11 November 2021
EMA/708926/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Nexviadyme

International non-proprietary name: avalglucosidase alfa

Procedure No. EMEA/H/C/005501/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Administrative information

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|---|---|
| Name of the medicinal product: | Nexviadyme |
| Applicant: | Genzyme Europe BV<br>Paasheuvelweg 25<br>1105 BP Amsterdam<br>NETHERLANDS |
| Active substance: | Avalglucosidase alfa |
| International Non-proprietary Name: | avalglucosidase alfa |
| Pharmaco-therapeutic group (ATC Code): | Not yet assigned |
| Therapeutic indication(s): | Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency). |
| Pharmaceutical form(s): | Powder for concentrate for solution for infusion |
| Strength(s): | 100 mg |
| Route(s) of administration: | Intravenous use |
| Packaging: | vial (glass) |
| Package size(s): | 1 vial, 10 vials, 25 vials and 5 vials |

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# List of abbreviations

| | |
|---|---|
| 4-MUG | 4- methylumbelliferone-α-D-glycopyranoside |
| 6MWT | 6 minute walk test |
| Ab | Antibody |
| ACE | angiotensin I-converting enzyme |
| ADA | anti-drug antibodies |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| AGLU | Algluccosidase alfa |
| ALT | alanine aminotransferase |
| ANX | Anion Exchange |
| AS | Active Substance |
| AST | aspartate aminotransferase |
| ATC | Anatomic Therapeutic Chemical |
| AUC | Area under the concentration-time curve |
| AUC0-24H | Area under the concentration from time 0 to 24 hours |
| AUC0-inf | Area under the serum concentration-time curve from time zero extrapolated to infinity |
| $AUC_{2W}$ | area under the curve over the dosing interval (2 weeks) |
| AVAL | avalglucosidase alfa |
| bisM6P | bis-mannose-6-phosphate-tetra-mannose glycan |
| BMI | Body Mass Index |
| Boc-AOAA | tert-(butoxylcarbonyl)aminooxyacetic acid (Boc aminooxyacetic acid) |
| BSE/TSE | *Bovine Spongiform Encephalopathy* / Transmissible Spongiform Encephalopathies |
| CE-SDS | Capillary electrophoresis sodium dodecyl sulfate |
| CHMP | Committee for Evaluation of Human Medicinal Products |
| CHO | Chinese hamster ovary |
| CI | Confidential Interval |
| CIM6Pr | cation-independent mannose-6-phosphate receptor |
| CIMPR | cation-independent mannose-6-phosphate receptor |
| CK | Creatine Kinase |

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|---|---|
| Cl | Clearance |
| Cmax | Maximum concentration |
| CoA | Certificate of Analysis |
| CPPs | Critical Control Parameters |
| CPV | continued process verification |
| CQA | Critical Quality Attributes |
| CRIM | cross-reactive immunological material |
| CV | Coefficient of variation |
| DBS | donor bovine serum |
| DCU | dicyclohexylurea |
| DDD | Defined Daily Dose |
| DHFR | dihydrofolate reductase |
| DHP | diphenhydramine |
| DPAS | Difficulty Physical Activity Score |
| DSC | Differential scanning Calorimetry |
| EAIR | Exposure Adjusted Incidence Rate |
| EC50 | Half Maximal Effective Concentration |
| ECG | electrocardiogram |
| ELISA | Enzyme linked immunosorbent assay |
| EMA | European Medicines Agency |
| EOP | End-Of-Production |
| EPAR | European Public Assessment Report |
| EQ-5D-5L | Five-Level EuroQoL in 5 dimensions |
| EQ-5D-VAS | Five-Level EuroQoL– Visual Analogue Scale |
| ERT | Enzyme Replacement Therapy |
| ETP | Extension Treatment Period |
| FBS | Fetal bovine serum |
| FP | Finished Product |
| FT-IR | Fourier transmission infrared (spectroscopy) |
| FVC | Force Vital Capacity |
| GAA | acid α-glucosidase |

| | |
|---|---|
| GAAKO | GAA knock-out |
| GAM6 | Alglucosidase alfa |
| GD | Gestation Day |
| GLP | Good Laboratory Practice |
| GMFCS-E&R | Gross Motor Function Classification System - Expanded and Revised |
| GMFM-88 | Gross Motor Function Measure-88 |
| GSD | glycogen storage disease |
| GSGC | Gait, Stair, Gower's Maneuver, and Chair composite functional assessment |
| Hex4 | hexose tetrasaccharides |
| HHD | Hand-Held Dynamometry |
| HIC-HPLC | Hydrophobic Interaction Chromatography High Performance Liquid Chromatography |
| HPLC | High Performance Liquid Chromatography |
| HRM | hypertrophic cardiomyopathy |
| HRQOL | health related quality of life |
| IARs | Infusion Associated Reactions |
| ICF | International Classification of Functioning, Disability, and Health |
| ICH | International Conference of Harmonisation |
| IgE | immunoglobulin E |
| IgG | immunoglobulin G |
| IMP | Investigational Medicinal Product |
| INN | International non-proprietary name |
| IOPD | infantile-onset Pompe disease |
| IPCs | In-Process Controls |
| IRT | Interactive Response Technology |
| IV | intravenous |
| KPAs | Key Process Attributes |
| KPPs | Key Process Parameters |
| LLOQ | Lower limit of quantitation |
| LOPD | late-onset Pompe disease |
| LS | Least Squares |
| LVM | left ventricular mass |

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|---|---|
| LVMI | left ventricular mass index |
| M6P | bis-mannose-6-phosphate-Man6 glycans |
| MA | Marketing Authorisation |
| MALDI-TOF MS | Matrix-assisted laser desorption-ionization – time of flight mass spectrometry |
| MCB | Master Cell Bank |
| MCID | Minimal Clinical Important Difference |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEP | Maximum Expiratory Pressure |
| MID | Minimally important difference |
| MIP | Maximum Inspiratory Pressure |
| mITT | modified intent-to-treat |
| MMRM | Mixed Model Repeated Measures |
| MRI | Magnetic resonance imaging |
| MWCO | Molecular Weight Cut Off |
| NAb | neutralising antibodies |
| NAS | New Active Substance |
| NCA | Non-compartmental analysis |
| NeoGAA | Avalglucosidase alfa |
| NHS | N-hydroxysucciminide |
| NI | Non Inferiority |
| NOAEL | No-observable adverse effect level |
| NORs | Normal Operating Ranges |
| NtA | Notice to Applicants |
| PAD | Pharmacologically active dose |
| PAP | primary analysis periods |
| PAR | Proven acceptable ranges |
| PCSA | potentially clinically significant abnormality |
| PD | Pharmacological |
| PDIS | Pompe disease impact scale |
| PDSS | Pompe disease symptom scale |
| PedsQL | PedsQL Pediatric Pain Questionnaire |

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|---|---|
| PFT | pulmonary functional testing |
| PGIC | Patients' Global Impression of Change |
| PIP | Paediatric Investigation Plan |
| PK | Pharmacokinetic |
| PND | postnatal day |
| p-NP | p-nitrophenol |
| p-NP-α-Glu | p-nitrophenyl-α-D-glucopyranoside |
| Pompe PEDI | Pompe pediatric evaluation of disability inventory |
| PoPK | population pharmacokinetic |
| PP | Per Protocol |
| PPQ | Process Performance Qualification |
| PS | Primary standard |
| PV | Process validation |
| QC | Quality Control |
| QMFT | Quick Motor Function Test |
| qow | every other week |
| QTPP | Quality Target Product Profile |
| rhGAA | recombinant human acid alfa-glucosidase |
| R-PACT | Rasch-built Pompe-specific Activity Scale |
| RP-HPLC | Reverse Phase - High Performance Liquid Chromatography |
| SA | Sialic Acid |
| SAE | Serious Adverse Event |
| SAM6 | avalglucosidase alfa |
| SAP | Statistical Analysis Plan |
| sCIMPR | Soluble cation-independent mannose-6-phosphate receptor |
| SD | Standard deviation |
| SDS-PAGE | Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis |
| SE | Standard Error |
| SE-HPLC | Size Exclusion High Performance Liquid Chromatography |
| SF-12 | Medical Outcomes Study 12 Item Short Form Health Survey |
| SF-36 | 36-Item Short Form Health Survey |

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|---|---|
| SmPC | Summary of Product Characteristics |
| SMQ | standardized MedDRA query |
| SOC | System Organ Class |
| SPR | Surface Plasmon Resonance |
| SV-AUC | Sedimentation velocity analytical ultracentrifugation |
| T1/2 | Time to maximal serum concentration<br>TMB Tetramethylbenzidine |
| t1/2z | terminal half-life |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TK | Toxicokinetic |
| ULN | Upper Limit of Normal |
| UV | Ultrafiltration/ Diafiltration step |
| UV | Ultra violet |
| Vz | Volume of distribution in the terminal phase calculated using the terminal slope (Lambda z) |
| WBC | Whole Blood Count |
| WCB | Working Cell Bank |
| WFI | Water for Injection |
| WHO | World Health Organisation |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Genzyme Europe BV submitted on 11 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Nexviadyme, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 November 2019.

Nexviadyme, was designated as an orphan medicinal product EU/3/14/1251 on 26 March 2014 in the following condition: Treatment of glycogen storage disease type II (Pompe's disease).

The applicant applied for the following indication: Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *1.3. Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0174/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0174/2020 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *1.5. Applicant's request(s) for consideration*

### 1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

### 1.5.2. New active Substance status

At the time of the initial submission, the applicant requested the active substance, avalglucosidase alfa contained in Nexviadyme to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

During the procedure, following the CHMP request, the applicant submitted data to support a claim for the active substance avalglucosidase alfa contained in the above medicinal product to be considered as a new active substance in comparison to alglucosidase alfa previously authorised in the European Union as Myozyme, as the applicant claimed that avalglucosidase alfa differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

## *1.6. Protocol assistance*

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 22 October 2015 | EMEA/H/SA/3170/1/2015/PA/I | *Dr Elmer Schabel and Dr Hans Ovelgönne* |
| 8 December 2015 | EMEA/H/SA/3170/1/2015/PA/III | *Dr Karl-Heinz Huemer and Prof. Brigitte Blöchl-Daum* |
| 31 May 2018 | EMEA/H/SA/3170/1/2018/FU/1/201/PA/I | *Dr David Brown and Mr Christian Gartner* |
| 13 December 2018 | EMEA/H/SA/3170/3/2018/PA/II | *Dr Kolbeinn Gudmundsson, Dr Karl-Heinz Huemer and Dr Armando Magrelli* |

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- Starting material and proposed specifications.
- Switch from non-irradiated to irradiated serum in the manufacturing process of alglucosidase alfa.
- Proposed analytical methods and plan to re-evaluate the proposed acceptance criteria.
- Release testing strategy and omission of testing of process-related impurities.
- Comparability analysis.
- Overall strategy for future process validation of the commercial manufacturing process and the intended up-scaling.

- Process and analytical control strategy for neoGAA.
- Functional assays to measure specific activity of neoGAA.
- Assays that could serve as the potency method for QC release testing and for stability testing of neoGAA.
- Release testing and methods for identity test.
- Evaluations to establish the acceptance criteria.
- Impurity control strategy.
- Mutagenic impurities assessment and the allowable limits calculated for one impurity.
- Control strategy.
- Demonstration of process consistency.
- Degradation pathway studies to provide information of the ability-indicating attributes of the product, in particular the active substance material and design.

Non-clinical:

- Acceptability of the non-clinical toxicity studies to support clinical development in both adult and paediatric patients.

Clinical:

- Acceptability of the proposed development plan in LOPD and IOPD to support the proposed indication and the inclusion of paediatric patients.
- Safety database.
- Selection of dose and dose frequency for the Phase 3 Study EFC14028 in LOPD patients naïve to treatment.
- Study design of the Phase 3 Study EFC14028 to support an MAA, in particular with regards to study population, study duration and endpoints selected, their frequency and timing, and immunogenicity assessments.
- Further questions on this study concerned the choice of primary endpoint in LOPD patients to demonstrate superiority of neoGAA over alglucosidase alfa and to support a specific label claim of superiority, sample size, analysis plan of the primary endpoint and proposed interim analysis.
- Study design of the Phase 2 IOPD Switch Study ACT14132 to support an MAA in terms of dosing cohorts and regimen, endpoints, study population and duration.
- Adequacy of the Phase 1/2 Study TDR12857 and the nonclinical data to support initiation of clinical trials in paediatric patients with IOPD and LOPD.
- Adequacy of the clinical development to show clinical significance.
- Approach to separate primary analysis period and the extension period, and the statistical methods for the latter.

Multidisciplinary Quality and Clinical:

- Orphan similarity.

## *1.7. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: Alexandre Moreau

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| The application was received by the EMA on | 11 September 2020 |
| The procedure started on | 1 October 2020 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 21 December 2020 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 21 December 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 4 January 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 28 January 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 18 March 2021 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 26 April 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 6 May 2021 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 20 May 2021 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 22 June 2021 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 7 July 2021 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | 20 July 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nexviadyme on | 23 July 2021 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of avalglucosidase alfa contained in Nexviadyme (see Appendix on NAS) | 23 July 2021 |

## *1.8. Steps taken for the re-examination procedure*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: John Joseph Borg

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|---|---|
| The Applicant submitted written notice to the EMA, to request a re-examination of Nexviadyme CHMP opinion of 23 July 2021., on | 27 July 2021 |
| The CHMP appointed Kristina Dunder as Rapporteur and John Joseph Borg as Co-Rapporteur on | 16 September 2021 |
| The Applicant submitted the detailed grounds for the re-examination on | 13 September 2021 |
| The re-examination procedure started on | 14 September 2021 |
| The Rapporteur's re-examination assessment report was circulated to all CHMP members on | 11 October 2021 |
| The Co-Rapporteur's assessment report was circulated to all CHMP members on | 3 October 2021 |
| The AHEG was convened to address questions raised by the CHMP on<br>The CHMP considered the views of the AHEG as presented in the minutes of this meeting | 26 October 2021 |
| The detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP on | 8 November 2021 |
| The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application recommended the granting of the marketing authorisation on | 11 November 2021 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The applicant applied for the following indication: long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

### 2.1.2. Epidemiology

Pompe disease (also known as acid maltase deficiency or glycogen storage disease [GSD] type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alfaglucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells leading to a variety of symptoms, clinical decline, and ultimately, death. In addition to being a lysosomal storage disorder, Pompe disease is also a neuromuscular disease, a metabolic myopathy, and a glycogen storage disorder.

The estimated global incidence of Pompe disease is 1:40,000, with variations in incidence reported between different ethnic groups (Martiniuk, 1998, Am J Med Genet; Ausems, 1999, Eur J Hum Genet; Poorthuis, 1999, Hum Genet; Hirschhorn, 2001, The Metabolic and Molecular Bases of Inherited Disease). All presentations of Pompe disease are caused by the same underlying deficiency of lysosomal GAA. However, there is significant heterogeneity in the clinical presentation of Pompe disease, and the disease manifests as a broad clinical spectrum with a continuum of clinical signs and symptoms (Chen, 2000, Mol Med Today; Hirschhorn, 2001, The Metabolic and Molecular Bases of Inherited Disease; van den Hout, 2003, Pediatrics; Kishnani, 2004, J Pediatr).

Pompe disease has been classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form of the disease to a more slowly progressing late-onset form with symptom onset any time after infancy through adulthood; there is considerable variability and overlap between these two extremes.
The majority of patients with Pompe disease are classified with late-onset Pompe disease (LOPD).

### 2.1.3. Biologic features, Aetiology and pathogenesis

Defects in both alleles of the gene for GAA, located on chromosome 17q25, result in reduced or absent enzyme activity. The deficiency in lysosomal GAA in Pompe disease results in the accumulation of glycogen to a variable extent in all muscles of patients with the disorder, leading to impaired contractile function. It is hypothesized that rupture of enlarged lysosomes leads to spill-over of lysosomal enzymes into the muscle cell cytoplasm, leading to eventual destruction of the muscle cell with fibrosis and fatty replacement as a consequence and progressive dysfunction of portions of muscle or even entire muscles. Imaging techniques such as total body MRI (magnetic resonance imaging) have shown that even Pompe disease patients who do not appear to have clinical

evidence of skeletal muscle involvement may have evidence of fatty replacement of parts of their muscles on MRI. T2 imaging can reveal large amounts of fatty infiltration with or without (+/-) fibrosis on MRI of their lower limbs, yet patients appear to be walking quite normally due to adaptive compensatory mechanisms.

Currently, over 500 mutations of GAA, including missense, nonsense, splicing defect, and frameshift mutations, have been found. According to the variety of mutations, clinical presentation of Pompe disease is heterogeneous in timing, severity, and ranges of symptoms observed.

Infantile-onset Pompe disease, which represents up to one third of the cases, presents in the first months of life and is characterized by virtually complete absence of acid alpha-glucosidase (GAA)-activity (GAA activity is less than 1%). Although GAA activity is <1% in all IOPD patients, two groups have to be differentiated. Patients may synthesize a non-functional form of GAA or are completely unable to form any kind of native enzyme. The former patients are designated as cross-reactive immunological material (CRIM)-positive, whereas the latter are classified as CRIM-negative.

The majority of Pompe patients become manifest after infancy with late-onset Pompe disease (LOPD), which shows a more variable course as compared with IOPD (Byrne et al., 2011; van der Ploeg et al., 2008). Longer disease duration of between 10-15 years, as well as FVC ≤80% predicted, are risk factors for more rapidly progressive disease (van der Beek, 2012, Orphanet J Rare Dis) and more than half of LOPD patients will eventually require ventilation after 10-15 years of symptomatic disease progression. The main cause of death in this group of patients is respiratory failure, a process in which dysfunction of the diaphragm is considered to play an important role (Wens, 2015, BMC Pulm Med). Patients who are symptomatic during childhood have a more rapidly progressive form of the disease and will often require ventilation at a younger age (van der Beek, 2011, Mol Genet Metab).

### 2.1.4. Clinical presentation, diagnosis and prognosis

Pompe disease is caused by biallelic mutations of the acid α-glucosidase (GAA) gene located on chromosome 17q25, that result in deficiency of the lysosomal enzyme GAA.

Severity of disease depends on the amount of residual enzyme GAA activity.

In classic infantile-onset Pompe disease (IOPD), GAA activity less than 1%causes marked accumulation of glycogen not only in skeletal muscle, but also in heart and other tissues contrary to milder forms with later onset (LOPD). Affected patients present with creatinine kinase elevation, hypertrophic cardiomyopathy (HCM), failure to thrive, muscular hypotonia and axial muscle weakness during the first six months of life. IOPD is rapidly progressive, and the majority of untreated subjects die within the first year of life due to a combination of ventilatory and cardiac failure without achieving any motor milestones such as turning, sitting, or standing. Survival beyond the age of 18 months is exceptional. Classic IOPD should be distinguished from non-classic or late-infantile Pompe disease that also manifests during infancy but has no or much less severe cardiac hypertrophy (Hahn et al., 2019).

Although GAA activity is <1% in all IOPD patients, two groups have to be differentiated. Patients may synthesize a non-functional form of GAA or are completely unable to form any kind of native enzyme. The former patients are designated as cross-reactive immunological material (CRIM)-positive, whereas the latter are classified as CRIM-negative. In the years since approval of ERT, it

has also become clear that IOPD is a multisystemic disorder, and that individuals receiving this kind of treatment develop clinical symptoms not known in the pre-ERT era. Features of this new IOPD phenotype include cardiac, speech, hearing, musculoskeletal, respiratory, swallowing, and neurocognitive symptoms.

Initial symptoms of LOPD typically include muscle weakness with a limb-girdle distribution, which often manifests as difficulties in climbing stairs, walking, running, and rising from a chair or lying position. Shortness of breath and respiratory dysfunction due to involvement of respiratory muscles, fatigue, exercise intolerance, and muscle pain are also common and may present at any time in the illness (Müller-Felber et al., 2007; Schüller et al., 2012; van der Beek et al., 2009, 2012; Wokke et al., 2008). Over time, progressive loss of muscle strength reduces mobility and interferes with the ability to independently complete activities of daily living, including toileting and dressing, resulting in decreased quality of life (Hagemans et al., 2004, 2005; Müller-Felber et al., 2007). Many LOPD patients ultimately end up confined to a wheelchair and require ventilation, and LOPD is also associated with increased mortality relative to the general population (Güngör et al., 2011). Although Pompe disease manifestations vary between individuals, studies in both IOPD and LOPD patients (Ausems et al., 1999) have confirmed that respiratory failure precedes death in nearly all subjects. The most common cause of death in patients with Pompe disease, regardless of age of disease onset and/or the severity of skeletal muscle weakness is respiratory failure (Hirschhorn et al., 2001; Güngor et al., 2011; Winkel et al., 2005).

### 2.1.5. Management

Currently the only treatment option for Pompe disease patients and standard-of-care is long-term enzyme replacement therapy (ERT) with alglucosidase alfa, globally approved for the treatment of all subsets of Pompe disease under the tradenames of Myozyme and Lumizyme. Enzyme replacement therapy (ERT) substitutes a deficient enzyme by intravenous infusion of the recombinant human enzyme at regular intervals. The enzyme is taken up into the cells via the mannose-6-phosphate receptor and transported to the lysosome.

Approval of alglucosidase alfa was based on early clinical trials demonstrating its ability to reduce cardiac hypertrophy and prolong invasive ventilator-free survival in infants with IOPD (Trials ALGLU01602 and ALGLU01702) and to stabilize respiratory function and improve walking distance in children and adults with LOPD (ALGLU02704).

Development and approval of ERT has profoundly changed the natural course of the disease, revealing new phenotypes in patients with classical IOPD who survive with ERT, and considerably extending productivity and quality of life for patients with LOPD. However, it is recognized that the progressive decline in muscle function in patients with Pompe disease is not completely abrogated with alglucosidase alfa ERT.

Studies in LOPD patients suggest that some patients on alglucosidase alfa continue to exhibit some decline in respiratory function, albeit at a slower pace than prior to treatment. Responses to treatment in LOPD patients vary between individuals and there might be room for improvement.

With respect to IOPD patients, literature data (Chien et al, 2015) indicate that some patients treated with Myozyme exhibit declines in motor function and mobility starting at 18-24 months of age, despite an initial decrease in CK levels. An effect that is likely due to reduced uptake of alglucosidase alfa in skeletal tissue compared to uptake in cardiac tissue. However, the reasons for the variable efficacy of ERT and the progression of disease with time are manifold and only imperfectly understood. Known factors include age at start of therapy and pre-treatment muscle pathology,

CRIM-status and antibody titers, distribution of type I and II fibers, and altered autophagy ( Kishnani et al., 2012).

Implementation of ERT has uncovered multisystemic character of IOPD, not known in the pre-ERT era. Although ERT has substantially improved the prognosis of IOPD, mortality is still considerable, and decline of motor function with time is frequent in long-term survivors. Thus, further huge efforts are necessary to improve the outcome of children affected by this most severe form of Pompe disease indicating an unmet medical need in the IOPD patients deteriorating on Myozyme.

## 2.2. About the product

The rationale for ERT in lysosomal storage disorders in general, and Pompe disease in particular, is that lysosomes are accessible to exogenous or extracellular proteins. The feasibility of using ERT in Pompe disease has been supported by studies in cultured skeletal muscle cells and fibroblasts, and in animal models of Pompe disease and efficacy was established in clinical trials with alglucosidase alfa.

The cation-independent mannose-6-phosphate receptor (CIM6Pr) plays an essential role in cellular binding, uptake and lysosomal targeting of exogenously administered alglucosidase alfa (Ghosh, 2003, Nat Rev Mol Cell Biol). This is supported by preclinical studies demonstrating a decrease in alglucosidase alfa uptake and reduced glycogen clearance in a muscle specific CIM6Pr/GAA double knockout mouse (Bali, 2004, ASHG). Furthermore, reports from the literature indicate that the CIM6Pr is present in relatively low levels in human skeletal muscle compared to that of cardiac tissue (Wenk, 1991, Biochem Internat) and that bis-phosphorylated glycans have a significantly higher affinity for the CIM6Pr as compared to the mono-phosphorylated forms (Tong, 1989, J Biochem). Therefore, greatly increasing the level of bis-M6P on alglucosidase alfa may provide a mechanism to drive uptake into the skeletal muscle.

Avalglucosidase alfa (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan) is a second-generation ERT for Pompe disease that has been specifically designed for enhanced receptor targeting and enzyme uptake with the aim of improving clinical efficacy and patient convenience. Avalglucosidase alfa is a modification of alglucosidase alfa (Myozyme and Lumizyme) that results in the conjugation of a number of hexamannose structures containing two terminal synthetic bis-mannose-6-phosphate-Man6 glycans (M6P) conjugated to alglucosidase alfa through an aminoxy nitrogen to carbon double bond. Compared to alglucosidase alfa, which contains only a single M6P molecule for each alglucosidase alfa molecule, each avalglucosidase alfa molecule contains approximately 13 to 18 M6P glycans.

## 2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment, as the product was not considered to be of major public health interest: Like alglucosidase alfa, avalglucosidase alfa is an enzyme replacement therapy. It does not exert a novel mechanism of action. Having additional therapeutic options for LOPD patients is valuable, but this is not considered sufficient to argue an unmet medical need and accelerated access. The subpopulation for whom an unmet need might exist (i.e. IOPD population worsening on alglucosidase/Myozyme) was not included in the pivotal trial. Moreover, formally, only non-inferiority against the established treatment has been demonstrated; superior efficacy was not shown.

## *2.4. Quality aspects*

### 2.4.1. Introduction

The finished product (FP) is presented as a powder for concentrate for solution for infusion containing 100 mg of avalglucosidase alfa as active substance (AS). Other ingredients are: histidine, histidine hydrochloride monohydrate, glycine, mannitol, polysorbate 80.

The product is available in type I glass vial with a stopper (elastomeric rubber), seal (aluminium) and a flip off cap (packs of 1, 5, 10 or 25 vials) as described in section 6.5 of the SmPC.

### 2.4.2. Active Substance

#### *2.4.2.1. General information*

The active substance (AS), avalglucosidase alfa (INN) is a recombinant human α-glucosidase (alglucosidase alfa, rhGAA) conjugated with multiple copies of glycan E13, a synthetic bis-mannose-6-phosphate-tetra-mannose glycan (bisM6P). The alglucosidase alfa is the secreted 110 kDa form of the molecule, which lacks the signal peptide and contains 896 amino acids and seven asparagine-linked glycosylation sites.

The bisM6P moieties are conjugated to sialic acid residues on alglucosidase alfa. As a result, approximately 7 hexamannose structures, each containing two terminal bis-M6P moieties, are conjugated to the oxidized sialic acid residues. Avalglucosidase alfa has on average a 15-fold increase in mannose-6-phosphate (M6P) moieties compared to alglucosidase alfa, which contains a single mole of M6P for each mole of enzyme.

Binding to M6P receptors on the cell surface has been shown to occur via carbohydrate groups on the acid alpha-glucosidase molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity to degrade glycogen.

#### *2.4.2.2. Manufacture, characterisation and process controls*

Manufacturing and testing of avalglucosidase alfa AS, are performed by Genzyme Flanders bvba, Cipalstraat 8, 2440 Geel, Belgium. Good Manufacturing Practice (GMP) compliance has been documented for all sites involved.

***Description of manufacturing process and process controls***

*Glycan E13 intermediate*

Glycan E13 intermediate is manufactured from starting materials applying a synthesis route using classical synthetic carbohydrate chemistry. The proposed starting material is acceptable. Reprocessing as declared is acceptable; no alternative commercial process is declared. The glycan E13 synthesis route remained the same throughout development (relevant changes are outlined in the dossier).

During the manufacturing process, Normal Operating Ranges (NORs) are applied. Proven acceptable ranges (PAR) were studied only to assess the criticality of the process parameters.

Overall, the manufacturing process description is acceptable. In-Process Controls (IPCs) are clearly defined. The quantity of each single starting material, solvent, reagent, catalyst employed in the synthesis is declared, as well as the operating temperatures. The typical yield of each step is reported in the dossier. The final yield of the manufacturing process is reported in the dossier, as well. The analytical methods used to monitor the IPCs have been described.

*Avalglucosidase alfa*

The AS manufacturing process consists in the bioproduction of alglucosidase alfa by a Chinese hamster ovary (CHO) cell culture in perfusion mode followed by purification steps. The purified enzyme is then oxidized and conjugated with an intermediate glycan E13, which is obtained by chemical synthesis. The conjugated enzyme, avalglucosidase alfa, is finally purified and formulated.

The cell culture process consists of a series of expansion steps (starting from thawing of the WCB vial) providing sufficient inoculum for the production bioreactor in which alglucosidase alfa is produced Harvest may be pooled and further processed. All the information concerning the production of the recombinant enzyme alglucosidase alfa starting from the cell bank system (Master Cell Bank (MCB), WCB and End-Of-Production (EOP) cells) is included in the dossier and of sufficient quality (the construction of the expression vector, the cell bank system and the cell bank characterization/ monitoring have been described in sufficient detail). Genetic stability has been confirmed.

Purification of alglucosidase alfa is performed using a series of chromatographic operations as well as depth and membrane filtration techniques starting from the harvest material collected in the harvest pool/depth filtration feed tank.

The sialic acids on the enzyme are oxidized with periodate before reacting with the reactive group (aminooxy) on the purified synthetic M6P-glycan to obtain the oxime conjugate which defines avalglucosidase alfa. This conjugation step leads to multiple copies of M6P bearing glycans. Additional purification, filtration and formulation steps are included after the conjugation to deliver avalglucosidase alfa AS.

***Control of materials***

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while Certificate of Analysis (CoAs) or specifications (including test methods) for non-compendial raw materials have been presented. CoAs for serum have been submitted.

Extractable and Leachable risk assessment was performed taking into account concepts and principles of ICH Q9 including criticality of the material, place of use in production process, applied process parameters. Overall, no high-risk components or materials were identified. The results are deemed acceptable.

As regards cell substrate and cell banking system, alglucosidase alfa is expressed in an independently derived CHO cell line. The vector map is provided. The expressing cells were cloned. The final clone was selected as it presented appropriate expression and genetic stability. From this clone, a cell banking system was established for commercial production. The generation of the

MCB and the first three WCBs was appropriately described. The results of the tests performed on each of these banks were provided. An EOP Cell Bank was constituted in culture Genetic integrity of MCB, WCB and EOP cells was confirmed by southern blot, copy number analysis and DNA sequence analysis. A protocol has been presented for preparation and qualification of future working cell banks.

***Control of critical steps and intermediates***

Analytical methods are in place to control impurities. Potential related substances in the intermediates have been discussed. The specification of intermediates includes limits for routine control of known, unknown and total impurities in-line with batch data.

Specification of Glycan E13 intermediate initially proposed by the applicant included appearance, identification, quantification of related substances, quantification of residual solvents, quantification of elemental impurities, mutagenic impurity assessment and quantification of endotoxins. The glycan E13 specification have been updated with regards to the agreed glycan purity and total impurities acceptance criteria and aligned with batch data.

An overview of the process controls (Critical Control Parameters (CPPs) and IPCs) within the avalglucosidase alfa manufacturing process has been provided. IPCs may have acceptance criteria or action limits. The manufacturing steps considered critical and controlled by CPPs and IPCs, are the following: harvest phase of production bioreactor, followed by all the downstream steps. The proposed avalglucosidase alfa control strategy (pre-oxidation intermediate in addition to avalglucosidase alfa AS/FP) in comparison to the current commercial alglucosidase alfa AS release acceptance criteria is acceptable. Section 3.2.S.2.4 has been updated to include the proposed specification (with acceptance criteria and action limits) and description of the analytical methods and validation summaries. Maximum Holding times of process intermediate are sufficiently illustrated.

***Process validation***

The process validation is divided into two major sections of WCB vial thaw to pre-oxidation and intermediate and pre-oxidation intermediate to avalglucosidase alfa AS. Due to the complexity and length of the process, Process Performance Qualification (PPQ) is performed in several separate studies for a single unit operation or a combination of process steps. Validation of the entire process is assured through the successful execution of all combined validation studies supplemented with process development and comparability data.

The process from WCB vial thaw to pre-oxidation intermediate was validated in the year 2008. Since then, the process was modified several times, and these modifications were validated one by one. The validated state was maintained with continued process verification (CPV) to ensure the intermediate batches used for the process validation of pre-oxidation intermediate to AS are from the validated process. Overall, the validation data for the steps from WCB vial thaw to UF/DF-3 are considered sufficient and appropriate.

The purification process from pre-oxidation intermediate through AS was validated on PPQ batches, derived from separate validated batches of glycan E13 and separate pre-oxidation intermediate batches. The results of successful consecutive PPQ runs provide evidence that the avalglucosidase alfa manufacturing process from the pre-oxidation intermediate to DS is consistent, reproducible and controlled to generate process intermediates and DS of intended

quality. All evaluated parameters complied with their respective pre-defined validation acceptance criteria, action limits and monitoring ranges.

Overall, the separate validation studies in combination with comparability data demonstrate that the manufacturing process for avalglucosidase alfa AS is reproducible, consistent and produces AS of intended quality.

Intermediate hold studies were performed to evaluate the in-process and/or storage conditions throughout the manufacturing process, including both microbial control and chemical hold. Data supporting cleaning and storage conditions of the resins and membranes have been provided. The shipping of the AS at temperature-controlled conditions was validated by real transport of three consecutive runs.

Glycan E13

Justified routine control of organic impurities has been included in the glycan E13 intermediate specifications. Results of three batches of the updated intermediate specifications Glycan E13 have been provided. All results comply with the proposed limits.

***Manufacturing process development***

*Process development history and process characterisation studies:*

The initial small-scale manufacturing process for alglucosidase alfa (rhGAA) was developed on 30 L/60 L bioreactor scale. Genzyme scaled up the initial 30 L/60 L perfusion process multiple times in preparation for commercial manufacture of alglucosidase alfa. The cell culture process was first increased to 160 L scale, then to 2000 L scale and subsequently to 4000 L scale. References to scale are based on the bioreactor working volume. Only the 4000 L scale is the manufacturing scale used for clinical and commercial manufacturing of avalglucosidase alfa.

The manufacturing process development for the avalglucosidase alfa AS process from the oxidation step onwards has been operated at different scales and locations during clinical GMP production, with some modifications introduced at each scale. Briefly, changes were made in the upstream material, the process has been optimization, and a new salt form of the glycan introduced. Process development and respective process changes were supported by process development studies including characterisation studies.

*Control strategy:*

The Quality Target Product Profile (QTPP) for avalglucosidase alfa is well defined. Critical Quality Attributes (CQA) are acceptable. An overview of the CPPs, KPPs (Key Process Parameters), IPCs and KPAs (Key Process Attributes) for commercial manufacturing of avalglucosidase alfa is given. The rationale and the impact on product quality, is sufficiently elaborated. Overall, the control strategy is acceptable.

*Comparability:*

Comparability studies were performed for each process change. The processes were found to be comparable with the respective previous process.

The results demonstrated the biochemical comparability of avalglucosidase alfa through the development process including process transfer and scale-ups.

*Glycan:*

Overall, manufacturing process development section for the manufacture of Glycan E13 is acceptable.

***Characterisation***

*Elucidation of structure and other characteristics:*

Summary of the characterization tests (primary structure confirmation, post-translational modifications, glycosylation, secondary and higher order structure and biological activity) performed on the PPQ batches, the primary standard (PS) and historical batches are provided. Data show comparability to the PS and also consistency over the development.
Characterization analyses provided further information on:
- the avalglucosidase alfa protein structure, e.g., peptide mapping, molecular weight determination non-reduced and reduced purity,
- secondary and tertiary structure by circular dichroism, solution structure by analytical ultracentrifugation; free thiol content,
- post-translational modifications, e.g., oxidation deamidation and glycosylation including oligosaccharide profiling, peptide map and monosaccharide composition,
- and function, e.g., enzyme kinetic parameters, cellular uptake, and M6P receptor binding.

The primary structure is consistent with the primary amino acid sequence encoded by the cDNA. The avalglucosidase alfa molecule contains 13 cysteine residues, 12 of which are involved in disulfide linkages. The disulfide bond configuration of avalglucosidase alfa was confirmed by peptide mapping the consistency of the secondary and higher order structure of avalglucosidase alfa was confirmed. The 7 asparagine-linked glycosylation sites in avalglucosidase alfa are asparagine residues 84, 177, 334, 414, 596, 826, and 869. These are the target conjugation sites for the synthetic glycan E13. The molecular weight of the protein after glycan conjugation was confirmed.

All the modifications which could lead to the formation of charge variants (glycosylation, phosphorylation, deamidation) were characterized by oligosaccharide profiling, site specific glycosylation analysis and mannose-6-phosphate content.

As regards the biological characterisation studies, the enzymatic activity of avalglucosidase as well as its ability to bind to the M6P receptor and be internalized by the cell is demonstrated. There is no impact of glycan conjugation on enzymatic activity.

Overall, the active substance has been sufficiently characterized.

*Impurities:*

The actual and potential impurities of avalglucosidase alfa AS, which may arise from raw materials, manufacturing process, avalglucosidase alfa variants, and avalglucosidase alfa degradation, are separated into process-related and product-related impurities. The purification process for avalglucosidase alfa has been designed to produce highly purified avalglucosidase alfa and to remove potential impurities. On the whole, the proposed impurity control strategy is endorsed.

Process related protein impurities have been quantified and confirmed to be decreased at each purification column step. For process related impurities related to E13 glycan synthesis, only

impurities specified at levels in E13 glycan above the applicable ICH safety limits are considered impurities which require control in the AS.

Product related impurities of avalglucosidase alfa AS include processed forms of alglucosidase alfa which are sufficiently controlled at characterisation level or in the AS specification.

The quality and toxicological information relevant for the evaluation of the actual and potential mutagenic impurities, as well as the acceptable limit and the control strategy have been defined.

On the whole, the proposed impurity control strategy is endorsed.

#### *2.4.2.3. Specification*

The specification for avalglucosidase AS include general tests for, identity, concentration, potency, purity, impurities, and safety tests.

The specification limits are based on results of batches used in clinical trial and batches obtained with the final commercial process. Recommendations of NfGs on Production and quality control of medicinal products derived by recombinant DNA technology (3AB1a) and Specifications: Test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96) are followed.
In general, the specification provided is acceptable.
The potency of avalglucosidase alfa is attributed to the enzymatic activity of the molecule as well as its ability to bind to the M6P receptor and be internalized by the cell.

Based on correlation data as well as a controlled manufacturing process, the proposed release assay panel versus the proposed characterization tests, relative to the critical quality attributes of the product, was justified.

Deamidation and isoaspartic acid isomerization were both observed during forced degradation studies performed at elevated temperature (37°C) at low and high pH conditions. Since deamidation levels for all Processes batches have been very low at the AS storage conditions, testing for deamidation as part of release and stability for the commercial process is not proposed. This is acceptable. Furthermore, degradation of avalglucosidase alfa is primarily controlled by the proposed acceptance criteria for aggregation, which indirectly provides a control for deamidation as deamidation only occurs under conditions where avalglucosidase alfa heavily aggregates. Oxidized species were assessed during characterization and oxidation conditions are well-controlled during the process. In order to establish the acceptance criteria of avalglucosidase AS, lots have been used to treat patients in clinical trials have been taken into account,

The acceptance criteria for bioburden and bacterial endotoxins are acceptable.

***Analytical methods***

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

***Batch analysis***

Batch analyses are presented AS batches manufactured according to all processes used, The information provided on the batches is sufficient. All release results for all avalglucosidase alfa AS and nanofiltrate batches (unformulated bulk) are within the defined acceptance criteria for the avalglucosidase alfa AS and nanofiltrate.

***Reference materials***

The reference standards are sufficiently described. The PS was subjected to full analytical, biological and physico-chemical characterization.

The primary standard, once established, is used to qualify all future working standards or a new primary standard if necessary. The primary standard will also be used for analytical testing for the purpose of characterization, where necessary.

The acceptance criteria for the annual (re-)qualification of the primary standard are deemed acceptable.

***Container closure system***

Avalglucosidase AS is stored in a single-use polyethylene bag.

#### *2.4.2.4. Stability*

Stability studies based on ICH guidelines have been conducted for the active substance. Relevant parameters were selected to study the stability profile of the active substance.

The analytical methods were validated and are described in the relevant sections of the dossier. The data from primary stability and supporting stability studies support the proposed shelf life at the designated storage condition in the proposed container closure system.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

## 2.4.3. Finished Medicinal Product

#### *2.4.3.1. Description of the product and pharmaceutical development*

Avalglucosidase alfa FP is a sterile lyophilized powder for injection administered by intravenous (IV) infusion following reconstitution with WFI and dilution. It is supplied in vials with a nominal strength of 100 mg/vial. The AS and the FP consist of the same formulation - an aqueous buffered solution, pH 6.2, containing 10 mg/mL avalglucosidase alfa protein, L-histidine, mannitol, glycine, and polysorbate 80.

Prior to lyophilization, the nominal fill volume is 10.0 mL. An overfill is introduced. Each vial is filled with a target fill volume of 10.3 mL of AS in order to ensure that 10.0 mL of solution can be withdrawn following reconstitution.

The primary packaging is 20 mL Type I clear colourless glass vial closed with a 20 mm siliconized grey elastomeric stopper with an outer FluroTec coating (no product contact) , crimped with an aluminium seal and a flip off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Each pack contains 1, 5, 10 or 25 vials.

**Table 1. Qualitative and quantitative composition of Avalglucosidase Alfa Finished Product (100 mg/vial)**

| Component * | Function | Reference to Quality Standards |
|---|---|---|
| Avalglucosidase alfa | Active pharmaceutical ingredient | Custom specification |
| L-Histidine | Buffer | USP-NF/Ph. Eur./JP |
| L-Histidine hydrochloride monohydrate | Buffer | Ph. Eur./JP |
| Glycine | Lyoprotectant, bulking agent, and tonicity modifier | USP-NF/Ph. Eur./JP |
| Mannitol | Lyoprotectant, bulking agent, and tonicity modifier | USP-NF/Ph. Eur./JP |
| Polysorbate 80 | Stabilizer | USP-NF/Ph. Eur./JP |
| | Solvent | USP/Ph. Eur./JP |

* Nitrogen (USP, Ph. Eur.) is used following lyophilizer vacuum release at the end of the lyophilization cycle to overlay the drug product vials prior to capping.

The components of the finished product, active substance and excipients, are adequately described. The choice of the excipients and their concentrations are justified.

Development of a buffer and pH system, with specified concentrations of stabilizing/lyoprotectant agent and surfactant, is sufficiently described. Compatibility of excipients and the robustness of the formulation has been demonstrated by formulation development studies to assess impact of excipients on quality attributes. A lyophilisation cycle, based on experience with a similar product has been established, which is considered acceptable. The final formulation was shown to be robust and to ensure stability of avalglucosidase alfa in liquid (AS) and lyophilized (FP) states when stored at recommended storage conditions of 2-8°C. One single formulation has been used over the course of development of avalglucosidase alfa.

No overages have been used for this FP. However, an overfill of 0.3mL is included to withdraw the desired amount of 10 mL.

Physicochemical and biological properties are sufficiently discussed. After reconstitution, the product is a clear, colourless to pale yellow solution, and essentially free of visible particles.

Avalglucosidase alfa has been manufactured according to fiveseveral processes variantsprocesses throughout the clinical and commercial development Process characterization studies were conducted at laboratory and industrial scales to support the changes and identify critical parameters that were relevant for process validation. The CPPs and the applied control strategy are described and are considered acceptable. Comparability assessments demonstrated that the lots produced by commercial process have characteristics and stability profile comparable to lots produced by previous processes. Extractables/Leachables from fill-finish line were tested and a filter validation is provided. Bacterial retention test and chemical compatibility of the FP and the used filters is provided.

### *2.4.3.2. Manufacture of the product and process controls*

*Manufacturers*

Manufacturing and release activities of avalglucosidase alfa FP is conducted at EU GMP compliant sites. The FP is released in the EEA by Genzyme Ireland Limited, Waterford, Ireland.

A batch range has been defined. The FP manufacturing process is standard and starts with AS pooling and mixing. The AS solution is then sterilized by filtration immediately prior to filling. Upon completion of the lyophilization cycle, vials are stoppered and capped, and visual inspection is performed before secondary packaging and labelling.

The level of detail in the description of the FP manufacturing process is deemed sufficient. List of IPCs is endorsed and process parameter ranges are supported by manufacturing process development. Controls of critical steps and intermediates is sufficiently described.

Validation of the avalglucosidase alfa FP manufacturing process was performed in accordance with EMA "Guideline on process validation for finished product –information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/749073/2016). Process validation (PV) was performed on manufacturing process validation, aseptic process validation (including media fills) and simulated shipping validation. The process parameters met proven acceptable ranges as defined by process development, demonstrating the manufacturing process is consistent throughout the different steps. Process maximum holding times for bulks, filtration/filling time and transport arrangements have been justified / validated. Efficacy of aseptic processing was satisfactorily addressed.

***Control of Excipients***

Pharmacopoeia grade excipients (Ph. Eur.) are used in the production of AS and FP. No novel excipients or excipients of human or animal origin are used in the avalglucosidase alfa FP. All excipients are tested using analytical procedures to full compendial monograph requirements.

### *2.4.3.3. Product specification*

The avalglucosidase FP specifications were established in line with ICH Q6B and include general testing, tests for protein content, safety, purity, impurities and potency.

Acceptance criteria setting is based on a combination of several factors: clinical experience, release and stability data, current compendia or regulatory guidelines, and product-specific knowledge. Overall the proposed specifications are considered justified and sufficient to deliver product with consistent quality.

A sufficiently detailed release and shelf life specification is presented. Parameters for lyophilized and reconstituted product are given in tabular format, including reference to used methods and specified limits for release and stability. All parameters are sufficiently justified.

*Impurities*

No elemental impurity above the ICH Q3D limits was detected and no extractable/leachable compound was identified to present a risk for the patient.

A full assessment of the risk for the presence of nitrosamine impurities in the FP has been presented, including the intermediates (alglucosidase alfa and glycan E13), the AS, excipients, manufacturing process/equipment and packaging. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the AS or the related FP. Therefore, no additional control measures are deemed necessary.

***Analytical methods***

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Analytical procedures that are common with the AS are discussed in the AS section. Analytical procedures dedicated to FP are mostly compendial and thus do not require specific validation, except for Dot Blot and HPLC (M6P content) methods which were validated as per ICH Q2 requirements. The Dot Blot method can serve as an identity test for FP in lieu of peptide map testing for AS, as previously agreed during EMA scientific advice. Compendial methods were verified in accordance with compendial requirements. Verification data for sterility and endotoxin testing have been provided.

***Batch analysis***

Batch analysis data from Process A, Process B, Process C1, Process C2A, and Process C2B, respectivelyof the finished product were provided. Among them, four batches were manufactured at the commercial site using the intended commercial process. The results are within the specifications and confirm consistency of the manufacturing process.

***Reference materials***

The reference standard used is the same as for testing AS.

***Container closure system***

The primary packaging materials consist of a clear colourless glass vial that meets the European Pharmacopoeia (Ph. Eur.) specifications for Type I glass and a 20 mm siliconized Type I grey elastomeric chlorobutyl stopper. The stoppers are crimped to the vials with an aluminium seal with plastic Flip-Off cover (non-product contact).

The secondary packaging components of FP are vial cartons.

The suitability of the selected primary packaging material for its intended use is supported by stability study results, container closure integrity testing and extractables/leachables studies. Avalglucosidase alfa FP contains no preservative. Sterility is sufficiently investigated by CCIT testing after manufacture and after storage (stability). Light protection is provided by secondary packaging (vial cartons), however the product is not sensitive to photo stress.

The containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life.

The product is intended to be administered at final concentration of 0.5 mg/mL to 4 mg/mL via intravenous infusion using water for injections (for reconstitution) and 5% dextrose solution (for dilution).

### *2.4.3.4. Stability of the product*

A 4-year shelf life is claimed for avalglucosidase alfa FP, when stored at 2-8°C.

Stability studies are carried out in accordance with current ICH/CPMP guidelines on a suitable number of batches representative of the final commercial product. The containers used in the stability studies are the same as those proposed for routine storage. Relevant parameters were selected to study the stability of the finished product. The analytical methods were appropriately validated.

Overall, little or no change has been observed for the FP stored under long-term and accelerated conditions, thus supporting the shelf-life and storage conditions for routine storage. Additionally, photostability study was performed and demonstrated that the FP is not sensitive to light exposure. Temperature cycling stability study is also ongoing with one batch; up to date (24 months available), no change in the stability profile was observed.

In-use stability studies support the instructions for use and handling in the SmPC which states that the reconstituted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and diluted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and up to 9 hours (including infusion time) when stored at room temperature (up to 25°C).

A post-approval stability protocol and stability commitment is provided.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

#### *2.4.3.5. Adventitious agents*

Material of animal origin used in host cell line culture, cell line development, cell banking, and the manufacturing process included. Concerning BSE/TSE risk, the data provided are satisfactory, and the risk is considered negligible due to the certified suitability or safety of the source materials, as well as dilution effects and the poor capability of CHO cells to express prion proteins.

The cells banks were assayed for adventitious and endogenous agents according to ICHQA5 guideline. No viral particles were observed other than retroviral-like particles normally seen in the MCB and EPC cell types. The starting material does not include any human material.

The virus validation studies performed in addition to the initial studies of the centralized procedure of alglucosidase alfa (Myozyme) have been submitted and support the viral clearance of the Avalglucosidase alfa manufacturing process.

Virus validation studies have been performed to meet the CPMP/BWP/268/95 guideline. The reduction factors for all 5 purification steps, using worst case parameters concerning viral clearance, were satisfactory regarding the virus removal/inactivation (the choice of model viruses complies with CPMP/BWP/268/95 guideline).

The overall viral safety of avalglucosidase alfa is considered acceptable.

#### *2.4.3.6. GMO*

Not applicable.

### 2.4.4. Discussion on chemical, pharmaceutical and biological aspects

***Quality Development***

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

In response to a major objection raised, the applicant has provided an adequate risk evaluation concerning the presence of nitrosamine impurities in the finished product, that there is no risk identified. The major objection is therefore considered resolved.

### 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

### 2.4.6. Recommendation(s) for future quality development

Not applicable.

## *2.5. Non-clinical aspects*

### 2.5.1. Introduction

Avalglucosidase alfa was evaluated in a series of non-clinical pharmacology, pharmacokinetic, and toxicology studies. These studies were conducted to evaluate the nonclinical safety and characterize efficacy in the in vivo animal models. Since the clinical route of administration is intravenous (IV) infusion, all nonclinical studies also administered avalglucosidase alfa via the IV route.

### 2.5.2. Pharmacology

A GAA knockout mouse model was used to evaluate safety and efficacy of SAM6 (NeoGAA) (Genzyme Corporation, Framingham, Massachusetts, U.S.A.; Raben, et al. 1998; Raben et al., 2000). The homozygous disruption of the GAA gene (6neo/ 6neo) results in lack of enzyme activity, reduced autophagy and glycogen accumulation in a manner similar to the adult form of Pompe disease in humans.

Throughout the preclinical programme, four studies were carried out to evaluate efficacy of enzyme replacement therapy with SAM6 in the GAA knockout mouse model. The approved recombinant human (rh)GAA (Myozyme) was used as a comparator.

The aim of the pharmacodynamics program of SAM6 (neoGAA3) was to evaluate glycogen clearance in the clinically relevant target tissues, the heart and skeletal muscle and the diaphragm.

#### *2.5.2.1. Primary pharmacodynamic studies*

Using the GAA knockout mouse model, the pharmacodynamic effects of SAM6, GAM6 (neoGAA3b) and rhGAA were compared in 3-6 months old GAA knockout mice to evaluate the glycogen clearance in the skeletal and cardiac muscle (**Study-07-1948**). After four weekly administrations of recombinant SAM6, GAM6 or rhGAA tissue specific reduction in glycogen deposition was evaluated. Common effects in animals treated with human enzymes are hypersensitivity reactions. In order to prevent the induction of hypersensitivity by the study medication, all groups received 5 mg/kg

diphenhydramine (DPH) intraperitoneally 10-20 minutes prior to SAM6, GAM6 or rhGAA application. SAM6 and GAM6 were approximately 3- to 7-fold more efficacious compared to rhGAA on a dose basis. Comparisons between SAM6 and GAM6 indicate that SAM6 is more potent at equivalent doses of GAM6 in the heart and quadriceps muscle. Interestingly, mild multifocal myocardial necrosis was seen in a single mouse in the 20mg/kg SAM6 group. Histopathologic examination in other tissues did not reveal any SAM6 related adverse effects. A consequence of lysosomal glycogen accumulation in GAA knockout mice is found in target tissues including liver, kidney, lung, and muscle tissue. Cytoplasmic swelling and vacuolation was assessed with specific PAS staining and found to be reduced in hearts of high dose SAM6 treated animals comparable to GAM6 or rhGAA application. No appreciable difference was observed in other tissues at other concentrations of SAM6, GAM6 or rhGAA. While there is a clear dose dependent effect for SAM6, GAM6 and rhGAA in reduction of glycogen content in the heart, this is not seen in other tissue. Interestingly, there is a 3.4 fold difference in the reduction of glycogen between the quadriceps and triceps in the highest SAM6 dose. Whether these differences in SAM6 distribution are significant for various skeletal muscles has not been evaluated.

Based on the hypothesis that higher amounts of mannose-6-phosphate (bisM6P) on rhGAA will improve absorption into target tissues, consecutive enhancement in clearance of glycogen was investigated in quadriceps, triceps, psoas and diaphragm of in 3-6 month old GAA knockout mice (**Study-09-3981**). The glycogen clearance was compared between rhGAA, and SAM6 containing variable levels of bisM6P in GAA knockout mice following 4-weekly dose administrations. The SAM6 conjugates were dosed at 20 mg/kg and rhGAA at 100 mg/kg for intravenous administration. Hypersensitivity reactions were prevented by administration of 5 mg/kg diphenhydramine (DPH) intraperitoneally, 10-20 minutes prior to test article application and repeated if necessary. Seven days after the last dose, animals were sacrificed and frozen tissues collected for glycogen content analyses. In parallel, blood samples were processed and evaluated for anti-rhGAA antibodies. The glycogen clearance in all tissues was comparable between rhGAA and SAM6 conjugates. Consistently, 20 mg/kg SAM6-1 was less potent than 100 mg/kg rhGAA in quadriceps, triceps and psoas. The overall variability of tissue glycogen clearance hindered a robust statistic evaluation. Anti-rhGAA antibodies were detected in all animals of all groups. Taken together, SAM6-1 containing two glycans was significantly less potent than the other SAM6-conjugates in all tissues except the diaphragm. Conversely, these data indicate that three or more glycans are required to obtain a substantial increase in potency of SAM6 relative to rhGAA. However, the differences in glycogen clearance were not consistent across all muscle tissues examined in this study. The variability of tissue glycogen levels in the diaphragm hampered establishing a clear and significant pattern of rank order of potency among treatment groups. Thus, there were no consistent differences between the potency of SAM6-2 through SAM6-5.

Glycogen clearance following administration of 4-weekly doses of rhGAA and neoGAA was investigated in GAA knockout mice (**Study-10-00587**). Diphenhydramine was administered to prevent a test article related hypersensitivity reaction prior to the 4- weekly doses of vehicle, 20, 60, or 100 mg/kg rhGAA or 4, 12, 20 mg/kg neoGAA. The study was terminated 7 days after the last dose. The heart, quadriceps, triceps, diaphragm and psoas muscles were collected and analysed for glycogen clearance. Blood samples were used for antibody analysis. No statistically significant differences were observed in glycogen reduction in the heart, quadriceps and diaphragm tissue following administration of neoGAA (SAM6) compared to rhGAA administered at 5-fold higher doses. Dose dependency and comparability were less conclusive in psoas and triceps. The level of glycogen reduction in the highest dose group of rhGAA was significantly better than 20mg/kg neoGAA. Taken together, the amount of glycogen reduction was strongly dependent on muscle type, and neoGAA

was not superior to rhGAA, in particular in the triceps and psoas. Interestingly, tibialis anterior and soleus muscle were collected, but no results were provided in terms of glycogen reduction.
Anti-rhGAA antibodies were detected in all animals of all groups. Due to expected hypersensitivity response, 5 mg/kg DPH was administered intraperitoneally prior to test article administration starting from the second administration. Beside this prophylactic administration, a second dose of 5 mg/kg DPH was given to animals showing signs of hypersensitivity after test article administration. Four animals died during the study. One animal died of unknown reason when receiving the fourth dose of vehicle. Another animal received the second dose of neoGAA (4 mg/kg) and died approximately 30 minutes thereafter. The third animal received rhGAA (20mg/kg) and died after the second dose. Although the cause of death is unknown, the event coincided with the second dose of DPH and maybe indicative for a hypersensitivity reaction. Lastly, one animal died the day after the last dose of neoGAA (12 mg/kg) and the reason is unknown. The reason for death is unknown in all cases, but timing of death is consistent with enzyme administration in two out of four cases, indicating a causal relationship to hypersensitivity against the test article.

**Study 11-02367** investigated the effect of different levels of sialic acid in neoGAA on reduction of glycogen content in various tissues of the GAA knockout mice. The test articles were applied in 4-weekly intravenous doses (4 and 12 mg/kg groups), containing either 5.5 mol/mol (neoGAA-5SA) or 7.2 mol/mol sialic acid (neoGAA - 7SA). The glycogen content was determined in heart, quadriceps, and triceps muscle. Dose concentration analysis was performed on dose retains from the first and fourth doses. Overall, no differences were found between neoGAA-5SA and neoGAA-7SA in any of the examined tissues (heart, quadriceps, and triceps). While there was no glycogen clearance at the 4 mg/kg dose level in skeletal muscle, at 12 mg/kg glycogen was reduced also in skeletal muscle. In triceps, 12 mg/kg neoGAA-7SA was significantly more effective than 12 mg/kg neoGAA-5SA. An explanation for the latter observation is not provided. Overall, the content of sialic acid (5.5 or 7.2 mol/mol) in rhGAA had no significant effect on glycogen clearance in this study.

#### *2.5.2.2. Secondary pharmacodynamic studies*

No secondary pharmacodynamic studies have been conducted. This was considerable acceptable by the CHMP.

#### *2.5.2.3. Safety pharmacology programme*

Safety pharmacology was implemented in the 26-week toxicity study of SAM 6 (avalglucosidase alfa) in cynomolgus monkeys (**Study 0658-11097**). The criteria were compatible with the ICH S7A and S7B guidelines and represent the core battery. The observations indicated that there were no SAM6-related changes in neurobehavioral, electrocardiogram (ECG) parameters, heart rate, core body temperature, activity or respiratory rate following administration at the highest dose administered 200 mg/kg IV. The mean Area Under the concentration time curve $(AUC)_{0\text{-}inf}$ exposure following the thirteenth infusion at the no observable adverse effect level (NOAEL) was 28161 µg.h/mL.

#### *2.5.2.4. Pharmacodynamic drug interactions*

No pharmacodynamic drug interactions studies have been conducted. This was considered acceptable since avalglucosidase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis, thus unlikely to be candidate for cytochrome P450 mediated drug-drug interactions.

## 2.5.3. Pharmacokinetics

In order to investigate the pharmacokinetic properties of avalglucosidase three dedicated single dose PK studies and two biodistribution studies were conducted in GAA knockout mice. In addition, toxicokinetic data were collected in the scope of the repeat-dose toxicity studies conducted in mice and cynomolgus monkeys.

Qualification of the 4-MUG (4- methylumbelliferone-α-D-glycopyranoside) assay (**Study 13GSTR088**) to detect avalglucosidase alfa in sera and tissues of non clinical species included analysis of mouse and monkey serum as well as tissues from CD1 and GAA knockout mice. No avalglucosidase alfa activity was detected in the tissues of GAA knockout mice; however, endogenous alglucosidase alfa was detected in wild-type mice. The tissue-specific LLOQ was determined by measurement of tissue homogenates from GAA knockout mice spiked with avalglucosidase alfa. Overall, the assay was qualified for the quantitation of avalglucosidase alfa in mouse heart, quadriceps, triceps, psoas, diaphragm, liver, and serum, rat serum, dog serum, and in monkey liver and serum (**Study DIV1922**). The 4-MUG assay for quantification of avalglucosidase in CD-1 mouse (**Study DOS1648**) and cynomolgus monkey (**Study 11GSTR069**) serum was validated regarding intra-assay precision, inter-assay precision and accuracy, selectivity, dilution linearity and freeze/thaw stability. A quantification range from 1000 to 45000 ng/mL and 300 to 4883 ng/mL was successfully validated for mouse and monkey serum, respectively. A similar assay was set up for the measurement of alglucosidase alfa activity.

An anti-neoGAA antibody (Ab) ELISA was successfully validated for the determination of anti-neoGAA antibody titers in CD-1 or GAA knockout mouse and cynomolgus monkey serum. Validation was performed in sera spiked with anti-neoGAA antibodies. The impact of avalglucosidase alfa present in the samples was also evaluated and drug tolerance was established at > 10 µg/mL avalglucosidase alfa. Similarly, an ELISA assay was successfully set up for the determination of anti-rhGAA antibody titers in CD-1 or GAA knockout mouse serum.

Pharmacokinetic parameters after a single IV administration of 20 mg/kg of avalglucosidase alfa and alglucosidase alfa were comparatively evaluated in two separate studies in GAAKO mice (**Studies 08-2344 and 10-00813**). Samples were analysed 5, 15, 30, 60, 120, 240 and 360 minutes post dose. Although the absolute values of pharmacokinetic (PK) parameters differed between the studies, reduced T1/2 and VZ were observed in the avalgucosidase alfa treated groups as compared to alglucosidase. Clearance (CL) tended to be higher in avalglucosidase alfa treated animals. Systemic exposure (AUC) was higher in the alglucosidase groups of both studies, whereas no equivocal trend could be observed for Cmax, which was either higher or lower for each of the molecules when comparing the results of both studies.

An additional single dose PK study was conducted in GAAKO mice in order to comparatively evaluate the properties of avalglucosidase containing either 5.5 or 7.2 mol/mol sialic acid (**Study 10-00540**). No significant differences in any of the evaluated PK parameters were observed between the two investigated molecules.

Toxicokinetic parameters after repeated IV administration (once per week for four weeks) of 4, 40 and 120 mg/kg avalglucosidase alfa were evaluated in CD-1 mice in the scope of an exploratory toxicology study (**Study 10-00183**). Toxicokinetic analysis was conducted after the first and last administration. TK evaluation revealed an increase in exposure, decrease in clearance and increase in T1/2 with increasing dose. In addition, T1/2 and VZ were statistically significantly decreased after four administrations of 120 mg/kg when compared to the first administration. In the 4 mg/kg and in the 40 mg/kg groups no relevant differences between the first and last dose were detected.

Toxicokinetic evaluation was also included in a juvenile toxicity study in Crl:CD1 mice administered 10, 50 or 100 mg/kg avalglucosidase alfa every other week for a total of 9 weeks (in summary 5 or 6 administrations) (**Study JUV0033**). An approximate dose relation was observed with regard to Cmax for all dose groups. In contrast, AUC increased disproportionally with increasing dose. Slightly higher exposure was observed in female animals as compared to males.

The repeat-dose toxicity studies in cynomolgus monkeys also comprised toxicokinetic evaluation.

In an exploratory study (**Study # 1213-004**), cynomolgus monkeys were administered 4, 40 or 120 mg/kg avalglucosidase alfa once weekly for four weeks. Avalglucosidase alfa levels were below the detection limit in the 4 mg/kg dose group. Exposure in the 40 mg/kg and 120 mg/kg dose groups was dose-related (Cmax: 192 ± 63.3 and 862 ± 302 µg/mL, respectively) and clearly increased in the 120 mg/kg group after the fourth infusion (1273 ± 214 µg/mL). Thus, AUC0-inf (3155±911 vs 5900 ± 660 µg▪hr/mL) and AUC0-inf/dose (26.3 ± 7.59 vs 49.2 ± 5.50 µg▪hr/mL/dose) were statistically significantly elevated after the fourth infusion as compared to the first infusion of 120 mg/kg. In contrast, Vz and CL decreased with increasing numbers of infusions.

In a 26-week, GLP-compliant, repeat-dose toxicity study (**Study # 0658-11097**) cynomolgus monkeys were administered 0, 50 or 200 mg/kg avalglucosidase alfa every second week via 6-hour IV infusion. Exposure to avalglucosidase alfa was dose-dependent (Cmax: 566 ± 157 and 3892 ± 506 µg/mL; AUC0-inf/dose: 48.5 ± 13.6 and 93.6 ± 14.3 µg▪hr/mL/dose after the first infusion) and increased with increasing numbers of infusions (Cmax: 861 ± 189 and 5284 ± 1440 µg/mL; AUC0-inf/dose: 74.2 ± 19.5 and 141 ± 53.5 µg▪hr/mL/dose after the thirteenth infusion). In addition, increasing t1/2 and decreasing CL was observed.

Observations in both studies indicate that saturation has been reached by repeated administrations of the high dose.

In order to investigate the influence of increasing plasma levels of the glycan linker as a consequence of avalglucosidase alfa degradation on the toxicity of avalglucosidase alfa, a study was conducted in cynomolgus monkeys (**Study TXC1530**). Animals were administered with 50 mg/kg avalglucosidase alfa every other week for 13 weeks, additionally spiked with 0, 3, 6 or 12.55 mg/kg of Genz-669342 (glycan). No influence of the glycan on T1/2 or exposure was observed.

Tissue levels after one single administration of 20 mg/kg avalglucosidase alfa or alglucosidase alfa were evaluated in GAA knockout mice (**Study 10-00818**). Specifically, liver, heart, triceps, quadriceps, tibialis anterior, diaphragm, brain, spleen, and kidneys were investigated 1, 6 or 24 hours post dose. 51.15% - 68.36% of the injected dose of avalglucosidase alfa were detected in the liver within 24 hours. Moreover, avalglucosidase alfa was found in heart (0.32% - 0.38%), quadriceps (0.03% - 0.05%) and triceps (0.02%). Comparable alglucosidase levels were detected in the heart (0.2% – 0.37%), quadriceps (0.03-0.04%) and triceps (0.01% - 0.03%). Overall, similar tissue distribution was observed for both molecules. Statistically significantly higher tissue levels of avalglucosidase alfa were only found in the heart at the 6- and 24-hour time points after administration.

An additional tissue distribution study combined with an in vivo micronucleus test was conducted (**Study 09-3559**). GAA knock out mice were administered not only a single dose but up to three doses of 50 mg/kg avalglucosidase given in 4 hour-intervals. Tissues were evaluated 6 hours after administration of 50 mg/kg, or 24 hours after the first dose of 50, 100 or 150 mg/kg. Enzyme activity was evaluated in bone marrow only. Liver, heart, triceps, quadriceps, tibialis anterior, diaphragm, psoas, spleen, and kidneys were collected, but not analysed. Avalglucosidase activity increased in a dose-dependent manner in the bone marrow, from 121.2 ± 27.9 µg/g wet tissue over 218.9 ± 58.2

µg/g wet tissue to 369.1 ± 70.5 µg/g wet tissue, following one, two or three administrations, respectively. In addition, the tissue activity in the bone marrow increased from 6 to 24 hours after a single administration.

No dedicated studies on the metabolism of avalgucosidase were conducted in animals. However, in vitro studies with human hepatocytes were performed to investigate whether hydrazine-structure containing degradation products may be formed upon breakdown of avalglucosidase alfa.

Excretion and pharmacokinetic drug interaction studies were not specifically investigated for avalglucosidase alfa, which is acceptable considering that the active substance is a protein.

## 2.5.4. Toxicology

The toxicology program was designed to determine the safety profile of avalglucosidase alfa in a series of toxicology studies in the mouse, rabbit, and monkey. Completed studies include repeat-dose toxicology studies of 14-days (mouse and monkey), 1- (mouse and monkey) and 6-months (monkey) in duration. Although genotoxicity studies are not required by ICH Guidelines, an exploratory in vivo micronucleus test was conducted in mice. Developmental and reproductive toxicology studies included fertility (mouse), embryo-fetal toxicity (mouse and rabbit), and pre- and post-natal developmental toxicity (mouse) studies. A juvenile toxicity study was conducted in 21-day old mice. Local tolerance was evaluated in the repeat-dose toxicity studies.

### *2.5.4.1. Single dose toxicity*

No single dose studies have been conducted to evaluate the toxicity of avalglucosidase alfa. Any evaluation of acute toxicity was determined after the first dose administration in the repeat-dose studies. This is considered acceptable by the CHMP.

### *2.5.4.2. Repeat dose toxicity*

In an exploratory, repeat-dose toxicity study (**Study # FFA00125**), CD-1 mice were dosed 50 mg/kg rhGAA, avalglucosidase alfa sialic acid modification (SAM, corresponds to avalglucosidase alfa) or galactose modification of alglucosidase alfa (GAM) IV every other day for 14 days (n=10/sex and group). Findings with unknown relation to the test article were increased reticulocyte counts, increased serum calcium, phosphorus, and potassium in avalglucosidase alfa-treated males; macroscopic findings in the male reproductive tract upon rhGAA and avalgucosidase treatment; increased spleen weights in rhGAA alfa-treated male and avalglucosidase alfa-treated male and female mice; multifocal liver necrosis and inflammatory infiltrates upon treatment with avalglucosidase.

A second exploratory study (**Study # Study 10-00183**) was conducted in order to evaluate potential toxicities of avalglucosidase. Alfa CD-1 mice were administered 4, 40 or 120 mg/kg neoGAA (n=9 animals/sex/group) once weekly for four weeks. Upon occurrence of anaphylaxis, animals were treated with DPH. Animals were observed for clinical signs, gross pathology, histopathology, TK parameters and anti-drug antibodies. Three animals of the 4 mg/kg dose group died or were euthanized on study day 22 after administration of neoGAA. The Applicant attributed the deaths of these animals to hypersensitivity reactions. It remains elusive why the severity of the hypersensitivity response was exceptionally high in the low dose group while it was manageable by DPH administration in other dosing groups. Overall, the hypersensitivity reactions are considered a

phenomenon related to species-specific reaction to the administered protein and the related observations are therefore not followed up further. Sporadic changes in organ weights, organ-to-body weight ratios and organ-to-brain weight ratios in neoGAA treated male animals were not accompanied by microscopic changes and are thus not considered of toxicological relevance, in accordance with the Applicant's conclusion. TK evaluation revealed an increase in exposure, decrease in clearance and increase in T1/2 with increasing dose. In addition, T1/2 and VZ were statistically significantly decreased after four administrations of 120 mg/kg when compared to the first administration. Anti-neoGAA antibodies were detected in all animals except for the vehicle group with mean titers of 462,196 (± 494,596), 1,761,493 (± 2,223,027), and 1,862,543 (± 2,731,156) for Groups 2, 3 and 4, respectively.

The findings of **Study # FFA00125** were not confirmed in this second study. However, administration schemes clearly differed between the two studies, i.e. administration every other day versus once weekly. According to the proposed SmPC, avalglucosidase alfa will be administered every other week and, thus, the once weekly administration is regarded as a more relevant administration scheme. Overall, the proposed NOAEL set to 120 mg/kg is acceptable.

A non-GLP, 28-day repeat dose toxicity study (**Study # 1213-004**) was conducted in cynomolgus monkeys for exploratory purposes. Animals were administered 4, 40 or 120 mg/kg avalglucosidase alfa once weekly. Animals were observed for clinical signs, haematology, coagulation, clinical chemistry, and urinalysis, gross pathology, histopathology, TK parameters and anti-drug antibodies. No adverse findings related to avalglucosidase alfa were observed. With regard to toxicokinetics, avalglucosidase alfa levels were below the detection limit in the 4 mg/kg dose group. Exposure in the 40 mg/kg and 120 mg/kg dose groups was dose-related (Cmax: 192 ± 63.3 and 862 ± 302 µg/mL, respectively) and clearly increased in the 120 mg/kg group after the fourth infusion (1273 ± 214 µg/mL). Thus, AUC0-inf (3155±911 vs 5900 ± 660 µg▪hr/mL) and AUC0-inf/dose (26.3 ± 7.59 vs 49.2 ± 5.50 µg▪hr/mL/dose) were statistically significantly elevated after the fourth infusion as compared to the first infusion of 120 mg/kg. In contrast, Vz and CL decreased with increasing numbers of infusions. These observations indicate that saturation has been reached by repeated administrations of the high dose. Anti-drug antibodies were detected at dose-dependent levels in all animals that received avalglucosidase alfa.

A 26-week, GLP-compliant, repeat-dose toxicity study (**Study # 0658-11097**) was conducted in cynomolgus monkeys. Animals were administered 0, 50 or 200 mg/kg avalglucosidase alfa every second week via 6-hour IV infusion (n=6/sex/group). Evaluation included mortality, clinical observations, physical examinations, body weight, food consumption, electrocardiographic, central nervous system and ophthalmologic examinations, respiratory rates, heart rate, core body temperature, haematology, clinical chemistry, coagulation and urinalysis. No test-article related adverse events were observed. Exposure to avalglucosidase alfa was dose-dependent (Cmax: 566 ± 157 and 3892 ± 506 µg/mL; AUC0-inf/dose: 48.5 ± 13.6 and 93.6 ± 14.3 µg▪hr/mL/dose after the first infusion) and increased with increasing numbers of infusions (Cmax: 861 ± 189 and 5284 ± 1440 µg/mL; AUC0-inf/dose:74.2 ± 19.5 141 ± 53.5 µg▪hr/mL/dose after the thirteenth infusion). Together with increasing t1/2 and decreasing CL, the occurrence of saturation kinetics is conceivable. Anti-drug antibodies were detected in all animals administered with avalglucosidase alfa with levels increasing in dependence of the dose and number of administrations. Overall, the proposed NOAEL set to 200 mg/mL is considered acceptable.

#### *2.5.4.3. Genotoxicity*

Despite not necessarily required for biotechnology derived pharmaceuticals, an exploratory in vivo micronucleus test into a biodistribution study was conducted in GAAKO mice receiving 0, 50, 100 or 150 mg/kg on one single day. No induction of micronuclei by avalglucosidase alfa was observed within 24 hours.

#### *2.5.4.4. Carcinogenicity*

No carcinogenicity studies have been conducted. A risk assessment based on literature, data reviews and in silico search. In addition, an evaluation of potential release of the linker moiety of Genz-669342 and other hydrazine containing compounds from avalglucosidase alfa. Overall, no evidence for a carcinogenic potential of avalglucosidase alfa was detected.

#### *2.5.4.5. Reproductive and developmental toxicity*

In order to address potential effects of avalglucosidase on reproduction and development the Applicant performed a fertility- and early embryonic development to implantation study in mice, an embryo-fetal development study in mice and rabbits as well as a pre- and post-natal development study in mice.

A GLP-compliant study of fertility- and early embryonic development was conducted in mice (**Study FER0511**) administered 10, 20 or 50 mg/kg avalglucosidase IV every other day either 10 weeks before mating through cohabitation (male animals) or 2 weeks prior to mating until G7 (female animals). Upon the occurrence of anaphylactic reactions (dose number 6 in male and dose number 2 in female animals), all animals were administered with DPH. Several male and female animals died after repeated administrations of avalglucosidase alfa. However, no relation to dose could be established and hypersensitivity reactions was assumed to be the cause of death. Other clinical observations included decreased motor activity, hyperreactivity to touch and ataxia. Also these findings did not appear to be dose-related, but were definitely related to the test article as no such observations were made in the vehicle or DPH control groups. The time needed for mating was higher than controls in the groups of male and female animals receiving 50 mg/kg avalglucosidase alfa, but within the historical range of the testing facility. Some deviations from control groups were observed in the weights of male reproductive organs; however, no dose relation was established in the context of these findings. Sperm evaluation and histopathology of testes and epididymides did not reveal any abnormalities. No avalglucosidase alfa-related effects were observed on female reproductive organs, fertility and pregnancy outcomes. The NOAEL set at the highest dose of 50 mg/kg is therefore acceptable. DPH administration started after dose number 6 for males and dose number 2 for females. Thus, as the first deaths of female animals occurred at dosing day 9, i.e. after the fourth avalglucosidase alfa dose, all deaths of female animals occurred when DHP treatment was already initiated.

A GLP-compliant study in pregnant CD-1 mice (**Study TER0685**) was conducted to assess potential effects of avalglucosidase alfa on early embryonic development. Mice were dosed with 10, 20 and 50 mg/kg once daily starting from GD 6 through 15. No mortality or hypersensitivity reactions were observed throughout the whole study period. In addition, no clinical signs, body weight changes or other macroscopic findings related to administration of avalglucosidase alfa were observed. With regard to ovarian and uterine examinations, no abnormalities were observed in the 10 and 20 mg/kg dosing groups. In contrast, the number of post-implantation losses and late resorptions was increased in the 50 mg/kg dosing group. No fetal malformations were recorded in any of the dosing

groups. Toxicokinetic evaluation revealed that maternal plasma levels for avalglucosidase alfa increased in a disproportionate manner with increasing dose levels. From the 10 to the 50 mg/kg dose level exposure increased by 9.90-fold (Cmax) and 12.8-fold (AUC0-24h). Whereas the tissue levels in maternal liver and placenta also increased dose-dependently, no or only very low levels of avalglucosidase alfa were detected in fetal livers. As fetal livers containing low levels of avalglucosidase were evenly distributed between control and treatment groups, no placental transfer of avalglucosidase is presumed and measured values are considered likely to be endogenous alglucosidase. Overall, the maternal NOAEL of 50 mg/kg and the developmental NOAEL of 20 mg/kg are agreed upon.

An additional GLP-compliant embryo-fetal development study was conducted in NZW rabbits (**Study TER0686**). Two preceding dose range finding studies were performed in non-pregnant (**Study DDO1378**) and pregnant rabbits (**Study TEP0366**). For the pivotal embryo-fetal development study time-mated NZW rabbits were administered 30, 60 and 100 mg/kg avalglucosidase alfa daily via IV infusion from gestation day (GD) 6 through 19. Animals were observed until GD 29. Maternal adverse effects observed were limited to reduced food consumption and lower mean body weights in the 60 and 100 mg/kg dosing groups. Body weight loss was statistically significant from GD 19 to 20 in the 100 mg/kg group and food consumption statistically significantly differed to controls during GD 13 to 20 in the 60 and 100 mg/kg groups. Thus, the maternal NOAEL was determined at 30 mg/kg/day. No malformations or developmental variations that could be attributed to administration of avalglucosidase alfa were observed. The fetal NOAEL was therefore determined to be the highest administered dose, i.e. 100 mg/kg/day. Toxicokinetic evaluation revealed dose-proportionate or slightly disproportionate exposure, whereby a higher dose-related increase was observed regarding AUC0-24 (4 to 6-fold) than regarding Cmax (3-fold). No accumulation was observed when comparing samples collected on GD 6 and 19.

A pre- and postnatal development study (GLP-compliant) was conducted in CD1 mice (**Study DPN0378**). Pregnant mice were administered 10, 20 or 50 mg/kg avalglucosidase alfa via IV bolus every other day from GD 6 through Day 19 or 20 post partum. In addition, starting from dose number 5, animals were prophylactically given 5 mg/kg DPH via intraperitoneal injection. Administration to mice that did not deliver a litter was stopped on GD 22. F1 pups were exposed to avalglucosidase alfa exclusively via their mothers (gestation and lactation). Three deaths of F0 female mice occurred and were distributed over all three dosing groups. Thus, these deaths were not dose-depended and can be considered to be not test article-related. Apart from that no noteworthy clinical observations were made in F0 animals. No influence of the test article on the number of pregnancies, litter-size and –viability or other related parameters was reported. In the F1 generation no deaths related to avalglucosidase alfa occurred. In addition, no clinical observations or any effects on sexual maturation, mating, behaviour, reproductive capacity or gross pathology were reported. Some statistically significant differences in body weight gains between various dosing groups occurred but were limited to specific time intervals and not persistent and therefore not considered relevant. Overall, the NOAEL of 50 mg/kg every other day for pre- and postnatal development is supported.

#### *2.5.4.6. Toxicokinetic data*

Toxicokinetic data have been collected from pharmacokinetics, repeated dose toxicity and reproductive and development toxicity studies and are discussed under the corresponding sections.

#### *2.5.4.7. Local Tolerance*

The assessment of local tolerability was incorporated into repeat-dose toxicology studies in cynomolgus monkeys by macroscopic and microscopic evaluation of the IV infusion sites. No findings related to avalglucosidase alfa administration were observed.

#### *2.5.4.8. Other toxicity studies*

Antibody formation to avalglucosidase alfa was evaluated in the scope of various repeat-dose toxicity studies.

Avalglucosidase alfa is not likely to cross the blood brain barrier by its relatively high molecular size. This property is intrinsic to lyosomal enzymes, such as alglucosidase alfa or avalglucosidase alfa. In addition, no behavioural or CNS-related effects were observed in repeat-dose toxicity studies in mice or monkeys. Similarly, in clinical studies no indications for dependence or abuse potential were reported. No specific studies have been conducted to investigate potential for dependence and this is considered acceptable by the CHMP.

In silico evaluation was performed for a number of impurities that were, as a consequence, adequately classified based on their properties as known mutagenic carcinogens or known mutagens. Other impurities were classified due to structural alerts for mutagenicity unrelated or related to the drug substance.

An in vitro bacterial reverse mutation assay was performed for N-hydroxysuccinimide that was classified class 3 after in silico evaluation. No increase in the number of revertant bacterial colonies of 5 Salmonella typhimurium strains was identified with or without S9 activation up to a dose level of 5000 µg/plate. Therefore N-hydroxysuccinimide was classified a Class 5 impurity.

In a series of additional studies, toxicity of the glycan-linker complex Genz-669342 was evaluated. These studies included an in vivo repeat-dose toxicity evaluation in monkeys, a bacterial reverse mutation test and an in vitro chromosome aberration test in human lymphocytes. No concerns regarding toxicity, mutagenicity or genotoxicity were identified from the study results. In the in vivo repeat-dose toxicity studies no adverse effects were observed at levels of up to 12.5 mg/kg administered every other week for 13 weeks.

## 2.5.5. Ecotoxicity/environmental risk assessment

According to "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2), no ERA studies have been submitted. This is acceptable since avalglucosidase alfa, is an enzyme consisting of naturally occurring amino acids linked to a glycan molecule.

## 2.5.6. Discussion on non-clinical aspects

The GAA knock out mouse model is suitable to mimic the adult form of Pompe disease. The reduction of elevated tissue glycogen levels serves as a solid parameter to document efficacy of enzyme replacement therapy. In all non-clinical pharmacological studies using the GAA knockout mouse, SAM6 (avalglucosidase alfa) revealed glycogen clearance from target tissues, particularly the heart, quadriceps and triceps. Based on dose comparison, avalglucosidase alfa is 3 to 7-fold more potent. However, the amount of glycogen clearance was similar to that of Myozyme in two studies.

Importantly, at least a concentration of 12 mg/kg IV is considered to be effective in glycogen reduction in the diaphragm and skeletal muscles. Of note, the reduction of glycogen varies dependent on the skeletal muscles investigated in non-clinical studies (07-1948). This tissue variability was argued to be dependent on the expression level of the cation independent mannose-6-phosphate receptor (CIMPR), which is most prominently expressed in the heart. Thus, avalglucosidase alfa triggered glycogen reduction was best seen in the heart followed by quadriceps and diaphragm. An increase in SAM6 dosage from 12 to 20 mg/kg had no influence on further glycogen reduction in quadriceps and triceps. This plateau effect and reduced effects seen in other skeletal muscles is referred to lower CIMPR expression levels in type II fibres.

The amount of sialic acid within avalglucosidase alfa (in the range of 5.5 to 7.2 mol/mol sialic acid) does not contribute to significant differences in potency to reduce glycogen accumulations in GAA knockout mice. Similarly, at least three glycan residues within avalglucosidase alfa were needed to obtain potent glycogen clearance in target tissues in GAA knockout mice.

Although pharmacologically relevant, the distribution of SAM6 into the brain was not investigated. No information on a potential reduction of glycogen or autophagy in the brain is available.

Pharmacokinetic evaluations after single and repeated administrations of avalglucosidase alfa reveal dose-dependent exposure in mice and monkeys. When comparing the doses administered, alterations in pharmacokinetic parameters become only apparent after repeated administrations of high doses (120 mg/kg), including a more than dose-proportional exposure, increasing $T_{1/2}$ and increasing CL, which points towards saturation. High variability was observed in clearance, $V_z$ and systemic exposure ($C_{max}$ and AUC) among studies in which animals were treated with the same doses, being these differences higher in study 08-2344 compared to studies 10-00813 and 10-00540 performed in mice and between studies 1213-004 and 0658-11097 in monkeys. It is acknowledged that the high variability observed in PK parameters among studies might be caused by the inter-study variability and, in case of monkeys, also by the smaller number of animals tested in Study 1213-004 compared to Study 0658-11097. The PK profile (prolongation in half-life and increased systemic exposure, with a corresponding decrease in clearance with increased dose levels) is similar among studies and high ranges of $AUC_{0\text{-}2w}$ and $C_{max}$ values were also observed in humans

Although knockout and wild-type mice have not been administered the same doses of avalglucosidase in the single dose PK studies, exposure in wild-type animals seem higher when projecting results from knockout animals to wild-type animals. The CHMP further noted that discrimination between endogenous alglucosidase alfa and administered avalglucosidase alfa is not possible with the employed method of quantification.

Pharmacokinetic parameters after repeated dosing of avalglucosidase were only analysed in CD1, and not in GAA knockout mice. The tissue distribution studies involved only single dose administration of 20 mg/kg and up to three administrations of 50 mg/kg in 4 hour-intervals. These study designs do not reflect the clinical dosing schedule of 20 or 40 mg/kg every other week as a life-long treatment. Especially in the case of avalglucosidase alfa that has been modified to target, among other tissues, the skeletal muscles more efficiently, a repeat-dose biodistribution study mimicking the clinical dosing schedule might have been useful to elucidate the effectiveness of the modification. In such study, potential accumulation of avalglucosidase alfa might have been detected and relevant information would have been collected on the enzyme levels to which GAA knock out mice are restored as compared to normal levels after chronic treatment.

Exposure was comparable at similar dose levels (40 mg/kg and 50 mg/kg, however, once every second week in patients and once weekly monkeys) in monkeys and patients. As exposure in

monkeys increased more than dose proportionally exposure at the 200 mg/kg dose level in repeat-dose toxicity studies is considered a sufficient safety margin.

Tissue distribution in heart, quadriceps and triceps after one single administration of 20 mg/kg avalglucosidase and alglucosidase, respectively, was similar for both molecules. Essentially, the amount of the total injected dose detected in the heart was ranged from 0.2-0.38% and from 0.03%-0.05% in the quadriceps. The percentage detected in triceps ranged from 0.01-0.03%. Statistically significantly higher tissue levels of avalglucosidase as compared to alglucosidase were found in the heart at the 6- and 24-hour time points after administration. The biodistribution study showed the addition of bis-M6P on alglucosidase alfa structure does not alter the biodistribution pattern of alglucosidase alfa, but increments the distribution to organs with higher CIMPR expression levels, as heart. Therefore, distribution of avalglucosidase alfa to other tissues may depend on their CIMPR expression levels. Since biodistribution of 83% of the total injected dose of avalglucosidase alfa is characterized and no significant differences in target organs of toxicity were observed, biodistribution is considered sufficiently characterized.

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Based on the nature of the product, the results of repeat-dose toxicity studies and an exploratory in vivo genotoxicity study in mice, as well as, clinical experience with a similar product (Myozyme), genotoxic and carcinogenic potential is not suspected for avalglucosidase alfa.

Overall, avalglucosidase was well tolerated by mice and monkeys in pharmacology and repeat-dose toxicity studies employing doses of up to 120 mg/kg or 200 mg/kg, respectively. Unscheduled deaths that occurred in mice were attributed to hypersensitivity reactions to the administered human protein. Hypersensitivity reactions were in general well manageable by DHP administration. However, deaths related to anti-drug reactions also occurred after DPH administration had started. Nevertheless, no causes of death other than immunologic responses were determined. Based on the coincidence with the avalglucosidase alfa administration (3 hours postdose), timing of death is most likely related to allergic reaction. Anti-drug antibodies were detected in all PD and toxicity studies. It was, however, not specified whether these anti-drug antibodies were of neutralizing character, which could have had an influence on the outcome of the PD and toxicity studies.

Avalglucosidase alfa caused no adverse effects in a combined male and female fertility study in mice up to 50 mg/kg IV every other day (9.4 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD).

In an embryo-fetal toxicity study in mice, administration of avalglucosidase at the highest dose of 50 mg/kg/day (17 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD) produced increased postimplantation loss and mean number of late resorptions. No effects were seen at 20 mg/kg/day (4.8 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD). Avalglucosidase alfa does not cross the placenta in mice, suggesting that the embryo-fetal effects at 50 mg/kg/day were related to maternal toxicity from the immunologic response. No malformations or developmental variations were observed.

No adverse effects were observed in an embryo-fetal toxicity study in rabbits administered avalglucosidase alfa up to 100 mg/kg/day IV (91 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD).

There were no adverse effects in a pre- and postnatal developmental toxicity study in mice following administration of avalglucosidase alfa once every other day. The NOAEL for reproduction in the dams and for viability and growth in the offspring was 50 mg/kg every other day IV.

The proposed limits of analysed impurities (residual glycans and E11) were considered acceptable by the CHMP and in line with previous scientific advices.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, avalglucosidase alfa is not expected to pose a risk to the environment.

***Assessment of paediatric data on non-clinical aspects***

A GLP-compliant juvenile toxicity study was conducted in CD1 mice (**Study JUV0033**) that received a total of 5 doses of 20, 50 or 100 mg/kg avalglucosidase alfa every other week from postnatal day (PND) 21 through PND 77. A fertility cohort consisting of male animals was administered up to PND 91. The recovery period ended on PND 111 or 112. Starting from the second dose, animals were also administered with 5 mg/kg DPH. 25 unscheduled deaths were reported, of which 21 were classified as related to avalglucosidase alfa administration. Although the causes of deaths were not elucidated, hypersensitivity reaction to the test article were considered as causative by the applicant. Dead animals were evenly distributed among all dose groups, with slightly more deaths observed in the lowest dose group. A significant increase in total leucocytes and specifically lymphocytes, segmented neutrophils and basophils was detected in male animals of higher dose groups. No effects on other endpoints evaluated were observed. These endpoints included clinical observations, body weight, food consumption, macroscopic and microscopic observations, development, sexual maturation, male and female reproductive organs, mating and fertility. Toxicokinetic evaluation of PND 77 revealed a dose-dependent, disproportionate increase of avalglucosidase alfa serum levels. Over the entire dose range, Cmax was 5.88-fold higher in females and 5.11 fold higher in males. AUC0-24 was 11.5 fold higher in females and 14.8 fold higher in males of the high dose group as compared to the lowest dose. Thus, also a gender difference in terms of exposure was observed. The presence of anti-avalglucosidase antibodies was determined on PND 48, 76 and 110/111 in 5 animals of each dosing group and each gender. Almost all animals that received avalglucosidase alfa had detectable anti-drug antibodies at each time point investigated. The NOAEL of 100 mg/kg once every other week determined in the juvenile toxicity study corresponds to exposure values of Cmax of 3120 µg/mL and AUC0-24 of 8140 µg•h/mL in males; Cmax of 2480 µg/mL and AUC0-24 of 5400 µg•h/mL in female. The highest dose tested in juvenile animals is not enough to discard a potential risk for IOPD patients at 40 mg/kg based on exposure margin and this has been reflected in the SmPC.

## 2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of avalglucosidase alfa have been adequately documented and meet the requirements to support this application.

# *2.6. Clinical aspects*

## 2.6.1. Introduction

***GCP aspects***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

| Study ID | No. of study centres / locations | Design | Study Posology | Study Objective | Subjs by arm entered/ compl. | Duration | Gender M/F Median Age | Diagnosis Inclusion criteria | Primary Endpoint |
|---|---|---|---|---|---|---|---|---|---|
| TDR12857 | 17/7 | Phase 1/2 open-label, ascending dose study with repeated (n=13) IV infusions of AVAL qow | 5, 10, or 20 mg/kg qow for a total of 13 infusions. | Primary: Safety and tolarability of AVAL in patients with LOPD and repeatedose PD, PK profiles | Group 1 10/9<br><br>Group 2 14/12 | 41 weeks (total of 13 infusions) | Group 1 3/7 44.8<br><br>Group 2 9/5 46.7 | Group 1: Naïve, patients with LOPD, ⩾ 18 years of age<br>Group 2: Patients with LOPD pre-treated with ALGLU⩾ 18 years of age | Safety<br>AEs, Physical examination, Clinical laboratory, Vital signs, 12-lead ECG Immunogenicity<br>PK<br>Cmax, tmax, AUClast, AUC, t1/2, CL, Vd<br>PD<br>Skeletal muscle glycogen content, Skeletal muscle MRI, etc. |
| ACT14132] | 10/5 France (2); Japan (2); Taiwan (1); United Kingdom (2); and US (3). | multistage phase 2 open-label, ascending dose cohort, repeated intravenous infusion study with long-term open label extension treatment period (ETP). | - Stage 1/Cohort 1: 20 mg/kg qow<br>- Stage 1/Cohort 2: 40 mg/kg qow<br>- Stage 2/Cohort 3: 40 mg/kg qow or pre-study dose<br>- **ETP**/Cohort 1: 20 mg/kg qow | Primary:safety profile of AVAL in patients with IOPD pre-treated with ALGLU | Cohort 1 6/6<br><br>Cohort 2 5/5<br><br>Cohort 3 AVAL/ AVAL: 5/5<br><br>ALGLU/AVAL: 6/6 | PAP: 25 weeks<br><br>ETP: up to a total of 3 years (extended to 7 years amended protocol 02 [dated 24-Mar-2020]) | Cohort 1 5/1<br><br>Cohort 2 3/2<br><br>Cohort 3 AVAL/AVAL: 2/3<br><br>ALGLU/ AVAL: | Pediatric patients with IOPD pre- treated with ALGLU and clinical decline (Stage 1) or sub-optimal clinical response (Stage2) in re= spiratory function, motor skills, cardiac parameters, and/or new onset of ptosis. | Safety<br>AEs/TEAEs, including infusion-associated reactions (IARs)<br>Physical examinations<br>Clinical laboratory evaluations<br>Vital sign measurements, ECG, Immunogenicity |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | - **ETP**/Cohort 2 & 3: 40 mg/kg qow | | | | | | |
| EFC14028 | 69/26<br><br>55 centers enrolled at least 1 patient | Phase 3, Randomized double-blind, 12-month **PAP** study.<br>Long-term, open label **ETP**. | 20 mg/kg i.v. qow | Primary:<br>Effect of AVAL treatment on respiratory muscle strength measured by FVC%, compared to ALGLU | AVAL<br>PAP: 51/51<br>ETP: 51/48[1]<br><br>ALGLU<br>PAP: 49/44<br>ETP: 44/43 | PAP: 49 weeks<br><br>ETP: 5-years | AVAL<br>27/24<br><br>ALGLU<br>25/24 | Treatment-naïve LOPD patients ⩾ 3 years of age | Change in FVC% predicted in the upright position from baseline to 12 months (Week 49) |

## 2.6.2. Clinical pharmacology

In the avalglucosidase alfa clinical development program to date, the PK of avalglucosidase alfa has been characterized in 3 studies in LOPD patients and in 1 study in IOPD (see Table 7). A total of 123 adult and 23 paediatric patients were enrolled in the clinical studies.

Pharmacokinetics was investigated in 75 avalglucosidase alfa treated LOPD patients from 3 studies (TDR12857, LTS13769 and EFC14028), including only one paediatric patient, and in 16 IOPD patients, all enrolled in study ACT14132. In addition, a population pharmacokinetic (PopPK) analysis was conducted using pooled data from the 3 studies in LOPD patients.

Avalglucosidase alfa was administered by IV infusion over the dose range of 5 to 20 mg/kg qow in LOPD patients, and 20 to 40 mg/kg qow in IOPD patients. Infusion duration was dose-dependent with a median duration of 4 hours and 7 hours at 20 mg/kg and 40 mg/kg, respectively.

Blood sampling schedules were implemented in all clinical studies (up to 48 hours in TDR12857, 24 hours in LTS13769, 8 hours in EFC14028 and 12 hours in ACT14132) to allow for a non-compartmental analysis (NCA).

Although NCA was used to assess the PK of avalglucosidase alfa in each individual study conducted in patients with LOPD, population PK modelling (PopPK analysis (POH0703)) was the primary approach to describe the absorption, distribution and elimination/excretion profile in LOPD patients and determine the effect of intrinsic (baseline characteristics, laboratory parameters, and immunogenicity) and extrinsic (patients previously treated with alglucosidase alfa versus treatment-naïve patients) factors on the PK of avalglucosidase alfa.

**Table 2 Avalglucosidase alfa pharmacokinetic and pharmacodynamic assessments in clinical studies and analyses**

| Study type | Study code | Dose or dose range<br>Treatment duration | Number enrolled[a] |
|---|---|---|---|
| **In vitro** | | | |
| Metabolism - Human plasma and human hepatocytes | PDD0035 | Not applicable | Not applicable |
| | MIV0740 | Not applicable | Not applicable |
| **Pharmacokinetics, pharmacodynamics, and initial tolerability in patients** | | | |
| Safety - Phase 1/2 | TDR12857 (NEO-1) | 5, 10 and 20 mg/kg qow for 24 weeks | 24 |
| **Pharmacokinetics in efficacy/safety studies in LOPD patients** | | | |
| Efficacy – Phase 3 | EFC14028 (COMET) | 20 mg/kg qow for 49 weeks | 51 |
| Long-term safety and PK | LTS13769 (NEO-EXT) | 5, 10 and 20 mg/kg qow | 19 |
| **Pharmacokinetics in efficacy/safety studies in IOPD patients** | | | |
| Safety - Phase 2 | ACT14132 (mini-COMET) | 20 or 40 mg/kg qow for 6 months | 16 |
| **Population pharmacokinetics and pharmacokinetic/efficacy analyses in LOPD patients** | | | |
| Population PK | POH0703 | 5 to 20 mg/kg qow | 75 |
| Exploratory PK/efficacy | POH0817 | 20 mg/kg qow | 51 |

IOPD: infantile-onset Pompe disease; LOPD: late-onset Pompe disease; qow: every other week

a Number of patients on avalglucosidase alfa during primary analysis period (no PK evaluation during the extension treatment period). For population PK analysis, the number corresponds to the number of patients included in the analysis with patients enrolled in TDR12857 and LTS13769 counted only once.

The pharmacological (PD) activity of avalglucosidase alfa was assessed during PAP and ETP through urinary hexose tetrasaccharides (Hex4), skeletal muscle magnetic resonance imaging (MRI), glycogen content in quadriceps muscle tissue, serum creatine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The PD evaluations are summarized by study in Table 8.

**Table 3 Pharmacodynamic evaluations by clinical study**

Table 2 - Pharmacodynamic evaluations by clinical study

| Study | Number of patients per study period | Hex4 | Skeletal muscle MRI | Skeletal muscle glycogen content | Creatine kinase/AST/ ALT |
|---|---|---|---|---|---|
| TDR12857 | 24 | Every 2 weeks | At screening and after last administration | At screening and after last administration | Every 2 weeks |
| LTS13769 | 19 | At 6 months, yearly thereafter | Every 2 years | Every 2 years[a] | Monthly then quarterly after first 3 years since enrollment |
| EFC14028 | PAP:51<br>ETP[b]: 44 | Quarterly for 1.5 year then every 6 months | NA | NA | Monthly |
| ACT14132 | PAP: 16<br>ETP[b]: 3 | Every 2 weeks | NA | At screening and after last administration[c] | Monthly then quarterly after first 1 year |

NA: not applicable; ETP: extension treatment period; PAP: primary analysis period

a Muscle biopsy not required in patients in whom the prior muscle biopsy, obtained in the TDR12857 study, had a glycogen content <5% unless the patient showed significant clinical decline

b Include patients treated with alglucosidase alfa in the primary analysis period who switched to avalglucosidase alfa in the extension treatment period. Do not include patients who received avalglucosidase alfa in the primary analysis period

c Optional

Study TDR12857, as well as the primary analysis periods (PAPs) of studies EFC14028 and ACT14132 have been completed. The extension study LTS13769 for patients from study TDR12857 and ETPs of ACT14132 and EFC14028 are ongoing, and PD results up to the cut-off date predefined for each study are also provided.

### *2.6.2.1. Pharmacokinetics*

#### *Absorption*

**LOPD population**

Avalglucosidase alfa exposure parameters in LOPD patients at 20 mg/kg qow are summarized in Table 9. After a 4-hour IV infusion of 20 mg qow, mean Cmax (CV%) and $AUC_{2W}$ were 273 µg/mL (24.2%) and 1220 µg.h/mL (28.6%), respectively.

For patients previously treated with alglucosidase alfa at 20 mg/kg qow, no accumulation of avalglucosidase alfa was observed following 5, 10 and 20 mg qow. This finding is consistent with the short t1/2z documented for avalglucosidase alfa.

The PK parameters obtained from NCA are presented by clinical study in Table 10 and Table 11.

**Table 4 Simulated post-hoc avalglucosidase alfa exposures in LOPD patients receiving 20 mg/kg (POH0703)**

| | $C_{max}$ (µg/mL) | $AUC_{2W}$ (µg.h/mL) |
|---|---|---|
| n | 70 | 70 |
| Mean (CV%) | 273 (24.2%) | 1220 (28.6%) |
| Median (Min-max) | 264 (135-432) | 1190 (582-2370) |

$AUC_{2W}$: area under the plasma concentration curve over the dosing interval; $C_{max}$: maximum plasma concentration

**Table 5 Summary of PK studies (TDR12857, EFC14028 and ACT14132) in patients (non-compartmental analysis)**

| Study (Report Location) | Study design | Subjects (M/F) Type Age range | Dose | Previous treat. | PK parameters Mean (CV%) or Median (range) for $t_{max}$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $t_{max}$ (h) | | $C_{max}$ (µg/mL) | | $AUC_{last}$ (µg.h/mL) | | $t_{1/2z}$ (h) | | CL (L/h) | | $V_{ss}$ (L) | |
| | | | | | n | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 |
| TDR12857 (5.3.3.2) | Open-label, ascending dose | 24 (14/10) LOPD 20-78 | 5 mg/kg | Naïve | 4[a] | 1.7 (1.5-2.6) | 1.4 (1.4-1.6) | 82.3 (8) | 89.1 (12) | 259 (15) | 264 (19) | 0.78 (47) | 0.78 (6) | 1.26 (16) | 1.23 (19) | 2.62 (15) | 2.40 (13) |
| | | | | AGA | 4 | 1.8 (1.4-2.6) | 2.0 (1.5-2.6) | 77.4 (29) | 97.1 (38) | 246 (33) | 306 (26) | 0.67 (45) | 1.53 (34) | 1.57 (23) | 1.24 (28) | 3.71 (41) | 2.88 (24) |
| | | | 10 mg/kg | Naïve | 3 | 2.3 (2.2-2.3) | 2.4 (2.4-2.5) | 190 (21) | 162 (16) | 529 (15) | 565 (16) | 0.83 (59) | 0.86 (28) | 1.24 (31) | 1.18 (15) | 2.48 (25) | 2.67 (4) |
| | | | | AGA | 4 | 2.3 1.8-2.4) | 2.5 (2.3-3.4) | 168 (22) | 164 (12) | 631 (19) | 642 (7) | 1.03 (61) | 0.71 (15) | 1.28 (19) | 1.23 (5) | 3.21 (26) | 3.06 (4) |
| | | | 20 mg/kg | Naïve | 3 | 3.8 (3.8-4.0) | 3.9 (3.8-4.5) | 302 (36) | 350 (30) | 1520 (53) | 1560 (41) | 0.78 (28) | 1.03 (24) | 0.989 (28) | 0.917 (23) | 2.90 (15) | 2.93 (8) |
| | | | | AGA | 6[b] | 3.8 (3.7-4.7) | 3.8 (3.7-5.6) | 321 (39) | 299 (16) | 1500 (33) | 1530 (29) | 0.88 (27) | 1.06 (41) | 1.06 (19) | 0.998 (21) | 3.31 (22) | 3.29 (23) |
| EFC14028 (5.3.5.1) | Randomized, double-blind | 51 (27/24) LOPD 16-78 | 20 mg/kg | Naïve | 49[c] | 4.0 (2.5-6.3) | 4.0 (2.2- 7.3) | 259 (28) | 242 (34) | 1290 (33) | 1250 (35) | 1.34 (42)[d] | 1.55 (57) | 1.22 (27)[d] | 1.37 (39) | 6.66 (28)[d] | 7.62 (30) |

| Study (Report Location) | Study design | Subjects (M/F) Type Age range | Dose | Previous treat. | PK parameters Mean (CV%) or Median (range) for $t_{max}$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $t_{max}$ (h) | | $C_{max}$ (µg/mL) | | $AUC_{last}$ (µg.h/mL) | | $t_{1/2z}$ (h) | | CL (L/h) | | $V_{ss}$ (L) | |
| | | | | | n | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 | W1 | W25/49 |
| ACT14132 (5.3.5.1) | Open-label, ascending dose | 16 (10/6) IOPD 1-12 | 20 mg/kg[e] | AGA | 5 | 4.4 (3.9-5.3) | 4.0 (3.8-4.8) | 189 (30) | 175 (38) | 923 (38) | 805 (37) | 0.70 (41) | 0.60 (43) | 0.673 (33) | 0.696 (29) | 3.55 (26) | 3.52 (34) |
| | | | 40 mg/kg[e] | AGA | 5[f] | 7.0 (6.0-7.3) | 7.1 (5.7-8.0) | 403 (43) | 297 (20) | 2630 (37) | 1930 (18) | 1.15 (46) | 1.04 (24%) | 0.562 (27) | 0.683 (51) | 4.50 (20) | 5.35 (42) |
| | | | 40 mg/kg[g] | AGA | 5[f] | 6.8 (6.7-7.2) | 6.9 (5.0-7.4) | 250 (18) | 356 (24) | 1720 (15) | 2200 (24) | 0.81 (31) | 1.19 (40) | 0.529 (28) | 0.526 (24) | 4.30 (33) | 4.02 (35) |

AGA: alglucosidase alfa; IOPD: infantile-onset Pompe disease; LOPD: late-onset Pompe disease

*a* n=3 at week 25,

*b* n=5 at Week 25

*c* n=48 at Week 49

*d* n=47

*e* decliners

*f* n=4 at Week 1

*g* suboptimal responders

**Table 6 Summary of PK study LTS13769 in patients (non-compartmental analysis)**

| Study (Report Location) | Study design | Subjects (M/F) Type Age range | Previous treat. | Dose | Week | PK parameters Mean (CV%) or Median (range) for $t_{max}$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | n | $t_{max}$ (h) | $C_{max}$ (µg/mL) | $AUC_{last}$ (µg.h/mL) | $t_{1/2z}$ (h) | CL (L/h) | $V_{ss}$ (L) |
| LTS13769 (5.3.5.2) | Open-label, treatment extension study | 19 (9/10) LOPD 20-78 | Naïve | 5 mg/kg | 26 | 3 | 1.73 (1.70-1.95) | 105 (42) | 361 (42) | 0.81 (21) | 1.01 (55) | 2.78 (49) |
| | | | | | 52 | 3 | 1.75 (1.33 -1.83) | 86.1 (21) | 299 (29) | 0.73 (26) | 1.1 (38) | 3.01 (33) |
| | | | | Switch 20 mg/kg | Re-baseline | 3 | 3.63 (3.57-4.05) | 331 (10) | 1810 (16) | 1.68 (17) | 0.686 (24) | 3.69 (23) |
| | | | | | 208 | 2 | 4.21 (3.83-4.58) | 256 (7) | 1370 (25) | 1.26 (37) | 0.914 (42) | 4.87 (25) |
| | | | AGA | 5 mg/kg | 26 | 3 | 1.87 (1.57-2.70) | 77.1 (10) | 254 (5) | 0.86 (30) | 1.33 (9) | 4.13 (17) |
| | | | | | 52 | 3 | 1.62 (1.60-2.40) | 81.8 ((28) | 247 (17) | 1.14 (41) | 1.38 (7) | 4.27 (31) |
| | | | | | 104 | 2 | 1.66 (1.62-1.70) | 93.8 (15) | 316 (41) | 1.95 (NA) | 0.93 (NA) | 3.13 (NA) |
| | | | | Switch 20 mg/kg | Re-baseline | 1 | 4.45 | 218 | 1220 | 1.37 | 0.968 | 5.89 |
| | | | | | 208 | 3 | 3.92 (3.78-4.23) | 300 (18) | 1530 (12) | 1.29 (28) | 0.962 (2) | 3.36 (87) |
| | | | Naïve | 10mg/kg | 26 | 1 | 2.33 | 170 | 645 | 0.70 | 1.22 | 4.01 |
| | | | | | 52 | 1 | 2.32 | 178 | 633 | 0.83 | 1.27 | 4.29 |
| | | | | Switch 20 mg/kg | Re-baseline | 0 | NA | NA | NA | NA | NA | NA |
| | | | | | 208 | 1 | 3.82 | 240 | 1100 | 1.97 | 1.61 | 7.73 |

| Study (Report Location) | Study design | Subjects (M/F) Type Age range | Previous treat. | Dose | Week | PK parameters Mean (CV%) or Median (range) for $t_{max}$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | n | $t_{max}$ (h) | $C_{max}$ (µg/mL) | $AUC_{last}$ (µg.h/mL) | $t_{1/2z}$ (h) | CL (L/h) | $V_{ss}$ (L) |
| | | | AGA | 10 mg/kg | 26 | 3 | 2.30 (2.28-3.58) | 175 (17) | 677 (13) | 1.07 (58) | 1.20 (7) | 4.56 (2) |
| | | | | | 52 | 3 | 2.33 (2.30-2.40) | 186 (19) | 794 (14) | 1.02 (45) | 1.03 (13) | 3.92 (10) |
| | | | | | 104 | 1 | 2.53 | 185 | 873 | 0.91 | 0.98 | 4.06 |
| | | | | Switch 20 mg/kg | Re-baseline | 2 | 4.31 (3.77-4.85) | 278 (15) | 1530 (8) | 0.89 (11) | 1.01 (13) | 5.06 (26) |
| | | | | | 208 | 3 | 3.85 (3.80-3.92) | 282 (1) | 1500 (2) | 1.65 (2) | 1.04 (8) | 5.61 (11) |
| | | | Naïve | 20 mg/kg | 26 | 2 | 3.67 (3.50-3.83) | 601 (86) | 2230 (67) | 1.59 (5) | 0.772 (52) | 3.87 (57) |
| | | | | | 52 | 3 | 3.75 (3.17-4.17) | 247 (20) | 1370 (37) | 1.56 (17) | 1.09 (28) | 5.79 (27) |
| | | | | | 104 | 3 | 3.83 (3.25-4.0) | 577 (109) | 2120 (89) | 1.78 (13) | 0.97 (54) | 4.74 (55) |
| | | | | | 156 | 3 | 4.50 (3.92-4.55) | 260 (22) | 1480 (36) | 1.60 (8) | 1.14 (13) | 3.84 (87) |
| | | | | | 208 | 2 | 3.84 (3.75-3.92) | 226 (0.3) | 1120 (14) | 1.72 (9) | 1.25 (9) | 6.52 (4) |
| | | | | | 260 | 3 | 3.75 (3.67-4.35) | 216 (16) | 1280 (30) | 1.97 (33) | 1.2 (17) | 6.81 (3) |

| Study (Report Location) | Study design | Subjects (M/F) Type Age range | Previous treat. | Dose | Week | PK parameters Mean (CV%) or Median (range) for $t_{max}$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | n | $t_{max}$ (h) | $C_{max}$ (µg/mL) | $AUC_{last}$ (µg.h/mL) | $t_{1/2z}$ (h) | CL (L/h) | $V_{ss}$ (L) |
| | | | AGA | | 26 | 5 | 3.93 (3.75-4.63) | 279 (37) | 1430 (41) | 1.12 (32) | 1.10 (13) | 5.79 (11) |
| | | | | | 52 | 5 | 4.28 (3.87-4.80) | 278 (31) | 1280 (43) | 1.06 (41) | 1.30 (31) | 6.98 (37) |
| | | | | | 104 | 5 | 3.97 (3.85-4.75) | 284 (28) | 1530 (35) | 1.27 (46) | 1.05 (14) | 5.73 (20) |
| | | | | | 156 | 4 | 3.93 3.75 (3.93) | 318 (28) | 1590 (41) | 1.21 (39) | 0.98 (11) | 4.94 (12) |
| | | | | | 208 | 4 | 4.17 (3.92-4.32) | 234 (21) | 1270 (30) | 1.31 (40) | 1.23 (12) | 6.61 (11) |
| | | | | | 260 | 2 | 3.76 (3.73-3.78) | 203 (4) | 1070 (17) | 0.80 (5) | 1.29 (28) | 6.46 (33) |

AGA: alglucosidase alfa; LOPD: late-onset Pompe disease; NA: not applicable

**IOPD population**

Avalglucosidase alfa exposure parameters in IOPD patients at 20 mg/kg and 40 mg/kg qow are summarized in Table 6. After a 4-hour IV infusion of 20 mg/kg, mean Cmax and $AUC_{2W}$ ranged from 175 to 189 µg/mL, and 805 to 923 µg.h/mL, respectively. After a 7-hour IV infusion of 40 mg/kg, avalglucosidase alfa exposure were in the same range in decliners and suboptimal responders with mean Cmax between 250 and 403 µg/mL and $AUC_{2W}$ from 1720 to 2630 µg.h/mL.

**Table 7 Avalglucosidase alfa exposures in IOPD patients at 20 mg/kg and 40mg/kg qow (ACT14132)**

| Dose | Population | $C_{max}$ (µg/mL) | | | | $AUC_{2W}$ (µg.h/mL) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 | | Week 25 | | Week 1 | | Week 25 | |
| 20 mg/kg | Decliner | n=5 | 189 (30) 217 (128-247) | n=5 | 175 (38) 182 (72.3-241) | n=5 | 923 (38) 946 (549-1320) | n=5 | 805 (37) 783 (383-1110) |
| 40 mg/kg | Decliner | n=4 | 403 (43) 423 (212-555) | n=5 | 297 (20) 275 (237-388) | n=4 | 2630 (37) 2680 (1580-3590) | n=5 | 1930 (18) 1740 (1630-2340) |
| 40 mg/kg | Suboptimal responder | n=4 | 250 (18) 246 (200-308) | n=5 | 356 (24) 352 (252-443) | n=4 | 1720 (15) 1630 (1530-2100) | n=5 | 2200 (24) 2470 (1480-2680) |

Mean (CV%) Median (minimum-maximum)

Following 20 and 40 mg/kg qow, Cmax and AUC2W appeared similar after single and repeated administrations indicating no accumulation of avalglucosidase alfa over time which is consistent with the short documented t1/2z. See Table 12.

***Distribution***

In vitro protein binding studies as conducted for small molecules are not applicable for ERT.

**LOPD population**

Avalglucosidase alfa PK was described by a 3-compartment model (POH0703). The distribution volume of central compartment characterized the main kinetic phase while the 2 distribution volumes of concatenated peripheral compartments characterized the late kinetic phase. The late phase occurred at very low concentrations (ie, ≤0.05% the mean Cmax at 20 mg/kg qow) and had a negligible impact of the overall PK profile of avalglucosidase alfa. For this reason, the peripheral compartment volumes of distribution had a marginal contribution of the overall distribution volume of avalglucosidase alfa. The typical population PK model predicted central compartment volume of distribution of avalglucosidase alfa was 3.35 L. See Table 13.

**Table 8 Avalglucosidase alfa population PK parameter estimates from the final model in LOPD patients (P0H0703)**

| Study (Report location) | Study included | Number and type of patients | Dose | Covariates tested | Final PK parameter estimates (%RSE) | Inter-individual variability (CV%) (%RSE) | Residual variability (%) (%RSE) |
|---|---|---|---|---|---|---|---|
| POH0703 (5.3.3.5) | TDR12857; LTS13769; EFC14028 | 75 patients 16 to 17 years of age with late-onset Pompe disease | 5, 10, 20 mg/kg every other week | age, gender, race, creatinine clearance, estimated glomerular filtration rate, albumin, alanine amino transferase, aspartate amino transferase, total bilirubin and dose | **$CL_L$ (L/h)**: 0869 (0.09%)<br>**V1 (L)**: 3.35 (0.07%)<br>**Km (µg/mL)**: 0.451 (0.120%)<br>**Vm (µg/h)**: 9.82 (0.019%)<br>**QPC (L/h)**: 0.020 (<0.330%)<br>**Q2 (L/h)[a]**: 0.254 (fixed parameter)<br>**V2 (L)[a]**: 296 (fixed parameter)<br>**Q3 (L/h)**: 1.87 (fixed parameter)<br>**V3 (L)[a]**: 1.31 (fixed parameter) | **$CL_L$**: 30.2 (20.5%)<br>**V1**: 12.7 (32.1%)<br>**Km**: 43.1 (10.1%)<br>**Vm**: 36.6 (34.8%)<br>**QPC**: 234 (1.21%) | σp: 12.5% (<0.01%) |

$CL_L$: linear clearance, CV: coefficient of variation; Km: Michaelis-Menten rate constant; Q2: 2-way clearance in between central compartment and compartment 2; Q3: 1-way clearance from compartment 2 to compartment 3; QPC: clearance from peripheral compartment 3 to central compartment, RSE: relative standard error, V1: distribution volume of central compartment; V2: distribution volume of peripheral compartment 2, V3: distribution volume of peripheral compartment 3; Vm: maximum rate of clearance; σp: residual variability for the proportional part

**IOPD population**

After avalglucosidase alfa 20 mg/kg and 40 mg/kg qow, mean steady state volume of distribution ranged between 3.5 and 5.4 L (see Table 10).

***Elimination***

No specific elimination and excretion studies were conducted. Avalglucosidase alfa is expected to be cleared from the plasma by cellular uptake.

The metabolic pathway of avalglucosidase alfa has not been characterized. As a glycoprotein, avalglucosidase alfa is expected to be degraded into small peptides or amino acids via non-saturable catabolic pathways.

***Dose proportionality and time dependencies***

**LOPD population**

Following 5, 10 and 20 mg/kg qow, no major deviation in dose proportionality was observed for Cmax and $AUC_{2W}$ (see Table 14). This is consistent with the limited contribution of the non-linear clearance in the overall clearance of avalglucosidase alfa.

**Table 9 Dose proportionality ration in avalglucosidase alfa exposures from 5 to 20 mg/kg in LOPD patients – study TDR12857**

| R-fold | Population | $C_{max}$ | | | $AUC_{2w}$ | | |
|---|---|---|---|---|---|---|---|
| | | Week 1 | Week 13 | Week 25 | Week 1 | Week 13 | Week 25 |
| 2 (5 to 10 mg/kg) | Naïve | 2.3 | 1.5 | 1.8 | 2.0 | 1.9 | 2.1 |
| | AGA[a] | 2.2 | 1.7 | 1.7 | 2.6 | 2.3 | 2.1 |
| 4 (5 to 20 mg/kg) | Naïve | 3.7 | 3.6 | 3.9 | 5.9 | 5.8 | 5.9 |
| | AGA[a] | 4.1 | 3.2 | 3.1 | 6.1 | 4.8 | 5.0 |

AGA: alglucosidase alfa

*a* patients previously treated with alglucosidase alfa

**IOPD population**

Following 20 and 40 mg/kg qow, no major deviation in dose proportionality was observed for Cmax and $AUC_{2W}$ (see Table 10).

***Intra and inter-individual variability***

**LOPD population**

In LOPD patients receiving 20 mg/kg qow, the total variability (CV%) of avalglucosidase alfa based on individual estimates using PopPK was 24.2% and 28.6% for Cmax and AUC2W, respectively (see Absorption, Table 5). Based on PopPK analysis of avalglucosidase alfa in LOPD patients, inter-patient variability in avalglucosidase alfa clearance, distribution volume of central compartment, Km, Vm and QPC was moderate to large (coefficient of variation of 30.2%, 12.7%, 43.1%, 36.6% and 234%, respectively). The residual (intra-individual) variability was small with a coefficient of variation of 12.5%.

**IOPD population**

In IOPD patients receiving 20 and 40 mg/kg qow, the total variability (CV%) of avalglucosidase alfa, determined in a small number of patients per group (4 to 5), Cmax and AUC2W ranged from 18% to 43%, and from 15% to 38%, respectively (see Table 10).

***Special populations***

Considering intrinsic factors such as renal and hepatic impairment, gender, weight, race and age, no major differences in terms of drug exposure could be observed. The PopPK analysis included 75 LOPD patients aged 16 to 78 years (with 1 patient <18 years of age and 16% of patients ≥65 years of age). Data are presented in Table 15.

**Table 10 Avalglucosidase alfa exposure by age category at 20 mg/kg qow in the LOPD (P0H703)**

| Covariate | | n | $C_{max}$ (µg/mL) | $AUC_{0\text{-}2week}$ (µg.h/mL) |
|---|---|---|---|---|
| Age (years) | < 18 | 1 | 247 | 980 |
| | 18 – 64 | 59 | 274 (24.9%)<br>262 [135-432] | 1200 (29.0%)<br>1160 [582-2370] |
| | ≥65 | 10 | 269 (21.5%)<br>267 [157-370] | 1350 (25.9%)<br>1330 [818-2100] |

Mean (CV%) Median [minimum-maximum]

The lack of further studies in severe and renal hepatic impairment is considered acceptable by the CHMP since the main pathway of elimination of avalglucosidase alfa is catabolism.

***Pharmacokinetic interaction studies***

No interaction studies have been performed. Because it is a recombinant human protein, avalglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

***Pharmacokinetics using human biomaterials***

See above.

### *2.6.2.2. Pharmacodynamics*

***Mechanism of action***

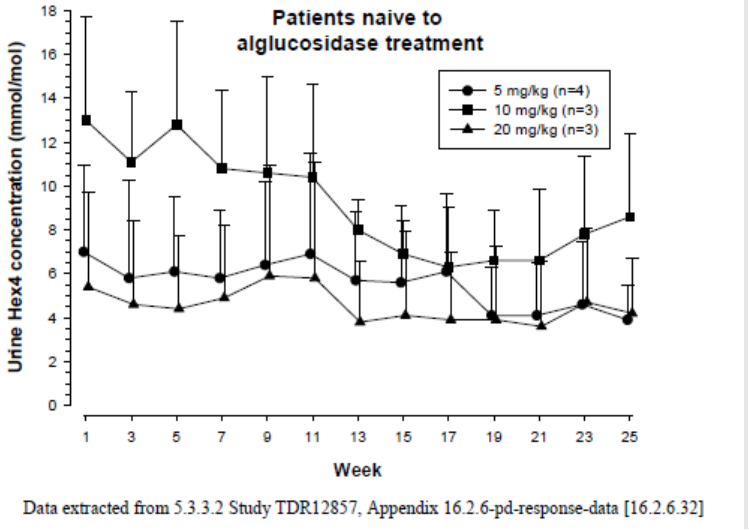
Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) that provides an exogenous source of GAA. Avalglucosidase alfa is a modification of alglucosidase alfa in which approximately 7 hexamannose structures each containing 2 terminal mannose-6-phosphate (bis-M6P) moieties are conjugated to oxidized sialic acid residues on alglucosidase alfa. Avalglucosidase alfa has a 15-fold increase in mannose-6-phosphate (M6P) moieties compared with alglucosidase alfa. Binding to M6P receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity.

***Primary and Secondary pharmacology***

**LOPD population**

In the Phase 1/2 TDR12857 study, urinary Hex4 was assessed on a bimonthly basis in LOPD patients after administration of avalglucosidase alfa at 5, 10 and 20 mg/kg qow for 25 weeks. As illustrated in Figure 4 for patients naïve to alglucosidase alfa treatment, decrease in urinary Hex4 was initiated within 2 weeks after the first avalglucosidase alfa administration (Week 3). At Week 25, mean decreases by 13.2% to 36% were observed in naïve patients with no clear relationship to dose level. The greatest reduction was observed in the group of patients (10 mg/kg) with the highest baseline values (mean ± SD: 13.0 ± 4.75 mmol/mol versus 7.0 ± 3.92 and 5.4 ± 4.3 mmol/mol at 5 mg/kg and

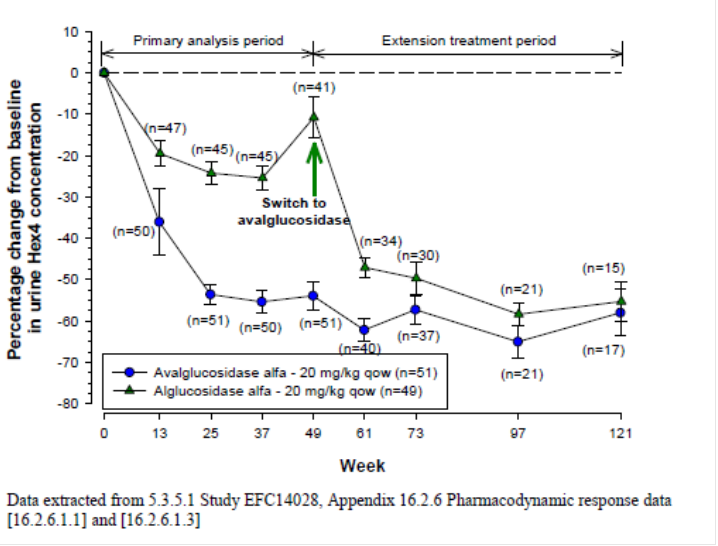
20 mg/kg, respectively). A similar response was documented in patients previously treated with alglucosidase alfa with mean decreases of the same magnitude (7.5% to 20.5%) and no evidence of dose response. In the long-term safety study LTS13769, the decrease in Hex4 levels was maintained with a same magnitude up to 6 years in patients treated with avalglucosidase alfa 20 mg/kg qow.




Data extracted from 5.3.3.2 Study TDR12857, Appendix 16.2.6-pd-response-data [16.2.6.32]

**Figure 1 Mean (SD) urinary Hex4 over time after 5,10 and 20 mg/kg qow in LOPD patients naïve to alglucosidase alfa treatment (TDR12857)**

In the PAP of Phase 3 study EFC14028, urinary Hex4 was assessed on a quarterly basis in LOPD patients after administration of avalglucosidase alfa or alglucosidase alfa at 20 mg/kg qow for 49 weeks. In the extension treatment period (ETP), patients treated with alglucosidase alfa in the PAP switched to avalglucosidase alfa 20 mg/kg qow with urinary Hex4 assessed on a quarterly basis for 6 months and then every 6 months. A slightly higher mean baseline value of urinary Hex4 was observed in the avalglucosidase alfa group (mean ± SD: 12.71 ± 10.10 mmol/mol) than in the alglucosidase alfa group (8.74 ± 5.04 mmol/mol) but median values were similar (8.55 mmol/mol versus 7.30 mmol/mol). Mean (SE) percentage changes from baseline in urinary Hex4 are illustrated for the PAP and ETP in Figure 5. In the PAP, a greater mean decrease in urinary Hex4 was reported in patients treated with avalglucosidase alfa 20 mg/kg qow than in patients treated with alglucosidase alfa 20 mg/kg qow reaching -53.9% as compared to -10.8% at Week 49. In patients with available data up to Week 121 in the ETP, alglucosidase alfa patients switching to avalglucosidase alfa 20 mg qow reached within 6 months same levels of decrease in Hex4 as patients already treated with avalglucosidase alfa during PAP.




Data extracted from 5.3.5.1 Study EFC14028, Appendix 16.2.6 Pharmacodynamic response data [16.2.6.1.1] and [16.2.6.1.3]

**Figure 2 Mean (SE) percentage change from baseline in urinary Hex4 over time after avalglucosidase alfa or alglucosidase alfa 20 mg/kg qow in LOPD patients (primary analysis and extension treatment periods – EFC 14028)**

**IOPD population**

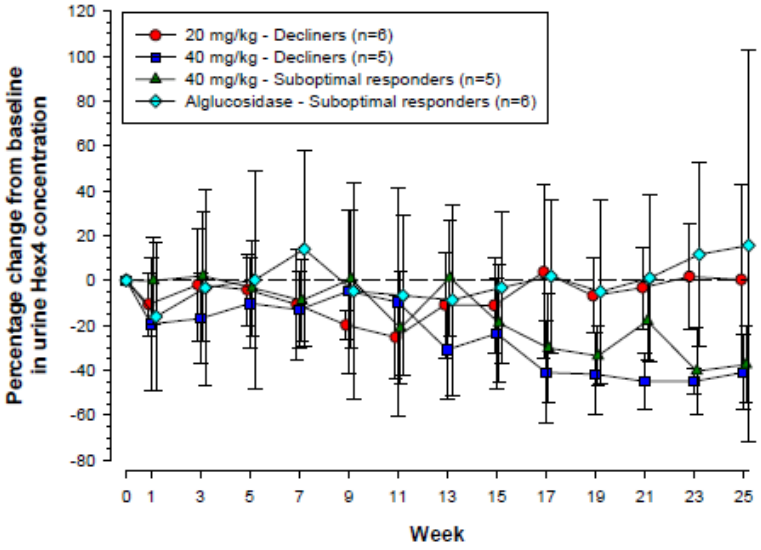
In the PAP of Phase 2 ACT14132 study, urinary Hex4 was assessed on a bimonthly basis in IOPD patients after administration of avalglucosidase alfa at 20 and 40 mg/kg qow or alglucosidase alfa at previously received stable dose (range: 20 mg qow up to 40 mg/kg qw) for 25 weeks. In the ETP urinary Hex4 was assessed every 6 months. Of note, all patients had shown incomplete responses to alglucosidase alfa while receiving a stable dose for a minimum of 6 months immediately prior to study entry. Mean value of urinary Hex4 levels at baseline was higher in clinical decliners to alglucosidase alfa treated with avalglucosidase alfa 20 mg/kg qow (80.25 mmol/mol) compared to clinical decliners and suboptimal responders to alglucosidase alfa treated with avalglucosidase alfa 40 mg/kg qow (63.43 and 54.81 mmol/mol, respectively) (Table 16). In suboptimal responders treated with a stable alglucosidase alfa qow or qw dose, the mean value of urinary Hex4 levels at baseline was 52.16 mmol/mol.

**Table 11 Urinary Hex4 at baseline, week 25 and week 49 after avalglucosidase alfa 20 mg/kg and 40 mg/kg qow or alglucosidase alfa stable qow or qw dose in patinets with IOPD (ACT14132)**

| Evaluation | Decliners | | Suboptimal responders | |
|---|---|---|---|---|
| | Avalglucosidase alfa | | | Alglucosidase alfa |
| | 20 mg/kg | 40 mg/kg | 40 mg/kg | Stable dose[a] |
| **Baseline** | 5 | 5 | 5 | 6 |
| Urinary Hex4 (mmol/mol) | 80.25 (48.38)<br>73.12 [16.1; 143.3] | 63.43 (30.71)<br>71.31 [20.0; 97.3] | 54.81 (50.41)<br>42.54 [11.9; 141.0] | 52.16 (33.93)<br>69.17 [4.2; 80.6] |
| **Week 25** | 6 | 5 | 5 | 5 |
| Urinary Hex4 (mmol/mol) | 77.94 (38.68)<br>87.14 [7.6; 119.2] | 39.59 (23.34)<br>34.63 [7.5; 68.4] | 32.03 (28.12)<br>23.53 [8.3; 79.8] | 41.94 (46.35)<br>25.50 [10.6; 121.8] |
| % change from baseline | 0.34 (42.09)<br>2.43 [-52.7; 60.9] | -40.95 (16.72)<br>-33.20 [-62.6; -24.4] | -37.48 (17.16)<br>-36.38 [-61.9; -15.1] | 15.65 (87.20)<br>-19.81 [-61.9; 151.5] |
| **Week 49** | 6 | 5 | | |
| Urinary Hex4 (mmol/mol) | 53.97 (22.01)<br>60.57 [14.0; 76.3] | 59.11 (68.98)<br>33.90 [4.8; 178.7] | NA | NA |
| % change from baseline | -22.98 (22.75)<br>-15.33 [-54.3; 3.5] | -19.19 (78.01)<br>-46.41 [-76.3; 116.2] | | |

Descriptive statistics are: Mean (SD) Median (minimum; maximum)
Data extracted from 5.3.5.1 Study ACT14132, Appendix 16.2.6 [16.2.6.1.1]
NA: not available (data from the extension treatment period not available at the cut-off date)
a 20 mg/kg qow (1 patient), 40 mg/kg qow (2 patients), 20 mg/kg qw (1 patient), 30 mg/kg qw (1 patient) and 40 mg/kg qw (1 patient)

A trend for greater mean decreases were observed in decliners and suboptimal responders to alglucosidase alfa treated with avalglucosidase alfa 40 mg/kg qow as compared to decliners to alglucosidase alfa treated with avalglucosidase alfa 20 mg/kg qow (Figure 6).




Data extracted from 5.3.5.1 Study ACT14132, Appendix 16.2.6 Pharmacodynamic response data [16.2.6.1.1]

**Figure 3 Mean (SD) percentage change from baseline in urinary Hex4 over time after avalglucosidase alfa 20 and 40 mg/kg qow or alglucosidase alfa in IOPD patients (primary analysis period- ACT14132)**

At Week 25, the mean decrease ranged from 37% to 41% at 40 mg/kg qow as compared to 0.34% at 20 mg/kg qow. All patients treated with avalglucosidase alfa 40 mg/kg qow showed decreases in Hex4 from baseline to Week 25 while decrease was less pronounced and response more variable at 20 mg/kg qow. Patients treated with 40 mg/kg qow showed also a more pronounced and less variable decrease in urinary Hex4 as compared to clinical decliners treated with a stable dose of alglucosidase alfa (range: 20 mg qow up to 40 mg/kg qw).

Decliners to alglucosidase alfa treated with avalglucosidase alfa 20 mg/kg qow showed a similar response to that of suboptimal responders treated at a stable alglucosidase alfa dose of 20 mg/kg qow to 40 mg/kg qw (ie, including higher than recommended dosages). This is consistent with a stabilization of the pathological process in muscles that is observed in IOPD patients previously treated with alglucosidase alfa.

In both LOPD and IOPD population, no results considering secondary pharmacologic parameters were submitted. This was considered acceptable by the CHMP.

## 2.6.3. Discussion on clinical pharmacology

A 3-compartment model with linear and non-linear Michaelis Menten kinetics was used to investigate the PK profile of avalglucosidase alfa. In a typical LOPD patient receiving avalglucosidase alfa qow, the PK is characterized by a linear plasma clearance of 0.869 L/h, a half-life (associated to linear clearance) of 2.7 hours, and a distribution volume of the central compartment of 3.35 L. A shorter terminal half-life ranging between 1.34 and 1.55 hour was documented with the NCA after avalglucosidase alfa 20 mg/kg qow. Avalglucosidase alfa PK characterization was performed in patients with IOPD using NCA. Following avalglucosidase alfa 20 mg/kg and 40 mg/kg qow, mean steady state volume of distribution ranged from 3.5 to 5.4 L and mean plasma clearance from 0.526 to 0.696 L/h. Mean t1/2z ranged from 0.60 to 1.19 h at 40 mg/kg.

The PK data obtained from patients with IOPD and LOPD so far demonstrate similar exposure to avalglucosidase alfa upon repeated injection (no accumulation). Pharmakokinetic dose-proportionality has been sufficiently examined (5, 10, 20 mg/kg in LOPD, and 20 and 40 mg/kg in IOPD) and also PK data in special populations considering renal/hepatic impairment, gender, race, weight and age have not shown major differences. However, the population PK analysis did not include patients below 16 years, mainly due to lack of recruitment in the LOPD studies. This is further discussed under 2.6.6.

Inter-patient variability of Cmax and $AUC_{2W}$ ranged from 18% to 43%, and from 15% to 38%, which is probably linked to the small number of subjects investigated in these studies. During the procedure, direct comparison of PK data from both avalglucosidase and alglucosidase treated patients were requested by the CHMP to conduct a reliable assessment regarding the exposure relevant for safety evaluation... In study ACT14132, no PK samples were collected in the IOPD patients treated with alglucosidase alfa (20 - 40 mg/kg every week) and thus no direct comparison could be performed with patients treated with avalglucosidase alfa 20 mg/kg or 40 mg/kg qow. Therefore, inter-study comparison data for IOPD patients have been provided. Exposure levels of avalglucosidase alfa (AVAL) and alglucosidase alfa (ALGLU) were found similar for both

doses (20 and 40 mg/kg every week) indicating a similar PK profile of avalglucosidase and alglucosidase in LOPD patients.

PD biomarkers of Pompe disease used in these studies showed the ability of avalglucosidase alfa to reduce the burden of glycogen accumulation (Hex4) and muscle damage (CK, ALT and AST) and support the pharmacological activity of avalglucosidase alfa in the intended population. In treatment-naïve LOPD patients aged 16 to 78, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline for patients treated with Nexviadyme 20 mg/kg every other week and alglucosidase alfa 20 mg/kg every other week was -53.90% (24.03) and -10.8% (32.33), respectively, in week 49. In paediatric IOPD patients (<18 years of age) treated with Nexviadyme at 40 mg/kg every other week, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline was -40.97% (16.72) and -37.48% (17.16), respectively, after 6 months. In patients previously declining treated with Nexviadyme at 20 mg/kg every other week, mean (SD) percentage change was 0.34% (42.09). These results were considered clinically relevant and reported in the SmPC.

Based on supporting data from study TDR12857 as well as experience from alglucosidase alfa, other ERT used in the same disease, a dose of 20 mg/kg qow was used in the Phase 3 study EFC14028 conducted in LOPD patients, which is justified. Accordingly, in the phase 2 study ACT14132, which was conducted in IOPD patients, the dosing regimen was aligned to the 20 mg/kg qow. A higher dose of 40 mg/kg qow was also used mainly driven by an observation of current medical practice with Myozyme without providing any further justification. According to literature, the measurement of urinary Glc4/Hex4 levels represents a robust biomarker of disease burden, and additionally, a reduction of Hex4 concentrations correlates also with a better clinical outcome. Even though the effect is not statistically significant, the 40 mg/kg dose tested in IOPD patients showed a sustained and less variable reduction of urinary Hex4 levels in long term follow-up data observed during the ETP. However, the lack of statistical significance together with the small sample size (see number of patients investigated) still remains a strong limitation in the interpretation of these results. This is further discussed in section 2.6.6.

**Immunogenicity assay**

A sufficiently thorough programme was conducted to establish proper qualification and/or validation of the immunogenicity assays employed to analyse avalglucosidase alfa patient sera for anti-drug antibodies (ADA's) and neutralising antibodies (NAb's).

Originally, ADA's were assessed in the Phase 1/2 trial ( and its initial long-term extension (Study LTS13769, until June 2016) by employing a qualified enzyme linked immunosorbent assay (ELISA) .Positive results were confirmed by a separate radio-immunoprecipitation assay.Samples that were confirmed positive for ADA's were then titered by employing the same qualified ELISA approach . To support the Phase 3 study EFC14028, the long-term extension study LTS13769 (samples obtained after June 2016), and the IOPD Phase 2b study ACT14132, the previously developed ELISA format was updated to utilize a floating cut point and a drug competition confirmatory assay. A bridging study was conducted that demonstrated high comparability between the original and the later ADA assays; concordance between the different approaches was 97%.

Samples that were positive for ADA's were subsequently evaluated for the NAb's. This was accomplished by testing the inhibition of the catalytic activity of avalglucosidase alfa (by cleavage of the fluorophore 4-MU from the avalglucosidase alfa substrate 4-MU-α-D-glucoside), and by testing the inhibition of cellular uptake of fluorophore-labelled avalglucosidase alfa in human fibroblasts. The enzymatic approach for analysing NAb's was first qualified, and then validated. Cellular avalglucosidase alfa uptake was originally quantified by flow cytometry. This NAb assay was employed for analysing ADA-positive patient sera obtained from the Phase 1/2 trial TDR12857 and its initial long-term extension (LTS13769, samples collected until June 2016). Because of the high variability that was observed with this first generation assay, cellular avalglucosidase alfa uptake and its inhibition by NAb's in patient sera obtained from the phase 3 study EFC14028, the long-term extension study LTS13769 (after June 2016), and the IOPD Phase 2b study ACT14132, was then analysed by a validated cellular imaging approach. Bridging between these two cellular uptake approaches was conducted, with concordance established in 5 out of 6 historic NAb-positive patient sera.

Furthermore, a method that allows to discriminate whether ADA's specific to Myozyme also cross-react with avalglucosidase alfa was qualified. In this assay, ADA's specific to Myozyme were at first depleted (by fixing Myozyme-specific ADA's that had complexed biotinylated Myozyme to streptavidin magnetic beads and then selectively removing these complexes; depletion was then tested in a previously validated ELISA to screen for Myozyme-ADA's). Subsequently, sera were tested for ADA's specific to avalglucosidase alfa by employing ELISA. Finally, an assay to detect symptom-driven IgE-ADA was validated.

Overall, the qualifications and validations of the assays employed to analyse patient sera for avalglucosidase alfa ADA's (IgM + IgG and, when symptom driven, IgE) and NAb's are acceptable; no concerns were identified.

The impact of immunogenicity and ADA development on the risk of Infusion Associated Reactions (IARs)/hypersensitivity is further discussed in 2.6.8.7.

## 2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacological profile of avalglucosidase alfa in human studies has been adequately documented and meet the requirements to support this application.

## 2.6.5. Clinical efficacy

The primary support for the efficacy of avalglucosidase alfa in the treatment of Pompe disease comes from the pivotal randomized **phase 3 study EFC14028** comparing avalglucosidase alfa to alglucosidase alfa in treatment naïve LOPD patients. Additional evidence of efficacy comes from the **phase 2 study ACT14132** in previously treated IOPD patient > 6 months. **Phase 1/2 TDR12857** and **LTS13769** studies provide supportive efficacy data on the long-term effect of avalglucosidase alfa.

• Study EFC14028 (COMET) is a pivotal Phase 3, randomized, double-blind, comparator controlled study in treatment-naïve patients 3 years of age or older with LOPD. The study comprises a primary analysis period (PAP) followed by an extended treatment period (ETP).

• Study ACT14132 (Mini-COMET) is a Phase 2 open-label, ascending-dose study of avalglucosidase alfa in patients under 18 years of age with IOPD previously treated (treatment experienced) with alglucosidase alfa for at least 6 months. The study comprises a primary analysis period (PAP) followed by an extended treatment period (ETP).

• Study TDR12857 (NEO-1) is a Phase 1/2, open-label, ascending-dose study of avalglucosidase alfa in both treatment-naïve and previously alglucosidase alfa-treated adult patients with LOPD.

• Study LTS13769 (NEO-EXT) is an open-label treatment extension study enrolling patients who completed study TDR12857.

LTS13769 and the ETP of studies EFC14028 and ACT14132 are ongoing, the study-specific data cut-off dates are as follows: EFC14028: 19 March 2020, ACT14132: 30 September 2019 and LTS13769: 27 February 2020.

#### *2.6.5.1. Dose response study(ies)*

No formal dose-finding studies have been conducted.

**LOPD population**

The dose selected for the LOPD Phase 3 Study EFC14028 (20mg/kg) is based on results from the ascending-dose study TDR12857. This clinical study was intended to assess in man the safety and tolerability of AVAL, and characterize its PD and PK profiles following repeated-dose administrations. Additionally, the effect of AVAL on exploratory efficacy endpoints was assessed. TDR12857 was a multicenter, multinational, open-label, ascending dose, repeated every other week (qow) intravenous (IV) infusion study of AVAL (3 dose levels) in late-onset Pompe disease patients ≥18 years of age naïve to treatment (Group 1, n=10) or previously treated with alglucosidase alfa ≥ 9 months (Group 2, n=14). The groups were initiated simultaneously. Eligible patients in each group received an IV infusion of AVAL at doses of 5, 10, or 20 mg/kg of body weight every other week (qow) for 24 weeks. AVAL was generally safe and well tolerated at dose levels of 5, 10, and 20 mg/kg in both treatment-naïve late-onset Pompe disease patients (Group 1) and in late-onset Pompe disease patients previously treated with alglucosidase alfa (Group 2) in this study. No deaths or life-threatening serious adverse events (SAEs) were reported. Six-minute walk test distances were generally stable or tended to increase with AVAL without relationship to patient group or dose level. There were increases across all Group 1 dose levels for percentage predicted force vital capacity (FVC), MEP (maximum expiratory pressure), and maximum inspiratory pressure (MIP) at Week 25 relative to baseline, with the exception of the 5 mg/kg dose group where FVC values remained stable. In Group 2, FVC, MEP, and MIP either remained stable or displayed small increases, with no clear dose-relationship. Across both groups, patients remained stable or demonstrated improvements via a number of functional assessments. Improvements in scores were observed for both groups in the QMFT and HHD evaluations without relationship to patient group or dose level; decreased general and cognitive fatigue was observed at 20 mg/kg AVAL in Group 1 patients. The GSGC and GMFM-88 assessments showed minimal changes for both groups and all dose levels.

**IOPD population**

The proposed dose of 40 mg/kg in IOPD patients is based on the results from the paediatric Phase 2 study ACT14132 (Mini-COMET) and recent publications of clinical experience in IOPD patients receiving alglucosidase alfa doses greater or at higher frequency than the label dose of 20 mg/kg qow (Chien, 2015, J Pediatr; Case, 2015, Neuromusc Disord). Literature generally indicates good tolerance and safety experience of alternate dosing regimen.

Study ACT14132 is a multistage (stage 1: declining patients, stage 2: insufficient clinical response) phase 2 open-label, ascending dose (20 or 40 mg/kg qow) cohort study. The patient must have a documented GAA deficiency, age <18 years, cardiomyopathy at the time of Pompe disease diagnosis, and having received a stable dose of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry, with documented evidence of clinical decline (Stage 1) or suboptimal clinical response (Stage 2).

All patients were treated for 25 weeks during the PAP, thereafter, all patients had the option to receive long term treatment with avalglucosidase alfa in an ETP at a dose of 20 mg/kg qow (Cohort 1) or 40 mg/kg qow (Cohorts 2 and 3). While stage 1 can be considered as a limited dose-finding study for patients with severe forms of IOPD, the second stage allowed a direct treatment comparison of the highest acceptable dose of AVAL (40 mg/kg qow, based on data from cohorts 1 & 2) and alglucosidase alfa at the at the current stable dose in patients with advanced disease.

During the PAP, GMFM-88 mean scores increased modestly from baseline to Week 25 in all 4 treatment groups. Of note, the highest increase was seen in Cohort 3, the alglucosidase alfa group. According to the Applicant, this may be attributed to younger patient age and a smaller proportion of subjects within the group with suboptimal motor response at baseline. Consistently with the results of the Gross Motor Function Measure-88, the greatest degree of change in the QMFT – total score was observed in the alglucosidase alfa group. All patients remained within the normal ranges or improved their left ventricular mass (LVM) and left ventricular mass index (LVMI) echocardiography Z-scores. A trend for improvement of the eyelid position measurement could potentially be observed in the 40 mg/kg qow avalglucosidase alfa groups as compared to the 20 mg/kg qow or alglucosidase alfa groups, which showed stabilization or decline in the measurements. Pulmonary function tests were performed only in few patients able to reliably undergo testing, and no trends were observed for the patients with available data.

### *2.6.5.2. Main study(ies)*

## EFC14028/COMET

The study design is represented in **Figure** 7.

Study EFC14028 is a Phase 3, multicenter, multinational, randomized, double blinded study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa (Myozyme/Lumizyme, both 20 mg/kg qow) in treatment-naïve patients aged 3 years or older with late onset Pompe disease (LOPD).

The study includes two main periods: a blinded treatment period (primary analysis period [PAP]) and an open-label avalglucosidase alfa long-term follow up phase (extension treatment period [ETP]). Patients in the alglucosidase alfa arm were switched to avalglucosidase alfa treatment at the end of the PAP. Patients remained blinded to the randomized treatment until after database was locked and the primary analysis completed. Randomization in a 1:1 ratio employed stratification factors based on baseline FVC, gender, age, and country (Japan or ex-Japan).

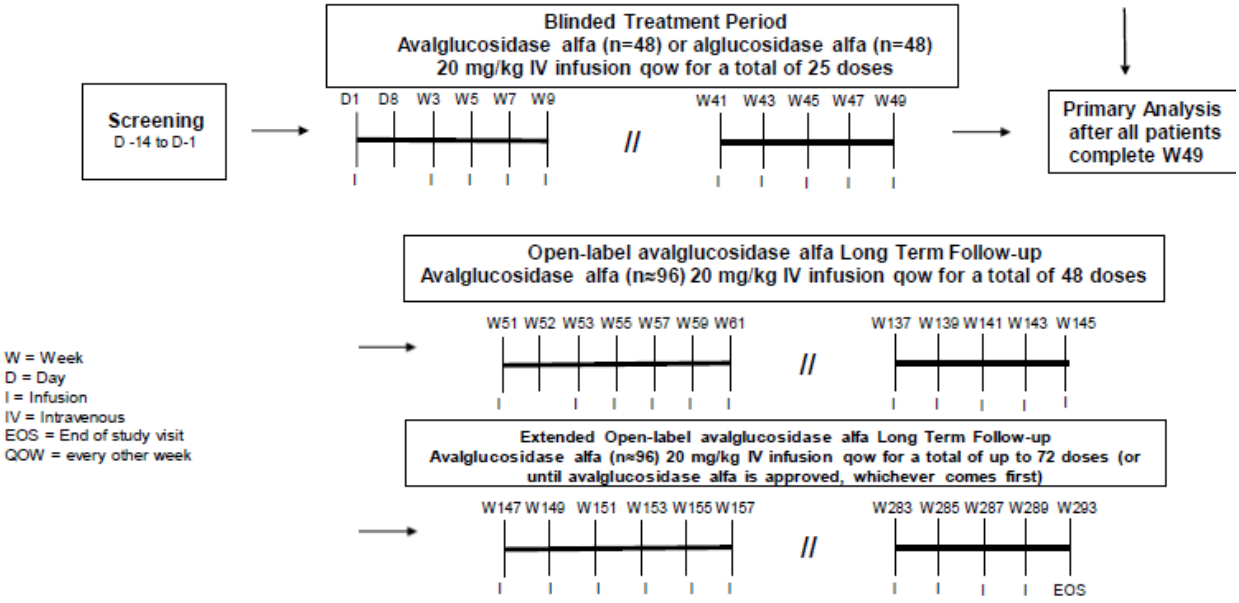



**Figure 4 Study design**

***Methods***

- **Study Participants**

A total of 100 patients were randomized; 51 patients received AVAL, 49 patients received ALGLU. All eligible patients had a confirmed diagnosis of Pompe's disease (GAA deficiency and/or two GAA gene mutations), were 3 years of age or older, able to

walk 40 m on the 6-minute walk test without stopping and without an assistive device and had a % predicted FVC within the range of 30% to less than 85% in the upright position. Patients were excluded if they required any invasive ventilation or if they had previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease.

**Main inclusion criteria**

The patient must have signed informed consent prior to performing any study-related procedures. If the patient was legally minor, signed written consent was obtained from parent(s)/legal guardian and assent obtained from patients, if applicable.

The patient must have had confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations.

**Main exclusion criteria**

Patient was/had: <3 years of age, Pompe-specific cardiac hypertrophy, wheelchair dependent, not able to ambulate 40 meters without stopping and without an assistive device, invasive ventilation, not able to successfully perform repeated FVC measurements in upright position of ≥30% predicted and ≤85% predicted, previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease, pregnant or breast feeding.

- **Treatments**

Route of administration: Intravenous (IV)

Dose regimen: 20 mg/kg once every 2 weeks (qow) for both treatment groups (avalglucosidase alfa and alglucosidase alfa).

- **Objectives**

The primary objective of study EFC14028 was to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by forced vital capacity (FVC)% predicted in the upright position, as compared to alglucosidase alfa.

The primary statistical objective was to test the non-inferiority (NI) of avalglucosidase alfa versus alglucosidase alfa at 5% level of significance. The non-inferiority (NI) of avalglucosidase alfa to alglucosidase alfa was to be investigated first before progressing to investigation of superiority.

Secondary objectives were to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health related quality of life (SF-12). Other objectives were to determine the PK, exploratory PD, pharmacogenetics and effect of avalglucosidase alfa treatment on motor function (GMFM-88 and GSGC), upper extremity muscle strength (HHD), health related quality of life (EQ-5D-5L and PedsQL Generic Core Scale), and patient-reported outcomes (PDSS/PDIS, R-PAct, and PGIC).

- **Outcomes/endpoints**

Primary, secondary and other endpoints are summarised below.

| | **Phase 3 EFC14028** |
|---|---|
| Primary Endpoint | % predicted FVC |
| Secondary Endpoints | • Functional endurance (6MWT)<br>• Inspiratory muscle strength (MIP)<br>• Expiratory muscle strength (MEP)<br>• Lower extremity muscle strength (HHD)<br>• Motor function (QMFT)<br>• Health-related quality of life (SF-12) |
| Exploratory/Tertiary/Other Endpoints | • Motor function (GMFM-88 and GSGC)<br>• Upper extremity muscle strength (HHD)<br>• Health-related quality of life (EQ-5D-5L and PedsQL Generic Core Scale)<br>• Patient reported outcomes (PDSS/PDIS, R-PAct, and PGIC) |

- **Sample size**

Sample size calculations were based on non-inferiority test of the primary efficacy endpoint of change from baseline to Week 49 in FVC (% predicted) upright position, with the following assumptions: primary endpoint is normally distributed with a common standard deviation (SD) of 5.1% predicted, which is estimated based on the data from previous Phase 3, placebo-controlled LOTS trial (AGLU02704); mean treatment difference (avalglucosidase alfa–alglucosidase alfa) of 2.0% predicted, assumed based on a conservative estimate when comparing studies AGLU02704 and TDR12857; a 2-sided 5% significance level; expected percent of missing data of up to 10% (estimated based on studies AGLU02704 and EMBASSY), a non-inferiority margin of 1.1% predicted, which is based on the estimated alglucosidase alfa effect from the placebo-controlled study AGLU02704.

A total sample size of 96 (1:1 randomization ratio) will provide approximately 80% power to demonstrate non-inferiority of avalglucosidase alfa versus alglucosidase alfa, when the true treatment difference (avalglucosidase alfa–alglucosidase alfa) is 2.0% predicted. If the non-inferiority criterion is met, a test for superiority will be performed. If the true difference between avalglucosidase alfa and alglucosidase alfa is 3.6% predicted, the study will have more than 85% power to demonstrate superiority of avalglucosidase alfa to alglucosidase alfa.

- **Randomisation and Blinding (masking)**

Randomisation and treatment allocation are described in a standard manner in the trial protocol in sufficient detail. No concern regarding potential bias arises from those descriptions. Treatment assignment and randomization was planned to be performed using a centralized treatment allocation system/IRT. During the double-blind period, approximately 96 patients were to be randomly assigned across sites to 1 of 2 treatment arms, avalglucosidase alfa or alglucosidase alfa at 20 mg/kg qow in a 1:1

ratio. Randomization was planned to be performed within each of the following 6 strata: Age <18; Age ≥18, all genders and FVC (% predicted), Japan; Age ≥18, male and FVC (% predicted) <55%, ex-Japan; Age ≥18, female and FVC (% predicted) <55%, ex-Japan; Age ≥18, male and FVC (% predicted) ≥55%, ex-Japan and Age ≥18, female and FVC (% predicted) ≥55%, ex-Japan.

To control the number of patients with high baseline FVC (% predicted), the percent of enrolled patients with baseline FVC (% predicted) of 80% to 85% was planned to be capped at 15% of the total population. The Interactive Response Technology or IRT (centralized treatment allocation system) was to generate the patient randomisation list and to allocate the treatment number and the corresponding treatment kits to the patients accordingly. Investigator and assigned study site personnel were planned to have access to blinded IRT menu/reports, whereas the unblinded pharmacist or unblinded designee were planned to have access to unblinded reports. The treatment kits were to be allocated using the IRT every 2 weeks starting at Visit 2 (Day 1/Day 2).

- **Statistical methods**

Analysis populations

*Modified intent-to-treat population*
The mITT population was planned to include randomized patients who receive at least 1 infusion (partial or total). The mITT population were to be used for all efficacy analyses unless otherwise specified. Analyses using the mITT population were to be performed according to the treatment arm allocated by randomization, regardless of the actual treatment received.

*Per-protocol population*
The PP population was planned to consist of mITT patients who met all of the following criteria:

- Meet all of the inclusion and exclusion criteria (See protocol Section 7.1 and 7.2),
- Received at least 80% of planned # of doses,
- Had a valid FVC (% predicted) assessment at Week 49,
- No major protocol deviations that potentially impacting on primary study objective.

The following criteria have been identified a priori as major deviations that will potentially impact on primary study objective. Additional major deviations could be identified during the study. These were planned to be reviewed and approved by sponsor prior to database lock and unblinding of treatment assignment.

- Patient receives doses 2 times higher than the protocol planned dose,
- Patient receives treatment different from the randomized assignment during the PAP,
- The treatment assignment is unblinded before the planned unblinding (completion of PAP) not due to safety reasons specified in the protocol.

The reason for excluding patients from the PP population were planned to be summarized by randomized treatment group and presented in data listing. PP population was planned to be used for sensitivity analysis of the primary efficacy endpoint in PAP only.

*Safety population*

The safety population was to be analyzed according to treatment received. In PAP, safety population was supposed to include randomized patients who receive at least 1 infusion in PAP. In ETP, safety population was supposed to include patients who receive at least 1 infusion in ETP, and was also supposed to include paediatric patients who were directly enrolled to ETP. Overall safety of avalglucosidase alfa was planned to be based on patients who receive at least 1 infusion during either PAP or ETP.

*Additional analysis populations*

- The ETP population was planned to consist of patients who receive at least one avalglucosidase alfa dose during the ETP.
- The pharmacokinetic population was planned to consist of patients from safety population in PAP who have evaluable drug concentration data.
- The pharmacodynamics or pharmacogenetic analysis population for the parameter of interest were planned to consist of mITT patients having evaluable pharmacodynamic data for the parameter of interest.
- The ADA evaluable population was planned to consist of patients from safety population who had at least one ADA sample taken post-baseline after drug administration that was appropriate for ADA testing with a reportable result. Patients with missing or non-reportable baseline samples and reportable post-baseline samples were planned to be considered as evaluable.

Analysis methods

Standard descriptive statistical anaylses were planned and carried out for patient demographics, baseline characteristics, medicinal product exposure and compliance as well as for use of concomitant medications. Analyses were planned by study treatment arm. Summary statistics for continuous variables were planned to minimally include n, mean, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages were to be presented. Graphical displays were planned to be provided as appropriate. Where considered meaningful, separate descriptions were planned to be provided for PAP and ETP.

*Efficacy analysis*

All efficacy endpoints were planned to be summarized descriptively at each study visit, as well as the last observation available during the PAP. All efficacy analyses were planned to be performed based on the mITT population. Corresponding analysis were to be performed in the PP population for the primary efficacy endpoint for sensitivity purposes.

A sequential test strategy for the primary efficacy endpoint and key secondary endpoints was implemented to control Type 1 error rate at 5% in a strong sense. Testing was planned to proceed according to the following order and was planned to be stopped once there was a non-significant result:

1. The primary efficacy endpoint of FVC (% predicted) was to be tested for NI of avalglucosidase alfa versus alglucosidase alfa first.

2. If NI was demonstrated, the superiority of the avalglucosidase alfa versus alglucosidase alfa in FVC (% predicted) was planned to be tested with the same overall 5% significance level.

3. If the superiority of avalglucosidase alfa versus alglucosidase alfa was demonstrated on the primary efficacy endpoint, the hypothesis testing for the following secondary efficacy endpoints was planned to proceed according to the following order:

a) Change from baseline to Week 49 in total distance walked in 6MWT (a superiority test with a two-sided alpha of 0.05),

b) Change from baseline to Week 49 in % predicted of MIP (a superiority test with a two-sided alpha of 0.05),

c) Change from baseline to Week 49 in % predicted of MEP (a superiority test with a two-sided alpha of 0.05),

d) Change from baseline to Week 49 in summary score of lower extremity strength by HHD (a superiority test with a two-sided alpha of 0.05).

The primary efficacy endpoint of change from baseline in FVC (% predicted) in upright position to Week 49 was planned and analyzed in the mITT population using a mixed model for repeated measures (MMRM) with change from baseline as outcome variable. The MMRM included the baseline FVC (% predicted) and age (both as continuous variables), gender (male, female), treatment group, visit, and treatment-by-visit interaction as fixed effects. The model was fitted using restricted maximum likelihood. The difference between treatment groups was planned to be estimated based on least square (LS) means at the Week 49 visit within the mixed model for repeated measures (MMRM) model. A 2-sided 95% confidence interval (CI) using the estimate and variance of the LS mean difference was to be provided. If the lower bound of the 2-sided 95% CI for the difference of avalglucosidase alfa and alglucosidase alfa was found to be larger than -1.1, the study was to be considered to have met its primary objective.

Each of the secondary endpoints were planned to be analyzed based on the MMRM model, similar to that described for the primary endpoint, using the mITT population (with the exception of SF-12, which was planned to be analyzed for a subset of mITT patients with age ≥18 years). The difference between treatment groups was to be assessed with Least squares (LS) mean difference at Week 49 estimated within the framework of the corresponding MMRM model. P-values and 2-sided 95% CIs were planned to be provided.

According to a very detailed plan presented in the SAP, several sensitivity analyses were planned to be conducted to assess the robustness of the primary efficacy analysis results with regards to missing data. This included a tipping point analysis and further analyses performed to address potential deviation from certain planning assumptions. Wilcoxon-Mann Whitney test, Linear Mixed Effects Model, and covariate-adjustment regression models were planned to be used for this purpose. In addition, responder analyses, analyses of changes in respiratory support, and correlation analyses between FVC (% predicted) change and other efficacy parameters were planned to be carried out.

Subgroup analyses for the primary efficacy endpoint of FVC % predicted and key secondary efficacy endpoint 6MWT were planned to be performed. Those were planned to include age group (<18 years, ≥18 years but <45 years, and ≥45 years old), gender, baseline FVC groups (<55%, and ≥55%), race, and ethnicity. Due to the limited power in these subpopulations, treatment difference within the subgroups expected to be difficult to interpret. Therefore, the focus of this analysis was planned on assessment of interaction between subgroup covariate and the treatment. If the p-value for the interaction term was found to be less than 0.1, nature of interaction was planned to be explored.

Exploratory efficacy endpoints were to be summarized descriptively and analyzed using a similar method as used for the primary efficacy endpoint. These analyses were planned in the mITT population.

Two further analyses were planned to evaluate the effect of avalglucosidase alfa in treatment experienced patients. One of them was a piecewise linear mixed effect model for % FVC (predicted) and 6MWT to be fitted for all patients who switched from alglucosidase alfa in PAP to avalglucosidase alfa in ETP. The other analysis was supposed to be conducted in % FVC (predicted) comparing the value from Week 49 to Week 97, by using a within-patient test in the treatment group who switched from alglucosidase alfa in PAP to avalglucosidase alfa in ETP. The change in % FVC (predicted) from Week 49 to Week 97 and the associated 95% CI were to be calculated from the MMRM with fixed term for visit and random term for subject. This MMRM analysis was planned to be based on % FVC (predicted) data from Week 49 and subsequent visits in ETP.

*Safety analysis*
The analysis of the safety variables was planned to be essentially descriptive and no inferential testing was planned. All safety analyses were planned to be performed on the safety population, unless otherwise specified, using the following common rules:

- The baseline value is the last available value before the start of first infusion in PAP or ETP, except possibly ECG parameters.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
    - o PCSA criteria will determine which patients had at least 1 PCSA during the treatment epoch, taking into account all evaluations performed during the period, including non-scheduled or repeated evaluations.
    - o The number of all such patients will be the numerator for the on-treatment PCSA percentage; the denominator will be the number of patients assessed for that given parameter in the treatment epoch in the safety population.

In PAP analysis, the safety analyses were planned to be carried out with patients by the actual treatment received, irrespective of the treatment the patient has been randomized to. In ETP analysis and overall evaluation of avalglucosidase alfa safety, the safety analyses were planned to be carried out by the following 4 groups:

- Group 1 included data in PAP and ETP among subjects who received avalglucosidase alfa in PAP and ETP,
- Group 2 included data in ETP among subjects who received alglucosidase alfa in PAP and received avalglucosidase alfa in ETP,
- Group 3 included data in PAP and/or EPT among subjects who received avalglucosidase alfa in that period,
- Group 4 included data in PAP and/or EPT among paediatric subjects who received avalglucosidase alfa in that period.

***Results***

- **Participant flow**

A total of 100 patients with LOPD were randomized and were exposed to investigational medicinal product (IMP): 51 patients in the avalglucosidase alfa group and 49 patients in the alglucosidase alfa group. 95 patients overall, 51 (100%) in the avalglucosidase alfa group and 44 (89.8%) in the alglucosidase alfa group, completed the PAP. See Table 17.

All 95 patients entered the ETP. There were 5 (5.0%) and 4 (4.0%) premature discontinuations in respective PAP and ETP periods of the study and 91 patients were continuing in the study at the time of the data cut-off. Treatment discontinuation was due to AEs in the majority of cases (see also safety section); two patients withdrew consent due to other reasons. Overall, the drop-out rate is low and does not affect the validity of results.

**Table 12. Participants flow**

| Background therapy | Age group | Clinical study Treatment group | Enrolled | mITT/ Efficacy set | Completed main treatment period[a] | Ongoing in ETP[a,b] |
|---|---|---|---|---|---|---|
| | | **EFC14028** | | | | |
| treatment-naïve | adult | • avalglucosidase alfa | 50 (100.0%) | 50 (100.0%) | 50 (100.0%) | 47 (94.0%) |
| treatment naïve | pediatric | • avalglucosidase alfa | 1 (100.0%) | 1 (100.0%) | 1 (100.0%) | 1 (100.0%) |
| treatment naive | adult | • alglucosidase alfa[c] | 49 (100.0%) | 49 (100.0%) | 44 (89.8%) | 43 (87.8%) |

- **Recruitment**

The study started in November 2016 and is ongoing.

- **Conduct of the study**

Three (5.9%) patients in the avalglucosidase alfa group and 2 (4.1%) patients in the alglucosidase alfa group reported protocol deviations. In the ETP, 12 patients missed a total of 13 infusions due to site access restrictions related to the COVID-19 pandemic. No patient missed any infusion in the PAP for that reason. None of the deviations led to the exclusion of patients from the per protocol (PP) population.

Eighteen (35.3%) patients in the avalglucosidase alfa group and 19 (38.8%) patients in the alglucosidase alfa group reported other major or critical protocol deviations. The most common was study procedure performed against protocol instructions (12 [23.5%] patients in the avalglucosidase alfa group and 11 (22.4%) patients in the alglucosidase alfa group) and failure to report adverse event (AE)/adverse event of special interest (AESI)/SAE/pregnancy/overdose to Sponsor within the protocol-specified time window (3 [5.9%] patients in the avalglucosidase alfa group and 6 [12.2%] patients in the alglucosidase alfa group). Patient safety and data integrity was not affected by the deviations in this study.

The blind was broken for 1 patient in the alglucosidase alfa group for regulatory purposes (due to the reporting of an unexpected serious adverse reaction suspected by the Investigator to be related to study treatment, cerebral artery thrombosis later updated to acute myocardial infarction based on final autopsy report. Accidental unblinding have also occurred in 2 other patients.

- **Baseline data**

Results are presented in Table 18 and Table 19.

**Table 13 Baseline demographics characteristics – in PAP-mITT population**

| Parameter | Statistics | avalglucosidase alfa (N=51) | alglucosidase alfa (N=49) | Total (N=100) |
|---|---|---|---|---|
| Age (years) | Number | 51 | 49 | 100 |
| | Mean (SD) | 46.0 (14.5) | 50.3 (13.7) | 48.1 (14.2) |
| | Median | 47.7 | 48.9 | 48.5 |
| | Min ; Max | 16 ; 78 | 20 ; 78 | 16 ; 78 |
| Age (years) - categorized | Number | 51 | 49 | 100 |
| | < 18 | 1 (2.0) | 0 | 1 (1.0) |
| | ≥ 18 and < 45 | 23 (45.1) | 19 (38.8) | 42 (42.0) |
| | ≥ 45 | 27 (52.9) | 30 (61.2) | 57 (57.0) |
| Gender, n(%) | Number | 51 | 49 | 100 |
| | Male | 27 (52.9) | 25 (51.0) | 52 (52.0) |
| | Female | 24 (47.1) | 24 (49.0) | 48 (48.0) |
| Race, n(%) | Number | 51 | 49 | 100 |
| | American Indian or Alaska Native | 0 | 0 | 0 |
| | Asian | 3 (5.9) | 0 | 3 (3.0) |
| | Black or African American | 1 (2.0) | 2 (4.1) | 3 (3.0) |
| | Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| | White | 47 (92.2) | 47 (95.9) | 94 (94.0) |
| | Not Reported | 0 | 0 | 0 |
| Ethnicity, n(%) | Number | 51 | 49 | 100 |
| | Hispanic or Latino | 3 (5.9) | 12 (24.5) | 15 (15.0) |
| | Not Hispanic or Latino | 44 (86.3) | 32 (65.3) | 76 (76.0) |
| | Unknown | 0 | 0 | 0 |

| Parameter | Statistics | avalglucosidase alfa (N=51) | alglucosidase alfa (N=49) | Total (N=100) |
|---|---|---|---|---|
| | Not reported | 4 (7.8) | 5 (10.2) | 9 (9.0) |
| Regions, n(%) | Number | 51 | 49 | 100 |
| | Europe | 31 (60.8) | 21 (42.9) | 52 (52.0) |
| | North America | 14 (27.5) | 20 (40.8) | 34 (34.0) |
| | Latin America | 2 (3.9) | 7 (14.3) | 9 (9.0) |
| | Asia-Pacific | 4 (7.8) | 1 (2.0) | 5 (5.0) |
| Weight (kg) | Number | 51 | 49 | 100 |
| | Mean (SD) | 77.8 (22.1) | 79.3 (18.2) | 78.5 (20.2) |
| | Median | 75.9 | 78.6 | 76.4 |
| | Min ; Max | 38 ; 129 | 46 ; 139 | 38 ; 139 |
| Height (cm) | Number | 51 | 49 | 100 |
| | Mean (SD) | 170.9 (9.7) | 172.0 (8.9) | 171.5 (9.3) |
| | Median | 169.8 | 171.5 | 170.3 |
| | Min ; Max | 145 ; 193 | 158 ; 191 | 145 ; 193 |
| BMI ($kg/m^2$) | Number | 51 | 49 | 100 |
| | Mean (SD) | 26.39 (6.79) | 26.69 (5.42) | 26.54 (6.13) |
| | Median | 25.40 | 27.40 | 26.45 |
| | Min ; Max | 14.0 ; 42.7 | 16.9 ; 44.6 | 14.0 ; 44.6 |
| Alcohol Habit, n(%) | Number | 51 | 49 | 100 |
| | Never | 21 (41.2) | 17 (34.7) | 38 (38.0) |
| | Occasional | 18 (35.3) | 20 (40.8) | 38 (38.0) |
| | At least monthly | 4 (7.8) | 3 (6.1) | 7 (7.0) |
| | At least weekly | 5 (9.8) | 5 (10.2) | 10 (10.0) |
| | At least daily | 3 (5.9) | 4 (8.2) | 7 (7.0) |
| Randomization Strata, n(%) | Number | 51 | 49 | 100 |
| | Age<18 | 1 (2.0) | 0 | 1 (1.0) |
| | Age≥18, Japan | 1 (2.0) | 0 | 1 (1.0) |
| | Age≥18, male and FVC<55%, ex-Japan | 10 (19.6) | 11 (22.4) | 21 (21.0) |
| | Age≥18, female and FVC<55%, ex-Japan | 5 (9.8) | 5 (10.2) | 10 (10.0) |
| | Age≥18, male and FVC≥55%, ex-Japan | 15 (29.4) | 14 (28.6) | 29 (29.0) |
| | Age≥18, female and FVC≥55%, ex-Japan | 19 (37.3) | 19 (38.8) | 38 (38.0) |

**Table 14 Baseline values of key efficacy parameters – in PAP-mITT population**

| Parameter | Statistics | avalglucosidase alfa (N=51) | alglucosidase alfa (N=49) | Total (N=100) |
|---|---|---|---|---|
| Predicted FVC (%), upright | Number | 51 | 49 | 100 |
| | Mean (SD) | 62.5 (14.4) | 61.6 (12.4) | 62.1 (13.4) |
| | Median | 65.5 | 60.8 | 63.2 |
| | Min; Max | 32; 85 | 39; 85 | 32; 85 |
| Distance Walked from 6MWT (m) | Number | 51 | 49 | 100 |
| | Mean (SD) | 399.3 (110.9) | 378.1 (116.2) | 388.9 (113.5) |
| | Median | 415.7 | 387.0 | 403.5 |
| | Min; Max | 118; 630 | 138; 592 | 118; 630 |
| 6MWT (% predicted) | Number | 51 | 49 | 100 |
| | Mean (SD) | 57.3 (15.0) | 55.3 (16.6) | 56.3 (15.8) |
| | Median | 61.0 | 56.6 | 59.1 |
| | Min; Max | 19; 86 | 23; 102 | 19; 102 |
| % Predicted MIP (%) [a], upright | Number | 50 | 49 | 99 |
| | Mean (SD) | 59.9 (47.1) | 60.6 (41.0) | 60.3 (44.0) |
| | Median | 47.6 | 51.1 | 48.1 |
| | Min; Max | 9; 263 | 18; 234 | 9; 263 |
| % Predicted MEP (%) [a], upright | Number | 50 | 49 | 99 |
| | Mean (SD) | 65.77 (38.97) | 74.83 (35.22) | 70.25 (37.25) |
| | Median | 54.21 | 68.00 | 59.56 |
| | Min; Max | 28.7; 232.5 | 19.7; 201.1 | 19.7; 232.5 |
| HHD (Lower extremity) composite score | Number | 50 | 46 | 96 |
| | Mean (SD) | 1330.45 (625.44) | 1466.16 (604.91) | 1395.48 (616.23) |
| | Median | 1193.50 | 1427.50 | 1290.00 |
| | Min; Max | 323.0; 3522.0 | 329.0; 3218.0 | 323.0; 3522.0 |
| % Predicted HHD (Lower extremity) composite score | Number | 50 | 46 | 96 |
| | Mean (SD) | 40.05 (21.76) | 45.02 (23.27) | 42.43 (22.52) |
| | Median | 30.51 | 40.60 | 38.61 |
| | Min; Max | 7.1; 112.7 | 9.6; 119.4 | 7.1; 119.4 |

| Parameter | Statistics | avalglucosidase alfa (N=51) | alglucosidase alfa (N=49) | Total (N=100) |
|---|---|---|---|---|
| HHD (upper extremity) composite score | Number | 46 | 47 | 93 |
| | Mean (SD) | 1535.95 (673.60) | 1608.56 (633.95) | 1572.65 (651.32) |
| | Median | 1380.00 | 1501.00 | 1439.00 |
| | Min; Max | 350.5; 3869.0 | 347.0; 3102.0 | 347.0; 3869.0 |
| % Predicted HHD (upper extremity) composite score | Number | 46 | 47 | 93 |
| | Mean (SD) | 69.44 (33.46) | 74.35 (34.91) | 71.92 (34.11) |
| | Median | 57.37 | 65.82 | 62.20 |
| | Min; Max | 14.8; 173.9 | 13.9; 148.4 | 13.9; 173.9 |
| QMFT | Number | 51 | 46 | 97 |
| | Mean (SD) | 41.29 (10.15) | 42.30 (10.58) | 41.77 (10.32) |
| | Median | 41.00 | 43.50 | 41.00 |
| | Min; Max | 17.0; 63.0 | 19.0; 63.0 | 17.0; 63.0 |
| SF-12 (PCS) | Number | 50 | 48 | 98 |
| | Mean (SD) | 35.95 (7.82) | 36.76 (9.40) | 36.35 (8.60) |
| | Median | 35.01 | 36.04 | 35.40 |
| | Min; Max | 17.8; 55.9 | 16.3; 57.3 | 16.3; 57.3 |
| SF-12 (MCS) | Number | 50 | 48 | 98 |
| | Mean (SD) | 48.31 (10.11) | 50.58 (8.69) | 49.42 (9.46) |
| | Median | 47.53 | 52.24 | 50.21 |
| | Min; Max | 24.2; 70.8 | 30.4; 65.0 | 24.2; 70.8 |
| GMFCS [n (%)] | Number | 51 | 49 | 100 |
| | Level I | 10 (19.6) | 14 (28.6) | 24 (24.0) |
| | Level II | 36 (70.6) | 27 (55.1) | 63 (63.0) |
| | Level III | 5 (9.8) | 8 (16.3) | 13 (13.0) |
| | Level IV | 0 | 0 | 0 |
| | Level V | 0 | 0 | 0 |
| Walking Device on 6MWT [n (%)] | Number | 51 | 49 | 100 |
| | Straight cane | 4 (7.8) | 3 (6.1) | 7 (7.0) |
| | Wide-based cane | 1 (2.0) | 1 (2.0) | 2 (2.0) |
| | One crutch | 0 | 2 (4.1) | 2 (2.0) |
| | Two crutches | 0 | 0 | 0 |
| | Standard walker | 0 | 0 | 0 |
| | Rolling walker | 0 | 3 (6.1) | 3 (3.0) |
| | Orthotics | 0 | 0 | 0 |
| | Other | 2 (3.9) | 1 (2.0) | 3 (3.0) |
| | None | 44 (86.3) | 39 (79.6) | 83 (83.0) |

- **Numbers analysed**

Results are presented in Table 20.

**Table 15 Patient disposition and Analysed populations**

| Parameter, n (%) | avalglucosidase alfa (N=51) | alglucosidase alfa (N=49) | Total (N=100) |
|---|---|---|---|
| mITT [b] | 51 (100) | 49 (100) | 100 (100) |
| Per Protocol | 46 (90.2) | 39 (79.6) | 85 (85.0) |
| Safety population [c] | 51 (100) | 49 (100) | 100 (100) |
| PK population [d] | 49 (96.1) | 0 | 49 (49.0) |
| ADA evaluable population [e] | 51 (100) | 48 (98.0) | 99 (99.0) |
| Number of randomized and treated patients at Week 97 | 24 (47.1) | 22 (44.9) | 46 (46.0) |

- **Outcomes and estimation**

Summary of the efficacy results are presented in Table 21.

**Table 16 Key efficacy results for study EFC14028**

| Primary endpoint | | Avalglucosidase alfa 20 mg/kg qow (N=51) | Alglucosidase alfa 20 mg/kg qow (N=49) | Avalglucosidase alfa vs alglucosidase alfa |
|---|---|---|---|---|
| FVC (percent predicted) | Mean baseline (SD) | 62.55 (14.39) | 61.6 (12.4) | |
| | LS Mean change (SE) | 2.89 (0.88) | 0.46 (0.93) | |
| | LS Mean difference (SE) | | | 2.43 (1.29) |
| | 95% CI | | | -0.13, 4.99 |
| | p-value for non-inferiority | | | 0.0074 |
| | p-value for superiority | | | 0.0626 |
| Secondary endpoints | | | | |
| 6MWT (distance walked in meters) | Mean baseline (SD) | 399.3 (110.9) | 378.1 (116.2) | |
| | LS Mean change (SE) | 32.21 (9.93) | 2.19 (10.40) | |
| | LS Mean difference (SE) | | | 30.01 (14.43) |
| | 95% CI | | | 1.33, 58.69 |
| | Nominal p-value | | | 0.0405 |
| MIP (percent predicted) | Mean baseline (SD) | 59.9 (47.1) | 60.65 (41.05) | |
| | LS Mean change (SE) | -0.29 (3.84) | -2.87 (4.04) | |
| | LS Mean difference (SE) | | | 2.58 (5.59) |
| | 95% CI | | | -8.54, 13.71 |
| | Nominal p-value | | | 0.6451 |
| MEP (percent predicted) | Mean baseline (SD) | 65.77 (38.97) | 74.83 (35.22) | |
| | LS Mean change (SE) | 2.39 (4.00) | 5.00 (4.20) | |
| | LS Mean difference (SE) | | | -2.61 (5.83) |
| | 95% CI | | | -14.22, 9.00 |
| | p-value | | | 0.6557 |
| Lower extremity HHD composite score | Mean baseline (SD) | 1330.45 (625.44) | 1466.16 (604.91) | |
| | LS Mean change (SE) | 260.69 (46.07) | 153.72 (48.54) | |
| | LS Mean difference (SE) | | | 106.97 (67.17) |
| | 95% CI | | | -26.56, 240.50 |
| | Nominal p-value | | | 0.1150 |

**Primary Endpoint**

- **Forced vital capacity**

Results are presented in Table 22, Table 23, Figure 8 and Table 24.

**Table 17 FVC(%Predicted) – in upright position: estimates and hypothesis tests of change from baseline by visit - Primary analysis- in PAP-mITT population**

| | Statistics [a] | Avalglucosidase alfa (N=51) | Alglucosidase alfa (N=49) | Difference |
|---|---|---|---|---|
| Week 13 | Estimate | 3.05 | 0.65 | 2.40 |
| | SE | 0.78 | 0.81 | 1.13 |
| | 95% CI | 1.50, 4.59 | -0.95, 2.26 | 0.16, 4.63 |
| | p-value for non-inferiority [b] | | | 0.0026 |
| | p-value for superiority | | | 0.0363 |
| Week 25 | Estimate | 3.21 | 0.57 | 2.64 |
| | SE | 0.80 | 0.84 | 1.17 |
| | 95% CI | 1.62, 4.80 | -1.10, 2.24 | 0.32, 4.96 |
| | p-value for non-inferiority [b] | | | 0.0018 |
| | p-value for superiority | | | 0.0259 |
| Week 37 | Estimate | 2.21 | 0.55 | 1.66 |
| | SE | 1.00 | 1.05 | 1.45 |
| | 95% CI | 0.23, 4.19 | -1.53, 2.64 | -1.22, 4.54 |
| | p-value for non-inferiority [b] | | | 0.0603 |
| | p-value for superiority | | | 0.2556 |
| Week 49 | Estimate | 2.89 | 0.46 | 2.43 |
| | SE | 0.88 | 0.93 | 1.29 |
| | 95% CI | 1.13, 4.65 | -1.39, 2.31 | -0.13, 4.99 |
| | p-value for non-inferiority [b] | | | 0.0074 |
| | p-value for superiority | | | 0.0626 |

**Table 18 FVC(%Predicted) – in upright position: estimates and hypothesis tests of change from baseline by visit - Primary analysis- in PAP-per protocol population**

| | Statistics [a] | Avalglucosidase alfa (N=46) | Alglucosidase alfa (N=39) | Difference |
|---|---|---|---|---|
| Week 13 | Estimate | 2.95 | 0.20 | 2.75 |
| | SE | 0.81 | 0.88 | 1.20 |
| | 95% CI | 1.34, 4.56 | -1.55, 1.95 | 0.36, 5.14 |
| | p-value for non-inferiority [b] | | | 0.0020 |
| | p-value for superiority | | | 0.0248 |
| Week 25 | Estimate | 3.02 | 0.62 | 2.40 |
| | SE | 0.82 | 0.90 | 1.22 |
| | 95% CI | 1.38, 4.65 | -1.17, 2.40 | -0.03, 4.83 |
| | p-value for non-inferiority [b] | | | 0.0053 |
| | p-value for superiority | | | 0.0528 |
| Week 37 | Estimate | 2.32 | 0.70 | 1.62 |
| | SE | 1.05 | 1.15 | 1.56 |
| | 95% CI | 0.23, 4.41 | -1.58, 2.98 | -1.48, 4.72 |
| | p-value for non-inferiority [b] | | | 0.0845 |
| | p-value for superiority | | | 0.3012 |
| Week 49 | Estimate | 2.87 | 0.19 | 2.69 |
| | SE | 0.93 | 1.02 | 1.38 |
| | 95% CI | 1.02, 4.73 | -1.83, 2.21 | -0.06, 5.44 |
| | p-value for non-inferiority [b] | | | 0.0076 |
| | p-value for superiority | | | 0.0555 |

*a* Based on MMRM model, the model includes baseline FVC (% predicted, as continuous), sex, age (in years at baseline), treatment group, visit, nteraction term between treatment group and visit as fixed effects.

*b* Non-inferiority margin is -1.1%

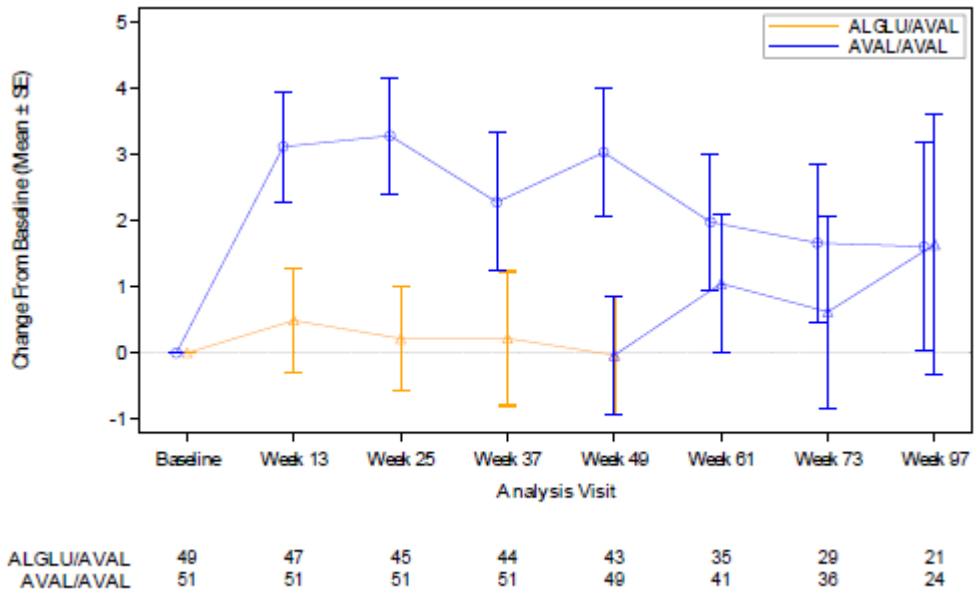



**Figure 5 Plot of Mean (SE) change from baseline of FVC (% Predicted) – in upright position over time up to week 97- in PAP and ETP – mITT population**

**Table 19 FVC(%Predicted)- in upright position: observed values and change from baseline by study visit- in PAP and ETP-mITT population**

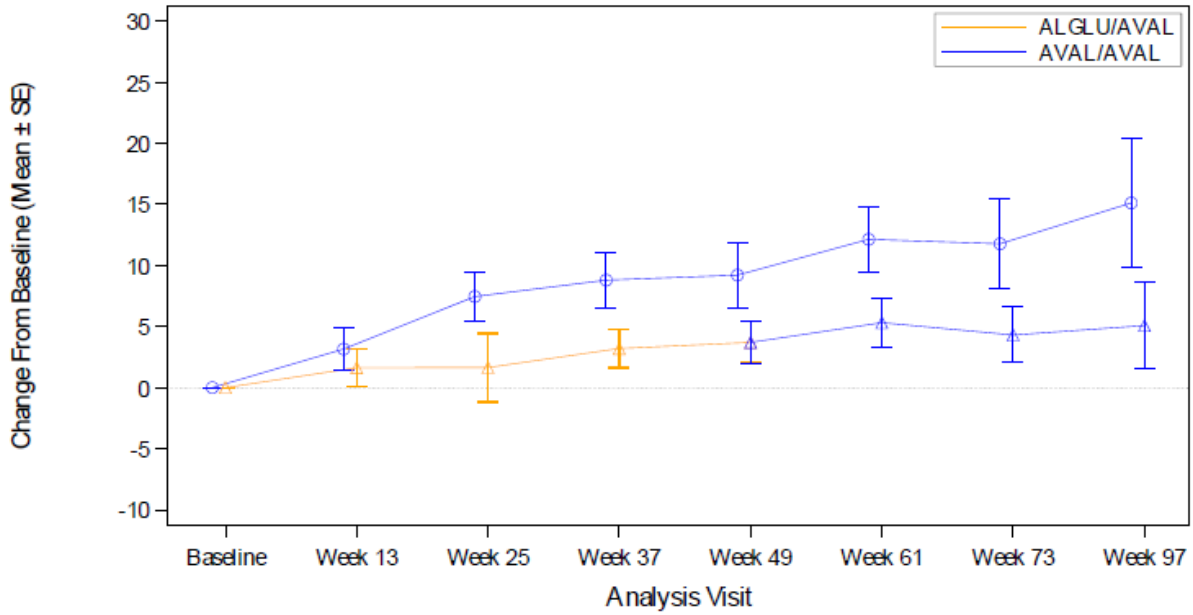
| Visit | Statistics | AVAL/AVAL (N=51) | | | ALGLU/AVAL (N=49) | | |
|---|---|---|---|---|---|---|---|
| | | Observed | Change from baseline | % change from baseline | Observed | Change from baseline | % change from baseline |
| | Min ; Max | 22.0 ; 94.3 | -24.5 ; 14.7 | -52.6 ; 19.5 | 32.5 ; 86.3 | -14.7 ; 16.0 | -23.2 ; 24.9 |
| Week 97 | Number | 24 | 24 | 24 | 21 | 21 | 21 |
| | Mean (SD) | 61.90 (18.11) | 1.60 (7.72) | 1.97 (14.58) | 63.01 (17.14) | 1.64 (8.97) | 2.39 (15.10) |
| | Median | 62.55 | 2.50 | 3.65 | 65.04 | 0.85 | 1.20 |
| | Min ; Max | 23.4 ; 87.2 | -23.2 ; 12.1 | -49.8 ; 23.8 | 37.6 ; 85.8 | -13.0 ; 20.8 | -22.9 ; 33.5 |
| Week 121 | Number | 17 | 17 | 17 | 15 | 15 | 15 |
| | Mean (SD) | 61.16 (15.68) | -0.45 (8.54) | -0.68 (16.28) | 62.05 (16.86) | 0.00 (7.54) | -0.35 (14.10) |
| | Median | 65.66 | -0.76 | -1.10 | 64.85 | 0.35 | 0.65 |
| | Min ; Max | 27.2 ; 84.3 | -19.3 ; 12.2 | -41.5 ; 19.3 | 34.9 ; 86.2 | -11.4 ; 12.0 | -24.6 ; 24.1 |
| Week 145 | Number | 11 | 11 | 11 | 9 | 9 | 9 |
| | Mean (SD) | 61.74 (16.67) | -1.27 (8.08) | -2.19 (15.41) | 58.12 (18.64) | -4.90 (8.14) | -8.81 (12.77) |
| | Median | 65.55 | -0.57 | -0.71 | 58.47 | -4.14 | -8.93 |
| | Min ; Max | 29.6 ; 80.1 | -16.9 ; 8.7 | -36.3 ; 15.4 | 33.6 ; 86.0 | -17.4 ; 6.7 | -25.5 ; 8.4 |
| Week 169 | Number | 1 | 1 | 1 | 2 | 2 | 2 |
| | Mean (SD) | 58.63 (NC) | -7.79 (NC) | -11.72 (NC) | 59.54 (39.29) | -1.23 (13.09) | -7.34 (24.70) |

**Other Secondary Endpoints**

- **Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP)**

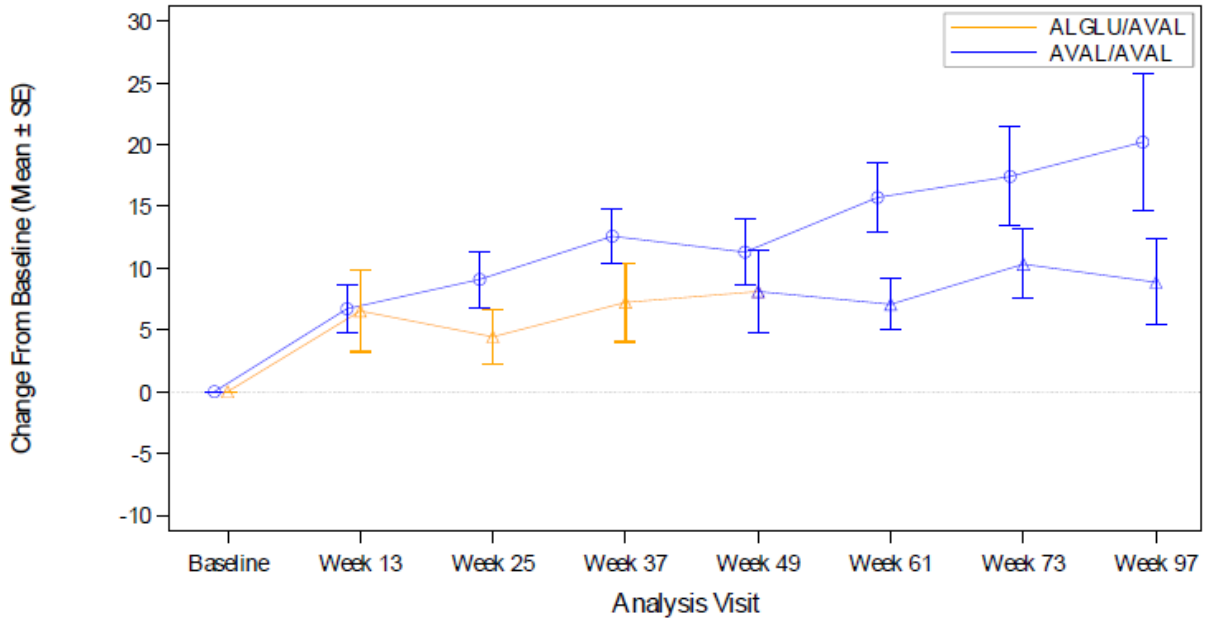
The LS mean (SE) changes from baseline in % predicted MIP was stable by Week 49 in both avalglucosidase alfa (-0.29% [3.84%]) and alglucosidase alfa (-2.87% [4.04%]) arms, with no clear treatment difference at any time point evaluated . Percent predicted MEP improved over baseline in both treatment arms, showing no treatment difference at Week 49 (avalglucosidase alfa, 2.39% ±4.00%; alglucosidase alfa, 5.00% ± 4.20%)

Following repeated queries and database lock, supraphysiologic baseline MIP and MEP values of 200 $cmH_2O$ or more were identified for 4 patients. As the anomalous values are not plausible in patients with Pompe disease, and likely due to errors in data entry, post hoc sensitivity analyses excluding these 4 patients were conducted for MIP and MEP. An LS mean increase (SE) of 8.70% (2.09) in MIP (LS mean difference +4.40% [95% CI: -1.63, 10.44]) was observed, confirming the benefit of avalglucosidase alfa 20 mg/kg qow on respiratory function. Similarly, an LS mean increase (SE) of 10.89% (2.84) in MEP (LS mean difference +2.51% [95% CI: -5.70, 10.73]) was observed, confirming the benefit of avalglucosidase alfa 20 mg/kg qow on MEP as well as MIP. Observed mean changes in MIP and MEP excluding patients with implausible baseline values are shown by treatment in Figure 9 and Figure 10, below.




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 47 | 43 | 43 | 42 | 41 | 31 | 27 | 19 |
| AVAL/AVAL | 48 | 46 | 48 | 48 | 46 | 39 | 34 | 22 |

**Figure 6 Plot of mean (SD) change from baseline of MIP (%predicted) – in upright position over time up to week 97 – in PAP and ETP-mITT population (age of 8 years or older) in study EFC14028**




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 47 | 43 | 43 | 42 | 41 | 31 | 27 | 19 |
| AVAL/AVAL | 48 | 46 | 48 | 48 | 46 | 39 | 34 | 22 |

Note: patients in the ALGLU/AVAL arm who received alglucosidase alfa in PAP period were switched to avalglucosidase alfa treatment after the 49 week PAP period.

4 patients (792000105001 and 792000205001 in Avalglucosidase alfa and 792000105002 and 840000505001 in Alglucosidase alfa) were excluded due to implausible MIP/MEP value of 200 $cmH_2O$ at baseline.

Source: 5.3.5.1 Study EFC14028 [Figure 8]

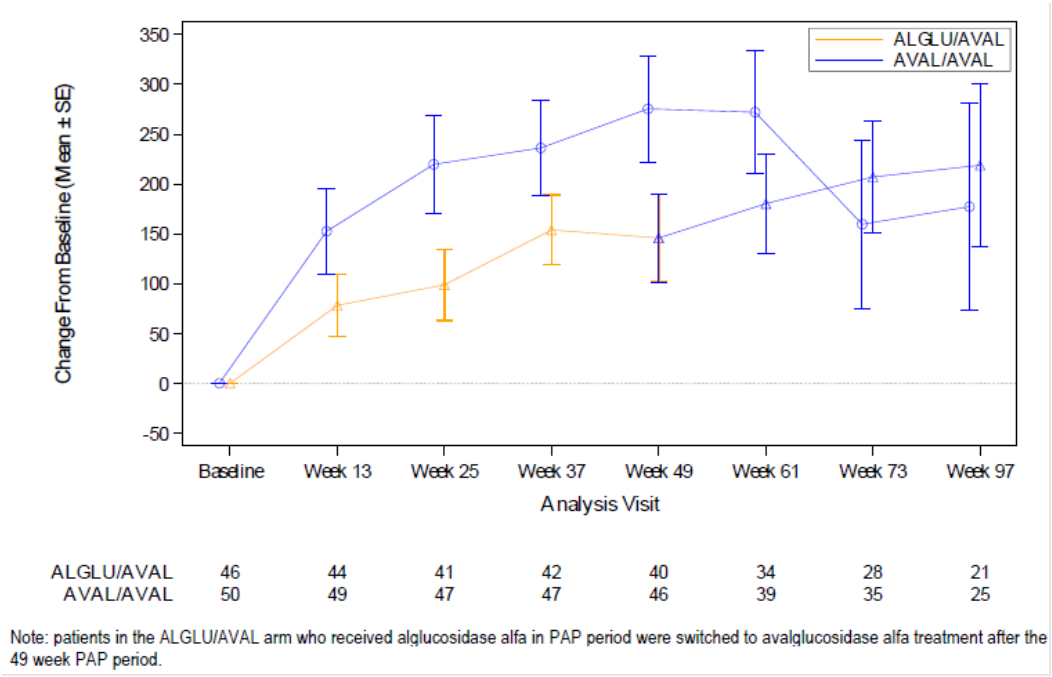
PGM=PRODOPS/GZ402666/EFC14028/CSR/REPORT/PGM/eff_meanchange_i_m_i_f.sas OUT=REPORT/OUTPUT/eff_meanchange_mep_i_m_i_f_i.rtf (13JUL2020 11:17)

**Figure 7 Plot of mean (SD) change from baseline of MEP (%predicted) – in upright position over time up to week 97 – in PAP and ETP – mITT population (age of 8 years or older) in study EFC14028**

- **Measurements of lower extremity muscle strength**

HHD composite scores for lower extremity muscle strength increased over baseline scores in both avalglucosidase alfa and alglucosidase alfa treatment groups. See Figure 11.

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). Mean plots over time to Week 49 showed a numerically higher treatment response with avalglucosidase alfa as compared with alglucosdidase alfa in changes from baseline in composite scores and summary scores (% predicted) of muscle strength. In those patients who had reached Week 97 at time of the data cut-off (19 March 2020), patients whose treatment switched from alglucosidase alfa to avalglucosidase alfa after Week 49 further improved HHD scores. Whereas patients treated continuously with avalglucosidase alfa showed higher variability, with lower mean scores observed in patients who had assessments at Week 97 by the cut-off date.




Note: patients in the ALGLU/AVAL arm who received alglucosidase alfa in PAP period were switched to avalglucosidase alfa treatment after the 49 week PAP period.

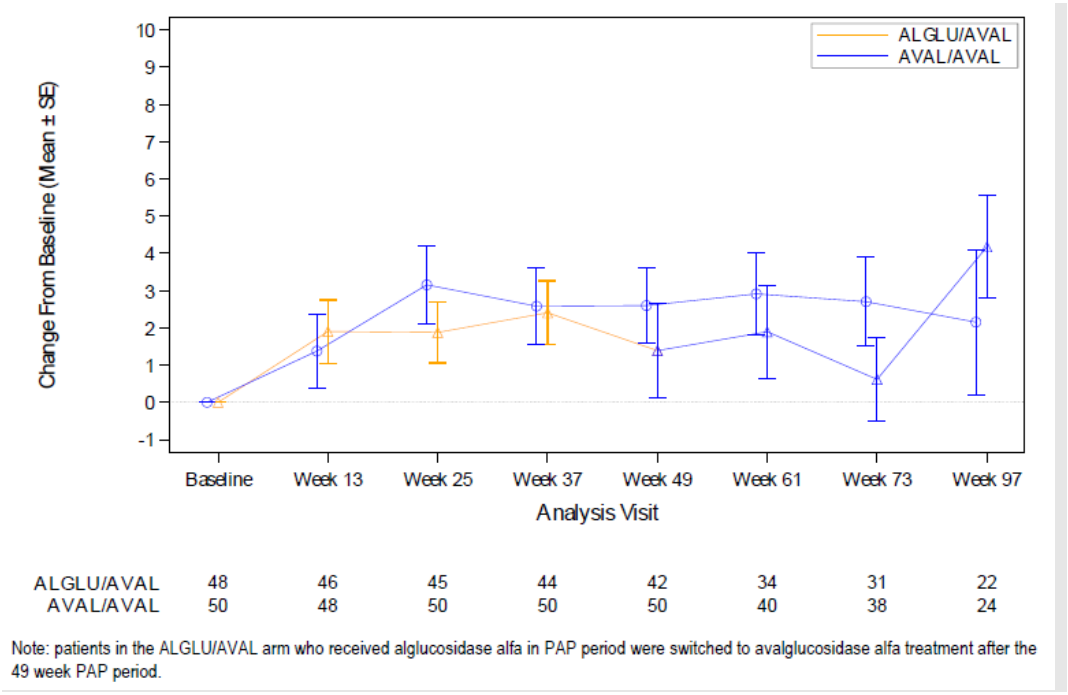
**Figure 8 Plot of mean (SD) change from baseline of HDD (lower extremity muscle strength in composite score) over time up to week 97 – in PAP and ETP – mITT 1 in study EFC14028**

- **Measurements of upper extremity muscle strength**

During the PAP, the LS mean change (SE) in HHD (upper extremity strength) (composite score) from baseline to Week 49 was 173.54 (38.04) in the avalglucosidase alfa group and 109.67 (38.98) in the alglucosidase alfa group; the difference was 63.87 (95% CI: -44.76, 172.51).

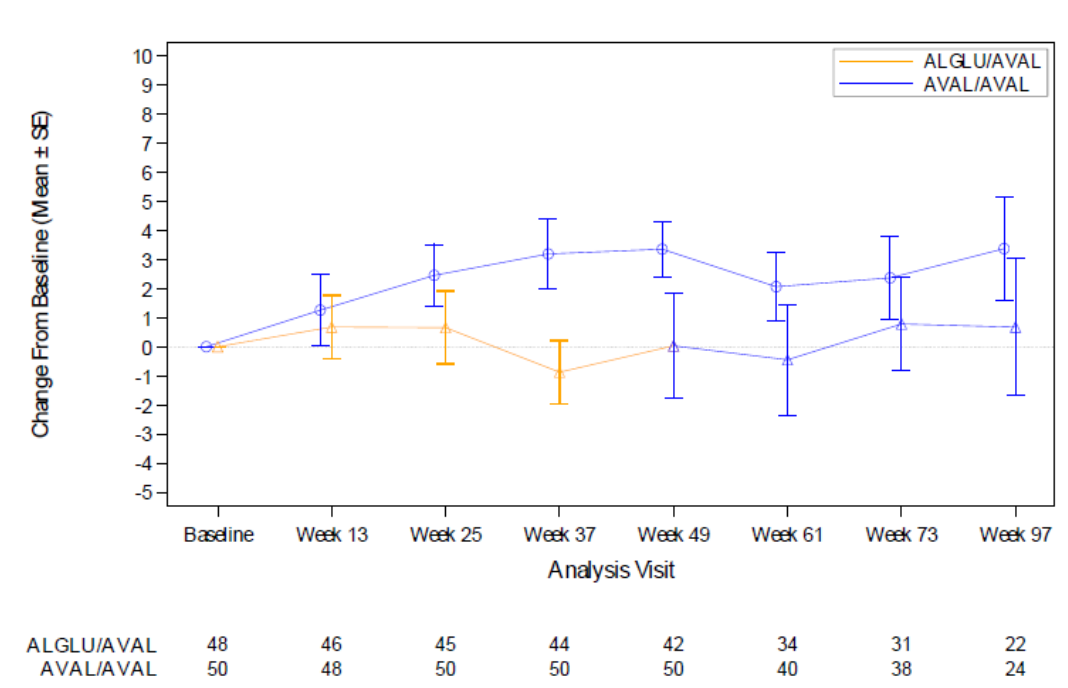
- **Efficacy results for health-related quality of life questionnaires**

The observed values in SF-12 show a gradual increase in mean PCS and MCS scores from baseline to Week 97 in both treatment groups, see Figure 12 and Figure 13.




Note: patients in the ALGLU/AVAL arm who received alglucosidase alfa in PAP period were switched to avalglucosidase alfa treatment after the 49 week PAP period.

**Figure 9 Plot of mean (SD) change from baseline of SF-12 (PCS score) –over time up to week 97 – in PAP and ETP – mITT population (age of 18 years or older) in study EFC14028**




Note: patients in the ALGLU/AVAL arm who received alglucosidase alfa in PAP period were switched to avalglucosidase alfa treatment after the 49 week PAP period.

**Figure 10 Plot of mean (SD) change from baseline of SF-12 (MCS score) –over time up to week 97 – in PAP and ETP – mITT population (age of 18 years or older) in study EFC14028**

## Study ACT14132/Mini-COMET

The study design is represented in Figure 14. ACT14132 is a multistage (stage 1: declining patients, stage 2: insufficient clinical response) phase 2 open-label, ascending dose (20 or 40 mg/kg qow) cohort study with long-term open label extension treatment period (ETP) at a dose of 20 mg/kg qow (Cohort 1) or 40 mg/kg qow (Cohorts 2 and 3).

**Figure 1 – Study design**

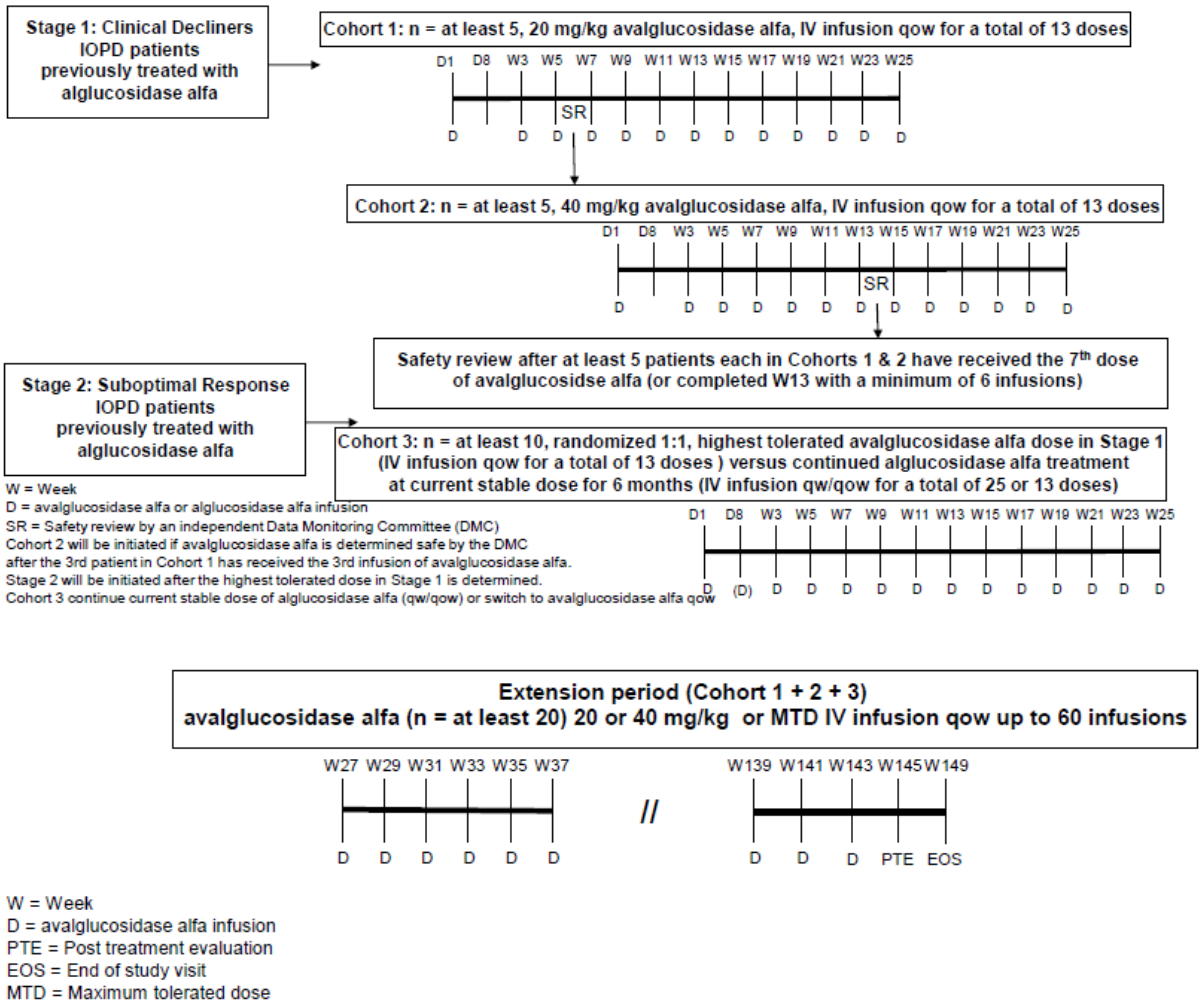



**Figure 11 Study design**

***Methods***

- **Study Participants**

Ten centers screened and enrolled at least 1 patient. Centers were from 5 geographic locations worldwide: France (2); Japan (2); Taiwan (1); United Kingdom (2); and United States (3). The patient must have had a documented GAA deficiency and cardiomyopathy at the time of Pompe disease diagnosis, aged <18 years, had been receiving a stable dose of alglucosidase alfa regularly for a minimum of 6 months

immediately prior to study entry, and had documented evidence of clinical decline (Stage 1) or suboptimal clinical response (Stage 2).

**Main inclusion criteria**

The patient must have signed informed consent prior to performing any study-related procedures. If the patient was legally minor, signed written consent was obtained from parent(s)/legal guardian and assent obtained from patients, if applicable.

*For patients participating in Stage 1: Clinical Decliners Dose Cohort 1 & 2*

The patient had evidence of clinical decline in at least 1 parameter related to Pompe Disease and NOT related to intercurrent illness as assessed by the Investigator: Respiratory Function, Motor Skills or Cardiac Parameters

*For patients participating in Stage 2: Suboptimal Responders Dose Cohort 3*

The patient had evidence of suboptimal clinical response in at least 1 of the following parameters related to Pompe Disease and NOT related to intercurrent illness as assessed by the Investigator: Respiratory Function, Motor Skills or New onset of ptosis.

**Main exclusion criteria**

Patient had/was: high antibody titer (anti-alglucosidase alfa antibody titer ≥1:25600) at 2 consecutive time points not less than 1 month apart, participating in another clinical study or had taken other investigational drugs within 30 days or 5 elimination half-lives of the investigational drugs from screening or randomization, whichever is longer, high risk for a severe allergic reaction to avalglucosidase alfa (ie, previous moderate to severe anaphylactic reaction to alglucosidase alfa and/or patient had immunoglobulin E (IgE) antibodies to alglucosidase alfa, and/or a history of high sustained immunoglobulin G (IgG) antibody titers to alglucosidase alfa), pregnant or breast feeding.

- **Treatments**

Avalglucosidase alfa was administered as an intravenous infusion at a dose of 20 mg/kg qow (Cohort 1 patients) or 40 mg/kg qow (Cohort 2 patients and Cohort 3 patients randomized to avalglucosidase alfa) for 25 weeks. Alglucosidase alfa was administered to Cohort 3 patients randomized to alglucosidase alfa for 25 weeks at their current stable dose (defined by dose of alglucosidase alfa administered regularly for a minimum of 6 months immediately prior to study entry. These doses were 20 mg/kg qow (1 patient), 40 mg/kg qow (2 patients), 20 mg/kg qw (1 patient), 30 mg/kg qw (1 patient) and 40 mg/kg qw (1 patient)). Of note, only 1 Cohort 3 patient randomized to alglucosidase alfa received the label dose of 20 mg/kg qow according to SmPC of Myozyme (INN: alglucosidase alfa).

After completing the PAP, all patients had the option to receive long-term treatment with avalglucosidase alfa in the ETP. Cohort 2 and 3 patients continued to receive avalglucosidase alfa at 40 mg/kg qow, including those Cohort 3 patients who received alglucosidase alfa treatment during the PAP. Cohort 1 patients continued to receive avalglucosidase alfa at 20 mg/kg qow unless they experienced further clinical decline at or after Week 25 when compared to prior to enrollment in ACT14132, and as defined by more rapid worsening of criteria of clinical decline, which was sustained on repeated study assessments. In this case, the patient could be managed per the discretion of the

Investigator, which could include return to treatment with commercially available alglucosidase alfa (and termination of trial participation) or increasing the avalglucosidase alfa dose to 40 mg/kg qow.

At time of data cut for the present analysis, 2 Cohort 1 patients had been switched to 40 mg/kg qow at Weeks 55 and 61, respectively.

- **Objectives**

The primary objective of study ACT14132 was to evaluate the safety profile of avalglucosidase alfa in patients with infantile-onset Pompe disease (IOPD) previously treated with alglucosidase alfa.

Secondary objectives were to characterize the pharmacokinetic profile of avalglucosidase alfa and to evaluate the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa.

Additional objectives were to determine exploratory PD, pharmacogenetics and effect of avalglucosidase alfa treatment on functional endurance, respiratory function, health related quality of life (HRQOL), pain, developmental disability, and hearing in patients with IOPD.

***Outcomes/endpoints***

Primary, secondary and other endpoints are summarised below.

| | **Phase 2 ACT14132** |
|---|---|
| Primary Endpoint | Safety |
| Secondary Endpoints | • Pharmacokinetics (PK)<br>• Gross Motor Function Measure-88 (GMFM-88) and Gross Motor Function Classification System – Expanded and Revised (GMFCS-E&R)<br>• Quick Motor Function Test (QMFT)<br>• Pompe Paediatric Evaluation of Disability Inventory (Pompe-PEDI) Functional Skills Scale: Mobility Domain<br>• Echocardiography (ECHO) endpoints: left ventricular mass index (LVMI) and left ventricular mass (LVM) Z-score<br>• Eyelid position measurements: Interpalpebral fissure distance (IPFD), margin reflex distance (MRD-1), margin pupil distance (MPD)<br>• Creatine kinase (CK) |

| | Phase 2 ACT14132 |
|---|---|
| Exploratory/Tertiary/Other Endpoints | • Pharmacodynamics (PD)<br>• Pharmacogenetics<br>• Functional endurance (6MWT)<br>• Respiratory function as assessed by ventilator use<br>• Pain (PedsQL pain questionnaire, VAS)<br>• Developmental disability (Bailey-III, Leiter-3)<br>• Hearing testing |

- **Sample size**

No formal sample size calculations have been performed. Sample size for this study was based upon empirical considerations.

- **Randomisation and blinding (masking)**

Patients who complied with all inclusion/exclusion criteria were enrolled in the study on a competitive basis. Depending upon the dose escalation status at the time of enrollment, patients were assigned to Cohort 1, Cohort 2, or Cohort 3. The site accessed the IRT system to obtain a treatment assignment and patient number. Only patients in Cohort 3 were randomized to receive either avalglucosidase alfa or alglucosidase alfa, using IRT. The trial protocol foresaw the option to implement a matched pairs design if 8 or more eligible patients are enrolled at the same time. If less than 8 patients were eligible at the beginning of the enrollment for Cohort 3, a stratified randomization design was planned to be used stratifying on gender. The actual randomization within Cohort 3 was obviously not following the optional matching strategy. Stratified randomisation by gender was eventually applied. Treatment condition was not blinded at the site level from an operation perspective. Nonetheless, some measures were taken to reduce bias for some observations where feasible, such as the central reading of echocardiograms in a blinded manner and the testing of laboratory parameters, with the exception of pharmacokinetic and immunogenicity measurements.

- **Statistical methods**

Analysis populations

The safety population was planned to be the primary population for Stage 1 and the overall study safety analysis. The safety population was to include patients who receive at least 1 infusion (partial or total). The safety population was to be analyzed according to treatment received. Overall safety of avalglucosidase alfa was planned to be based on patients who receive at least 1 infusion during either PAP or ETP. For Cohort 1 and Cohort 2, patients for whom it is unclear whether IMP was administered were to be included in the safety population. For cohort 3, randomized patients for whom it is unclear whether they took the IMP were to be included in the safety population as randomized.

The modified intent-to-treat (mITT) population was defined as all randomized patients in Cohort 3 who received at least 1 infusion and with evaluable baseline efficacy assessment. Patients were planned to be analyzed in the treatment group to which

they are randomized. The mITT population was planned as the primary population for Cohort 3 (Stage 2) efficacy analysis.

The PK population was planned to consist of patients from the safety population in PAP who have evaluable drug concentration data. PK analysis for Cohort 3 patients who switch to avalglucosidase alfa during the ETP were to be reported in the final CSR.

For Cohort 1 and Cohort 2, the PD or pharmacogenetic analysis populations for the parameter of interest were planned to consist of safety patients who have evaluable PD or pharmacogenetic data for the parameter of interest. For Cohort 3, the PD or pharmacogenetic analysis population for the parameter of interest were planned to consist of mITT patients who have evaluable PD or pharmacogenetic data for the parameter of interest.

The ADA evaluable population was planned to consist of patients from safety population who had at least one ADA sample taken post-baseline after drug administration that was appropriate for ADA testing with a reportable result. Patients with missing or non-reportable baseline samples and reportable post-baseline samples were planned to be considered as evaluable.

In general, all summary statistics were to be computed and displayed by study cohort and treatment arm. Summary statistics for continuous variables were planned to minimally include the number of available data (n), mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, n and percentages were to be presented and denominators for the percentages were to be based on the analysis population used. For categorical variables, frequencies and percentages were be presented. Graphical displays were planned to be provided as appropriate. The statistical analysis plan contained more detailed descriptions of the plans to analyse outcome data in a descriptive manner.

As regards inferential statistical methodology, the effect of switching to avalglucosidase alfa after having received alglucosidase alfa at current stable dose was assessed by comparative assessment of the defined composite score. The difference in average composite scores between avalglucosidase alfa and alglucosidase alfa patients was to be used as the test statistic. Null and alternative hypotheses for this efficacy endpoint were set up for statistical testing:

H0: Mean Composite Score for avalglucosidase alfa = Mean Composite Score for alglucosidase alfa; versus

HA: Mean Composite Score for avalglucosidase alfa $\neq$ Mean Composite Score for alglucosidase alfa

The control arm (alglucosidase alfa treatment) in Cohort 3 was planned to serve as a reference. If deemed appropriate, these analysis might have been repeated using Cohort 2 and/or Cohort 1 patients combined with Cohort 3 avalglucosidase alfa treated patients. Statistical inference was planned to be performed based on the re-randomization approach. Specifically, all possible randomization sequences that were consistent with the selected randomization design (i.e. randomization stratifying on gender) were to be generated. The test statistics were to be calculated for all randomization sequences, and the statistical significance level was to be calculated as the proportion of more or equally extreme scenarios than the observed one, among all

possible scenarios. Due to the small sample size and open-label nature, p-values were planned to serve as references only and any interpretations were suggested to be made with caution.

The plans foreseen and described in the SAP for descriptive statistical data analyses are considered adequate. The definitions of analysis populations are reasonable as well.

The sole inferential statistical analysis was carried out for an exploratory Composite Score constructed based on three efficacy endpoint domains: GMFM-88 and GMFCS-E and R, Ptosis, and Respiratory Function. The need for thorough methodological assessment regarding the corresponding re-randomisation test used for statistical comparison is seen limited due to the following reasons:

(i) according to the set of secondary trial objectives a "preliminary" comparative evaluation of efficacy data was targeted. Against this background, it is found unusual in this phase 1/2 setting to foresee the only inferential statistical comparison for an exploratory variable in relation to a secondary trial objective,

(ii) the construction of the exporatory composite endpoint lacks any methodological background justification in terms of validity and interpretational potential to describe a treatment difference comparing group means of that constructed score

(iii) the outcome of the statistical test (non-significance) cannot be considered sufficiently informative to draw any conclusion with sound interpretability. The Company's own warning in the corresponding results section that "the interpretation of the exporatory composite score needs to be performed with caution" underlines the limited value of this statistical comparison for B/R-assessment and regulatory decision making.

(iii) the outcome of the statistical test (non-significance) cannot be considered sufficiently informative to draw any conclusion with sound interpretability. The Company's own warning in the corresponding results section that "the interpretation of the exporatory composite score needs to be performed with caution" underlines the limited value of this statistical comparison for B/R-assessment and regulatory decision making.

### *Results*

### *Participant flow*

All patients completed the primary analysis phase. All but 3 patients (all from cohort 3 ALGLU arm) entered the ETP. Until data cut-off dose was increased from 20 to 40 mg/kg AVAL for two patients (Week 61 for one patient and Week 55 for the other patient). See Table 25.

**Table 20 Participant flow**

| Background therapy | Age group | Clinical study<br>Treatment group | Enrolled | mITT/ Efficacy set | Completed main treatment period[a] | Ongoing in ETP[a,b] |
|---|---|---|---|---|---|---|
| | | **ACT14132** | | | | |
| alglucosidase alfa | pediatric | • avalglucosidase alfa | 16 (100.0%) | 16 (100.0%) | 16 (100.0%) | 16 (100.0%) |
| alglucosidase alfa | pediatric | • alglucosidase alfa[d] | 6 (100.0%) | 6 (100.0%) | 6 (100.0%) | 3 (50.0%) |

- **Recruitment**

The study started in October 2017 and is ongoing.

- **Conduct of the study**

No protocol deviations related to randomization and drug-dispensing irregularities occurred during the study. One batch number recording error was reported.

Regarding critical or major deviations, no critical deviations were reported. A higher incidence of major protocol deviations in Cohort 1 was noted. This may have been due to a learning curve in the first patients treated in the study (associated with inclusion/exclusion criteria and informed consent procedures) or due to the longer duration of participation in the study (associated with assessments/procedures). Overall, 2 patients had multiple major protocol deviations. The deviations did not negatively impact patients' safety or data integrity. No patients were excluded from the mITT or Safety/PK population due to protocol deviations.

- **Baseline data**

*Baseline demographic characteristics*

Results are presented in Table 26.

**Table 21 Baseline demographic characteristics and growth parameters – in PAP- safety population**

| Parameter | Statistics | Cohort 1 (N=6) | Cohort 2 (N=5) | Cohort 3 | | Total (N=11) |
|---|---|---|---|---|---|---|
| | | | | avalglucosidase alfa (N=5) | alglucosidase alfa (N=6) | |
| Gender, n (%) | Number | 6 | 5 | 5 | 6 | 11 |
| | Male | 5 (83.3) | 3 (60.0) | 2 (40.0) | 2 (33.3) | 4 (36.4) |
| | Female | 1 (16.7) | 2 (40.0) | 3 (60.0) | 4 (66.7) | 7 (63.6) |
| Race, n(%) | Number | 6 | 5 | 5 | 6 | 11 |
| | White | 3 (50.0) | 2 (40.0) | 3 (60.0) | 4 (66.7) | 7 (63.6) |
| | Black or African American | 0 | 0 | 0 | 2 (33.3) | 2 (18.2) |
| | Asian | 3 (50.0) | 3 (60.0) | 2 (40.0) | 0 | 2 (18.2) |
| Ethnicity, n (%) | Number | 6 | 5 | 5 | 6 | 11 |
| | Hispanic or Latino | 0 | 1 (20.0) | 1 (20.0) | 1 (16.7) | 2 (18.2) |
| | Not Hispanic or Latino | 6 (100) | 4 (80.0) | 4 (80.0) | 5 (83.3) | 9 (81.8) |
| Weight (kg) | Number | 6 | 5 | 5 | 6 | 11 |
| | Mean (SD) | 28.5 (15.0) | 32.5 (21.5) | 26.8 (10.9) | 18.6 (7.3) | 22.3 (9.6) |
| | Median | 24.5 | 23.4 | 27.3 | 17.4 | 20.5 |
| | Min ; Max | 13 ; 50 | 10 ; 64 | 14 ; 43 | 10 ; 29 | 10 ; 43 |
| Age at study entry (years) | Number | 6 | 5 | 5 | 6 | 11 |
| | Mean (SD) | 7.6 (3.4) | 8.1 (4.1) | 6.9 (2.7) | 4.7 (3.2) | 5.7 (3.0) |
| | Median | 8.2 | 9.8 | 8.0 | 3.6 | 4.5 |
| | Min ; Max | 2 ; 11 | 1 ; 12 | 4 ; 10 | 1 ; 10 | 1 ; 10 |
| Age at study entry (years) - categorized | Number | 6 | 5 | 5 | 6 | 11 |
| | <6 | 1 (16.7) | 1 (20.0) | 2 (40.0) | 4 (66.7) | 6 (54.5) |
| | >=6 and <12 | 5 (83.3) | 4 (80.0) | 3 (60.0) | 2 (33.3) | 5 (45.5) |
| | >=12 and <18 | 0 | 0 | 0 | 0 | 0 |

Consistent with inclusion criteria, all infants had evidence of cardiac involvement at the time of diagnosis (specifically, cardiomegaly in 17 patients, arrhythmia 1, other 4), and the majority had hearing loss and muscle weakness as expected in this population. Besides the above there was no clear pattern in other medical history across cohorts and treatment arms.

All patients had early onset of symptoms (⩽6.5 months of age) and the majority were diagnosed and began treatment with alglucosidase alfa at a median age ranging between 1.94 and 4.63 months. Functional levels were heterogeneous at baseline across all patients, with, as expected due to the inclusion criteria for Cohort 3, less

severe motor dysfunction in Cohort 3 as evaluated by GMFCS E&R levels.

In this study patients were required to have previously received treatment with alglucosidase alfa. The dose of alglucosidase alfa prior to the study ranged from 20 mg/kg qow up to 42.6 mg/kg qw.

By cohort, Cohort 1 patients received prior treatment with alglucosidase alfa 20 mg/kg qow (3 patients) or qw (3 patients); Cohort 2 patients received 20 mg/kg qow (2 patients) or qw (2 patients) or 40 mg/kg qow (1 patient); Cohort 3 avalglucosidase alfa patients received prior treatment with alglucosidase alfa at doses of 20 mg/kg qow (1 patient), 25 mg/kg qw (2 patients), 35 mg/kg qw (1 patient), and 42.6 mg/kg qw (1 patient); Cohort 3 alglucosidase alfa patients received prior treatment (and PAP treatment) with alglucosidase alfa at doses of 20 mg/kg qow (1 patient), 20 mg/kg qw (1 patient), 40 mg/kg qow (2 patients), 30 mg/kg qw (1 patient), and 40 mg/kg qw (1 patient).

There are imbalances in demographics and patient characteristics at baseline between cohorts and treatment arms, most notably with respect to younger age of Cohort 3 patients in the alglucosidase alfa arm. The median age in this group was 3.6 years, more than 4 years younger compared to all other treatment groups. Higher numbers of male patients were included in Cohort 1 and Cohort 2 (Stage 1), while more female patients were enrolled in Cohort 3 (Stage 2), but stratification of randomization by gender produced a nearly balanced mix of male and female patients within Cohort 3 (Stage 2). There were more Asian patients enrolled in Cohort 1 and Cohort 2 (Stage 1) than in Cohort 3 (Stage 2) and more patients from minorities (2 Black or African American and 1 Hispanic or Latino out of 6 patients) in the Cohort 3 alglucosidase alfa arm. Due to the inclusion criteria for Cohort 3, patients in this Cohort had less severe motor dysfunction compared to patients in Cohort 1 or 2.

Of note, only 3 patient in Cohort 1 received the approved dose for alglucosidase alfa (20 mg/kg qow) prior to study. The dose for the other 3 patients was 20 mg/kg qw. Prior to study doses in the other two cohorts were even higher. Two patients even received 40 mg/kg qw, or higher.

The overall rate of patients maintaining compliance with the treatment regimen was 100% in both the PAP and the ETP.

- **Numbers analysed**

Results are presented in Table 27.

**Table 22 Disposition of patients and analysis poplations – all enrolled/randomised patients**

| Parameter, n (%) | Cohort 1 (N=6) | Cohort 2 (N=5) | Cohort 3 | | |
|---|---|---|---|---|---|
| | | | AVAL/AVAL (N=5) | ALGLU/AVAL (N=6) | Total (N=11) |
| Patients received decreased dose in PAP, i.e. decrease from 40 mg/kg qow to 20 mg/kg qow (Cohort 2 and avalglucosidase alfa patients in cohort 3) | NA | 0 | 0 | NA | NA |
| mITT population[c] | 6 (100) | 5 (100) | 5 (100) | 6 (100) | 11 (100) |
| Safety population[d] | 6 (100) | 5 (100) | 5 (100) | 6 (100) | 11 (100) |
| PD population[e] | 6 (100) | 5 (100) | 5 (100) | 6 (100) | 11 (100) |
| ADA evaluable population[f] | 6 (100) | 5 (100) | 5 (100) | 6 (100) | 11 (100) |

- **Outcomes and estimation**

A summary of main efficacy results are presented in Table 28.

**Table 23 Main efficacy data in study ACT14132- week 25**

| | Stage 1: declining patients | | Stage 2: insufficient clinical response | |
|---|---|---|---|---|
| | **Cohort 1** | **Cohort 2** | **Cohort 3** | |
| | Avalglucosidase alfa 20 mg/kg qow | Avalglucosidase alfa 40 mg/kg qow | Avalglucosidase alfa 40 mg/kg qow | Alglucosidase alfa previous dose |
| **GMFM-88 - Total % Score** | N=6 | N=5 | N=4 | N=6 |
| Mean baseline (SD) | 54.81 (31.44) | 67.43 (33.84) | 78.69 (20.99) | 50.44 (26.45) |
| mean change from baseline (SD) | 2.62 (9.33) | 3.54 (5.46) | 4.20 (4.32) | 6.82 (3.34) |
| **QMFT - Total Score** | N=6 | N=5 | N=4 | N=6 |
| Mean baseline (SD) | 23.33 (14.76) | 31.20 (19.98) | 30.75 (17.52) | 20.67 (12.03) |
| mean change from baseline (SD) | -0.17 (4.45) | 3.20 (4.55) | 4.25 (3.30) | 5.17 (4.54) |
| **Pompe-PEDI Functional Skills Scale: Scaled Score Mobility Domain** | N=6 | N=5 | N=3 | N=6 |
| Mean baseline (SD) | 44.27 (22.79) | 55.81 (17.02) | 46.19 (27.17) | 40.76 (14.11) |
| mean change from baseline (SD) | 6.19 (10.55) | 2.12 (4.04) | 2.60 (1.72) | 5.20 (5.95) |
| **Echo-LVM Z-score M-MODE** | N=5 | N=2 | N=5 | N=3 |
| Mean baseline (SD) | -1.10 (1.07) | 0.13 (2.39) | -0.78 (0.70) | -0.43 (0.92) |
| mean change from baseline (SD) | -0.60 (2.16) | -0.60 (0.71) | -0.58 (0.76) | 0.47 (1.76) |
| **Interpalpebral fissure distance (left non-FLASH; mm)** | **N=6** | **N=5** | **N=5** | **N=6** |
| Mean baseline (SD) | 8.50 (1.97) | 7.30 (1.04) | 7.50 (1.66) | 8.17 (1.40) |
| mean change from baseline (SD) | -0.67 (1.54) | 1.30 (1.48) | 1.30 (0.76) | -0.50 (0.77) |
| **6MWT (% predicted total distance)** | **N=3** | **N=3** | **N=3** | **N=3** |
| Mean baseline (SD) | 45.30 (18.54) | 63.43 (7.77) | 62.29 (19.71) | 45.15 (11.30) |
| mean change from baseline (SD) | -6.68 (10.85) | 5.60 (2.36) | 3.17 (12.52) | -3.64 (1.30 |
| **PedsQL - Total Score** | **N=5** | **N=4** | **N=5** | **N=5)** |
| Mean baseline (SD) | 67.18 (12.92) | 66.03 (16.56) | 56.68 (15.35) | 56.43 (10.46) |
| mean change from baseline (SD) | 0.86 (15.02) | -0.28 (14.26) | 2.40 (15.41) | -6.60 (14.95 |
| **Leiter-3 -Nonverbal IQ/Composite Score** | **N=5** | **N=3** | **N=4** | **N=3** |
| Mean baseline (SD) | 96.20 (29.75) | 105.75 (29.23) | 86.00 (15.68) | 89.67 (17.16) |
| mean change from baseline (SD) | 3.20 (7.60) | 4.33 (13.58) | 7.25 (2.06) | 0.00 (7.21) |

**Efficacy endpoints**

- **Gross Motor Function Measure-88 (GMFM-88) and Gross Motor Function Classification System - Expanded and Revised (GMFCS-E&R)**

During the PAP, GMFM-88 Total Percent Score mean values increased modestly from baseline to Week 25 in all 4 treatment groups. The highest increase was seen in Cohort 3, in the alglucosidase alfa group. See Figure 15.

Subgroup analyses indicated trends in differences mainly on motor function outcomes. Subgroup factors associated with improvement or stabilization on GMFM-88 and QMFT were female gender, non-Asian race years from diagnosis to ACT14132 study start of <8 years and GMFCS level of I. No difference within subgroups could however be identified in all other analyses, such as age at first infusion of avalglucosidase alfa or alglucosidase alfa in the ACT14132 study. Informative value of these subgroup analyses is however limited due to the small sample size of the individual treatment groups and overall study. Using defined minimally important difference (MID) definitions of change in GMFM-88 score based on GMFCS-E&R baseline functional level, individual patients could be classified as 'improved,' 'unchanged,' and 'worsening' on the GMFM-88 between baseline and Week 25. In Cohort 1, 3 patients were classified as 'improved,' 1 patient as 'unchanged', and 2 patients were classified as 'worsening' at Week 25. In Cohort 2, 2 patients 'improved', and 3 patients were 'unchanged.' In Cohort 3, avalglucosidase alfa group, 2 patients 'improved', 2 patients were 'unchanged', and no GMFM assessments were done for 1 patient (due to the patient being GMFCS level V). In Cohort 3, alglucosidase alfa group, 5 patients 'improved', and 1 patient was 'unchanged'.

Only 2 patients demonstrated 'worsening' on the GMFM-88 at Week 25 by the established MID definition, and both were in Cohort 1 and both had experienced clinical decline in motor skills as inclusion criteria to the study.

During the ETP, GMFM-88 changes grossly followed the trajectory observed for each patient from baseline to W25, with patients that classified as having 'improved' at W25 all having higher GMFM-88 total scores at their most recent visit. There was one exception related to a patient who improved between baseline and Week 25 and experienced a motor decline between Week 49 and Week 73. All patients classified as 'unchanged' at Week 25 remained within 2.6 points of Week 25 scores at their most recent visit in the ETP.

Of the 2 patients from Cohort 1 that were classified as 'worsening' at Week 25, both increased their dose of avalglucosidase alfa from 20 to 40 mg/kg. The first patient increased the dose at Week 61; GMFM Total Percentage score increased from the assessment before dose increase to the most recent visit, resulting in GMFM-88 scores at his most recent visit to be 2 points from baseline. The second patient increased the dose at Week 55 and demonstrated continued decline in GMFM-88 scores until the most recent visit at Week 73.

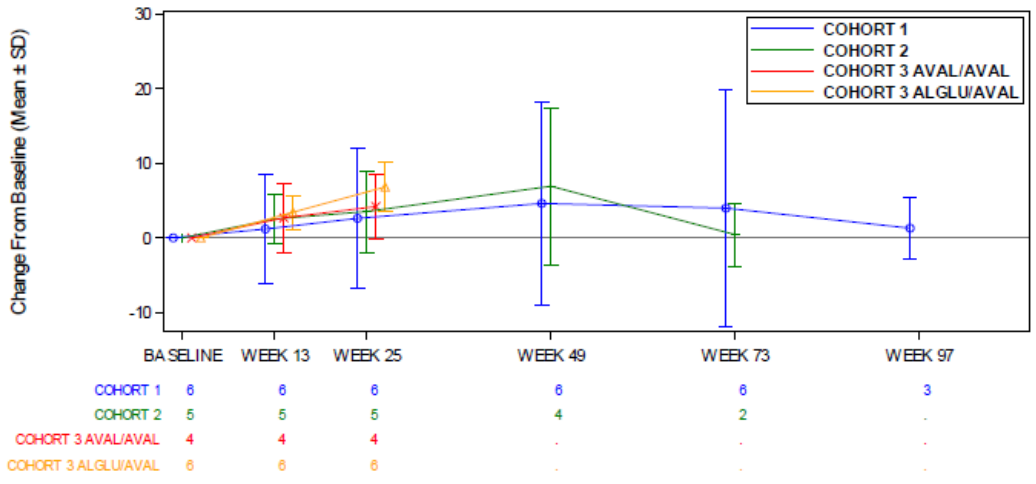



**Figure 12 Plot of Mean (SD) Change from baseline of Gross Motor Function Measure-88 (GMFM-88)- Total Percent score over time – safety population**

For **GMFCS-E&R** levels during the PAP, the distribution of levels in Cohort 1 and 2 and Cohort 3 avalglucosidase alfa patients showed modest changes in a few patients, with a resultant improvement in distribution of 1 level (from Level IV to Level III) by 1 patient each in Cohort 1 and Cohort 2 at Week 25 and a resultant decline in distribution of 1 level (from Level III to Level IV) by 1 patient in the Cohort 3 avalglucosidase alfa arm while there was no resultant change in GMFCS-E&R level in the Cohort 3 alglucosidase alfa patients.

- **Quick Motor Function Test**

Results are presented in Figure 16 and Table 29.

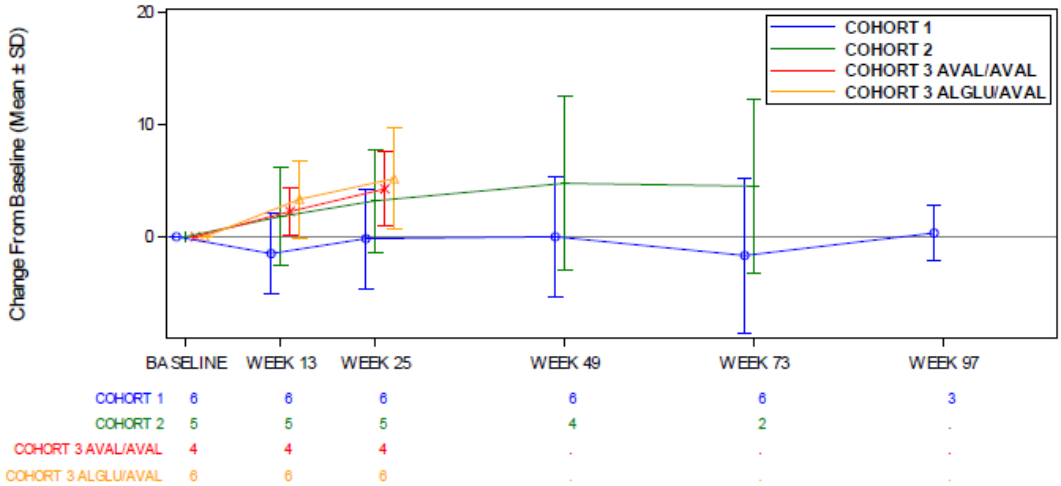



**Figure 13 Plot of mean (SD) Change from baseline of QMFT- total score over time- safety population**

**Table 24 Clinical response in quick motor function test at week 25, study ACT14132**

| Cohort | Treatment Assignment | GMFCS at Baseline | GMFM1 Total % Score Change from Baseline to W25 | Classification of GMFM Change |
|---|---|---|---|---|
| 1 | avalglucosidase alfa 20 mg/kg qow | III | -7,67 | Worsening |
| 1 | avalglucosidase alfa 20 mg/kg qow | II | -3,77 | Worsening |
| 1 | avalglucosidase alfa 20 mg/kg qow | V | 0,4 | Unchanged |
| 1 | avalglucosidase alfa 20 mg/kg qow | IV | 4,43 | Improvement |
| 1 | avalglucosidase alfa 20 mg/kg qow | IV | 2,96 | Improvement |
| 1 | avalglucosidase alfa 20 mg/kg qow | I | 19,37 | Improvement |
| 2 | avalglucosidase alfa 40 mg/kg qow | IV | -0,76 | Unchanged |
| 2 | avalglucosidase alfa 40 mg/kg qow | II | 0,81 | Unchanged |
| 2 | avalglucosidase alfa 40 mg/kg qow | IV | 12,79 | Improvement |
| 2 | avalglucosidase alfa 40 mg/kg qow | II | 0,83 | Unchanged |
| 2 | avalglucosidase alfa 40 mg/kg qow | I | 4,01 | Improvement |
| 3 | avalglucosidase alfa 40 mg/kg qow | I | 0,12 | Unchanged |
| 3 | avalglucosidase alfa 40 mg/kg qow | V | No data | No Data |
| 3 | avalglucosidase alfa 40 mg/kg qow | III | 5,74 | Improvement |
| 3 | avalglucosidase alfa 40 mg/kg qow | II | 9,57 | Improvement |
| 3 | avalglucosidase alfa 40 mg/kg qow | I | 1,35 | Unchanged |
| 3 | alglucosidase alfa | I | 9 | Improvement |
| 3 | alglucosidase alfa | V | 0,78 | Unchanged |
| 3 | alglucosidase alfa | III | 6,57 | Improvement |
| 3 | alglucosidase alfa | I | 8,78 | Improvement |
| 3 | alglucosidase alfa | I | 9,94 | Improvement |
| 3 | alglucosidase alfa | IV | 5,86 | Improvement |

- **Pompe Paediatric Evaluation of Disability Inventory (Pompe-PEDI)**

Results are presented in Figure 17.

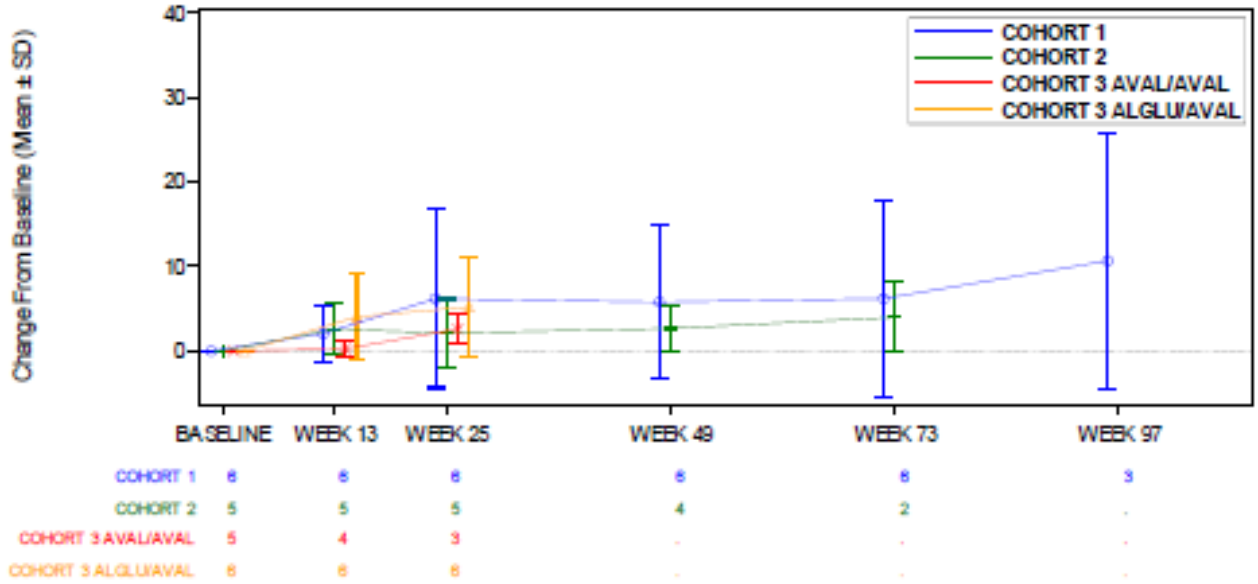



**Figure 14 Plot of mean (SD) Change from baseline of Pompe-PEDI Functional skill scale: mobility domain-scaled score over time- safety population**

- **Echocardiography**

At baseline, only 1 patient with evaluable echocardiography had an abnormal LVM Z-score (>2), which normalized by 25 weeks with avalglucosidase alfa 40 mg/kg qow. All other patients had normal LVM Z-scores at baseline, and scores remained stable through Week 25. Mean (SD) change in LVM (z score) from baseline to Week 25 was -0.60 (2.16) with avalglucosidase alfa 20 mg/kg qow and -0.60 (0.71) with avalglucosidase alfa 40 mg/kg qow in patients previously declining. In patients previously insufficiently controlled, mean (SD) change was -0.58 (0.76) with avalglucosidase alfa 40 mg/kg qow and +0.47 (1.76) with alglucosidase alfa at stable dose. In summary, all patients remained within the normal ranges or improved their LVM and LVMI Z-scores.

- **Eyelid position measurements**

A trend for improvement of the eyelid position measurement was observed in the 40 mg/kg qow avalglucosidase alfa groups (Cohort 2 and Cohort 3 avalglucosidase alfa arm) as compared to the 20 mg/kg qow avalglucosidase alfa group (Cohort 1) or alglucosidase alfa group (Cohort 3 alglucosidase alfa arm), respectively, who showed stabilization or decline in the measurements. This was more pronounced for the Interpalpebral Fissure Distance (both eyes, with and without flash) than for the Margin Reflex Distance (both eyes) or the Margin Pupil Distance (both eyes).

- **Hearing testing**

At baseline, the majority (approximately 75%) of 21 patients tested in study ACT14132 had abnormal hearing in at least 1 ear. A single patient in Cohort 1 (20 mg/kg) with normal hearing at baseline tested abnormal at Week 25; no change in hearing status was observed in Cohort 2 (40 mg/kg), while Cohort 3 results showed too few assessable patients (only 1 baseline value).

**Additional long-term efficacy data (cut-off 30 April 2021)**

Results are presented in Figure 18,  Figure 19, Figure 20 and Figure 21.

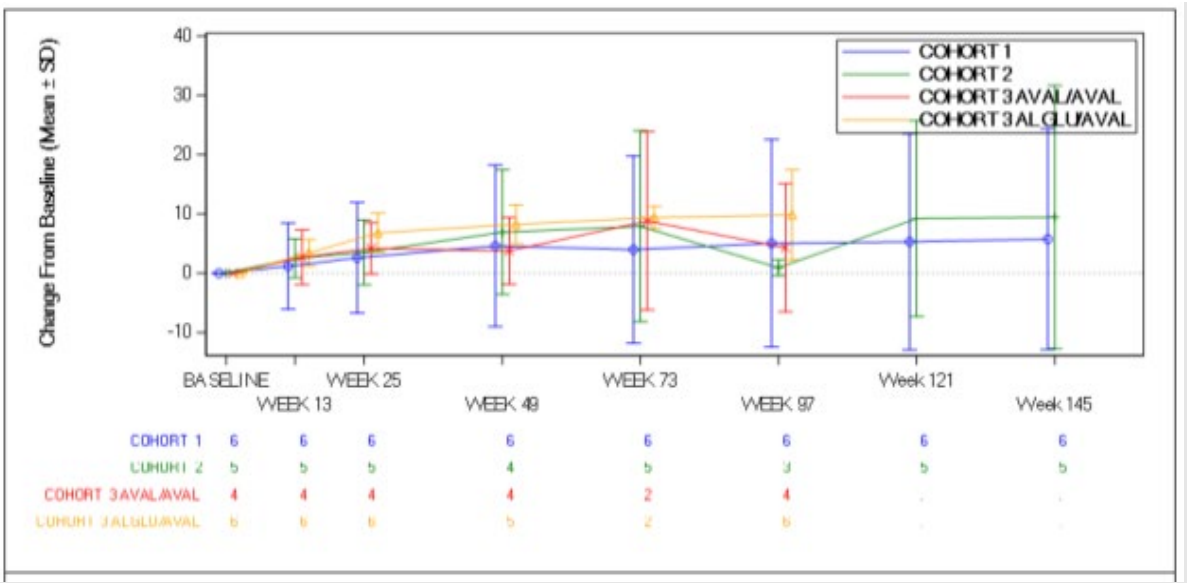



**Figure 15 Plot of Mean (SE) Change from baseline (up) and individual spaghetti Plot (down) of Gross Motor Function Measure-88 (GMFM-88)- Total Percent score over time – safety population**

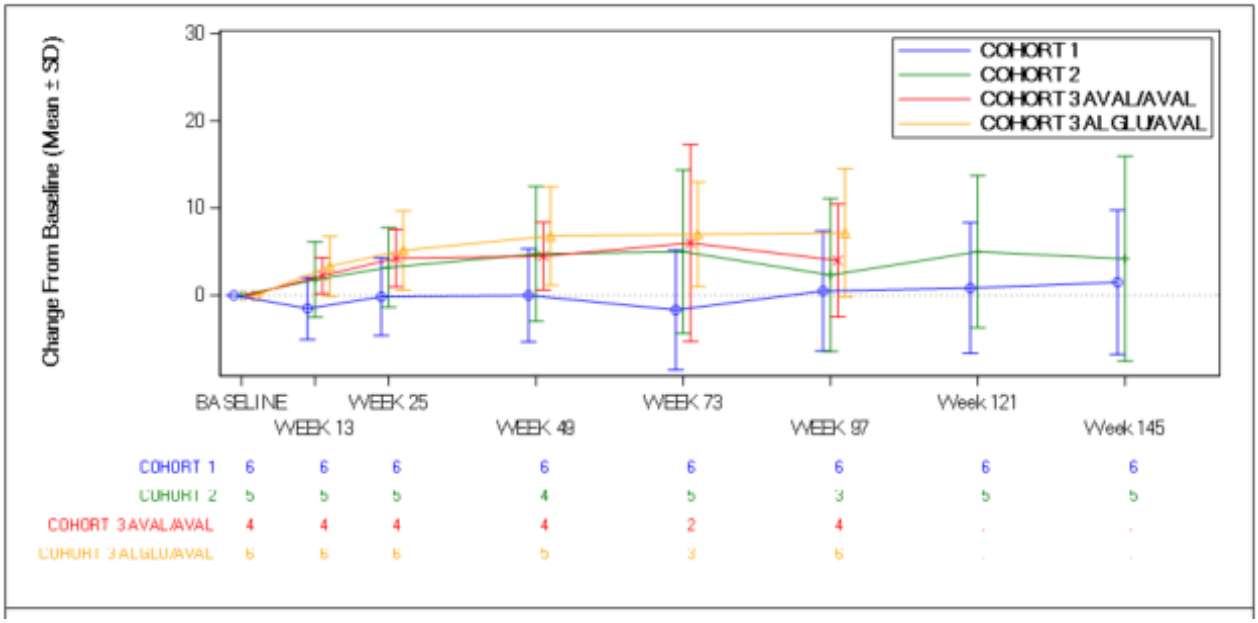



**Figure 16 Plot of Mean (SE) Change from baseline (up) and individual spaghetti Plot (down) of QMFT- Total Percent score over time – safety population**

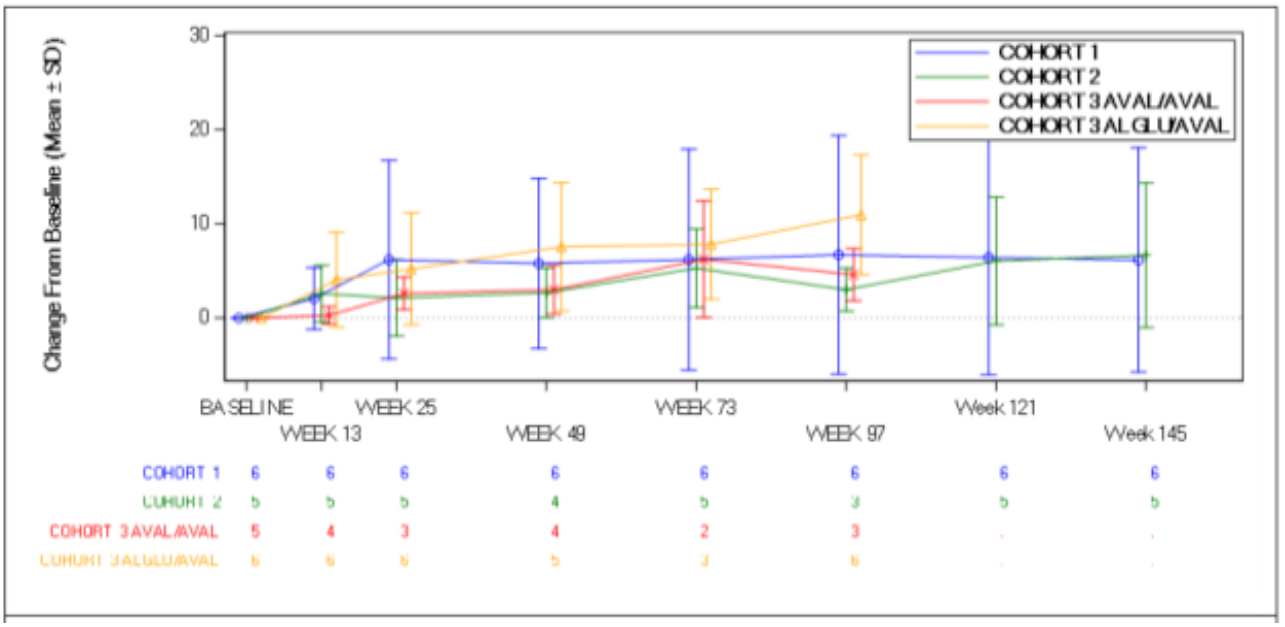



**Figure 17 Plot of Mean (SE) Change from baseline (up) and individual spaghetti Plot (down) of Pompe-PEDI Functional skills scale: Mobility domain-scaled score over time – safety population**

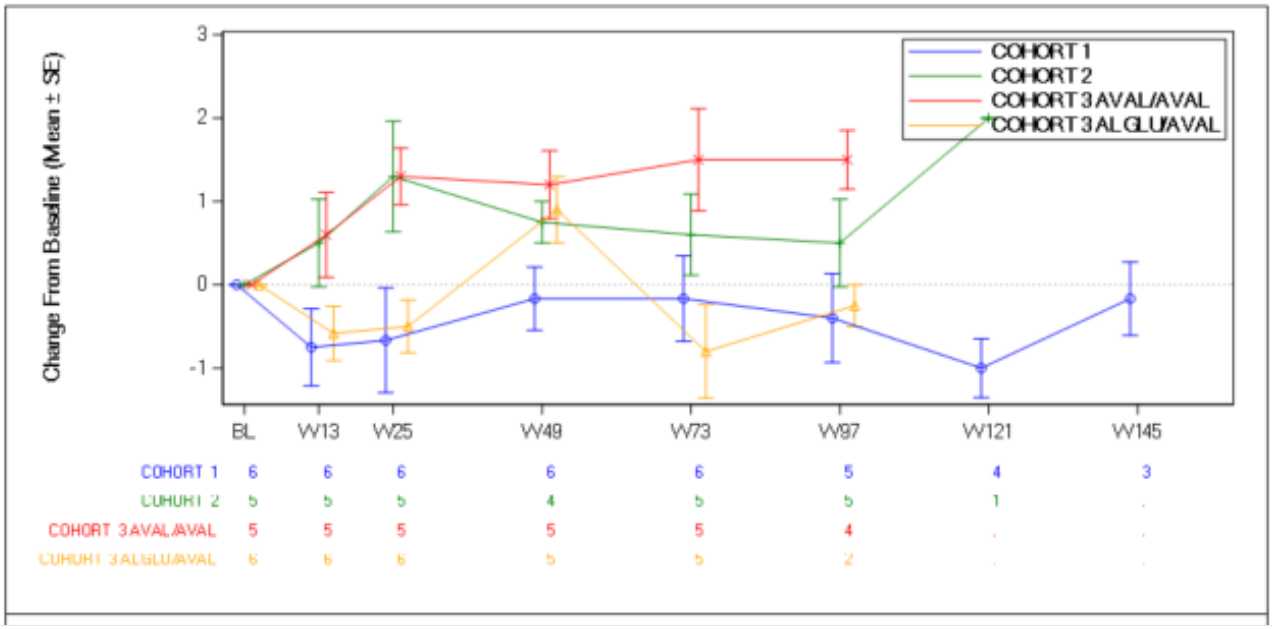



**Figure 18 Plot of Mean (SE) Change from baseline (up) and individual spaghetti Plot (down) of interpalpebral fissure distance (left non-FLASH) (mm) over time – safety population**

- **Ancillary analyses**

**Study EFC14028**

Results are presented in Figure 22 and Figure 23.

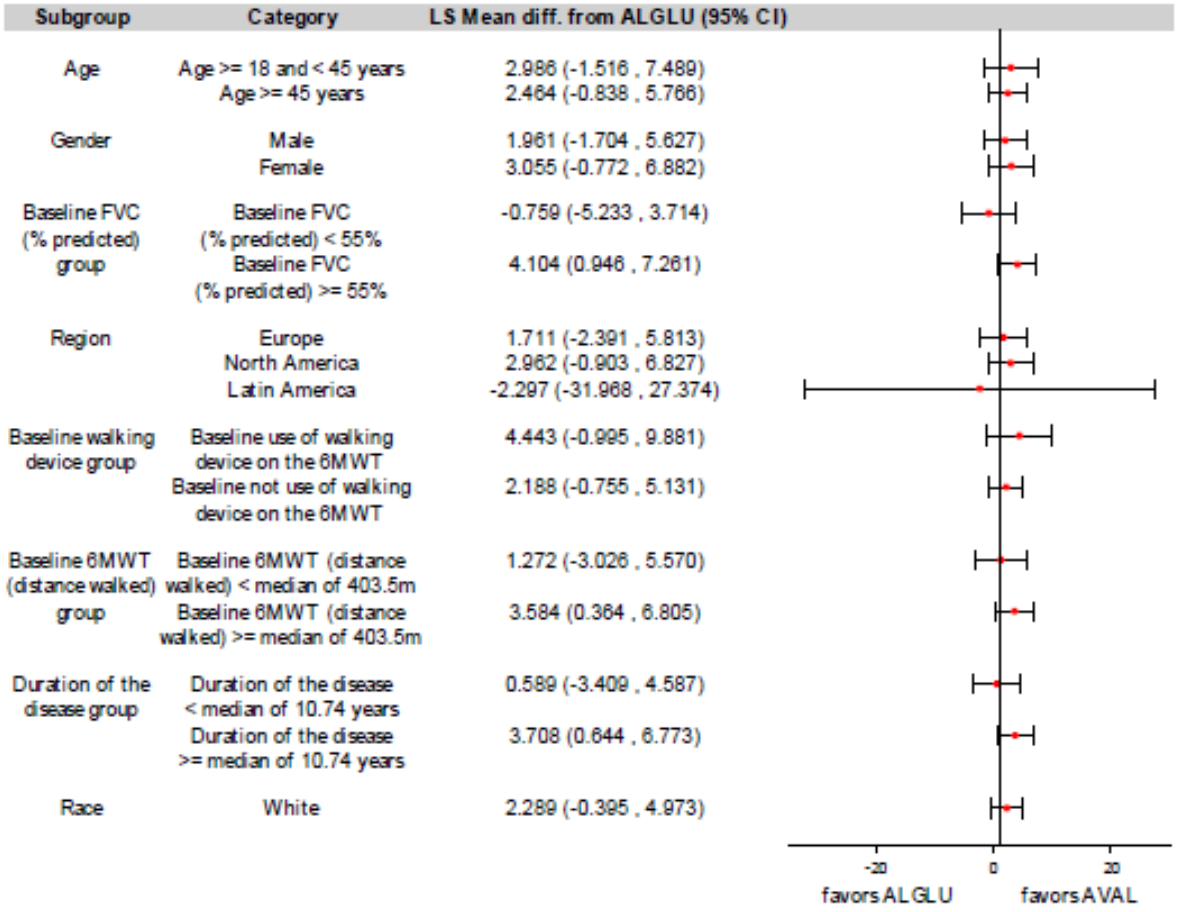



**Figure 19 Forest plot of FVC(%predicted)- in upright position change from baseline at week 49 for primary and subgroup analyses- mITT population, study EFC14028**

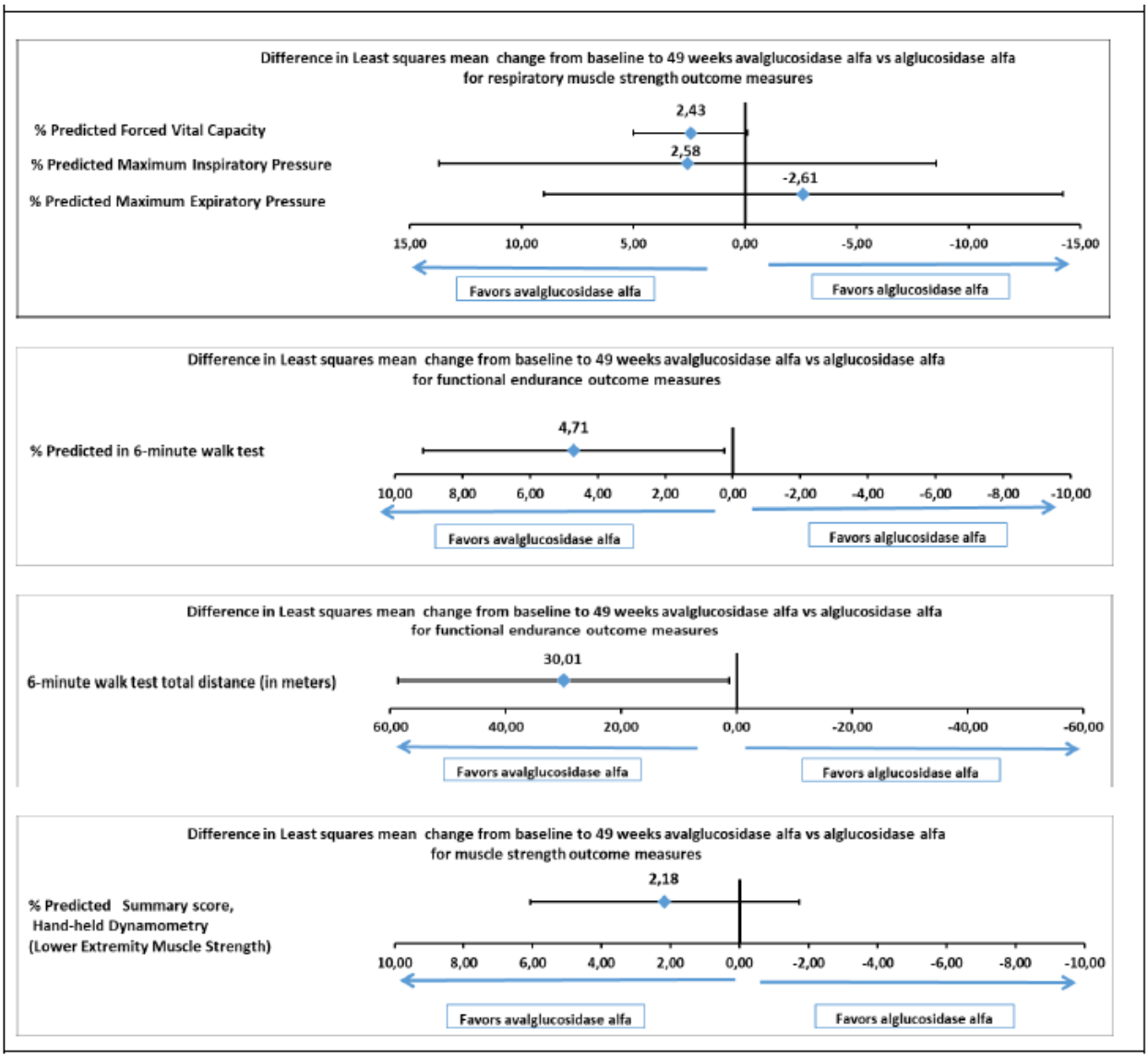



**Figure 20 Forest plots for the main benefits based on phase 3 study EFC14028**

### Study ACT14132

Subgroup analyses were conducted for the secondary and selected tertiary efficacy endpoints by: race, ethnicity, gender, prior alglucosidase alfa treatment duration age at first alglucosidase alfa infusion, age at first infusion of avalglucosidase alfa or alglucosidase alfa in the ACT14132 study, baseline use of non-invasive ventilatory support, baseline status on invasive ventilatory support, assistive device use, CRIM status, baseline GMFCS level, angiotensin I-converting enzyme (ACE) Genotype, status of inhibitory antibody, quartiles of peak IgG antibody titer, baseline LVM Z-Score, duration of Pompe disease at start of ACT14132 and prior use of alglucosidase alfa dose regimen.

Trends in differences mainly on motor function outcomes were observed. The following subgroup factors were associated with improvement or stabilization on GMFM-88 and QMFT: female gender, non-Asian race, years from diagnosis to ACT14132 study start of

<8 years and GMFCS level of I. No difference within subgroups could be identified in all other analyses.

Comparative assessment on an exploratory composite score was performed in addition to the above-mentioned other efficacy endpoints. Three domains were used to construct this score. Within each domain, the change from baseline to Week 25 was classified into improvement, unchanged, and worsening with respect to pre-defined minimally important difference (MID) in each domain. The corresponding score was determined based on both the baseline status and the change from baseline to Week 25. Results are presented in Table 30.

**Table 25 Composite Score Constructed Considering 3 Domains (GMFM-88 and GMFCS-E and R, Ptosis, and Respiratory Function): Estimates and Hypothesis Tests of Change from Baseline to Week 25 - Cohort 3 mITT population**

| Statistics | Avalglucosidase alfa (N=5 ) | Alglucosidase Alfa (N=6 ) | Difference |
|---|---|---|---|
| Composite score | | | |
| Estimate | 1.60 | 2.33 | -0.73 |
| SE | 0.68 | 0.67 | 0.96 |
| 95% CI | -0.28, 3.48 | 0.62, 4.05 | -2.90, 1.43 |
| Permutation p-value | | | 0.41 |
| | | | |
| Gross motor function score | | | |
| Estimate | 1.20 | 1.17 | 0.03 |
| SE | 0.37 | 0.31 | 0.48 |
| 95% CI | 0.16, 2.24 | 0.38, 1.96 | -1.05, 1.12 |
| | | | |
| Ptosis score | | | |
| Estimate | 0.20 | 0.83 | -0.63 |
| SE | 0.49 | 0.31 | 0.56 |
| 95% CI | -1.16, 1.56 | 0.04, 1.62 | -1.89, 0.63 |
| | | | |
| Respiratory score | | | |
| Estimate | 0.20 | 0.33 | -0.13 |
| SE | 0.20 | 0.33 | 0.41 |
| 95% CI | -0.36, 0.76 | -0.52, 1.19 | -1.06, 0.79 |

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Summary of Efficacy for trials EFC14028 and ACT14132**

<table>
<tr><td colspan="4"><u>Title: COMparative Enzyme replacement Trial with neoGAA versus rhGAA (COMET)</u></td></tr>
<tr><td>Study identifier</td><td colspan="3">EFC14028</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">A Phase 3 multicenter, multinational, 1:1 randomized, double-blinded study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa (Myozyme®/Lumizyme®) in treatment-naïve patients with LOPD. The study includes 2 main periods: the blinded treatment period (PAP) and the open-label avalglucosidase alfa long-term follow-up phase (ETP).</td></tr>
<tr><td colspan="3">Duration of main phase: 49 weeks<br>Duration of Run-in phase: not applicable<br>Duration of Extension 144 weeks (ongoing)</td></tr>
<tr><td>Hypothesis</td><td colspan="3">The primary efficacy endpoint (FVC% predicted change from baseline) was tested for non-inferiority (NI) of avalglucosidase alfa versus alglucosidase alfa first at 2-sided 5% level of significance. If the lower bound of the two-sided 95% confidence interval (CI) for the difference between treatment groups is larger than -1.1 (pre-defined NI margin), the study is declared positive. After the NI is demonstrated, the superiority of the avalglucosidase alfa versus alglucosidase alfa was to be tested with the same</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="3">PAP<br><u>Avalglucosidase alfa</u> 20 mg/kg qow, 51 (randomized) 51 (treated) 51 (completed)<br><br><u>Alglucosidase alfa</u> 20 mg/kg qow , 49 (randomized) 49 (treated) 44 (completed)</td></tr>
<tr><td colspan="3">ETP<br>Avalglucosidase alfa 20 mg/kg qow 44 (ongoing)</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td>Primary endpoint</td><td>Forced vital capacity (FVC)</td><td>FVC% predicted in the upright position from baseline to 12 months (Week 49).</td></tr>
<tr><td>Key Secondary endpoint</td><td>Six-minute walk test (6MWT)</td><td>6MWT (distance walked in meters) change from baseline to Week 49 (superiority test)</td></tr>
<tr><td>Secondary efficacy endpoints</td><td>Max. inspiratory pressure (MIP)</td><td>% predicted change from baseline to Week 49 for MIP (superiority test),</td></tr>
</table>

| | | | |
|---|---|---|---|
| | | Max. expiratory pressure (MEP) | % predicted change from baseline to Week 49 for MEP (superiority test) |
| | | Hand-held dynamometry (HHDM) | lower extremity muscle strength; lower extremity summary score and individual muscle group and % predicted from the muscle groups of Hip Flexion, Hip Extension, Hip Abduction, Hip Adduction, Knee Flexion, Knee Extension, Ankle |
| | | Quick motor function test (QMFT) | total score of the QMFT; observer administered test comprising 16 items specifically difficult for patients with Pompe disease. The items are scored separately on a 5-point ordinal scale (ranging from 0 to 4) with a total score of all items ranging between 0 and 64 |
| | | Health-related quality of life (SF-12) | 12-Item Short-Form Health Survey (SF-12) in patients ≥18 years of age; Change from baseline in PCS (physical component summary) and MCS (mental component summary). |
| Database lock | Primary Completion Date: 19 Mar 2020, Database Lock (DBL) date: 23 April 2020 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis in PAP (primary analysis period)** | | |
|---|---|---|---|
| Analysis population and time point | Modified Intent to treat (mITT): randomized patients who received at least 1 infusion<br>Time point: Week 49 | | |
| Descriptive statistics and estimate variability | Treatment group | Avalglucosidase alfa (AVAL)<br>20 mg/kg qow | Alglucosidase alfa (ALGLU)<br>20 mg/kg qow |
| | Number of Subjects | 51 | 49 |
| | FVC % | 2.89 | 0.46 |
| | standard error (SE) | 0.88 | 0.93 |
| Effect estimate per comparison | FVC % predicted | Comparison groups | Avalglucosidase alfa vs alglucosidase alfa |
| | | difference between groups (mean difference) | 2.43 |
| | | 95% CI | -0.13, 4.99 |
| | | P-value for non-inferiority<br>P-value for superiority | 0.0074<br>0.0626* |
| Notes | Statistical NI met (p=0.0074), exceeding the predefined NI margin of -1.1.<br>***Superiority statistical significance was not achieved for the avalglucosidase alfa arm (p=0.0626). Accordingly, all subsequent trial endpoints in the testing sequence were tested without multiplicity adjustment and thus, were not formally tested for statistical significance.** | | |

| **Analysis description** | **Secondary analysis in PAP (primary analysis period)** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Modified Intent to treat (mITT): randomized patients who received at least 1 infusion<br>Time point: Week 49 | | | |
| Effect estimate per comparison | | Avalglucosidase alfa 20 mg/kg qow | Alglucosidase alfa 20 mg/kg qow | Avalglucosidase alfa vs alglucosidase |
| 6MWT (distance walked in meters from baseline to Week 49) | Mean change | 32.21 | 2.19 | |
| | Mean difference | | | 30.01 |
| | 95% CI | 12.47, 51.94 | -18.48, 22.86 | 1.33, 58.69 |
| | Nominal p-value | | | 0.0405 |
| MIP (% predicted) from baseline to Week 49 | Mean change | -0.29 | -2.87 | |
| | Mean difference | | | 2.58 |
| | 95% CI | -7.94 , 7.36 | -10.92 , 5.17 | -8.54 , 13.71 |
| | Nominal p-value | | | 0.6451 |
| MEP (% predicted) from baseline to Week 49 | Mean change | 2.39 | 5.00 | |
| | Mean difference | | | -2.61 |
| | 95% CI | -5.59 , 10.36 | -3.36 , 13.36 | -14.22 , 9.00 |
| | Nominal p-value | | | 0.6557 |
| Lower extremity HHD composite score | Mean change | 260.69 | 153.72 | |
| | Mean difference | | | 106.97 |
| | 95% CI | | | -26.56, 240.50 |
| | Nominal p-value | | | 0.1150 |
| QMFT (total score) | Mean change | 3.98 | 1.89 | |
| | Mean difference | | | 2.08 |
| | 95% CI | | | 0.22, 3.95 |
| | Nominal p-value | | | 0.0288 |
| SF-12 (PCS) | Mean change | 2.37 | 1.60 | |

| | | | | |
|---|---|---|---|---|
| | Mean difference | | | 0.77 |
| | 95% CI | | | -2.13, 3.67 |
| | Nominal p-value | | | 0.5996 |
| SF-12 (MCS) | Mean change | 2.88 | 0.76 | |
| | Mean difference | | | 2.12 |
| | 95% CI | | | -1.46, 5.69 |
| | Nominal p-value | | | 0.2427 |

| | | |
|---|---|---|
| **<u>Title:</u> Paediatric open-label, ascending dose cohort study (Mini-COMET)** | | |
| Study identifier | ACT14132 | |
| Design | Multistage (stage 1: declining patients, stage 2: insufficient clinical response) phase 2 open-label, multicenter, multinational, ascending dose cohort repeated intravenous infusion study with long-term open label extension treatment period (ETP). | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension | PAP (primary analysis period): 25 weeks<br>not applicable<br>ETP: (extension treatment period): 7 years (ongoing) |
| Hypothesis | Since the primary objective of the study was safety and tolerability, there was no primary efficacy variable. Secondary objectives were to characterize the pharmacokinetic profile of neoGAA and to evaluate the preliminary efficacy of neoGAA in comparison to alglucosidase alfa. | |
| Treatments groups | **PAP**<br>Stage 1/Cohort 1<br><br>Stage 1/Cohort 2<br><br>Stage 2/Cohort 3 | <br>20 mg/kg avalglucosidase qow, 6 (randomized), 6 (treated), 6 (completed)<br><br>40 mg/kg avalglucosidase qow, 5 (randomized), 5 (treated), 5 (completed)<br><br>40 mg/kg avalglucosidase alfa qow (5 randomized, 5 treated, 5 completed)<br>**or**<br>avalglucosidase alfa at pre-study dose |
| | **ETP**<br>Cohort 1<br><br>Cohort 2 & 3 | <br>20 mg/kg avalglucosidase alfa qow,<br><br>40 mg/kg avalglucosidase alfa qow |

| | | | |
|---|---|---|---|
| Endpoints and definitions | Primary endpoint | Safety | adverse events (AEs)/treatment-emergent adverse events (TEAEs); physical examinations; clinical laboratory evaluations; vital sign measurements; 12-lead electrocardiogram (ECG) and immunogenicity assessments |
| | Secondary efficacy endpoints | GMFM-88 | Gross Motor Function Measure-88 (quantitative changes in gross motor function). No age cut-off for the GMFM-88. The GMFM-88 consists of 88 items organized into 5 dimensions: Lying and rolling (17 items), Sitting (20 items), Crawling and kneeling (14 items), Standing (13 items), Walking, running and jumping (24 items). |
| | | GMFCS-E&R | Gross Motor Function Classification System – Expanded and Revised; 5 level classification system for specific age ranges consisting of Levels I to V based on self-initiated movement, with emphasis on sitting, transfers, and mobility (Level I Walks without limitations, Level II Walks with limitations, Level III Walks using a hand-held mobility device, Level IV Self-mobility with limitations; may use powered mobility and Level V Transported in a manual wheelchair). |
| | | QMFT | Quick Motor Function Test ; to evaluate changes in motor function concurrently with the GMFM-88; observer administered test comprising 16 items specifically difficult for patients with Pompe disease. The items are scored on a 5-point ordinal scale (ranging from 0 to 4) with a total score of all items ranging between 0 and 64 points. |
| | | Pompe-PEDI | Pompe Paediatric Evaluation of Disability Inventory Functional Skills Scale: Mobility Domain, to measure change in mobility secondary to changes in muscle strength; the domain consists of 160 mobility items |
| | | ECHO | Echocardiography endpoints (left ventricular mass index [LVMI] and left ventricular mass [LVM] Z-score |
| | | eyelid position measurements | Interpalpebral fissure distance (IPFD), margin reflex distance (MRD-1), and margin pupil distance (MPD) |
| Database lock | Primary Completion Date: 30 September 2019 | | |
| **Results and Analysis** | | | |
| **Analysis description** | All efficacy endpoints were summarized descriptively by dose, cohort and treatment group. The mean composite scores between avalglucosidase alfa and alglucosidase alfa patients were compared. The control arm (alglucosidase alfa treatment) in Cohort 3 served as a reference. These analyses were also repeated using Cohort 2 and/or Cohort 1 patients combined with Cohort 3 avalglucosidase alfa treated patients. The nominal p- values were provided via re-randomization approach. | | |

| | | | | | |
|---|---|---|---|---|---|
| Analysis population and time point description | The safety population was the primary population for Stage 1 (Cohort 1, 2)<br>The mITT population was the primary population for Stage 2 (Cohort 3)<br>Comparative assessment on an exploratory composite score and several other Efficacy endpoints was conducted using the mITT population.<br><br>The safety population included patients who received at least 1 infusion (partial or total).<br>The modified intent-to-treat (mITT) population was defined as all randomized patients in Cohort 3 who received at least 1 infusion and with evaluable baseline efficacy assessment. | | | | |
| | Treatment group | Cohort 1 AVAL 20 mg/kg | Cohort 2 AVAL 40 mg/kg | Cohort 3 AVAL 40 mg/kg qow (N=5) | Cohort 3 ALGLU previous dose (N=6) |
| **GMFM-88** Total % Score Descriptive statistics and estimate variability | Number of Subjects | 6 | 5 | 4 | 6 |
| | Mean change from baseline (SD) | 2.62 (9.33) | 3.54 (5.46) | 4.20 (4.32) | 6.82 (3.34) |
| **QMFT** Total Score | Number of Subjects | 6 | 5 | 4 | 6 |
| | Mean change from baseline (SD) | -0.17 (4.45) | 3.20 (4.55) | 4.25 (3.30) | 5.17 (4.54) |
| **Pompe-PEDI** Functional Skills Scale: Scaled Score Mobility Domain | Number of Subjects | 6 | 5 | 3 | 6 |
| | Mean change from baseline (SD) | 6.19 (10.55) | 2.12 (4.04) | 2.60 (1.72) | 5.20 (5.95) |
| **Echo** LVM Z-score M-MODE | Number of Subjects | 5 | 2 | 5 | 3 |
| | Mean change from baseline (SD) | -0.60 (2.16) | -0.60 (0.71) | -0.58 (0.76) | 0.47 (1.76) |
| **Interpalpebral fissure distance** (left non-FLASH; mm) | Number of Subjects | 6 | 5 | 5 | 6 |
| | Mean change from baseline (SD) | -0.67 (1.54) | 1.30 (1.48) | 1.30 (0.76) | -0.50 (0.77) |

| Effect estimate per comparison | Comparison groups | | Avalglucosidase alfa (N=16)<br>Alglucosidase Alfa (N=6 )<br><br>Stage 1 safety population and Cohort 3 mITT population |
|---|---|---|---|
| | **GMFM-88** | difference between groups | -3.48 |
| | | 95% CI | |
| | | Permutation p-value | 0.38 |
| | **QMFT** | difference between groups | -3.03 |
| | | 95% CI | -7.51, 1.44 |
| | | Permutation p-value | 0.30 |
| | **Pompe-PEDI** | difference between groups | -1.24 |
| | | 95% CI | -8.31, 5.83 |
| | | Permutation p-value | 0.66 |
| | **ECHO** | difference between groups | -1.06 |
| | | 95% CI | -3.09, 0.98 |
| | | Permutation p-value | 0.29 |

#### *2.6.5.3. Clinical studies in special populations*

Clinical studies in special populations are limited to paediatric population. This is considered acceptable by the CHMP.

#### *2.6.5.4. In vitro biomarker test for patient selection for efficacy*

Patients were selected by confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations.

#### *2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)*

No analysis across trials have been conducted. This is considered acceptable by the CHMP.

#### *2.6.5.6. Supportive studies*

**TDR12857 (NEO-1)** was a phase 1, multicenter, multinational, open-label, ascending dose study with repeated intravenous (IV) infusions of neoGAA every other week (qow) for a total of 13 infusions.
The study population included 2 groups of late-onset Pompe disease patients ≥18 years of age who were naïve to treatment (Group 1) or previously treated for a minimum of 9 months with alglucosidase alfa (Group 2). The study was intended to assess in man the safety and tolerability of avalglucosidase alfa, and characterize its pharmacodynamic (PD) and PK profiles following repeated-dose administrations. Additionally, the effect of avalglusodisae alfa on exploratory efficacy endpoints was assessed.

The total study duration per patient was approximately 41 weeks from the time of screening until the end-of-study (EOS), including screening within 90 days, a 24-week treatment period (Weeks 1 to 25), post-treatment evaluation 2 weeks after the last infusion (Week 27), and an EOS visit 4 weeks after the last infusion (Week 29).

The study included male and female patients ≥18 years of age, with confirmed acid $\alpha$-glucosidase (GAA) enzyme deficiency from any tissue source and/or confirmed GAA gene mutation, and without known cardiac hypertrophy. The patients were able to ambulate 50 m (approximately 160 feet) without stopping and without an assistive device. The patients had a forced vital capacity (FVC) in the upright position of ≥50% predicted.

6MWT and % predicted FVC values in treatment-naïve (Group 1, n=10) or previously alglucosidase alfa-treated (Group 2, n=14) patients with LOPD were generally stable or increased slightly in both groups without clear relationship to dose level (doses employed were 5 mg/kg, 10 mg/kg and 20 mg/kg qow). Minimal change in respiratory parameters FVC, MIP and MEP, as well as 6MWT were observed at avalglucosidase alfa 5 mg/kg in both groups, while largest improvement in % predicted values of FVC, MIP, MEP and 6MWT was seen with avalglucosidase alfa dose of 20 mg/kg (+6.2%, +7.9%, +12% and +3.9%, respectively) in the treatment-naïve patients.

Study **LTS13769 (NEO-EXT)** is an open-label treatment extension study enrolling patients who completed study TDR12857. Among the 21 patients who completed the TDR12857 study, 19 patients were enrolled in the LTS13769 study. Among them, 2 patients prematurely discontinued; the reasons for treatment discontinuation were wishes to withdraw and other. Seventeen patients remained on IMP and were ongoing in the long-term safety study at the time of the data cut- (27 February 2020). Overall, patients 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.

## 2.6.6. Discussion on clinical efficacy

***Design and conduct of clinical studies***

The main evidence for safety and efficacy of avalglucosidase alfa is derived from a phase 3, randomized double-blind, study comparing avalglucosidase alfa (neoGAA) and alglucosidase alfa in treatment-naive patients (≥ 3 years of age) with LOPD (study EFC14028). The conduct of a double-blinded RCT in a sufficiently large number of LOPD patients is positively recognized. The trial provides an adequate basis for drawing robust conclusions on the comparative efficacy of avalglucosidase versus the approved ERT Myozyme in adult LOPD patients.

Data for the paediatric population comes from the phase 2 study ACT14132 in previously treated IOPD patients > 6 months. The study recruited 22 paediatric patients (5-6 patients per arm) to investigate the safety, immunogenicity and PK of subsequent treatment with avalglucosidase (20-40mg, every other week), collecting also some

preliminary efficacy data. Due to its design and small size the study cannot deliver firm conclusions on avalglucosidase´s efficacy in this setting.

The primary support for the efficacy of avalglucosidase alfa in the treatment of Pompe disease comes from the randomized **phase 3 study EFC14028** comparing in treatment naïve LOPD patients avalglucosidase alfa (AVAL) to alglucosidase alfa (ALGLU), which is currently the only approved ERT for Pompe disease.

***Study EFC14028 (COMET)***

The study design of EFC14028 was discussed and considered acceptable during the protocol assistance.

In this study, a total of 100 patients were 1:1 randomized; 51 patients received AVAL, 49 patients received ALGLU. All eligible patients had a confirmed diagnosis of Pompe's disease (GAA deficiency and/or two GAA gene mutations), were 3 years of age or older, were able to walk 40 m on the 6-minute walk test without stopping and without an assistive device, and had a percentage of the predicted FVC within the range of 30% to less than 85% in the upright position. Patients were excluded if they required any invasive ventilation or if they had previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease.

In the avalglucosidase alfa group, 27 (52.9%) patients were male and 24 (47.1%) patients were female and in the alglucosidase alfa group, 25 (51.0%) patients were male and 24 (49.0%) patients were female. The majority of the patients were "White". There was 1 Japanese and 1 paediatric patient, both in the avalglucosidase alfa group. Hispanic or Latino ethnicity was more frequent in the alglucosidase alfa (24.5%) than in the avalglucosidase alfa group (5.9%).

The mean age of included patients was 48 years; only 1 paediatric patient (aged 15 years) was included in the avalglucosidase alfa group. Patients were slightly younger (mean age (SD): AVAL 46 (14.5) vs. ALGLU 50.3 (13.7)) and fewer patients used a walking device at baseline in the avalglucosidase alfa group. The mean weight, height, and body mass index (BMI) were similar between both groups. The mean distance patients in the AVAL group were able to walk were 399 m on the 6-minute walk test compared to 378 m reached by patients in the ALGLU group – 21 meters less. Baseline FVC% predicted was also slightly better in the AVAL group (AVAL 62.5 vs. ALGLU 61.6).

The selected age cut-off of 3 years is considered appropriate due to evidence from literature that patients as young as 3 years old can adequately perform spirometry after approximately 15 minutes of instruction prior to the test (Eigen, 2001, Am J Respir Crit Care Med; Pesant, 2007, Pediatr Pulmonol).
Overall, this trial includes a less severely affected patient population in terms of respiratory function (mean % predicted FVC: 54.2 vs. 62.1) and mean walking distance (6MWT m: 325.1 vs. 388.9) compared with population of the phase 3 ALGLU02704 study with alglucosidase alfa. According to the Applicant, this is due to current availability of effective therapy (alglucosidase alfa) and hence, patients being treated earlier in their disease. The justification for including a less severely affected patient population in

terms of respiratory function as compared with the main study conducted with alglucosidase alfa is generally reasonable.

Due to the rarity of treatment naïve LOPD patients in the subpopulation of under the age of 18 years, only 1 paediatric patient has been included in the study. According to the original PIP a minimum of 4 paediatric patients (at least 1 patient from 3 to less than 6 years of age and at least 3 patients from 6 to less than 18 years of age) were required to be enrolled. Enrollment of patients aged 3 to <18 years in the study has been challenging, mainly due to exclusion criterion related to respiratory function (requirements that FVC% predicted ≤85%). According to literature (van Capelle et al. 2016) only about 50% of newly diagnosed paediatric LOPD patients have impaired lung function at time of diagnosis. Per clinical practice, these patients are treated early with ERT as physicians are not waiting for decline. Since study EFC14028 enrolled a treatment naïve population, treated patients were no longer eligible for participation in this study. Due to recruitment difficulties, the agreed PIP was modified to include 2 paediatric patients in an open label part of EFC14028 study. However, since only one additional 9 years old paediatric patient could be recruited (enrolled after the study cut-off date of 10 March 2020), study EFC14028 was subsequently removed from the latest agreed PIP. The lack of feasibility to generate sufficient paediatric data in LOPD population is thus agreed by the CHMP.

The duration of the study for each patient included an up to 14-day screening period, a 49-week blinded treatment period (PAP), an up to 144-week open-label treatment period (ETP) with avalglucosidase alfa for all patients regardless of prior randomization group, and an up to 4-week post treatment observation period. In order to allow study participants to continue to receive the investigational medicinal product (IMP) after Week 145, the study was extended to an additional period of up to 144 weeks in protocol amendment 3, dated 10-Apr-2019.

The study included two main periods: a blinded treatment period (PAP) and an open-label extension, in which patients in the alglucosidase alfa arm were switched to avalglucosidase alfa. The 12-month double-blind comparative treatment period for assessment of the primary endpoint was discussed during scientific advice and considered acceptable by CHMP. The usefulness of efficacy data of the switched patients is considered limited, but adds some information regarding safety, i.e. acceptability of switching from alglucosidase alfa to avalglucosidase alfa.

The study was conducted with a dose schedule of 20 mg/kg qow for both, the avalglucosidase alfa and alglucosidase alfa arm. This corresponds with the recommended labelled dosing for alglucosidase alfa. For avalglucosidase alfa, the dose selection was supported by the results from non-clinical studies and the safety and exploratory efficacy results from the ascending dose phase 1 study TDR12857. The limited number of patients included in each dose cohort of study TDR12857 (n=3-4 per cohort in the phase I trial) does not permit any valid conclusions on relative efficacy, but did not indicate dose-dependent increases in tolerability problems. The Applicant has not conducted any investigations of optimal dose intervals (e.g. qw as compared to qow) or formal dose finding trials. However, retrospectively considering the results of the pivotal study and

taking into account clinical experience gained with alglucosidase alfa, the dosing scheme is is deemed acceptable.

The primary efficacy assessment is based on forced vital capacity (FVC; % predicted). This is partly in line with the primary endpoint used in the registration trial for alglucosidase alfa (ALGLU02704/LOTS). In this placebo-controlled trial, a co-primary endpoint comprising the 6-minute walk test and % predicted FVC in the upright position was used. FVC is a well-established surrogate marker of pulmonary function, which is a relevant target in Pompe disease. Furthermore, the chosen surrogate endpoint is relevant since after 10-15 years of manifest disease many patients suffer from - and eventually die of respiratory insufficiency. Overall, FVC % predicted in the upright position from baseline to 12 months is considered suitable as primary endpoint.

The chosen secondary endpoints 6MWT, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP); % predicted, lower extremity muscle strength (hand-held dynamometry (HHD)), motor function (Quick Motor Function Test (QMFT)), and health-related quality of life Short Form-12 (SF-12) are considered suitable to demonstrate consistency in effect across several domains.

As avalglucosidase alfa was expected to be at least as efficacious as alglucosidase alfa, it was considered appropriate to firstly test for non-inferiority. If NI was demonstrated, superiority of avalglucosidase alfa versus alglucosidase alfa in FVC (% predicted) would be tested at the same overall 5% significance level. If the superiority of avalglucosidase alfa versus alglucosidase alfa was demonstrated on the primary efficacy endpoint, the hypothesis testing for several secondary efficacy endpoints would proceed according to a pre-defined order: superiority tests in 6MWT, MIP, MEP and HHD.
The primary efficacy endpoint of change from baseline in FVC (% predicted) in upright position to Week 49 was planned to be analyzed in the mITT population using a mixed model for repeated measures (MMRM) with change from baseline as outcome variable. The definition of the analysis sets can be endorsed, and the MMRM-based analyses for primary and secondary endpoints are considered adequate.
The difference between treatment groups was planned to be estimated based on least square (LS) means at the Week 49 visit within the MMRM model. A 2-sided 95% confidence interval (CI) using the estimate and variance of the LS mean difference was to be provided. If the lower bound of the 2-sided 95% CI for the difference of avalglucosidase alfa and alglucosidase alfa was found to be larger than -1.1, the study would be considered to have met its primary objective. Each of the secondary endpoints were planned to be analyzed based on the MMRM model, similar to that described for the primary endpoint, using the mITT population (with the exception of SF-12, which was planned to be analyzed for a subset of mITT patients with age $\geq$18 years). The difference between treatment groups was to be assessed with LS mean difference at Week 49 estimated within the framework of the corresponding MMRM model. P-values and 2-sided 95% CIs were planned to be provided.
The chosen hierarchical testing strategy is considered a suitable method to control for multiple testing. From the methological perspective, it is, however noted that stopping in this hierarchy due to a non-significant result limits the interpretability of subsequent

endpoint analyses. The plans described in relation to blinding measures are generally considered adequate.

***Study ACT14132 (Mini-COMET)***

Additional evidence of efficacy comes from the **paediatric Phase 2 study ACT14132** (Mini-COMET) in IOPD patients aged 6 months and older who previously experienced disease progression while on alglucosidase alfa. Study ACT14132 is a multistage (stage 1: declining patients, stage 2: insufficient clinical response) phase 2 open-label, ascending dose (20 or 40 mg/kg qow) cohort study with long-term open label ETP, at a dose of 20 mg/kg qow (Cohort 1) or 40 mg/kg qow (Cohorts 2 and 3). The MTD was established at 40 mg/kg after consultation of the Data Monitoring Committee (DMC). The Extension Period (ETP) was extended to 7 years in the amended protocol 02, dated 24.3.2020. The proposed design was discussed in a protocol assistance and considered overall acceptable.

The patient must have had a documented GAA deficiency, aged <18 years, cardiomyopathy at the time of Pompe disease diagnosis, having received a stable dose of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry, and documented evidence of clinical decline (Stage 1) or suboptimal clinical response (Stage 2).

The study population fulfilled the measures specified in the agreed PIP. Patients at high-risk for experiencing a severe allergic reaction to avalglucosidase alfa (i.e. patients who previously had severe anaphylactic reaction to alglucosidase alfa and/or a history of high sustained IgG antibody titers to alglucosidase alfa) were excluded from the phase 2 study in IOPD patients. This was of concern for the CHMP, since it could potentially confound the safety/immunogenicity and efficacy results for avalglucosidase alfa. Further data were provided to address this concern. It was shown that at baseline, 11 patients were ADA positive with anti-alglucosidase alfa antibodies with titers ranging from 100 to 800. During treatment, 6 anti-alglucosidase alfa ADA-positive patients had treatment boosted ADA with titers up to 25600, and 4 anti-alglucosidase alfa ADA-negative patients seroconverted. At Week 25, all patients receiving alglucosidase alfa were switched to avalglucosidase alfa 40 mg/kg qow regardless of ADA titers during PAP. Data also evidenced that high titer of anti-alglucosidase alfa antibodies was not a limitation to switching to avalglucosidase alfa. These findings were also valuable for all treatment-naïve patients in EFC14028, initially randomized to alglucosidase alfa who also switched to avalglucosidase alfa during the ETP, including those in the high titer category. Overall, the CHMP concluded that the impact of the exclusion criteria of study ACT14132 on the generalizability of the study findings regarding safety/immunogenicity and efficacy results was thus considered negligible.

All patients were treated for 25 weeks during Primary Analysis Period (PAP), thereafter, all patients had the option to receive long term treatment with avalglucosidase alfa in an Extended Treatment Period (ETP) at a dose of 20 mg/kg qow (Cohort 1) or 40 mg/kg qow (Cohorts 2 and 3).
While stage 1 can be considered a limited dose-finding study for patients with severe forms of IOPD, the second stage allowed a direct treatment comparison of the highest acceptable dose of AVAL (40 mg/kg qow, based on data from cohorts 1 & 2) and

alglucosidase alfa at the current stable dose (between 20 mg/kg qow and 40 mg/kg qw as prescribed by physician during the 6 months prior to study) in patients with advanced disease. In principle, such an additional trial stage is considered meaningful, even though the small sample size does not allow firm conclusions and the alglucosidase control-arm was treated at various different doses.

Twenty-two patients were enrolled: 6 in Cohort 1, treated with avalglucosidase alfa at 20 mg/kg qow for 6 months, 5 in Cohort 2, treated with avalglucosidase alfa at 40 mg/kg qow for 6 months, and 11 in Cohort 3, where they were randomized to receive avalglucosidase alfa at 40 mg/kg qow (5 patients) or alglucosidase alfa treatment at current stable dose (between 20 mg/kg qow and 40 mg/kg qw as prescribed by physician during the 6 months prior to study) (6 patients) for 6 months. The methods of treatment assignment to enrolled patients, including the randomisation procedure for Cohort-3-patients are adequately described and no concerns arise in relation to outcome interpretation. Nevertheless, inclusion in this study was sequential, with patients with declining condition being included first. Treatment condition was not blinded at the site level from an operation perspective. Nonetheless, some measures were taken to reduce bias for some observations where feasible, such as the central reading of echocardiograms in a blinded manner and the testing of laboratory parameters, with the exception of pharmacokinetic and immunogenicity measurements.

Unblinded conditions seem straight forward for safety evaluations in Cohort 1 and Cohort 2. Comparative assessment of preliminary efficacy endpoints in Cohort 3 would have benefitted from blinded conditions. However, in light of the limitations in interpretation of generated efficacy data there is little additional concern regarding potential bias caused by the open-label nature of the trial.

No patient discontinued in the PAP or up to the cut-off date. At the cut-off date, all patients were included in the ongoing ETP.

Patients were allowed to participate in the study with heterogeneous baseline functional levels. Cohorts 1 and 2 included the most severely affected patients. Cohort 3 treatment arms were imbalanced, with alglucosidase alfa-treated patients being younger in age and receiving dose regimens between 20 mg/kg qow and 40 mg/kg qw, being enrolled mostly with new onset of ptosis. Overall, avalglucosidase alfa-treated patients were older and were enrolled based on motor function plateau or respiratory criteria.
Medical/surgical histories were in line with underlying Pompe disease in a paediatric population. In line with inclusion criteria, all infants had cardiac involvement at the time of diagnosis, and the majority had hearing loss and muscle weakness as expected in this population.

The primary objective of the ACT14132 study was the assessment of safety and tolerability of administering avalglucosidase alfa. The secondary objectives were characterization of the pharmacokinetic profile of avalglucosidase alfa and evaluation of the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. Efficacy endpoints in ACT14132 included motor function (evaluated through functional and clinical outcome assessments and 6-minute walk test [6MWT]), respiratory function (evaluated through pulmonary functional testing [PFT] and ventilator use

questionnaire), quality of life, pain, cardiac function (echocardiography), eyelid position measurements, and cognitive and auditory function. These endpoints represent systems affected by Pompe disease where clinical decline or sub-optimal response to alglucosidase alfa was observed. The CHMP considers that due to its design and small size, the study is not able to deliver firm conclusions on a 40 mg/kg qw starting dose in the IOPD setting, as initially proposed by the applicant. In particular treatment naïve IOPD patients were not included in the study. This is further discussed below.

***Efficacy data and additional analyses***

***Study EFC14028 (COMET)***

The primary objective of the Phase 3 study EFC14028 was met by demonstrating non-inferiority of respiratory function as measured by % predicted FVC as compared to alglucosidase alfa at week 49. The LS mean change from baseline to Week 49 in % predicted FVC in the avalglucosidase alfa group (mITT) was 2.89; the corresponding value was 0.46 in the alglucosidase alfa group. The difference in mean change from baseline to week 49 of 2.43 (with a lower boundary of the 95% CI of -0.13) exceeded the predefined NI margin of -1.1, and thus meets the primary study objective of non-inferiority. A pre-planned sensitivity analysis of the primary efficacy endpoint in the PAP PP population indicates that the non-inferiority conclusion is robust.

In a second step, superiority of % FVC was tested, but the study could not demonstrate superiority of avalglucosidase alfa in this endpoint. Therefore, the further endpoints cannot be interpreted in a conclusive manner. Regarding secondary endpoints, the LS mean difference in distance walked in meters in the 6MWT (key secondary endpoint) was 30.01 (95% C.I.:1.33, 58.69).

Subgroup analyses for study EFC14028 (primary efficacy endpoint, % predicted FVC), performed by age group (<18 years, ≥18 years to <45 years, ≥45 years old), gender, baseline FVC groups (<55%, and ≥55%), region, baseline walking device use, baseline 6MWT distance, duration of disease at baseline, and race indicate consistency of results across subgroups.

Although some of the investigated efficacy parameters showed a positive trend for better outcome with avalglucosidase alfa, many of these endpoints were correlated and are measured in the same patients. Most importantly, however, demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in the primary endpoint % predicted FVC at Week 49 was missed at the required significance level. Accordingly, all subsequently conducted statistical tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate experimentwise type-1-error control. Hence, any reference in the discussion of trial outcome for these endpoints indicating an advantage of avalglucosidase alfa over alglucosidase alfa is not permissible and a conclusion of demonstrated superiority is not possible.

The LS mean difference in distance walked in meters in the 6MWT (key secondary endpoint) was 30.01 (95% C.I.:1.33, 58.69).

Subgroup analyses for study EFC14028 (primary efficacy endpoint, % predicted FVC), performed by age group (<18 years, ≥18 years to <45 years, ≥45 years old), gender, baseline FVC groups (<55%, and ≥55%), region, baseline walking device use, baseline 6MWT distance, duration of disease at baseline, and race indicate consistency of results across subgroups.

Due to sequential enrollment, data at Week 97 are available in 40% of the original trial population and only limited data beyond Week 97 is available. At the cut-off date of 19 March 2020, 91 patients were enrolled in the ongoing extension treatment period (ETP) and efficacy data at 97 weeks were available for 24 patients who had continuously received avalglucosidase alfa since study start and for 21 patients who switched from alglucosidase alfa to avalglucosidase alfa treatment after 49 weeks. Clinical outcomes in the extension treatment period were not included in the confirmatory testing strategy and only descriptive statistics were used for these endpoints. The observed mean change from baseline of the %predicted FVC numerically decreases over time in ETP in the (continued) avalglucosidase alfa group and improved in patients switching from alglucosidase alfa. Furthermore recent data (cut-off date 10 February 2021) show a plateau or even a slight decrease in the effect of avalglucosidase alfa in FVC and 6MWT. The applicant argued that the maintenance of efficacy in the long-term is however beneficial taking into account the natural decline in these parameters with age and progressing disease. Furthermore, based on published evidence, the applicant's assumption is that patients on alglucosidase alfa would either reach a stable plateau or slowly decline, then observing a positive change from switching to avalglucosidase alfa in clinical outcomes, further supporting that there is also a clinical benefit of switching from alglucosidase alfa to avalglucosidase alfa. The CHMP however noted that recent long term efficacy data from alglucosidase alfa are available indicating a sustained effect up to five years (see Myozyme SmPC). Data from avalglucosidase alfa study LTS13769, an open-label treatment extension study enrolling patients who completed the phase 1 study TDR12857 seem to show a stabilisation of the pulmonary and motor functions of the patients.

Taking into consideration the flattening effect of avalglucosidase alfa at Week 97 of the pivotal study and the available long term data for avalglucosidase alfa and alglucosidase alfa, a potential efficacy advantage of avalglucosidase alfa over algucosidase alfa in the long run of treatment remain to be demonstrated.

Notably, the overall performance of alglucosidase alfa in the COMET study was poorer than in the registration trial for alglucosidase alfa (ALGLU02704/LOTS). In the LOTS trial, the estimated change in FVC, expressed as a percentage of each patient's predicted value, was an increase of 1.2 percentage points at week 78 (1.73 at week 49) for the patients who received alglucosidase alfa (and a decrease of 2.2 percentage points for the patients who received placebo). This effect was even more pronounced in the key secondary endpoint, the 6MWT. In the present COMET study the LS mean change (SE) in 6MWT (distance walked in meters) from baseline to Week 49 was 2.19 (10.40) in the alglucosidase alfa group compared to a mean increase of 25.1 m on the 6-minute walk seen in the ALGLU02704/LOTS trial test at week 78. The CHMP was thus concerned about the observed poor performance of alglucosidase alfa that could potentially contribute to an overestimation of the observed effect of avalglucosidase alfa in the COMET study. The applicant argued that study AGLU02704 was conducted

approximately 15 years ago when no treatment was available for patients with Pompe disease, potentially affecting the baseline criteria of enrolled patients. Post-hoc analyses between Study EFC14028 and Study AGLU02704 revealed some key differences: a delayed time to an enzyme replacement therapy initiation in Study AGLU02704 compared to Study EFC14028 (median time from diagnosis to treatment 7.50 years vs 0.65 year, respectively) as well as greater severity of the disease in patients randomized in Study AGLU02704. Post-hoc analyses were conducted to estimate the impact of the selection differences in studies EFC14028 and AGLU02704 on the results/outcomes/patient trajectories. Although these post-hoc data need to be interpreted with caution, results observed in the alglucosidase alfa group in Study EFC14028 are likely influenced by a randomized population different to the one randomized in Study AGLU02704. Thus, the concern regarding potential underperformance of alglucosidase alfa in Study EFC14028 is sufficiently alleviated.

***Assessment of paediatric data on clinical efficacy***

***Study EFC14028 (COMET)***

Data are limited to 2 patients aged 16 and 9 years old. For the primary endpoint, improvement of % predicted FVC of 2.63% (from 84.79% at screening to 87.42% at Week 49) compared to a LS mean increase (SE) of 2.89 (0.88) % was reported in the older paediatric patient in the global study as well as improvement of 6MWT distance (%predicted) of 34 m (5.33%) (from 602 m [84.19%] at screening to 636 m [89.52%] at Week 49) compared to a LS mean increase (SE) of 32.21 m (9.93) (5.02% [1.54] for the secondary endpoint. A clinically meaningful improvement in the primary and key secondary endpoints from baseline to Week 49 was thus observed and was consistent with mean data observed in adult patients. The second paediatric patient, aged 9 years at study entry, was included in the study after cut-off date (19 March 2020) and, per protocol, directly entered the open-label period with avalglucosidase alfa 20 mg/kg qow. The patient recently completed Week 25 visit, an improvement in FVC (82.72%vs 84.51%), 6MWT (444m/70.28 vs 463.14m/72.24%) was also observed, confirming the benefit of avalglucosidase alfa in the broad range of patients with LOPD. Although these data are very limited, the CHMP previously acknowledged the lack of feasibility to generate sufficient paediatric data in LOPD population. A comprehensive justification for extrapolation of the efficacy from adult to paediatric LOPD patients was submitted by the applicant. Since the available efficacy data are comparable between adult and paediatric LOPD patients, the CHMP accepted such extrapolation. See further below.

***Study ACT14132 (Mini-COMET)***

During the PAP, GMFM-88 mean scores increased modestly from baseline to Week 25 in all four treatment groups. The highest increase was seen in Cohort 3, in the alglucosidase alfa group. According to the Applicant, this may be attributed to younger patient age and a smaller proportion of subjects within the group with suboptimal motor response at baseline.

Consistently to the results of the Gross Motor Function Measure-88, the greatest degree of change in the QMFT–total score was observed in the alglucosidase alfa group. In the

ETP, QMFT change from baseline remained in the same direction for all patients with available data at the most recent visit, with the exception of 1 patient in Cohort 2; this patient increased 1 point in score at Week 25 and at most recent visit had a change of 1 point from baseline.

All patients remained within the normal ranges or improved their left ventricular mass (LVM) and left ventricular mass index (LVMI) echocardiography Z-scores.

A trend for improvement of the eyelid position measurement could potentially be observed in the 40 mg/kg qow avalglucosidase alfa groups as compared to the 20 mg/kg qow or alglucosidase alfa groups which showed stabilization or decline in the measurements. Pulmonary function tests were performed only in few patients able to reliably undergo testing, and no trends were observed for the patients with available data. In addition to the above-mentioned other efficacy endpoints a comparative assessment on an exploratory composite score was performed. The 3 domains used to construct this score were the Gross motor function score, the Ptosis score and the Respiratory score. The composite scores for Cohort 3 were higher for the alglucosidase alfa arm than the avalglucosidase alfa arm, as well as compared to all avalglucosidase alfa treated patients in the PAP, although the difference was not significant. The outcome of this exploratory composite endpoint, however, cannot be considered sufficiently informative to draw any sound and firm conclusion on the efficacy of avalglucosidase alfa.

Overall the totality of the evidence on efficacy of avalglucosidase alfa in IOPD patient is very limited, especially because the primary objective of the study was to determine safety and no data are available in treatment naïve IOPD population. A comprehensive justification for extrapolation of the efficacy from LOPD to IOPD patients was submitted by the applicant. Since the pathophysiology of the disease, the mechanism of action, and the pharmacokinetic profile of enzyme replacement therapy (ERT) for Pompe Disease are comparable across the whole disease spectrum, the CHMP accepted such extrapolation.

Regarding long term data, at a cut off data of 30 April 2021, all 22 patients were still participating in the study, all were treated for at least 2 years, and stage 1 patients, previously declining with alglucosidase alfa, were treated for at least 3 years. In Cohort 1, 4 patients out of 6 have had a dose increase from 20 mg/kg to 40 mg/kg qow per predefined protocol criteria, and all Cohort 3 patients treated with alglucosidase alfa during the initial 6 months of the study had switched to avalglucosidase alfa treatment at 40 mg/kg qow. These long term data showed a slight improvement or stabilisation of the endpoints assessed but with substantial variation between patients. This effect is however was not consistently in favour of patients initially treated with avalglucosidase alfa 40 mg/kg, as claimed by the applicant. For instance, the assessment scale Pompe paediatric evaluation of disability inventory (Pompe PEDI) showed a more beneficial effect, or at least a comparable effect for Cohort 1 patients (initially treated with 20 mg/kg avalglucosidase alfa). Interestingly, best response in all endpoints but one (Intrapalpebral fissue distance) is demonstrated for patients participating in cohort 3, initially treated with alglucosidase alfa. While avalglucosidase alfa 40 mg/kg shows an acceptable safety profile, the efficacy data presented are not considered sufficient to

support the claimed 40 mg/kg starting dose for avalglucosidase alfa in IOPD patients. Clinical response varies greatly between patients and a clear dose response relationship could not be demonstrated. Moreover, a starting dose of 40 mg/kg avalglucosidase alfa in treatment naïve patients has not been investigated at all. However, uthe se of the 40mg/kg regimen could be agreed for those IOPD patients who show a less than optimal clinical response to the 20mg/kg (starting) dose. Following the CHMP recommendation, the applicant agreed to update the posology in IOPD patients, reflecting that for IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week should be considered in the absence of safety concerns (e.g severe hypersensitivity, anaphylactic reactions, or risk of fluid overload).

***Proposed Indication***

The claimed indication is "Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency)." Based on the submitted data, the CHMP considered acceptable the wording of the indication that includes both adult and paediatric LOPD population and IOPD population.

Pompe's disease is a genetic disease which is therefore present in patients from birth, the mutations are very diverse and there is no relationship between the mutation and the amount of residual enzyme activity. In both populations the root cause of the disease is the deficiency GAA activity, the difference between the infantile and adult forms being due to the amount of residual enzyme activity. In the infantile setting, this activity is absent or almost absent whereas there is residual activity in the adult type. Pompe's disease is heterogeneous and is characterised by muscular damage linked to glycogen storage. However, the damage is not totally identical in the infantile and adult forms, particularly with regard to cardiac damage, even though there may be some overlaps.

Nevertheless, since the available efficacy data for avalglucosidase alfa are comparable between adult and paediatric LOPD patients, the extrapolation of efficacy from adult LOPD to paediatric LOPD population is acceptable by the CHMP, especially since the lack of feasibility to generate sufficient paediatric data in LOPD population is acknowledged.

In addition, in order to justify that the data are transposable from LOPD to IOPD population, the applicant explained that alglucosidase alfa (Myozyme) has been approved across the spectrum of Pompe disease on the basis of survival data in the infantile form and motor and respiratory function data in adults and that therefore avalglucosidase which contains the same enzyme/protein should also be effective across the whole spectrum of Pompe disease. This reasoning is considered acceptable by the CHMP. This is further supported by the results of study EFC14028, which demonstrated non-inferiority of avalglucosidase in % predicted forced vital capacity (FVC) as well as a comparable safety profile in LOPD patients.

The CHMP also noted that a further study is planned to evaluate the safety and efficacy of avalglucosidase alfa patients with IOPD ≤6 months naïve to previous treatment with alglucosidase alfa. Study EFC14462 will be a phase 3 open label multinational, multicenter intravenous infusion study for avalglucosidase alfa in approximately 16 male and female treatment naïve patients ≤ 6 months of age with documented IOPD. The first patient is expected to be enrolled in Q2 2021. This study is expected to generate data to confirm efficacy and safety of avalglucosidase alfa in treatment-naive patients with IOPD and the CHMP considered acceptable to submit them as a post-authorisation commitment.

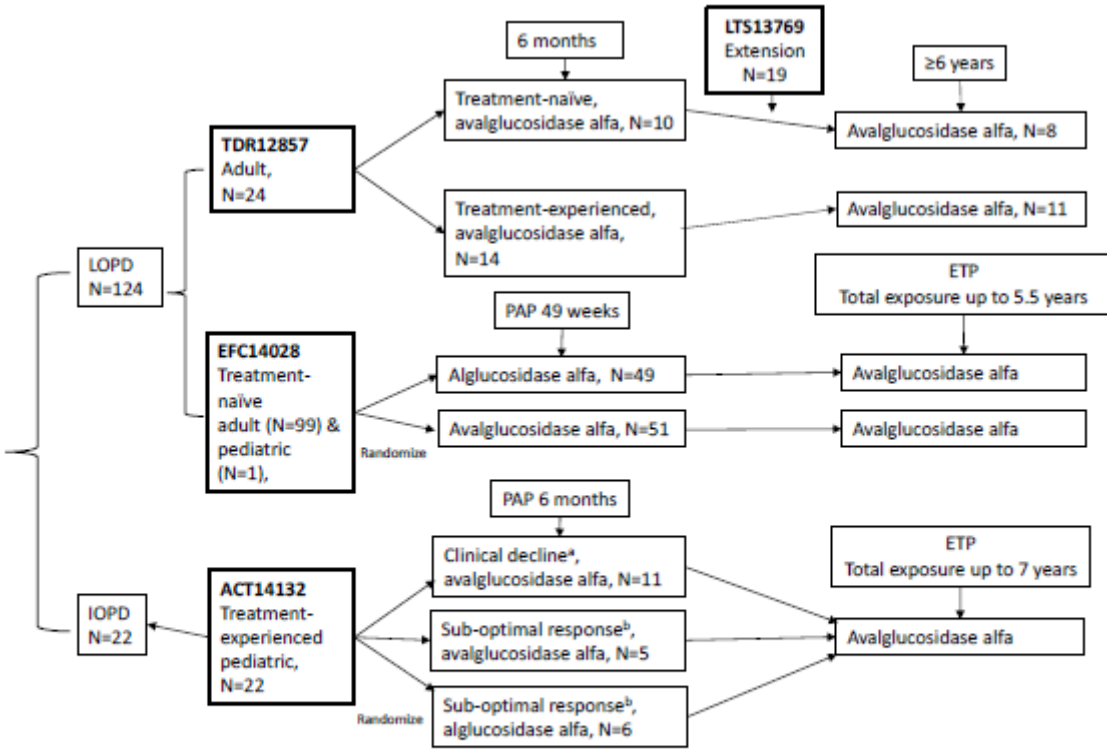
## 2.6.7. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy of avalglucosidase alfa was demonstrated in

patients with Pompe disease (acid α-glucosidase deficiency) in the proposed dosing regimens for adult and paediatric (0-18 years) population.

## 2.6.8. Clinical safety

The avalglucosidase alfa clinical development program was designed to demonstrate reductions in burden of the disease in children and adults with Pompe disease as compared with the standard-of-care ERT, alglucosidase alfa. To match the heterogeneity of the Pompe disease patient population, 4 clinical studies evaluated avalglucosidase alfa in a broad spectrum of patients. See Figure 24.




Note: Experienced=previously treated with ERT for Pompe disease; ETP=extended treatment period; IOPD=infantile onset Pompe disease; LOPD=late onset Pompe disease; Naïve=not previously treated with ERT for Pompe disease; PAP= primary analysis period.

a. Cohorts 1 and 2
b. Cohort 3

**Figure 21 Overview of the avalglucosidase alfa clinical development program**

They were Phase 3 study EFC14028, and Phase 2 study ACT14132, which are the studies to support the primary basis of approval, and the supportive Phase 1/2 study TDR12857 and its open-label long term extension study LTS13769. Study TDR12857 is completed, as well as the PAP of studies EFC14028 and ACT14132. Study LTS13769 and the ETP of studies EFC14028 and ACT14132 are ongoing, the study-specific data cut-off dates are as follows: EFC14028: 19 March 2020; ACT14132: 30 September 2019 and LTS13769: 27 February 2020.

The avalglucosidase alfa safety set consists of pooled avalglucosidase alfa safety data from the 4 clinical studies shown in Figure 1 up to the individual study's data cut-off date. Data across different doses of avalglucosidase alfa from 4 clinical studies were pooled to form the avalglucosidase alfa safety set and presented by the 5 patient populations: naïve patients (studies TDR12857/LTS13769, EFC14028); experienced patients/ previously treated with alglucosidase alfa (studies TDR12857, LTS13769, EFC14028, and ACT14132); adult patients (studies TDR12857/LTS13769 and EFC14028); paediatric patients (studies EFC14028 and ACT14132); patients (studies TDR12857/LTS13769, EFC14028, and ACT14132).

The statistical analyses and reporting from study LTS13769 include all data from lead-in study TDR12857 and its extension study, LTS13769.

#### *2.6.8.1. Patient exposure*

In total, 138 patients were treated with investigational medicinal product (IMP); 20/138 were paediatric patients. For all patients, mean cumulative exposure to avalglucosidase alfa was 274.2 patient years. Majority of patients (73.2%) had ≥48 weeks of exposure to avalglucosidase alfa; 17 patients (12.3%) had ≥240 weeks of exposure. Mean exposure was higher in naïve patients (122.35 weeks) than in experienced patients (88.87 weeks), and higher in adult patients (111.16 weeks) than in paediatric patients (59.47 weeks).

Highest total exposure was in patients ≥18 years to <45 years with 133.2 patient years.

#### *2.6.8.2. Adverse events*

Among the avalglucosidase alfa safety pool, a majority of patients (91.3% [126/138]), reported at least one treatment emergent adverse event (TEAE) during the treatment period, a greater proportion of these patients being alglucosidase alfa naïve patients (95.1% [58/61]) compared with experienced patients (88.3% [68/77]) (see Table 31). The same trend was observed for TEAEs or SAEs "potentially related" to avalglucosidase alfa (49.2% [30/61] vs 45.5% [35/77]; 8.2% [5/61] vs 0, respectively). See Table 31.

**Table 26 Overview of treatment-emergent adverse events - avalglucosidase alfa safety set**

| | Naïve patients (N=61) | Experienced patients (N=77) | Adult patients (N=118) | Paediatric patients (N=20) | All patients (N=138) |
|---|---|---|---|---|---|
| Any TEAEs , n (%) | 58 (95.1) | 68 (88.3) | 106 (89.8) | 20 (100) | 126 (91.3) |
| Person years | 23.2 | 14.0 | 34.7 | 2.5 | 37.2 |
| EAIR per 100 person years | 249.9 | 485.8 | 305.5 | 798.4 | 338.7 |
| TEAEs potentially related to avalglucosidase alfa[a], n (%) | 30 (49.2) | 35 (45.5) | 59 (50.0) | 6 (30.0) | 65 (47.1) |
| Person years | 78.9 | 64.3 | 123.6 | 19.6 | 143.2 |
| EAIR per 100 person years | 38.0 | 54.5 | 47.7 | 30.7 | 45.4 |
| Treatment-emergent SAEs , n (%) | 18 (29.5) | 17 (22.1) | 27 (22.9) | 8 (40.0) | 35 (25.4) |
| Person years | 112.7 | 106.9 | 203.6 | 16.0 | 219.6 |
| EAIR per 100 person years | 16.0 | 15.9 | 13.3 | 50.1 | 15.9 |
| Treatment-emergent SAEs potentially related to avalglucosidase alfa , n (%) | 5 (8.2) | 0 | 5 (4.2) | 0 | 5 (3.6) |
| Person years | 138.5 | 134.3 | 249.1 | 23.6 | 272.7 |
| EAIR per 100 person years | 3.6 | 0 | 2.0 | 0 | 1.8 |
| Severe TEAEs , n (%) | 14 (23.0) | 16 (20.8) | 25 (21.2) | 5 (25.0) | 30 (21.7) |
| Person years | 115.5 | 105.1 | 201.0 | 19.6 | 220.6 |
| EAIR per 100 person years | 12.1 | 15.2 | 12.4 | 25.5 | 13.6 |
| TEAEs leading to death , n (%) | 0 | 1 (1.3) | 1 (0.8) | 0 | 1 (0.7) |
| Person years | 145.5 | 134.2 | 256.1 | 23.6 | 279.7 |
| EAIR per 100 person years | 0 | 0.7 | 0.4 | 0 | 0.4 |
| TEAEs leading to permanent treatment discontinuation[b] , n (%) | 4 (6.6) | 0 | 4 (3.4) | 0 | 4 (2.9) |
| Person years | 145.2 | 134.3 | 255.8 | 23.6 | 279.5 |
| EAIR per 100 person years | 2.8 | 0 | 1.6 | 0 | 1.4 |

TEAE: treatment-emergent adverse event.
The patient year is calculated as time from first avalglucosidase alfa infusion to the time of first event; for patients without event, it is calculated as time from first avalglucosidase alfa infusion to the last administration + 4 weeks (28 days). EAIR = 100*number of patients/person year in each category.

*a* Potentially related to avalglucosidase alfa as assessed by the investigator as "Related" or "Possibly Related" in eCRF.

*b* Does not include the TEAE leading to death.

### Adverse events of special interest (AESI)

AESIs included infusion associated reaction (IAR), pregnancy, symptomatic overdose (EFC14028 and ACT14132) /overdose (LTS13769) and laboratory values meeting pre-specified criteria. Around 37.7% (52/138 patients) of patients receiving avalglucosidase alfa had 1 or more AESIs; no differences were seen between the four groups (naïve patients: 37.7%; experienced patients: 37.7%; adult patients: 39.0%; paediatric patients: 30.0%). Comparing avalgulcosidase alfa treated patients with alglucosidase treated patients in study EFC14028, during the PAP, 13 (25.5%) patients in the

avalglucosidase alfa group and 18 (36.7%) patients in the alglucosidase alfa group reported AESI with similar PT.

In total, 9 pregnancies were reported in the avalglucosidase alfa treated population as of 11 January 2021: 5 patient pregnancies and 4 partner pregnancies. This is further discussed in 2.6.8.6. There were no cases of (symptomatic) overdose reported.

### *2.6.8.3. Serious adverse event/deaths/other significant events*

Treatment emergent serious AEs were reported in 22.9% (27/118) of the adult and 40% (8/20) of the paediatric population. Most treatment emergent serious adverse events (TESAEs) from the paediatric population (25%) were classified in SOC Infections and Infestations. In the adult population, SOCs with most TESAEs were Respiratory, thoracic and mediastinal disorders (5.1%) and Nervous system disorders (4.2%). Five out of 138 subjects (3.6%) reported a total of 9 TESAEs potentially related to avalglucosidase, all of them were naïve adult subjects; neither paediatric patients nor experienced adult subjects reported TESAEs related to IMP. All but one TESAEs potentially related to avalglucosidase were manageable within one day, only respiratory distress lasted for 3 days, but was also manageable.

A tendency towards lower proportion of patients with TESAEs in the avalglucosidase alfa group (15.7%) than in the alglucosidase alfa group (24.5%) (data PAP EFC14028) was noticed, however, numbers of patients are currently too limited to provide robust and conclusive interpretation of the data.

Overall, the percentage of patients receiving avalglucosidase alfa and experiencing TESAEs potentially related to IMP was very low, and all of them were manageable.

According to patient narratives, in study EFC14028, 2 patients treated with alglucosidase and none in the avalglucosidase arm died: one subject had an acute myocardial infarction and another subject had an adenocarcinoma pancreas. Both events were not related to study treatment.

### *2.6.8.4. Laboratory findings*

**Blood pressure parameters**

During EFC14028 study, some of fluctuations in PCSAs for systolic and diastolic blood pressure and heart rate were related to concomitant IARs and some others led to the reporting of a related event, while the remaining ones were not considered as clinically significant.

**ECG parameters**

Eighty adult patients who had at least one ECG with a QRS duration >100 ms were identified. These included 2 patients who were never treated with avalglucosidase alfa and were not in the pooled datasets for the safety analyses in the avalglucosidase alfa safety set, defined as all randomized or enrolled patients who received at least 1 infusion (partial or total) of avalglucosidase alfa, regardless of the amount of treatment administered. Among the 69 adult patients who had at least one ECG with a QRS duration >100 ms, but no QRS duration ≥120 ms, 16 patients had at least one cardiac event. Amongst those, 3 patients had events that were assessed as related to treatment,

i.e.: tachycardia reported as IAR on day 72, resolved after 7 minutes, heart rate increased reported with other events as IAR on day 1009, resolved after 84 minutes, ventricular extrasystoles reported as IAR on day 351, resolved after 100 minutes. For the 11 adult patients who had at least one ECG with a QRS duration ≥120 ms, 4 patients had at least one cardiac event, amongst whom 1 patient with chest discomfort, causally related IAR on day 504, no difference in ECGs from before the infusion, resolved after 59 minutes .

Thirty-five adult patients who had at least one ECG with a QTc interval >450 ms (by Bazett's formula) were identified. One adult patient was never treated by avalglucosidase alfa and was not in the pooled datasets for the pooled safety analyses on avalglucosidase alfa treatment. Among the 35 adult patients who had at least one ECG with a QTc interval >450 ms (by Bazett's formula), 11 patients had at least one cardiac event. Amongst those, 3 patients had events that were assessed as related to treatment, i.e.: tachycardia reported as IAR on day 72, resolved after 7 minutes; ventricular extrasystoles reported as IAR on day 351, resolved after 100 minutes; chest discomfort, causally related IAR on day 504, no difference in EKGs from before the infusion, resolved after 59 minutes.

Two paediatric patients who had at least one ECG with a QRS duration >100 and <120 ms were identified. One patient had 2 cardiac events of pericardial effusion and heart rate increased; neither of the events was assessed as causally related by the investigator.

Twelve paediatric patients who had at least one ECG with a QTc interval >450 ms (by Bazett's formula) including 1 paediatric patient, who had not been treated by avalglucosidase alfa and is not in the pooled datasets for the pooled safety analyses on avalglucosidase alfa treatment. Among the 12 paediatric patients who had at least one ECG with a QTc interval >450 ms (by Bazett's formula), 2 patients had at least one cardiac event (1 patient had pericardial effusion and heart rate increased; 1 patient had presyncope); neither of these events was assessed as causally related by the investigator.

**Hematology**

In patients with normal baseline values, the number of patients who had PCSAs in hematology parameters are as follows: decreased WBC count (5 paediatric patients), increased WBC count (1 paediatric patient), increased lymphocytes (2 adult patients), increased eosinophils (1 paediatric patient), decreased hemoglobin (3 adult patients and 1 paediatric patient), increased hemoglobin (1 adult patient), decreased hematocrit (8 adult patients and 1 paediatric patient), increased hematocrit (1 paediatric patient), increased platelets (1 paediatric patient), increased monocytes (6 adult patients), increased RBC count (2 adult patients), and increased basophils (26 adult patients).

PCSAs of increased basophil counts were observed in 26 patients who received avalglucosidase alfa (26.3% [26/99])**.** Normal range values of basophil count for 25/26 patients (0-0.2 G/L) vs PCSA values defined as abnormal (<0.1 G/L which is below the ULN) were noted.

**Biochemistry parameters**

For patients who had normal baseline values for ALT and AST, 9 of 115 (7.8%) patients had post-baseline values of >3 × ULN for ALT and 7 of 107 (6.5%) patients had post-baseline values of >3 × ULN for AST. For ALT, 2 of 115 (1.7%) adult patients had post-baseline values >10 × ULN, and 1 of 107 (0.9%) adult patients had a post-baseline AST value of >10 × ULN. For ALP, 1 of 135 (0.7%) adult patients had post-baseline values >1.5 ULN. Four of 135 (3.0%) adult patients had a post-baseline value >1.5 ULN for total bilirubin; no patient had a postbaseline value >2 × ULN for total bilirubin. No patient met the criteria of a potential Hy's law case (ie, ALT ≥3 × ULN and total bilirubin >2 × ULN).

In the EFC14028 study PAP, the number of patients with PCSAs for ALT, AST, and creatinine was greater in the avalglucosidase alfa group in comparison to the alglucosidase alfa group. The Applicant also underlined that most of the PCSAs were observed in patients with elevated baseline values of ALT or AST, that reflects the muscle damage related to the underlying disease, explaining that only a few were considered as AESIs. Some increases in AST and ALT during TDR12857/LTS13769 were mentioned as unrelated to avalglucosidase alfa and considered as related to the underlying disease. While the Applicant also outlined a positive signal of the effect of avalglucosidase alfa on muscle damage through some decreased CK and liver function test values.

Over time, both mean values of ALT and AST tend to decrease with a narrowing in the range of the values. Intercurrent illnesses like infections treated with antibiotics, treatments with analgesics or treatment of manifestations and complications of the underlying Pompe disease are reported by some, but not for all patients. There was one related TEAE of Hepatic enzyme increased in one subject during study TDR12857/LTS13769. The subject recovered, remained in the study and had no recurrence of the event. Other patients with reported TEAEs of Alanine or Aspartate aminotransferase increased have also been reviewed suggesting no apparent pattern regarding time or contributing factors that raises concerns.

Total Bilirubin values were generally within the normal range throughout the treatment periods; there is a slight increase in the mean values for the patients who have been in the studies for a long time. The review of the 7 patients did not reveal for any of them a concurrent increase in ALT or AST and no reported liver-related medical history. The 5 patients from studies ACT14032 and EFC14028 had elevated Total Bilirubin values only on 2 or 3 occasions, which are separated in the studies by long periods with normal values. The 3 patients from study TDR12857/LTS13769 presented with elevated Total Bilirubin values more frequently, but not for all measurements of Total Bilirubin, and the non-elevated Total Bilirubin values are all within the normal range; the elevated values of Total Bilirubin have all been assessed by the investigators as clinically non Significant. The review suggested Gilbert's syndrome in two patients, although this was not reported in the medical history.

Over time, creatinine also showed no large variation during the course of the studies. The increase of creatinine in one subject in study TDR12857 was apparently an isolated event; the patient had no similar events during the remaining study duration. The review of a second patient from the same study with a TEAE Blood creatinine increased also appeared to be an isolated event.

**Urinalysis**

No patients had abnormal urinalysis parameters while on treatment that were considered clinically meaningful.

### *2.6.8.5. In vitro biomarker test for patient selection for safety*

No data have been submitted regarding in vitro biomarker test for patient selection for safety.

### *2.6.8.6. Safety in special populations*

No formal studies were conducted in special populations. According to the applicant, the disposition of avalglucosidase alfa, an ERT, is not expected to be impacted by renal or hepatic function. Furthermore based on the review of literature, non-clinical and clinical data the possibility of a risk of hepatic and/or renal toxicity from the breakdown of the synthetic linker is unlikely.

Five age groups were analysed: 0 to <6 years, ≥6 to <18 years, ≥18 to <45 years, ≥45 to <65 years, and ≥65 years. Highest percentages of both TEAEs and SAEs potentially related to avalglucosidase alfa were reported in age groups ≥45 to <65 years and ≥65 years with over 50% experiencing TEAEs potentially related to avalglucosidase alfa, and 4.3% and 11.8% experiencing SAEs potentially related to avalglucosidase alfa, respectively. No SAEs potentially related to avalglucosidase alfa were reported in children and adolescents.

There are no obvious differences between male and female regarding percentage of patients who had TEAEs that were potentially related to avalglucosidase alfa (47.3% [35/74]) and 46.9% [30/64], respectively) and those who experienced SAEs (24.3% [18/74] and 26.6% [17/64], respectively). SAEs potentially related to avalglucosidase alfa were very rare in both males and females (2.7% [2/74]) and 4.7% [3/64], respectively). Most subjects were white, hence, no comparisons could be made with other races. The percentage of all patients, who had TEAEs potentially related to avalglucosidase alfa by duration of the disease was also analysed.

Overall, none of the intrinsic factor subgroups analysed (age, gender, race, duration of disease) seem to be at higher risk for TEAEs.

No conclusion can be drawn from analysing extrinsic factor "region" as numbers of patients from different regions were very small.

In total, 9 pregnancies were reported in the clinical development program as of 11 January 2021: 5 patient pregnancies and 4 partner pregnancies. Of the 9 pregnancies, 4 resulted in live birth (2 patient and 2 partner pregnancies), 3 abortions (2 patient and 1 partner pregnancies), and 2 were of unknown outcome (2 partner pregnancies).

No patterns or trends in reported events associated with dependence or abuse were identified.

### *2.6.8.7. Immunological events*

In both LOPD and IOPD patients, the incidence of treatment emergent antibodies is quite high and there is also a clear trend for increased occurance of IARs as well as hypersensitivity, which correlates with the increase of ADA titers measured. See Table 32.

**Table 27 Summary of treatment-emergent adverse events by anti-avalglucosidase alfa antibodies peak titer category for naive patients - ADA evaluable population**

| | | Naïve patients (N=61) | | |
|---|---|---|---|---|
| | | Peak titer | | |
| **Category n (%)** | **Always negative (N=3)** | **100-800 (N=14)** | **1600-6400 (N=29)** | **>=12,800 (N=13)** |
| Patients with any TEAE | 3 (100) | 13 (92.9) | 27 (93.1) | 13 (100) |
| Patients with any serious TEAE | 1 (33.3) | 3 (21.4) | 10 (34.5) | 3 (23.1) |
| Patients with any protocol defined IAR | 1 (33.3) | 1 (7.1) | 5 (17.2) | 7 (53.8) |
| Patients with any hypersensitivity (narrow SMQ) | 2 (66.7) | 2 (14.3) | 8 (27.6) | 4 (30.8) |
| Patients with any anaphylactic reaction (broad SMQ) | 1 (33.3) | 0 | 2 (6.9) | 1 (7.7) |

TEAE: treatment-emergent adverse events that developed, worsen or became serious on or after the 1st infusion of avalglucosidase alfa study drug, and up to 28 days after last infusion; IAR: infusion associated reaction; SMQ: standardized MedDRA query.

Peak titer: highest ADA titer from first infusion of avalglucosidase alfa for naïve patients that were seroconverted.

| | | Naïve patients (N=61) | | |
|---|---|---|---|---|
| | | Peak titer | | |
| Category n (%) | Always negative (N=3) | 100-800 (N=14) | 1600-6400 (N=29) | >=12,800 (N=13) |

ADA evaluable population in avalglucosidase alfa safety set will be used for the immunogenicity analyses. It is defined as all randomized or enrolled patients who received at least 1 infusion (partial or completed) of avalglucosidase alfa and had at least one ADA sample taken post-baseline after avalglucosidase alfa infusion that is appropriate for ADA testing with a reportable result.
Naïve patients (in TDR12857, LTS13769, and EFC14028).

IAR events in %: ADA peak titer ≥12 800 (53.8%, 7 of 13 patients) compared to patients with ADA titer 1600-6400 (17.2%, 5 of 29 patients), ADA low response titer 100-800 (7.1%, 1 of 14 patients), and patients who were ADA negative (33.3%, 1 of 3 patients).

Hypersensitivity events in %: ADA titers: 100-800 peak titer (14.3%), 1600-6400 peak titer (27.6%) and ≥12 800 peak titer (30.8%)

Updated immunogenicity data covered the overall treatment period during which the majority of IOPD patients received 40 mg/kg qow avalglucosidase after the initial 25 week period. One additional patient had treatment-boosted anti-avalglucosidase alfa ADAs and 4 additional patients had treatment-induced anti-avalglucosidase alfa ADAs. Unlike observed before, one IOPD patient developed neutralizing anti-avalglucosidase alfa ADAs. Antiavalglucosidase alfa ADAs increased in some patients but none of the patients developed a high ADA response ≥12,800.

No fatal events, related SAEs nor anaphylaxis cases (as defined by Sampson upon case review) were reported to date and no patients have discontinued the study. All IARs were reported as non-serious and mild to moderate in severity and the majority of IARs events were reported by a few patients, without established relationship with ADA titers. However, limited number of IOPD patients hampers the interpretability of the results and due to the fact that immunogenicity of avalglucosidase in treatment-naïve IOPD patients has not been studied yet, robust data in order to support the dose of 40 mg/kg qow are still missing. Increasing amount of data from paediatric patients are needed to allow a meaningful assessment of ADA responses taking into account administered dose differences of avalglucosidase treatment in paediatric patients. Sufficient information about several approaches regarding immune modulation treatment strategies including rituximab, methotrexate and intravenous immunoglobulin in a prophylactic and therapeutic setting were provided as relevant ITI regiment for naïve or experienced patients.

### *2.6.8.8. Safety related to drug-drug interactions and other interactions*

No drug-drug interaction studies have been conducted, which is considered acceptable by the CHMP.

### *2.6.8.9. Discontinuation due to adverse events*

The rate of discontinuation in avalglucosidase treated patients was low: 4/138 patients had TEAEs that led to discontinuation of IMP; all were naïve, adult from 3 different studies (TDR12857, EFC14028, and LTS13769). In comparison, 3/49 patients in the alglucosidase group from study EFC14028 withdrew from the study; 2 patients due to IARs related to study treatment, the other one died of acute myocardial infarction which was not related to study treatment.

Events in two patients receiving avalglucosidase alfa were considered related to IMP and were the reason for discontinuation: one of them experienced TESAEs (respiratory distress and chest discomfort), the other one experienced non-serious TEAEs of ocular hyperaemia and erythema. All TEAEs related to avalglucosidase alfa leading to permanent treatment discontinuation are included in 4.4 and/or 4.8 of the proposed SmPC.

Overall, in both treatment groups, TEAEs related to IMP leading to discontinuation of study participation were IARs.

#### *2.6.8.10. Post marketing experience*

There is no postmarketing experience available since avalglucosidase alfa is not approved in any country at the present time.

## 2.6.9. Discussion on clinical safety

From all clinical studies, a safety pool of 138 patients treated with avalglucosidase administered by IV infusions (LOPD and IOPD patients) was analysed. The mean cumulative exposure to avalglucosidase alfa was 274.2 patient years. The majority of patients (73.2%) had ≥48 weeks of exposure to avalglucosidase alfa; 17 patients (12.3%) had ≥240 weeks of exposure.

Fifty percent of adult reported TEAEs potentially related to avalglucosidase treatment. In the adult population, these were mainly TEAEs of the System Organ Classes (SOCs) General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Gastrointestinal disorders, and Nervous system disorders.

The three of most frequent TEAEs (all patients) were nasopharyngitis, headache, and diarrhoea.

There was no difference in percentage of patients experiencing TEAEs potentially related to study drug neither in experienced (45.5%) vs naïve (49.2%) patients nor in patients receiving avalglucosidase alfa (45.1%) vs alglucosidase alfa (49.0%). These data from avalglucosidase alfa vs alglucosidase alfa are from PAP of study EFC14028 only.

These adverse events are consistent with those reported in patients treated with the active comparator alglucosidase alfa in thePAP of study EFC14028. Treatment emergent serious AEs were reported in 22.9% (27/118) of the adult and 40% (8/20) of the paediatric population. Most TEAEs from the paediatric population (25%) were classified in SOC Infections and Infestations but were unrelated to IMP. In the adult population, SOCs with most TEAEs were Respiratory, thoracic and mediastinal disorders (5.1%) and Nervous system disorders (4.2%). 5/138 subjects (3.6%) reported a total of 9 TESAEs potentially related to avalglucosidase, all of them were naïve adult subjects; neither paediatric patients nor experienced adult subjects reported TESAEs related to IMP. All but one TESAEs potentially related to avalglucosidase were manageable within one day; only respiratory distress lasted for 3 days, but was also manageable. The percentage of patients receiving avalglucosidase alfa and experiencing TESAEs potentially related to IMP was very low, and all of them were manageable.

In addition, IARs were reported by 26.1% of all patients studied, mostly 0-2 hours after infusion started; again, no difference was seen between the four groups (naïve, experienced, adult, paediatric). Most frequently reported IARs for all patients was pruritus, rash, and urticaria. Avalglucosidase alfa related TEAEs reported in ≤2 patients were further analysed to ensure that the SmPC adequately report TEAEs (PTs) <2% in all patients.

Anaphylactic reactions were reported by 8 patients, 4 naïve and 4 experienced patients. Hypersensitivity was experienced by 60 patients, and the percentage of patients experiencing hypersensitivity was comparable between naïve, experienced and adult patient group. Six of the 60 patients experiencing hypersensitivity had hypersensitivity events that were considered by the Investigator to be severe, a TESAE, or both. There was no difference between percentage of patients experiencing anaphylactic reactions in the avalglucosidase alfa group (3.9%) vs alglucosidase alfa group (4.1%) during the PAP of study EFC14028. Two cases of anaphylaxis leading to withdrawel of study drug and study drug interruption, respectively, occurred in study TDR12857. In study EFC14028, the applicant claims that a numerically lower risk of IARs was seen with avalglucosidase alfa. Percentage of patients reporting at least one IAR was indeed lower in the avalglucosidase alfa group (25.5%) than in the alglucosidase alfa group (32.7%) However, looking at the actual numbers (13/51 patients in the avalglucosidase group reported at least one IAR compared to 16/49 patients in the alglucosidase group), difference between the two groups is rather small and interpretation is limited due to the small sample size. Overall, data do not show a better safety profile in avalglucosidase group compared to alglucosidase treated patients and the limited data do not allow firm conclusions. Postmarketing data may further characterise the overall safety profile of avalglucosidase alfa versus alglucosidase alfa.

The percentage of abortions was relatively high. The review of the 2 patients in the clinical development program for avalglucosidase alfa as well as the 2 patients from the Pregnancy Sub-Registry in the Pompe Registry with spontaneous abortion, did not show any particular pattern. Of the 2 patients from the Pregnancy Sub-Registry, one was treated with alglucosidase alfa at the time when she was found to be pregnant, while the other patient was not being treated. The small sample sizes do not allow robust conclusions, while the numbers in comparison to the overall sample of the patients enrolled in either the study program or the Pompe Registry appear consistent with the numbers reported in the literature. In addition, the pre-clinical data do not provide any supportive evidence for a potential causal association of the reported miscarriages and the treatment with avalglucosidase alfa. The inclusion of an additional text in the SmPC Section 4.6 is thus not warranted. Pregnancies are listed as reasons for temporary treatment discontinuation and are not considered as protocol deviations in studies LTS13769 and EFC14028; lactating women are excluded per protocol. Moreover additional information on special populations of interest such as pregnant or lactating women treated with avalglucosidase alfa are planned to be collected as part of additional pharmacovigilance activities (see 2.7).

Overall, none of the intrinsic factor subgroups analysed (age, gender, race, duration of disease) seem to be at higher risk for TEAEs. No dosage adjustment is thus proposed in the SmPC. Further data are expected to be collected with the additional pharmacovigilance activities to further characterise the safety and this is considered acceptable by the CHMP (see 2.7).

Effects on the ability to drive or operate machinery are generally not expected based on the presented safety profile. However, in the proposed SmPC, dizziness was reported as IAR, which might affect the ability and use of machines on the day of the infusion. In the avalglucosidase alfa safety set, 13% reported TEAE dizziness. Section 4.7 of the SmPC mentioned that Nexviadyme may have a minor influence on the ability to drive and use machines.

The CHMP considers that no unexpected safety concerns arise from the safety data with avalglucosidase alfa. IARs, anaphylactic reactions, and hypersensitivity are sufficiently described in the proposed SmPC. Even if the Applicant concludes that IARs and hypersensitivity events are manageable, immunogenicity and the risk of IARs/hypersensitivity should be closely monitored in the post-marketing setting, especially due to the small number of patients (see section 2.7). In the ETS period of study ACT14132, only one patient out of 6, who

received 20 mg/kg avalglucosidase alfa, developed a transient ADA response, whereas in the cohort, who received 40 mg/kg, 5 out of 10 patients (50%) developed treatment emergent ADA response.

The limited number of IOPD patients hampers the interpretability of the results and due to the fact that immunogenicity of avalglucosidase in treatment-naïve IOPD patients has not been studied yet, robust data in order to support a starting dose of 40 mg/kg qow are still missing. Increasing amount of data from paediatric patients are needed to allow a meaningful assessment of ADA responses taking into account administered dose differences of avalglucosidase treatment in paediatric patients. Sufficient information about several approaches regarding immune modulation treatment strategies including rituximab, methotrexate and intravenous immunoglobulin in a prophylactic and therapeutic setting were provided as relevant ITI regimens for naïve or experienced patients. However, careful observation in the ongoing clinical trials and further studies is expected, especially with the use of the higher dose of 40 mg/kg. All these events shall be followed upon post-marketing and presented in the respective PSURs.

At this time point, no conclusion can be drawn on whether or not avalglucosidase alfa has a different or better safety profile than alglucosidase alfa. This is mainly due to the limited safety database.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

***Assessment of paediatric data on clinical safety***

For safety assessment, 20 paediatric patients treated with avalglucosidase alfa, 6 (30%) in the age range 0 to <6 and 14 (70%) in the age range ≥ 6 to <18 were included. All but one paediatric patient exposed to avalglucosidase alfa were part of study ACT14132. All paediatric patients were treatment-experienced, and all but one were diagnosed with IOPD (one patient with LOPD); no data on treatment naïve IOPD patients are available.

Even though the number of paediatric patients is limited, total number of patients exposed to IMP is relatively high, also for exposure more than 6 months. In comparison, only 22 patients treated with Myozyme provided safety data, none of them were treated more than 6 months. Therefore, it was suggested to establish a registry in order to follow all treated (and ideally some untreated) patients. The Sanofi Genzyme Pompe Registry was established in 2004 to track the natural history and treatment outcomes of patients, both treated and not. This registry is still ongoing. A total of 2254 patients were enrolled in the Pompe Registry as of 01 May 2020, 390 patients with IOPD and 1640 patients with LOPD.

Thirty percent of paediatric patients reported TEAEs potentially related to avalglucosidase treatment. In the paediatric population, most TEAEs reported were reported in the SOC Skin and subcutaneous tissue disorders.

In the paediatric population upper respiratory tract infections, rash, and pyrexia were the three most reported TEAEs.

No paediatric patient experienced anaphylactic reactions. A slightly higher percentage of paediatric patients experienced hypersensitivity as compared to the naïve, experienced and adult groups.

No unexpected safety concerns arise from the safety data with avalglucosidase alfa.

Data regarding the dosing regimen 40 mg/kg qow in IOPD patients (cohort 2 and avalglucosidase arm in cohort 3) are rather sparse. No conclusive pattern could be identified with regards to occurrence/increase of adverse events in comparison to 20 mg/kg qow treated paediatric patients.

***Home infusion***

To support home infusion, some clinical data, from a preliminary home infusion report with Myozyme in the Netherlands in adult LOPD patients, were presented.

To further justify the implementation of home infusion, the applicant presented new data from the ongoing studies related to immunologic events, IAR or emergency situations. As of 31 May 2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Only one case of non-serious events was reported at the first administration at home (eyelid edema and flushing), which was treated appropriately and resolved at the same day. After administration of further infusions at the study site under monitoring, home infusion could be resumed without occurrence of further IAR events. Current data do not indicate an increased risk of IARs or medication errors with home infusion in adults. For IOPD patients, no data on home infusion were available yet. Six unrelated non-serious AEs in 2 other patients in EFC14028 and 1 unrelated on-serious AE in 1 patient in LTS13769 were reported. No medication error occurred in the setting of home infusion.

The applicant proposed to reflect in section 4.2 of the SmPC the population eligible to receive home infusion. These are patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. The following criteria should be considered:

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may affect patient's ability to tolerate the infusion.

- The patient is considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.

- The patient must have received Nexviadyme infusions supervised by a physician with expertise in management of Pompe patients for a few months that could be in a hospital or in another appropriate setting of outpatient care. Documentation of a pattern of well-tolerated infusions with no IARs, or mild IARs that have been controlled with premedication, is a prerequisite for the initiation of home infusion.

- The patient must be willing and able to comply with home infusion procedures.

- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. The healthcare professional should be available at all times during the home infusion and a specified time after-infusion, depending on patient's tolerance prior to starting home infusion.

The SmPC also recommends that if the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately and appropriate medical treatment should be initiated (see section 4.4). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present. Dose and infusion rate must not be changed without consulting the responsible physician.

The CHMP acknowledged that home infusion is an established practice for some other ERTs. Based on the submitted data, the proposed SmPC recommendations regarding home infusion is considered acceptable by the CHMP. A mix-up with Alglucosidase alfa (Myozyme) will be counteracted with different colours of the brand name, outer packing and caps. In addition additional risk minimisations are introduced to ensure safe and effective use of avalglucosidase alfa under this specific setting. These actions are considered appropriate.

### 2.6.10. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Appropriate measures including additional pharmacovigilance activities and risk minimisation activities (see 2.7) have been put in place to ensure safe and effective use of the product in the recommended indication.

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

| | |
|---|---|
| Important identified risk | Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies |
| Important potential risks | Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies) |
| | Medication error in home infusion setting |
| | Immune complex related reactions |
| Missing information | Use in pregnant and lactating women |
| | Use in patients with renal or hepatic insufficiency |

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

### 2.7.2. Pharmacovigilance plan

| Study status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| Not applicable | | | | |
| Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| Not applicable | | | | |
| Category 3 - Required additional pharmacovigilance activities | | | | |

| | | | | |
|---|---|---|---|---|
| LTS13769<br>Ongoing | Evaluate long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies".<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q4 2022 |
| EFC14028 (COMET)<br>Ongoing | Primary objective is 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.<br>Secondary objectives are to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12).<br>The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including adverse events of special interest and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with neutralizing antibodies in ADA-positive patients) are evaluated 1 week following | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies"<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q1 2025 |

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|---|---|---|---|---|
| | the 1st infusion in ETP, then monthly through Week 73, then every 12 weeks up to the end of the follow-up. | | | |
| ACT14132 (Mini-COMET)<br>Ongoing | Primary objective is to evaluate the safety profile of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies".<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q4 2025 |
| EFC14462<br>Planned | Primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment.<br>Secondary objectives are to determine the effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival at 12 and 18 months of age, as well the change in LVM-Z score; AIMS score; body length, body weight, and head circumference Z scores; and urinary Hex4 at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies"<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q2 2027 |
| DIREGC07005 (Pompe Disease Registry)<br>Planned | The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression, and management of Pompe disease including patients | "Use in patients with renal or hepatic insufficiency" | Start of data collection<br>End of data collection | Q3 2021<br>Q4 2031<br>Q3 2032 |

| | | | | |
|---|---|---|---|---|
| | treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency. | | Final cumulative report submission | |
| AGLU03506 (Pompe Disease Pregnancy Sub-registry)<br>Planned | The primary objective of this Sub-registry is to track pregnancy outcomes, including complications and infant growth, in all women with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERT with alglucosidase alfa or avalglucosidase alfa.<br>This Sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated. | "Use in pregnant and lactating women" | Start of data collection<br>End of data collection<br>Final cumulative report submission | Q3 2021<br>Q4 2031<br>Q3 2032 |
| Post-Authorization Safety Study<br>Planned | This study aims at gathering more comprehensive safety information on avalglucosidase alfa in a structured way to further characterize the important identified risk of infusion associated reactions, including hypersensitivity and anaphylactic reactions, and the important potential risk of medication error in the setting of clinical/ hospital and home infusion. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies"<br>"Medication errors in home infusion setting" | Final protocol<br>Final report submission | Q1 or Q2 2022<br>Q2 2028 |

6MWT: 6-Minute Walk Test; ADA: Anti Drug Antibody; AIMS: Alberta Infant Motor Scale; ETP: Extended Treatment Period; ERT: Enzyme Replacement Therapy; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LVM-Z: Left Ventricular Mass Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure; PK: Pharmacokinetic; Q: Quarter; QMFT: Quick Motor Function Test; SF-12: 12 Item Short Form Health Survey.

## 2.7.3. Risk minimisation measures

| Safety concern | Risk minimization measures |
|---|---|
| Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies | **Routine risk minimization measures**:<br>Labeled in sections 4.4 and 4.8 of SmPC.<br>Labeled in section 2 of PL.<br>Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of adverse reactions are included in SmPC section 4.2.<br>Instructions to mitigate the infusion associated reactions are included in SmPC section 4.4.<br>How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 4.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (HCP guide for immunosurveillance service and Home infusion guide). |
| Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies) | **Routine risk minimization measures**:<br>Labeled in sections 4.4 and 4.8 of SmPC.<br>Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in section 4.4 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (HCP guide for immunosurveillance service). |
| Medication error in home infusion setting | **Routine risk minimization measures**:<br>Labeled in sections 4.2 and 6.6 of SmPC.<br>Labeled in sections 3 and 5 of PL.<br>Decision criteria to have a patient move to home are included in SmPC section 4.2, as well as the description of home infusion infrastructure, resources, and procedures.<br>The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in SmPC section 6.6.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (Home infusion guide). |
| Immune complex related reactions | **Routine risk minimization measures**:<br>Not applicable<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |

| Safety concern | Risk minimization measures |
|---|---|
| Use in pregnant and lactating women | **Routine risk minimization measures**:<br>Labeled in section 4.6 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |
| Use in patients with renal or hepatic insufficiency | **Routine risk minimization measures** Labeled in sections 4.2 and 5.2 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |

HCP: Healthcare Professional; IgE: Immunoglobulin E; IgG: Immunoglobulin G; PL: Package Leaflet; PSUR: Periodic Safety Update Report; SmPC: Summary of Product Characteristics.

### 2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reason: vial label does not have the space necessary to display all required information in a suitable and readable font size.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

### 2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nexviadyme (avalglucosidase alfa) is included in the additional monitoring list as it is a biological product, which will be authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Avalglucosidase alfa is intended for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA). Defects in both alleles of the gene for GAA, located on chromosome 17q25, result in reduced or absent enzyme activity, leading to progressive intralysosomal accumulation of undegraded glycogen. The resulting damage to affected cells produces a range of symptoms that characterize Pompe disease, including metabolic myopathy leading to neuromuscular dysfunction and ultimately death.

Currently, over 500 mutations of GAA, including missense, nonsense, splicing defect, and frameshift mutations, have been found. According to the variety of mutations, clinical presentation of Pompe disease is heterogeneous in timing, severity, and ranges of symptoms observed. The disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. The phenotypes range from a rapidly progressive infantile-onset form (IOPD) characterized by virtually complete absence (less than 1%) of acid alpha-glucosidase (GAA)-activity to a more slowly progressive late-onset form (LOPD).

Infantile-onset Pompe disease (IOPD), which represents up to one third of the cases, becomes manifest in the first months of life. Affected patients present with creatinine kinase elevations, hypertrophic cardiomyopathy (HCM), failure to thrive, muscular hypotonia and axial muscle weakness. IOPD is rapidly progressive, and the majority of untreated subjects die within the first year of life due to a combination of ventilatory and cardiac

failure without achieving any motor milestones such as turning, sitting, or standing. Survival beyond the age of 18 months is exceptional.

The majority of patients with Pompe disease present after infancy with late-onset Pompe disease (LOPD), which takes a more variable course. In untreated patients, undegraded glycogen accumulates in diaphragm and respiratory muscles, and respiratory function declines over time, leading to dependence to external ventilation and, ultimately, to respiratory failure which is the most common cause of death regardless of age of disease onset. Glycogen also accumulates in skeletal muscles, and motor function declines over time, leading to problems with activities of daily living, reduced mobility, and eventually dependence on wheelchair. Quality of life is usually severely affected by the burden of the disease.

The estimated global incidence of Pompe disease is 1:40 000, with variations in incidence reported between different ethnic groups and clinical forms. Avalglucosidase alfa gained Orphan designation in 2014 with an estimated number of affected patients below 1/10,000 people in the EU, equivalent to around 51,000 people.

### 3.1.2. Available therapies and unmet medical need

Development and approval of ERT has profoundly changed the natural course of the disease, revealing new phenotypes in patients with classical IOPD who survive with ERT, and considerably extending productivity and quality of life for patients with LOPD. However, it is recognized that the progressive decline in muscle function in patients with Pompe disease is not completely abrogated with alglucosidase alfa ERT.

Studies in LOPD patients suggest that some patients on alglucosidase alfa continue to exhibit some decline in respiratory function, albeit at a slower pace than prior to treatment. Responses to treatment in LOPD patients vary and there might be room for improvement in individual patients, but overall there is not a huge unmet medical need in this population.

With respect to IOPD patients, literature data (Chien et al, 2015) indicate that some patients treated with Myozyme exhibit declines in motor function and mobility starting at 18-24 months of age, despite an initial decrease in CK levels. The reasons for the variable efficacy of ERT and the progression of disease with time are manifold and only imperfectly understood. Known factors include age at start of therapy and pre-treatment muscle pathology, CRIM-status and antibody titers, distribution of type I and II fibers, and altered autophagy (Kishnani et al., 2012).

Although ERT has substantially improved the prognosis of IOPD, mortality is still considerable, and decline of motor function over time is frequent in long-term survivors. Thus, further efforts are necessary to improve the outcome of children affected by this most severe form of Pompe disease, indicating an unmet medical need in IOPD patients deteriorating on the available ERT.

### 3.1.3. Main clinical studies

Study EFC14028 (COMET) in LOPD population

The main evidence of efficacy comes from a single phase III multicenter, randomized, double-blind study comparing avalglucosidase alfa (n=51) to alglucosidase alfa (n=49) in treatment-naïve LOPD patients from 3 years of age. The study comprises a primary analysis period (49 weeks) followed by an extended treatment period. The primary objective of study EFC14028 was to determine the effect of avalglucosidase alfa treatment

on respiratory muscle strength as measured by forced vital capacity (FVC)% predicted in the upright position, as compared to alglucosidase alfa.

The primary statistical objective was to test the non-inferiority (NI) of avalglucosidase alfa versus alglucosidase alfa at 5% level of significance. The non-inferiority (NI) of avalglucosidase alfa to alglucosidase alfa was to be investigated first before progressing to investigation of superiority.

Secondary objectives were to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT, key secondary endpoint), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health related quality of life (SF-12).

Study ACT14132 (Mini-COMET) in IOPD population

Additional evidence of efficacy comes from a multicenter, multistage phase II, open-label, ascending dose cohort study in 22 patients under 18 years of age with IOPD, who were previously treated (treatment-experienced) with alglucosidase alfa for at least 6 months. The study comprises a primary analysis period (week 25) followed by an extended treatment period. The primary objective of the ACT14132 study was the assessment of safety and tolerability of administering avalglucosidase alfa. The secondary objectives were characterization of the pharmacokinetic profile of avalglucosidase alfa and evaluation of the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. Efficacy endpoints in ACT14132 included motor function (evaluated through functional and clinical outcome assessments and 6-minute walk test [6MWT]), respiratory function (evaluated through pulmonary functional testing [PFT] and ventilator use questionnaire), quality of life, pain, cardiac function (echocardiography) and eyelid position measurements.

## *3.2. Favourable effects*

LOPD population

- The main evidence of efficacy and safety is based on a randomized, double-blind, active controlled study including 100 patients. The active comparator was alglucosidase alfa, an approved medicinal product of established therapeutic value, and currently the standard of care.
- The primary objective of the Phase 3 study EFC14028 was met by demonstrating non-inferiority of respiratory function as measured by % predicted FVC as compared to alglucosidase alfa at week 49. In the mITT population, the LS mean change from baseline to Week 49 in % predicted FVC was 2.89 in the avalglucosidase alfa group and 0.46 in the alglucosidase alfa group. The difference in mean change (from baseline to Week 49) of 2.43 with lower boundary of 95% CI of -0.13 exceeded the predefined NI margin of -1.1 and thus achieved statistical significance (95% CI: -0.13, 4.99; p=0.0074)
- Results of a pre-planned sensitivity analysis of the primary efficacy endpoint done in the PP population support the non-inferiority conclusion: LS mean difference FVC% predicted at week 49 was 2.69 (95% CI: -0.06, 5.44; p=0.0076).
- The LS mean difference in distance walked in meters in the 6MWT (key secondary endpoint) was 30.01 (95% CI:1.33, 58.69).

- Subgroup analyses for study EFC14028 (primary efficacy endpoint, % predicted FVC), performed by age group (<18 years, ≥18 years to <45 years, ≥45 years old), gender, baseline FVC groups (<55%, and ≥ 55%), region, baseline walking device use, baseline 6MWT distance, duration of disease at baseline, and race indicate consistency of results across subgroups.

IOPD population

The descriptive results of study ACT14132 show positive trends (stabilization or improvement) in secondary and tertiary efficacy outcomes with avalglucosidase. During the primary analysis period (PAP), Gross Motor Function Measure-88 (GMFM-88) mean scores increased modestly from baseline to Week 25 in all four treatment groups (Cohort 1: 2.62, Cohort 2: 3.54, Cohort 3: AVAL: 4.20, AGLU: 6.82)

Home infusion

- As of 31 May 2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Few non-serious events was reported at the first administration at home (eyelid edema and flushing), which was treated appropriately and resolved at the same day. Current data do not indicate an increased risk of IARs or medication errors with home infusion in adults. No medication error occurred in the setting of home infusion.

## *3.3. Uncertainties and limitations about favourable effects*

LOPD population

- The pivotal trial was performed in adult LOPD patients, only two subjects were below the age of 18 years and included a 9 years old patient that was enrolled after the study cut-off date of 10 March 2020. Evidence for efficacy and safety of avalglucosidase in the paediatric population is limited to 22 previously treated IOPD patients > 6 months of age in the open-label phase 2 study (ACT14132).
- Demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in % predicted FVC at Week 49 was missed in Study EFC14028 at the 5% significance level (p= 0.0626). Since superiority could not be demonstrated for the primary endpoint, all subsequently planned statistical superiority tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate control of the experimentwise type-1-error.
- Despite some of the investigated efficacy parameters showed a positive trend for better outcome with avalglucosidase alfa; many of these endpoints were correlated and are measured in the same patients. Further significance testing was also hampered by the lack of demonstration of superiority in study EFC14028.
- The overall performance of alglucosidase alfa (i.e. LS mean change from baseline to Week 49 in FVC %: 0.46, in 6MWT: 2.19 meters) was notably poorer than in the registration trial for alglucosidase alfa (ALGLU02704/LOTS). In the LOTS trial the estimated change in FVC, expressed as a percentage of each patient's predicted value, was an increase of 1.2 percentage points at week 78 (1.73 at week 49) for the patients who received alglucosidase alfa. Furthermore, patients in the LOTS trial had a mean increase of 25.1 m on the 6-minute walk test by week 78. It is however acknowlegded that the results observed in the alglucosidase alfa group in Study EFC14028 are likely influenced by a randomized population different to the one randomized in Study AGLU02704.

- Data on long-term efficacy are limited. Extended treatment periods of the clinical trials are still ongoing. At the cut-off date of 19 March 2020, 91 patients were enrolled in the ongoing ETP; efficacy data at 97 weeks were available for 24 patients who had since study start continuously received avalglucosidase alfa and for 21 patients who switched from alglucosidase alfa to avalglucosidase alfa treatment after 49 weeks. After Week 49, FVC slightly decreased in patients continuing with avalglucosidase alfa.

IOPD population

- There is lack of data in treatment-naive IOPD patients under the age of 6 months.
- No formal dose-response studies have been performed. The 20 mg/kg dose was selected based on the clinical experience with alglucosidase alfa and results from non-clinical studies and the safety and exploratory efficacy results from the ascending dose phase 1 study TDR12857.
- The investigation in IOPD patients is limited to a pre-treated population in study ACT14132 (Mini-COMET), including 22 patients (Cohort 1 (n=6): 20 mg/kg AVAL, Cohort 2 (n=5): 40 mg/kg AVAL, Cohort 3 (n=11): 5 patients 40 mg/kg AVAL and 6 patients AGLU at various doses). The primary objective of the ACT14132 study was the assessment of safety and tolerability of avalglucosidase alfa. The secondary objectives were characterization of the pharmacokinetic profile and the evaluation of the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa.. The highest improvement was seen in Cohort 3, in the alglucosidase alfa group. Consistently to the results of the GMFM-88, the greatest degree of change in the Quick motor function test (QMFT)–total score was observed in the alglucosidase alfa group (5.17 vs. 4.25 in the AVAL group of Cohort 3). Due to its design and small size the study cannot deliver firm conclusions on avalglucosidase´s efficacy and safety in this setting. Moreover, the proposed higher starting dose in IOPD patients (40 mg/kg) has not been demonstrated to be more suitable than the 20 mg/kg dose proposed in LOPD patients.
- IOPD patients with higher anti-alglucosidase alfa antibody titers (≥1:25600) have been excluded from clinical studies.

Home infusion

- Home infusion is an established practice for some other ERTs. However limited data are available for avalglucosidase alfa and have been supplemented by the clinical experience with alglucosidase alfa. For IOPD patients, no data on home infusion are available. The risks related to home infusion is reflected in the RMP as important potential risk and will be reported in the PSURs.

## *3.4. Unfavourable effects*

LOPD and IOPD populations

- In the ETS period of study ACT14132, only one patient, who received 20 mg/kg avalglucosidase alfa, developed a transient ADA response, whereas in the cohort, who received 40 mg/kg, 5 out of 10 patients (50%) developed a treatment emergent ADA response.
- 50% of adult and 30% of paediatric patients reported TEAEs potentially related to avalglucosidase treatment.

- IARs were reported by 26.1% of all patients studied, mostly 0-2 hours after infusion started.
- Anaphylactic reactions were reported by 8 patients, 4 naïve and 4 experienced patients.
- Six of the 60 patients experiencing hypersensitivity had hypersensitivity events that were considered by the Investigator to be severe, a TESAE, or both.
- AVAL IAR events in %: ADA peak titer ≥12 800 (53.8%, 7 of 13 patients) compared to patients with ADA titer 1600-6400 (17.2%, 5 of 29 patients), ADA low response titer 100-800 (7.1%, 1 of 14 patients), and patients who were ADA negative (33.3%, 1 of 3 patients).
- AVAL Hypersensitivity events in %: ADA titers: 100-800 peak titer (14.3%), 1600-6400 peak titer (27.6%) and ≥12 800 peak titer (30.8%)

## *3.5. Uncertainties and limitations about unfavourable effects*

IOPD population

- The proposed higher starting dose of 40 mg/kg in IOPD patients is mainly based on recent publications of clinical experience in IOPD patients receiving alglucosidase alfa doses greater or at higher frequency than the label dose of 20 mg/kg qow (Chien, 2015, J Pediatr; Case, 2015, Neuromusc Disord). So far there are only very limited data with 40mg/kg avalglucosidase alfa from study ACT14132 (in total 10 patients in the PAP received the 40 mg/kg dose; cut-off date 30 April: during ETP all but 2 patients switched to the 40 mg/kg AVAL resulting in 20 patients currently treated with the highest dose of 40 mg/kg).
- So far, there are no data on avalglucosidase alfa in an ERT treatment naïve IOPD population. Treatment-experienced IOPD and LOPD patients appear to have some degree of attenuation of immunologic response, possibly due to development of immunologic tolerance given the shared protein structure of aval- and alglucosidase.
- Patients at high-risk for experiencing a severe allergic reaction to avalglucosidase alfa (i.e. patients who had previously severe anaphylactic reaction to alglucosidase alfa and/or a history of high sustained IgG antibody titers to alglucosidase alfa) were excluded from the phase 2 study in IOPD patients.

Paediatric LOPD and IOPD populations

- The number of paediatric patients is very limited: In total, 24 paediatric patients were treated with avalglucosidase alfa, 22 IOPD patients, and 2 paediatric/juvenile LOPD patients.

## *3.6. Effects Table*

Effects Table for avalglucosidase alfa in the long-term use as an Enzyme replacement therapy (ERT) for the treatment of patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

| Effect | Short Description | Unit | AVAL | ALGLU | AVAL vs ALGLU | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | | |
| FVC | Mean change in FVC from baseline to week 49 | % | 2.89 | 0.46 | 2.43 | 95%CI (-0.13;4.99; p (NI)=0,0074, p (superiority)=0.0626 | EFC14028 |
| 6MWT | Mean change in distance walked in meters | m | 32.21 | 2.19 | 30.01 | Superiority tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate control of the experimentwise type-1-error, since statistical superiority was missed for the primary endpoint. | EFC14028 |
| | | | | | | | |
| **Unfavourable Effects** | | **unit** | **20mg/kg AVAL** | **40mg/kg AVAL** | | | |
| ADA | Proportion of patients developing ADA | % (n) | 16.7% (1/6) | 50% (5/10) | | A dosing regimen of 40 mg/kg qow might be associated with a higher risk for ADA-mediated IARs and hypersensitivity events. | ETS period of study ACT14132 |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Despite some uncertainties regarding effect size and less severely affected studied population, efficacy of avalglucosidase alfa could be convincingly demonstrated in the phase 3 study in LOPD patients by showing non-inferiority in % predicted FVC compared to alglucosidase alfa. Although some of the investigated efficacy parameters showed a positive trend for better outcome with avalglucosidase alfa, many of these endpoints are correlated and are measured in the same patients. Most importantly, however, demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in the primary endpoint % predicted FVC at Week 49 was missed at the required significance level. Accordingly, all subsequently conducted statistical tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate experimentwise type-1-error control. Hence, any reference in the discussion of trial outcome for these endpoints indicating an advantage of avalglucosidase alfa over alglucosidase alfa is not permissible and a conclusion of demonstrated superiority is not possible.

Additional evidence for the paediatric population solely comes from phase 3 study EFC14028 and the phase 2 study ACT14132 in previously treated IOPD patient > 6 months. However, due to its design and small size of study ACT14132, the study cannot deliver firm conclusions on avalglucosidase´s efficacy and safety in this setting at the proposed starting dose of 40 mg/kg. In particular, only one patient, who received 20 mg/kg avalglucosidase alfa, developed a transient ADA response, whereas in the cohort, who received 40 mg/kg, 5 out of 10 patients (50%) developed a treatment emergent ADA response.

Long term data are limited. Ongoing clinical studies and the extension of the applicant existing Pompe disease and Pompe disease Pregnancy sub registries to further characterise the efficacy (especially in the paediatric population) and safety of avalglucosidase alfa are thus part of the additional pharmacovigilance activities. In addition, a further study is planned in IOPD patients ⩽6 months naïve to previous treatment with alglucosidase alfa (approximately 16 males and females) and is expected as post-authorisation commitment.

### 3.7.2. Balance of benefits and risks

The proposed indication includes paediatric IOPD and LOPD patients, in first and second line of treatment. Results from the pivotal study in adult LOPD naïve patients showed that avalglucosidase is non-inferior to alglucosidase alfa at a 20 mg/kg dose with an acceptable safety profile. Extrapolation from adult to paediatric **LOPD and IOPD patients** is considered acceptable, since the pathophysiology of the disease, the mechanism of action, and the pharmacokinetic profile of enzyme replacement therapy (ERT) for Pompe Disease are comparable across the whole disease spectrum.

In IOPD patients, the results of study ACT14132 show positive trends in secondary and tertiary efficacy outcomes with avalglucosidase. However, subgroups of patients receiving different concentrations of avalglucosidase alfa in study ACT14132 were very small and clinical response varies greatly between patients. Moreover, beneficial effects are not consistently in favour of patients initially treated with avalglucosidase alfa 40 mg/kg and a clear dose response relationship could not be demonstrated. Thus, a higher starting dose was not recommended by the CHMP. However, for IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week can be considered in the absence of safety concerns.

Overall, based on the submitted data, a positive benefit risk can be concluded for the LOPD and IOPD populations with recommended dose of 20 mg/kg for LOPD and a starting dose of 20 mg/kg with possible increase to 40 mg/kg in IOPD.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable

## 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nexviadyme is favourable in the following indication(s):

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Additional risk minimisation measures**

Prior to the launch of Nexviadyme in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority. The educational program is aimed at increasing the awareness about the immunosurveillance service and to support the correct and safe administration of the product in the home setting.

The MAH shall ensure that in each member state where Nexviadyme is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense and administer Nexviadyme are provided with the following educational package to be disseminated through professional bodies:

- Healthcare professionals (HCPs) guide for immunosurveillance service and

- Home infusion guide for HCPs

Guide for healthcare professionals for Immunosurveillance Service shall include the following key elements:

- Testing recommendations:
  - Baseline serum sample collection prior to the first infusion is strongly encouraged.
  - Immunoglobulin G (IgG) antibody titers should be regularly monitored and IgG anti-drug antibody (ADA) testing should be considered if patients do not respond to therapy.
  - Treated patients may be tested for inhibitory antibodies if they experience a decrease in clinical benefit despite continued treatment with Nexviadyme.
  - Adverse-event-driven immunologic testing, including IgG and Immunoglobulin E (IgE) ADA, should be considered for patients at risk for allergic reaction or previous anaphylactic reaction to Myozyme (alglucosidase alfa).
  - Adverse-event-driven immunologic testing should also be considered in patients who experience moderate/severe or recurrent infusion associated reactions (IARs) suggestive of hypersensitivity reactions, anaphylactic reactions.
- Testing practicalities of the testing service and contact details
  - Description of the testing services: available tests, indication for testing, sample type, Frequency of testing, collection time
  - Procedure for testing: diagram summarizing main steps for HCP requesting Specialty testing services

The Home Infusion guide for HCPs which will serve as training document to HCPs who will perform the infusion at home shall contain the following key elements:

- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.
- Details on the preparation and administration of Nexviadyme, including all the steps of preparation, reconstitution, dilution and administration
- Medical evaluation of the patient prior to administration of the infusion at home
- Information on signs and symptoms related to infusion associated reactions and recommended actions for the management of the ADRs when symptoms occur.

***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that avalglucosidase alfa is not to be qualified as a new active substance in itself.

Based on the review of the available data, the CHMP considers that avalglucosidase alfa in comparison to alglucosidase alfa previously authorised as a medicinal product in the European Union is not to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

Refer to Appendix on new active substance (NAS).

# 5. Re-examination of the CHMP opinion of 23 July 2021

On 23 July 2021, the CHMP concluded that Nexviadyme was not to be qualified as a new active substance (NAS) on the following basis:

Based on the review of the available data, the CHMP considers that avalglucosidase alfa in comparison to alglucosidase alfa previously authorised as a medicinal product in the European Union is not to be qualified as a new active substance in itself as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

Following this negative CHMP outcome on the new active substance claim, the applicant submitted detailed grounds for the re-examination of the negative CHMP conclusions on NAS claim.

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group (AHEG) inviting the experts to provide their views on specific questions related to the CHMP negative conclusions on NAS claim (see section 5.2).

The applicant presented their grounds for re-examination in writing and at an oral explanation (see section 5.1).

The detail of the CHMP's assessment of the Applicant's grounds and the final conclusions of the Committee are presented in section 5.3.

## *5.1. Detailed grounds for re-examination submitted by the applicant*

The submission contains detailed grounds for a request for re-examination of the CHMP opinion of 23 July 2021. The opinion recommends the granting of a marketing authorisation for Nexviadyme (avalglucosidase alfa) for the long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency) but denies new active substance status (NAS) for Nexviadyme (avalglucosidase alfa).

The request for re-examination is limited to the refusal of NAS status. The Applicant states that the detailed grounds contained in the submission demonstrate that Nexviadyme (avalglucosidase alfa) qualifies as a NAS.

The following sections (5.1.1 and 5.1.2) detail the applicant justifications why avalglucosidase alfa complies with the Notice to Applicants (NtA), Annex 1, definition of a NAS for biological substances, ie:

- "a …, biological … substance not previously authorised in a medicinal product for human use in the European Union; [Indent 1]
- …;

- a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process; [Indent 3]".

Tables and Figures are numbered as per applicant's submission.

### 5.1.1. Ground#1: criterion under Indent 1

**Ground #1: Based on the CHMP review of the available data, the CHMP considers that avalglucosidase alfa is not to be qualified as a new active substance in itself.**

The 23 July 2021 NAS assessment report attached to the CHMP opinion, states that in general Indent 1 does not apply because avalglucosidase alfa contains the same "primary molecular structure (amino acid sequence)" as alglucosidase alfa. The Applicant respectfully disagrees with this restrictive approach.

The approach seems to be an analogous application of the principle under the 2015 reflection paper for chemical substances that when an active substance exposes patients to the same therapeutic moiety as an existing product, it will not qualify as a NAS under Indent 1 (but Indent 3 may apply). The standard of same therapeutic moiety for a chemical is here replaced by the same primary molecular structure (of amino acid sequence for a proteinaceous biological active substance). The Applicant maintains that such an extrapolation is not justified.

In 2012 and 2015, the EMA issued two reflection papers on the determination of NAS status for chemical active substances. The papers were first published in draft to obtain comments from interested parties and provide further details on how Annex 1 of the Notice to Applicants can be applied. There is no similar reflection paper on the NAS criteria for biological active substances.

The Applicant submits that where the NAS determination under Indent 1 is not automatically made based on the full molecular structure of avalglucosidase alfa (as suggested by the simple wording of Indent 1), the following principles apply and are not mutually exclusive:

1. The entire structure of the active substance is in any event to be considered under Indent 1 when the added glycans are relevant for the therapeutic function or activity of the molecule. That relevance can be shown in different ways, which may of course overlap:

    a. The added glycans have a biological clinical function or impact. This is clearly supported by precedents. For instance, the EPAR for Rekovelle states:

    "In general, differences in glycosylation profile could only be considered relevant for NAS status, <u>if associated with a primary mode of action and a given function related to the indication</u>. This is not the case for FSH mechanism of action, as there is no impact on potency. Nevertheless, the differences in glycosylation profile might be considered relevant in terms of safety and/or efficacy when assessed at the non-clinical and clinical levels." (emphasis added)

    Similarly, the EPAR for Zinbryta states: "Glycosylation is generally not considered a distinctive attribute unless the primary mode of action is associated to a specific structure and a given function related to the indication." (emphasis added)

The principle that in the specific case of avalglucosidase alfa, enhanced cell uptake is relevant was also recognised during the assessment of the product. The Rapporteur stressed the relevance of significant impact of glycosylation on cellular binding (Rapporteur Day 80 report of 28 January 2021, p. 4-5). Similarly, the Co-Rapporteur invited further data on cell uptake (Co-Rapporteur Day 80 report, p. 7).

The relevance of a clinical function may also have been recognised in the 23 July 2021 NAS assessment report. The quality considerations on page 102 conclude that the glycan modifications are relevant under Indent 1 when they "have a clinical impact in terms of safety or efficacy" but the assessment under Indent 1 is then stopped without considering the impact on the clinical function under that same Indent.

Of course, this is a different test from Indent 3. There is no need under Indent 1 to demonstrate a significant difference in safety or efficacy properties. This is also clearly recognised in the above quoted passage from the Rekovelle EPAR.

b. The added glycans contribute to the biological activity of the active substance. Biological activity is defined as follows:

"The biological activity is the specific ability or capacity of the product to achieve a defined biological effect. Biological assays using different and complementary approaches to measure the biological activity should be considered, as appropriate. Depending on the biological properties of the product, different assay formats can be used (e.g. ligand or receptor binding assays, enzymatic assays, cell-based assays, functional assays), taking into account their limitations."

This makes clear that receptor binding is also relevant.

c. The added glycans in avalglucosidase alfa imply a "relevant difference" with alglucosidase alfa.

This is the criterion that was applied in the EPAR for Qarziba (under the quality aspects):

"It has been the policy of the CHMP that changes in the manufacturing process of a given product, or differences between the manufacturing processes of two different products (e.g. a biosimilar product and its Reference Medicinal Product) do not require a new INN, New Active Substance (NAS) status, and/or another qualification that the two active substances are somehow different. Such a status is only warranted if the differences in manufacturing processes result in relevant differences between the two products."

2. The demonstration of the above-mentioned functionality of the glycans can be based on any relevant data, including in vitro, non-clinical, and clinical data. There is nothing in Annex I that excludes reliance on such data. The evaluation under Indent 1 is thus not purely based on the quality aspects.

The Applicant provides an analysis of avalglucosidase alfa under Indent 1 and concludes that the substance qualifies as a NAS.

#### *5.1.1.1. Rationale for development of avalglucosidase alfa as an intentionally different molecular structure*

For any ERT for Pompe disease to be successful, the enzyme must not only be taken up by the target tissue, but it must be properly trafficked into the lysosome. The role for the CIMPR in lysosomal targeting of endogenous lysosomal proteins from the Golgi apparatus and targeting of exogenous proteins (i.e. ERTs including alglucosidase alfa) is well established. The CIMPR has 3 distinct binding domains that bind mannose-6-phosphate (M6P) moieties on the surface (at N-glycosylation sites) of proteins but the receptor has a much higher affinity for two terminal M6P (bis M6P) compared to a single M6P alone (KD in the nanomolar versus micromolar ranges, respectively).

Alglucosidase alfa has ~1 mol/mol of M6P and only ~10% of this is present as bis M6P, resulting in most of the enzyme having little to no affinity for the CIMPR. It was therefore hypothesized that increasing the amount of M6P, and bis M6P in particular, would result in increased CIMPR binding and subsequent cell uptake and lysosomal targeting. A glycoengineering approach was taken to identify glycan structures that would substantially increase CIMPR binding, cellular uptake and glycogen clearance in GAAKO mice resulting in an ERT significantly more potent than alglucosidase alfa. Such a molecule cannot be produced through manipulation of cell culture methods but is instead produced via chemical conjugation of a synthetic glycan to specifically oxidized sialic acids at the N-linked glycosylation sites present on alglucosidase alfa. The deliberate and methodical design of the oxidation and conjugation processes and the resulting molecule, avalglucosidase alfa, yielded an enzyme with ~15- fold higher M6P levels, almost entirely composed of bis M6P glycans. The conjugated glycans are unique structures which could not be generated through a recombinant biosynthesis process. As expected, this significant increase in bis M6P results in dramatically higher affinity for the CIMPR, significant increase in cellular uptake in vitro, increased potency at clearing glycogen in the GAAKO mouse, and better clinical outcomes and safety profile (including immunogenicity) for Pompe patients.

Given that efficient delivery of ERT to lysosomes is critical for glycogen clearance in Pompe disease, a key factor for significant improvement in therapeutic effect is the presence of sufficient levels of a high affinity glycan on the enzyme. Mutation of the amino acid sequence to alter the enzymatic activity would likely not alter the efficacy of alglucosidase alfa, however increasing the uptake and lysosomal targeting of the enzyme would. Therefore, a glycoengineering approach was taken to optimize CIMPR interaction. Since alglucosidase alfa contains a very low level of M6P (of which only a small fraction is from the higher affinity bis M6P glycan type) and displays low muscle cell uptake activity in vitro and in vivo, a variety of different methods to increase the M6P content was investigated. Broadly, two approaches were taken: (i) to increase the M6P content on alglucosidase alfa produced in culture (using different expression systems, cell lines and cell line engineering); and (ii) to chemically conjugate glycans to the purified alglucosidase alfa. Among those tested, only the enzyme generated using chemical conjugation of bis M6P glycan resulted in a molecule with significantly increased cellular uptake in vitro and enhanced potency at clearing glycogen in vivo. The choice was therefore made to abandon the alternative approach based on the manipulation of the cell culture and to further develop and optimize the glycan structure and conjugation process to generate an enzyme with the greatest cellular uptake.

Multiple glycans were tested, differing in M6P content (mono versus bis), structure (linear versus branched), and chain length, as was the type of linker and conjugation investigated (aminooxy or hydrazide linker to lysine, free cysteine, carbohydrate galactose and sialic acid residues, etc.). These extensive characterization studies revealed not only that 2 terminal M6P (bis M6P) are needed for optimal high affinity CIMPR binding, but that the orientation and length of the conjugated glycan chain are important as well. The results of these

studies led to the selection of glycan E13, a bisphosphorylated hexamannose, conjugated to oxidized sialic acid through its aminooxy linker structure (Figure 5). The complex manufacturing process was also optimized, particularly the conditions for oxidation and conjugation, to reliably generate a molecule with high levels of bis M6P, and thus high affinity for the CIMPR and increased muscle targeting. A summary of the resulting manufacturing process for avalglucosidase alfa is described below.

Avalglucosidase alfa is a modified human acid α-glucosidase (alglucosidase alfa) conjugated with multiple copies of glycan E13, a synthetic bis-mannose-6-phosphate-tetra-mannose glycan (bis M6P). Alglucosidase alfa is the secreted 110 kDa form of the molecule which lacks the signal peptide and contains 896 amino acids and seven asparagine-linked glycosylation sites.

After initial purification of alglucosidase alfa through multiple chromatography and filtration steps, an oxidation step is performed.

The sialic acids on the enzyme are oxidized with periodate before reacting with the reactive group (aminooxy) on the purified synthetic M6P-glycan to obtain the oxime conjugate which defines avalglucosidase alfa.

This conjugation step leads to multiple copied of M6P bearing glycans.
Additional purification, filtration and formulation steps are included after the conjugation to deliver avalglucosidase alfa AS.

#### *5.1.1.2. The N-linked glycan structures of avalglucosidase alfa significantly differ from the N-linked glycan structures of alglucosidase alfa*

As stated above, alglucosidase alfa has 7 N-linked glycosylation sites. Site-specific glycan LC-MS analyses have identified the 3 most prevalent glycoforms at each of these sites for avalglucosidase alfa and alglucosidase alfa (Table 1). The main glycoforms detected for each of these sites are starkly different between alglucosidase alfa and avalglucosidase alfa. Importantly, glycan E13 is conjugated to all 7 N-linked glycosylation sites in avalglucosidase alfa whereas only 2 of these sites have been shown to carry M6P or bis M6P moieties at variable levels in alglucosidase alfa. Complex sialylated N-glycans present on all 7 sites in alglucosidase alfa are exploited as the primary conjugation targets (shown in blue) to achieve the extensive bis-phosphorylation levels on avalglucosidase alfa. This results in the conjugation of at least 7glycans to each molecule of enzyme across the 7 sites (shown in green), redirecting the functional purpose of sialylated N-glycans by this modification to CIMPR binding and cellular targeting. Additionally, to further exemplify the unique aspects of avalglucosidase alfa N-linked glycosylation structure, a more detailed biochemical structure is presented in Figure 7 for the 3 major glycoforms at position Asn-84. Avalglucosidase alfa therefore has at least a 15-fold increase in M6P levels compared to alglucosidase alfa, almost entirely comprised of bis M6P moieties whereas only a small portion of alglucosidase alfa carries a single bis M6P moiety.

#### *5.1.1.3. In vitro data confirm that the glycan structure contributes to the biological activity of avalglucosidase alfa*

As for multiple ERT, the exogenous enzyme needs to be taken up by cells for effective treatment. Avalglucosidase alfa and alglucosidase alfa are both administered as an intravenous infusion. They depend primarily upon the CIMPR for routing to lysosomes to the target muscle cells where they exhibit catalytic activity. Thus, as stated previously as well as emphasized and in the White paper on "why avalglucosidase alfa glycosylation is innovative to support the claim for avalglucosidase alfa as a new active substance for

EMA" written by Gerald F. Cox, MD, PhD and previously submitted within response to D180, the CIMPR plays an essential role in receptor binding, cellular uptake and lysosomal targeting of exogenously administered ERTs for Pompe disease. The addition of multiple copies of the synthetic glycan translates to (i) an increased binding to the CIMPR and (ii) an improved cellular uptake which thus contributes to the biological activity of avalglucosidase alfa and provides a relevant functional difference when compared with alglucosidase alfa.

#### 5.1.1.3.1. Avalglucosidase alfa shows increased binding to the CIMPR compared to alglucosidase alfa

The targeted increase in the presence of bis M6P results in a dramatic increase in affinity of avalglucosidase alfa for the CIMPR when compared to alglucosidase alfa. The affinity of avalglucosidase alfa compared to alglucosidase alfa for the soluble CIMPR (sCIMPR) complex was assessed by affinity chromatography. The sCIMPR was immobilized on a Poros EP resin, which was then custom-packed into an analytical HPLC column. Avalglucosidase alfa and alglucosidase alfa samples were applied to this column and bound protein was eluted with M6P after a short buffer wash. A 4-step elution was used, with increasing concentrations of M6P for each step (0 mM: unbound / 0.26 mM: bound 1 / 0.8 mM: bound 2 / 5 mM: bound 3 / 20 mM: bound 4). Sample elution was monitored via fluorescence detection (Ex: 290nm/Em: 340 nm). Results are recorded as the peak area percentage that does not bind the column (Unbound) and the sum of the percentages of the highest affinity fractions (eluting with 5 and 20 mM M6P, Peaks 3 and 4, respectively). While 67% of alglucosidase alfa does not bind to sCIMPR at all and only 0.4% binds with high affinity, 82% of avalglucosidase alfa binds to sCIMPR with high affinity. Receptor column fractionation studies showed that no mono- or bis-phosphorylated glycans are present on alglucosidase alfa recovered from the unbound column fraction. These data demonstrate that the high levels of bis M6P on avalglucosidase alfa result in a drastic increase in high affinity CIMPR binding compared to alglucosidase alfa.

#### 5.1.1.3.2. Avalglucosidase alfa shows an increased cellular uptake when compared with alglucosidase alfa

The increased affinity for the CIMPR results in increased cellular uptake as demonstrated by cellular uptake assays in L6 myoblasts and Pompe fibroblasts.

The increase in cellular uptake was first demonstrated in L6 myoblasts during the early development of avalglucosidase alfa where a 20-fold increase in uptake was observed. Saturation of the CIMPR, which limits cellular uptake, is achieved at much lower doses for avalglucosidase alfa than for alglucosidase alfa (Figure 9 -). In these studies, maximal uptake of alglucosidase alfa is never achieved due to the high concentrations required to reach saturation, as measured by enzyme activity within cells. The increased affinity of avalglucosidase alfa for the CIMPR translates into dramatically higher cellular uptake, and thus saturation of the CIMPR. L6 myoblast uptake was also one of the criteria for glycan selection during the glycoengineering of avalglucosidase alfa. In those studies, avalglucosidase alfa (β-SAM6) was compared with other glycan conjugates in addition to alglucosidase alfa (rhGAA). Avalglucosidase alfa demonstrated the greatest cellular uptake with an approximately 15-fold increase compared to alglucosidase alfa, demonstrating maximal activity at much lower dosing to the cells (Figure 10). These initial studies demonstrate that the conjugation of bis M6P bearing glycans results in a significant increase in cellular uptake.

*Figure 9 - L6 myoblast cellular uptake of avalglucosidase alfa (filled circles) and alglucosidase alfa (open squares)*

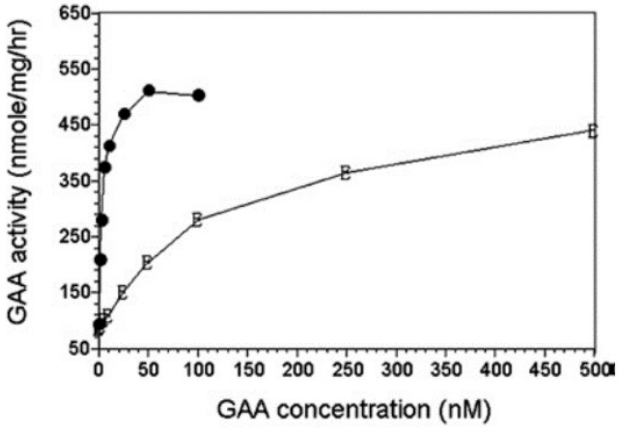
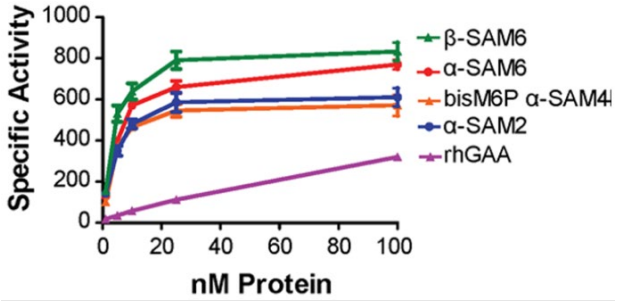



*Figure 10 - Cellular uptake assay comparing alglucosidase alfa (rhGAA) to avalglucosidase alfa (β-SAM6) and various other glycan conjugates (2)*




The effect of increasing levels of conjugated bis M6P on cellular uptake was further investigated in Pompe fibroblast cells using alglucosidase alfa conjugated with increasing amounts of glycan E13 (see module 3.2.S.3.1). The unconjugated material (alglucosidase alfa GZ-24) was used as a comparator (Figure 11 and Table 3). Increasing the number of conjugated glycans (up to 5) significantly increases cellular uptake in this assay (each conjugated glycan represents 2 moles/mole M6P and 1 mole/mole bis M6P). Note that maximal uptake is observed in these experiments from conjugated bis M6P levels which are more than 15-fold higher than those found on alglucosidase alfa (3 moles/mole conjugated bis-M6P on avalglucosidase alfa versus 0.2 moles/mole bis-M6P on alglucosidase alfa).

*Figure 11 - Cellular uptake assay with increasing glycan levels*

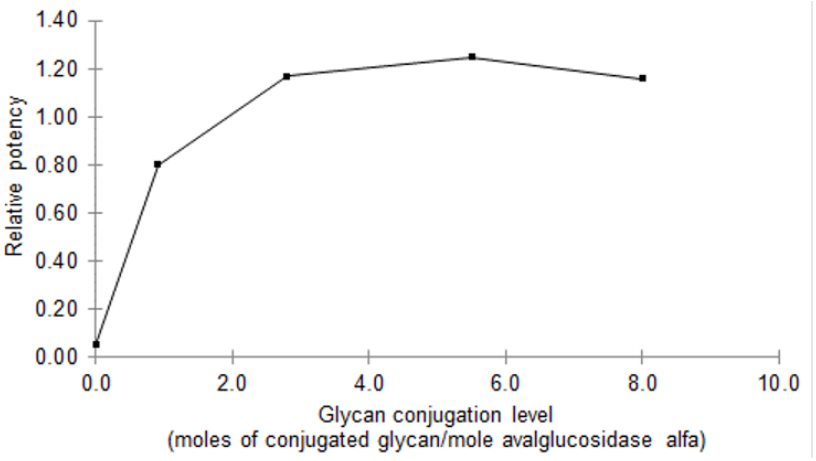


*Table 3 - Summary of relative potency values obtained from three plates of the cellular uptake assay*

| Lot Number | Plate 1 | Plate 2 | Plate 3 | Average | SD | %CV |
|---|---|---|---|---|---|---|
| GZ-24 | 0.05 | ND | 0.05 | 0.05 | 0.00 | 0.00 |
| 2x glycan/alglucosidase alfa molar conjugation ratio | 0.82 | 0.77 | 0.80 | 0.80 | 0.03 | 3.16 |
| 5x glycan/alglucosidase alfa molar conjugation ratio | 1.23 | 1.09 | 1.19 | 1.17 | 0.07 | 6.16 |
| 7x glycan/alglucosidase alfa molar conjugation ratio | 1.19 | 1.23 | 1.32 | 1.25 | 0.07 | 5.43 |
| 12x glycan/alglucosidase alfa molar conjugation ratio | 1.14 | 1.10 | 1.25 | 1.16 | 0.08 | 6.68 |
| Abbreviations: ND, not determined; SD, standard deviation; % CV, percent coefficient of variation | | | | | | |

Cellular uptake of avalglucosidase alfa and alglucosidase alfa was also directly compared in Pompe fibroblasts (Table 4). Results for total M6P content for these samples and estimated bis M6P content (theoretical) are included for reference. Relative cellular uptake was determined as the ratio of the EC50 of the assay standard divided by the EC50 of the sample. Avalglucosidase alfa was shown to be 9-10 times more potent than alglucosidase alfa in this assay (see module 3.2.S.3.1).

*Table 4 - Relative potency (EC50 reference/EC50 sample) of avalglucosidase alfa and alglucosidase alfa*

| Sample | Relative Potency | M6P content (moles/mole) |
|---|---|---|
| Alglucosidase alfa (GZ-31) | 0.1 | 0.9* (~0.2 moles/mole bisM6P) |
| Avalglucosidase alfa (GZ-36) | 0.9 | 14.9* (~7 moles/mole bisM6P) |
| *Average of 5 results of GZ-31 or GZ-36 primary standard qualification. | | |

These data establish the relationship between increasing bis M6P glycans and cellular uptake in vitro.

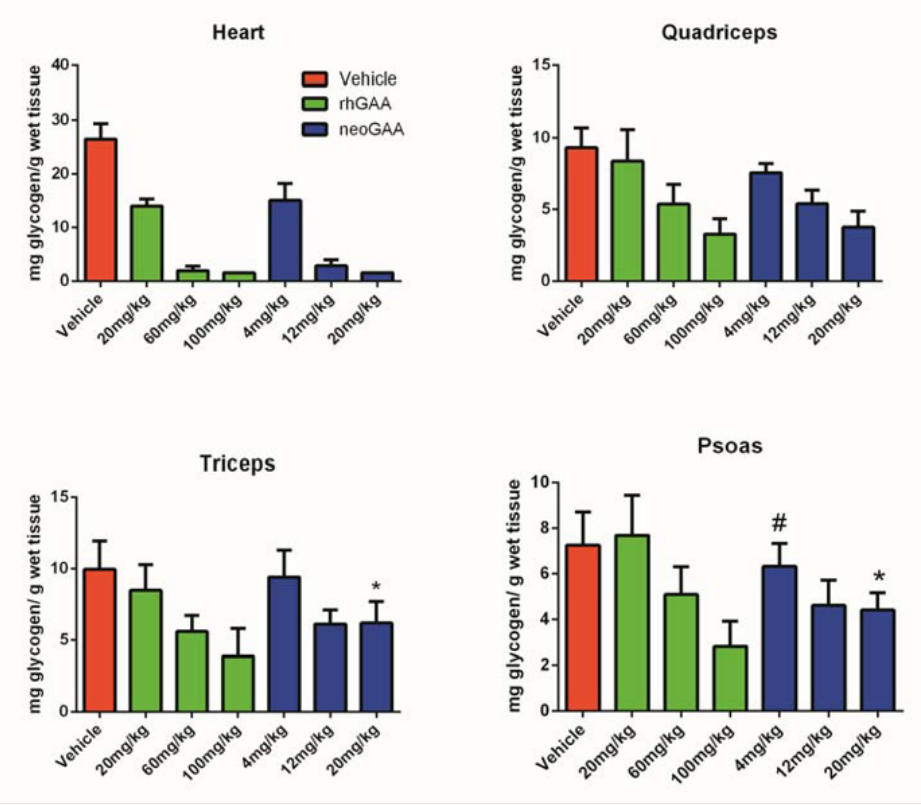
#### *5.1.1.4. Non-clinical data confirmed improved therapeutic impact of the glycan structure of avalglucosidase alfa compared to alglucosidase alfa*

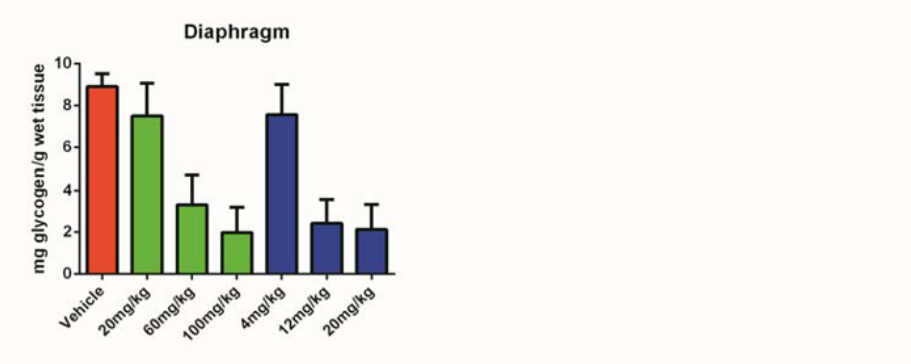
The biological functionality of the glycan structure is clearly confirmed by the pharmacodynamic and functional differences observed in a mouse model. In particular, nonclinical studies conducted in GAA knockout (GAAKO) mice have shown that avalglucosidase alfa is 3 to 7-fold more potent at reducing glycogen than alglucosidase alfa (section 4.3.1). Moreover, long-term avalglucosidase alfa administration results in significant improvement in motor function when compared with alglucosidase alfa in animal models (section 4.3.2). Therefore, the addition of the synthetic glycan provides a relevant difference with regard to the functionality of avalglucosidase alfa when compared with alglucosidase alfa.

#### 5.1.1.4.1. Avalglucosidase alfa is 3 to 7-fold more potent than alglucosidase alfa as measured by glycogen depletion in GAAKO mice

The pharmacodynamic effect of avalglucosidase alfa was evaluated in nonclinical studies in GAAKO mice. These mice lack GAA enzyme activity and accumulate glycogen in a manner similar to the human disease. In two studies, Studies 07-1948 and 10-00587, GAAKO mice were administered four weekly doses of avalglucosidase alfa at 4, 12 or 20 mg/kg or alglucosidase alfa at 5-fold higher doses of 20, 60 or 100 mg/kg. Glycogen content was assayed biochemically in the heart, diaphragm and other skeletal muscles and confirmed histologically in the heart and quadriceps. As shown in Figure 12, treatment with 20 mg/kg avalglucosidase alfa was ~ 5-fold more potent at reducing glycogen levels in the heart, diaphragm and quadriceps compared to 20 mg/kg alglucosidase alfa. In these tissues, treatment with 4 mg/kg avalglucosidase alfa resulted in glycogen levels similar to treatment with 20 mg/kg alglucosidase alfa. Following treatment with 20 mg/kg avalglucosidase alfa, heart glycogen levels were reduced to below the lower limit of quantitation of vehicle controls whereas treatment with 20 mg/kg alglucosidase alfa resulted in a reduction to only 53% of vehicle controls (Table 5). A similar increase in pharmacodynamic effect was observed in the quadriceps (40.3% versus 89.8%) and diaphragm (24.0% versus 84.2%) following treatment with 20 mg/kg avalglucosidase alfa compared to alglucosidase alfa, respectively. These data demonstrate that avalglucosidase alfa is ~5-fold more potent at reducing glycogen levels in the heart, diaphragm and quadriceps of GAAKO mice.

*Figure 12 - Glycogen content in tissues (mean + SD) following 4-weekly doses of avalglucosidase alfa (neoGAA) or alglucosidase alfa (rhGAA) to GAAKO mice (Study 10-00587)*






*p≤0.05 compared to 100mg/kg alglucosidase alfa.
# p≤0.05 compared to 20mg/kg alglucosidase alfa.

*Table 5 - Glycogen content as percent of vehicle controls (Study 10-00587)*

| | Heart | Quadriceps | Triceps | Diaphragm | Psoas |
|---|---|---|---|---|---|
| Alglucosidase alfa (20 mg/kg) | 52.9 | 89.8 | 85.3 | 84.2 | 106.0 |
| Avalglucosidase alfa (20 mg/kg) | 5.7* | 40.3 | 62.2 | 24.0 | 60.9 |

*, this represents the lower limit of quantitation of the assay of 1.5 mg/g wet tissue weight.

Glycogen depletion in the psoas and the triceps was not as efficient and shows greater variability (between animals and studies) than in the heart and other skeletal muscles in GAAKO mice administered avalglucosidase alfa or alglucosidase alfa. A plateau effect is observed in both tissues at higher doses of avalglucosidase alfa. This may be a result of the lower relative expression of the CIMPR in predominantly Type II muscle fibers (21, 22, 23). Despite this plateau effect, avalglucosidase alfa is ~3-fold more potent than alglucosidase alfa in these tissues, with significant glycogen reduction observed at 12 mg/kg avalglucosidase alfa (Figure 12).

The pharmacologically active dose (PAD) for avalglucosidase alfa is 4 mg/kg in the heart whereas the PAD for alglucosidase alfa is 20 mg/kg. In all other tissues, the PAD for avalglucosidase alfa is 12 mg/kg compared to 60 mg/kg for alglucosidase alfa. These data, together with the data from Study 07-1948, demonstrate that avalglucosidase alfa is 3 to 7-fold more potent than alglucosidase alfa as measured by glycogen depletion in the GAAKO mice.

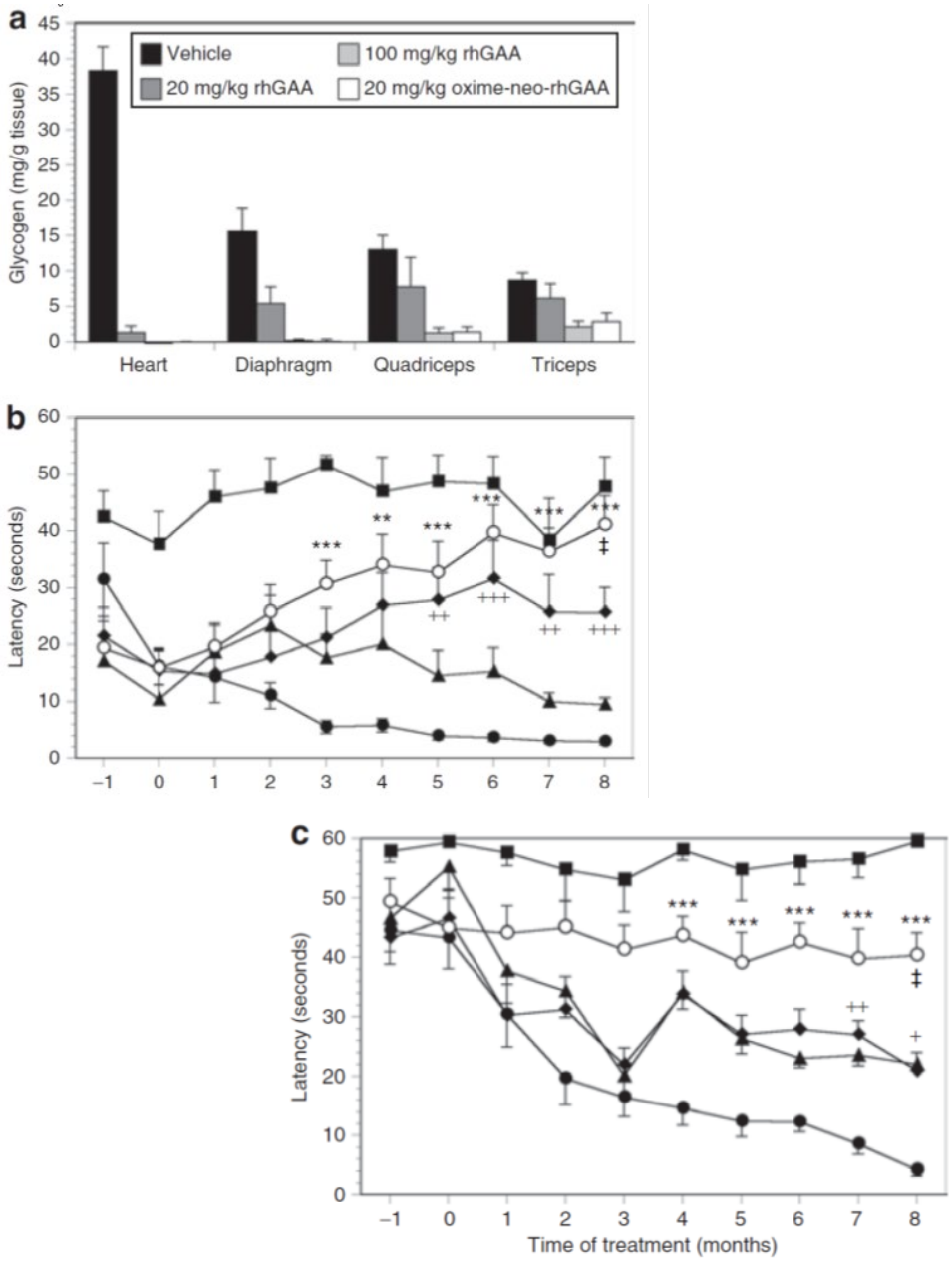
A third study in GAAKO mice evaluated the relationship of the number of conjugated glycans on avalglucosidase alfa to the extent of glycogen clearance in skeletal muscles (Study 09-3981). Animals were administered 4 weekly doses of 20 mg/kg avalglucosidase alfa with 2, 3, 4, 5 or 7 glycans per molecule, or 100 mg/kg alglucosidase alfa. Though a dose dependent relationship between cell uptake and the number of glycans on avalglucosidase alfa was observed in vitro, such a relationship between glycan number and extent of glycogen clearance was not observed at glycan levels of greater than 3 in vivo. Glycogen clearance was similar between cohorts administered avalglucosidase alfa with 3 or more glycans and animals treated with a 5-fold higher dose of alglucosidase alfa, further supporting the increased potency of avalglucosidase alfa over alglucosidase alfa. The plateau effect may be related to saturation of the CIMPR with this dosing regimen. This is supported by the short serum half-life for avalglucosidase alfa (~ 30 minutes) and alglucosidase alfa (~2 hours) which may not allow for receptor recycling to the plasma membrane during this timeframe. As in the previous studies, lower glycogen levels were observed in tissues with higher Type I muscle fibers (i.e. quadriceps and diaphragm). Though the effect is not equally penetrant, the totality of the nonclinical data

from GAAKO mice demonstrates that the unique structure of avalglucosidase alfa results in significantly better glycogen clearance compared to alglucosidase alfa.

#### 5.1.1.4.2. Avalglucosidase alfa treatment significantly improved motor function compared with alglucosidase alfa as measured by rocking rotarod and wire hang tests in GAAKO mice

Previous work has shown that long-term administration of avalglucosidase alfa to GAAKO mice resulted in significant improvement in motor function. Animals 5.5 months of age were administered 20 mg/kg avalglucosidase alfa, or 20 mg/kg or 100 mg/kg alglucosidase alfa every other week for 8 months. Glycogen content was measured at the end of the 8 months, demonstrating comparable clearance in animals treated with 100 mg/kg alglucosidase alfa and 20 mg/kg avalglucosidase alfa (Figure 13a). Animals were subjected to rocking rotarod and wire hang tests once a month during the study. GAAKO mice treated with 20 mg/kg avalglucosidase alfa performed substantially better in both tests (Figure 13b, c). Significant increases in rotarod performance were observed after 3 months of treatment and by 7 months the animals treated with avalglucosidase alfa performed as well as age-matched wild type mice. Animals administered 100 mg/kg alglucosidase alfa showed marked improvement in rotarod performance but not to the same extent as the avalglucosidase alfa group (at a five-fold lower dose). Similar results were observed in the wire hang test where treatment with avalglucosidase alfa prevented functional decline throughout the study. Animals administered 20 mg/kg or 100 mg/kg alglucosidase alfa displayed a significant decline in latency in the wire hang test over time. Therefore, the ~5-fold increase in potency of avalglucosidase alfa over alglucosidase alfa as measured by glycogen clearance is correlated with a greater than 5-fold improvement in motor function in GAAKO mice. This may seem paradoxical but note that glycogen content was only measured at the end of 8 months of treatment and represents the steady state level of maximal glycogen depletion at these doses. This does not reflect the length of time that it took to reach that steady state. The increased potency of avalglucosidase alfa, as a result of increased CIMPR binding, cellular uptake, and lysosomal targeting, leads to a faster depletion of glycogen which in turn has a stronger impact on preventing further muscle damage. This is best displayed by the wire hang tests where function is maintained with 20 mg/kg avalglucosidase alfa but decays with 100 mg/kg alglucosidase alfa.

*Figure 13 - Glycogen content (a) and assessment of motor coordination and muscle strength after enzyme therapy of young GAAKO mice by rocking rotarod (b) and wire hang (c) tests*



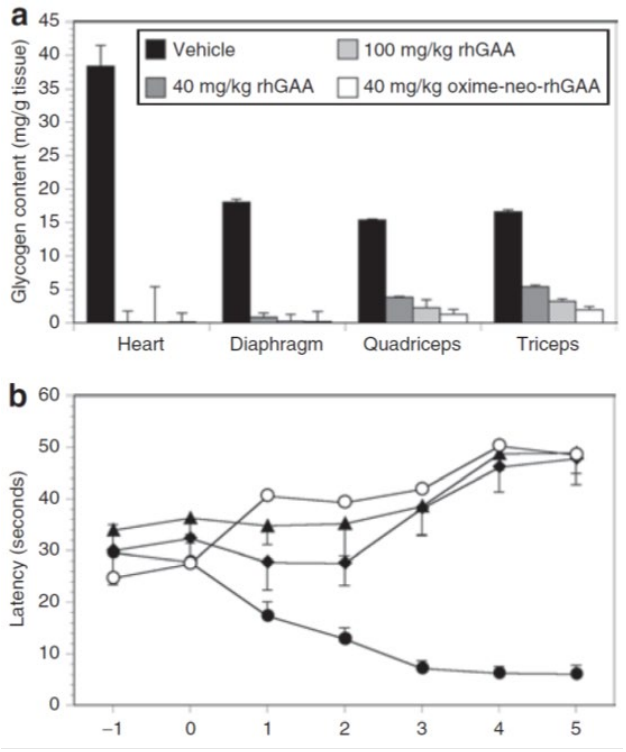

Zhu Y et al., Mol Ther. 2009 Jun;17(6):954-63.

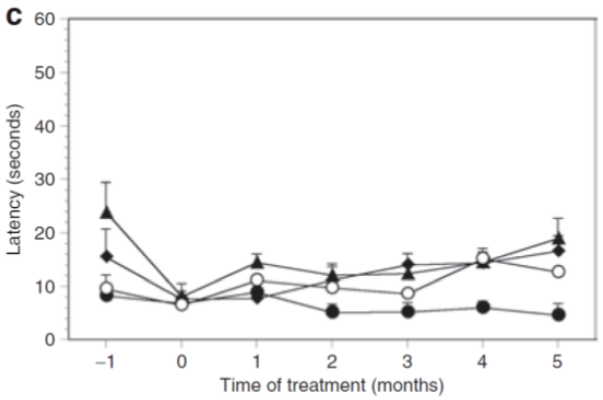
GAAKO mice treated with vehicle (closed circle), 20 mg/kg alglucosidase alfa (closed triangle), 100 mg/kg alglucosidase alfa (closed diamond), and 20 mg/kg avalglucosidase alfa (open circle) were tested monthly. Statistical analyses were performed between vehicle and enzyme-treated groups (vehicle versus 20 mg/kg avalglucosidase alfa, *P<0.05, **P<0.01, and ***P<0.001; vehicle versus 100 mg/kg alglucosidase alfa, +P<0.05, ++P<0.01, +++P<0.001), as well as between avalglucosidase alfa and alglucosidase alfa treated groups (P<0.01) for each timepoint. Data are presented as means ± SEM. Age-matched wild type mice as control group are indicated with closed squares.

The importance of clearing accumulated glycogen quickly and early was also demonstrated by a second long-term study in which 11-month old GAAKO mice were administered 40 mg/kg avalglucosidase alfa or 40 mg/kg or 100 mg/kg alglucosidase alfa weekly for 5 months. More frequent dosing and a higher avalglucosidase alfa dose were used because previous studies had demonstrated that older GAAKO mice were refractory to treatment compared to younger mice, (25)(23), likely as a result of accumulated muscle damage. As in the previous study in which younger mice (5.5 months) were evaluated following treatment, animals were subjected to rocking rotarod and wire hang tests once a month during the study (Figure 14).

Though all ERT treated groups made similar gains in function by the end of the study, the mice administered avalglucosidase alfa displayed a more rapid gain of muscle function in the rocking rotarod test compared to alglucosidase alfa treated mice. Only modest improvements in latency in the wire hang tests were seen in any group administered ERT suggesting the presence of significant irreversible muscle damage at the time of treatment initiation. Indeed, progressively higher levels of degeneration and regeneration, as measured by central localization of nuclei in the myofiber, were observed in GAAKO mice as a function of age (24). Little reduction in the number of centralized nuclei were observed in older GAAKO mice following weekly treatment with 40 mg/kg avalglucosidase alfa or 40 mg/kg or 100 mg/kg alglucosidase alfa (Figure 15a). However, a significant reduction was observed in younger mice administered 20 mg/kg avalglucosidase alfa or 100 mg/kg alglucosidase alfa every other week for 6 months (Figure 15b). These results correlate with the muscle function data, suggesting that glycogen clearance in younger mice leads to less muscle damage and better functional outcomes. These observations further substantiate the dogma that "earlier is better" with regard to initiating ERT. The earlier and faster that glycogen is cleared from the muscle, the more function is maintained, or can even be regained. With an early treatment start (5.5 months of age versus 11 months of age), as a result of a more rapid and effective clearance of glycogen by avalglucosidase alfa over alglucosidase alfa, avalglucosidase alfa is >5 times more effective at preserving muscle function compared to alglucosidase alfa in GAAKO mice.

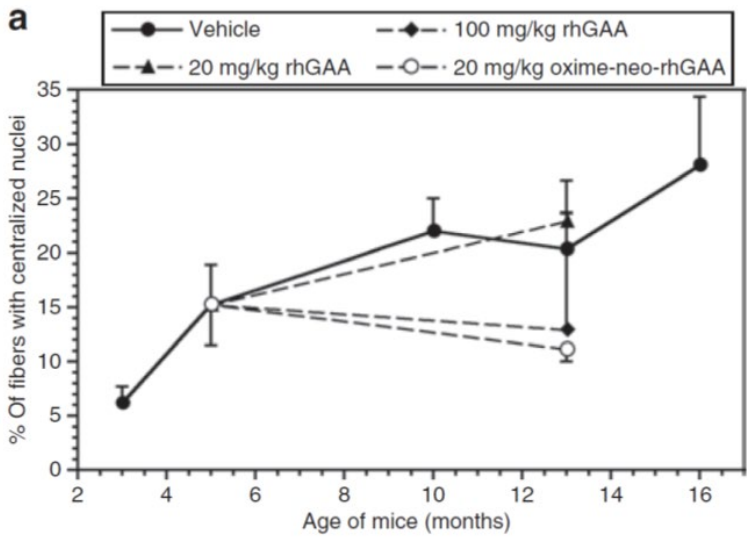
*Figure 14 - Glycogen content (a) and assessment of motor coordination and muscle strength after enzyme therapy of older, symptomatic GAAKO mice by rocking rotarod (b) and wire hang (c) tests*

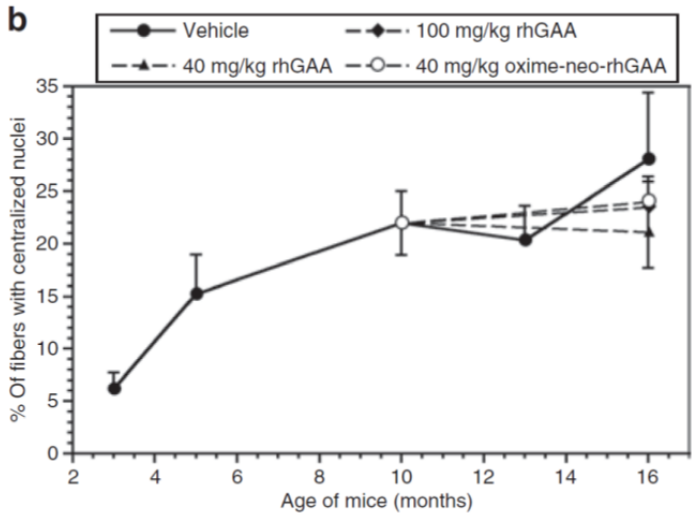





Zhu Y et al., Mol Ther. 2009 Jun;17(6):954-63.
GAAKO mice treated with vehicle (closed circle), 40 mg/kg alglucosidase alfa (closed triangle), 100 mg/kg alglucosidase alfa (closed diamond), and 40 mg/kg avalglucosidase alfa (open circle) were tested monthly. Data are presented as means ± SD.

*Figure 15 – Extent of degeneration and regeneration in GAAKO mouse muscle treated at 5.5 months (a) or 11 months (b) of age*






Zhu Y et al., Mol Ther. 2009 Jun;17(6):954-63.

Hematoxylin and eosin stained sections from three animals of each treatment group (at each time point) was scored for the number of myofibers harboring centralized nuclei. For each animal, 1,000-3,500 muscle fibers from different fields were examined. The results illustrated in figure a were from GAAKO mice treated every other week starting at 5.5 months of age and those in figure b were treated weekly starting at 11 months of age. Dashed lines represent the time periods the animals were treated. Data are presented as means ± SD.

The Applicant concludes that the provided evidence and discussion demonstrate that avalglucosidase alfa qualifies as a new active substance under Indent 1. Avalglucosidase alfa cannot be considered as a substance previously authorised in the EU for the following reasons: (i) avalglucosidase alfa is conjugated with multiple copies of glycan E13, a synthetic bis-mannose-6-phosphate-tetra-mannose glycan (bisM6P) and (ii) the N-linked glycan structures of avalglucosidase alfa significantly differ from the N-linked glycan structures of alglucosidase alfa. Since the (bis)M6P-bearing N-glycans enable binding to CIMPR, cellular uptake and lysosomal trafficking of rhGAA (steps that are a prerequisite for the functioning of the enzyme), they should be taken into account when assessing whether there are structural differences between avalglucosidase alfa and alglucosidase alfa

#### *5.1.1.5. The new active substance status is further confirmed by the orphan medicines principles on similarity*

The Applicant argues that the principles that apply for assessing similarity of medicines for purposes of the orphan medicines rules (and in particular the scope of the market exclusivity for orphan medicines), confirm the conclusion that avalglucosidase alfa is a NAS under Indent 1. The definition of similarity was further defined in 2018 to take into account the specific aspects of biological products. The revised Commission Regulation 847/2000 provides (in Article 3(3)(c)):

"(2) Biological medicinal products (other than advanced therapy medicinal products)

The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of that substance. The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element(s) significantly contributing to the functional characteristics of the active substance.

Such an additional structural element(s) can be conjugated, fused or linked by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids. …

(2.1) Proteinaceous substances:

If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) substances shall normally be considered similar. However, exceptionally some post-translational modifications may result in a non-similar substance if there is significant effect on the functional characteristics of the substance. If the difference in the amino acid sequence is not major, substances shall normally be considered similar.

Therefore, two pharmacologically related protein substances of the same group (for example, having differences related to e.g. N-terminal methionine, naturally extracted versus rDNA-derived proteins or other minor variants) shall normally be considered similar. However, the addition of a structural element may result in substances being considered non-similar if this significantly affects the functional characteristics of the substance."

These rules show that:

- For purposes of similarity, the "structural components of an active substance that are relevant for the functional characteristics of that substance" constitute the "principal molecular structural features."
- The principal molecular structure can include glycans when they contribute to the functional characteristics, for instance by improving binding capacity.

This was confirmed by the CHMP during the Protocol Assistance when the Applicant sought advice on orphan similarity in the context of a parallel development of an ERT for Pompe disease by a competitor (i.e., BMN-701). The advice that was provided in November 2015 states:

"It is acknowledged that the cation-independent mannose-6-phosphate receptor (CIM6Pr) plays an essential role in cellular binding, uptake and lysosomal targeting of exogenously administered alglucosidase alfa. As such, the molecule structures relevant for cellular binding should be taken into account as they can be considered important functional elements relevant to the MoA.

It thus might be concluded that the PMSF [principal molecular structural features] of BMN-701 and NeoGAA comprise, in addition to the parts responsible for enzymatic activity, those parts of the BMN-701 and NeoGAA molecule that bind the CIM6Pr."

and

"Based on the information presented, molecular structural differences in those parts of the BMN-701 and neoGAA which comprise the PMSF (particular to the functional elements responsible for receptor binding) are apparent, and this could be argued to be an acceptable basis to claim, in a future MAA, non-similarity in the context of the Orphan Regulation."

The Applicant fully recognizes that the principles of similarity under the orphan medicines rules do not directly apply to a NAS determination. Both assessments, however, relate to regulatory exclusivities that are intended to stimulate the development of new medicines. If one regime does not consider a product "similar", then it is hard to see how it could be deemed to be the "same" under the other regime that has a similar objective. And the standard for being considered the same (and thus denying NAS status) must also logically speaking be stricter than for similarity.

#### *5.1.1.6. The new active substance status is further confirmed by the EU principles governing biosimilar medicinal products*

The Applicant argues that, the NAS status is reviewed in the context of the global marketing authorisation concept, which itself is part of the regime on data and marketing protection for new medicines under Article 10 of Directive 2001/83 and Article 14(11) of Regulation 726/2004. Article 10 includes (in par. 2) the specific passage on different salts, esters, etc., which is the legal basis for the 2015 reflection paper on the NAS determination for chemical active substances (see section 3.2). Article 10 also includes in par. 4 the specific rule on similar biological medicines ("biosimilars"). To maintain consistency in the regulatory approach, it is thus also necessary to take into account the principles on biosimilars when making a NAS assessment for a biological active substance.

The current EMA guideline on similar biological medicinal products (CHMP/437/04 Rev 1) states that "intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach." Therefore, avalglucosidase alfa could not be considered as a biosimilar of alglucosidase alfa, and this should also be taken into account when assessing the NAS status. As the glycan structure is clearly added "to improve efficacy" through improved cellular uptake, the Applicant submits that also on that ground avalglucosidase alfa qualifies as a NAS.

#### *5.1.1.7. The new active substance status is further confirmed by the INN recommended by WHO and its ATC code classification of avalglucosidase alfa*

The Applicant argues that supporting the novelty of avalglucosidase alfa, the WHO approved 'avalglucosidase alfa' as a separate INN and did not designate an INN that would merely reflect differences in glycosylation profiles (e.g., "alglucosidase beta"). Each INN is a unique name that is in principle selected only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula).

In April 2021, the WHO International Working Group for Drug Statistics Methodology adopted a proposed Anatomical Therapeutic Chemical (ATC) Code for avalglucosidase alfa. The proposal is to classify avaglucosidase alfa under code A16AB22. This is different from the established classification of alglucosidase alfa under code A16AB07.

The deadline for objections to this separate classification expired on 1 September 2021. To the Applicant's best knowledge, the EMA and the European Commission have not submitted any objections.

The ATC coding system allows for classification of the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. It provides an aid to drug utilization monitoring and research.

The ATC classification is not an assessment of the safety or efficacy properties of an active substance. The ATC guidelines clearly state that "[t]he classification of a substance in the ATC/DDD system is … not a recommendation for use and it does not imply any judgements about efficacy or relative efficacy of drugs and groups of drugs.". The classification is thus not relevant under indent 3 for the NAS determination. The fifth level of the ATC code, however, is based on the chemical aspects (also of biological active substances) and is thus relevant for the NAS determination under indent 1. It follows that the separate ATC classification for avalglucosidase alfa at the fifth level confirms the NAS status under indent 1.

#### *5.1.1.8. The principles under the variation regulation confirm the new active substance status*

According to the Applicant, in the absence of clear guidance on how the NAS status of a biological active substance must be assessed, it is necessary to also take into account the standard for extensions under the variation's rules. The Applicant argues that the NAS review occurs in the context of the global marketing authorisation rule. The EU Court of Justice has held that the terms "any variations and extensions" under that rule refer to a "variation to the terms of [an MA]" or an "extension of [an MA]" within the meaning of the Variations Regulation 1085/2003. The Variations Regulation (now Regulation 1234/2008) must thus also be taken into account when assessing the NAS status.

This means that for assessing the NAS status of avalglucosidase alfa, it is relevant to consider whether replacing alglucosidase alfa with avalglucosidase alfa could meet the conditions for an extension of the Myozyme marketing authorisation under Annex I to Regulation 1234/2008. This would require demonstration of compliance with point 1 (c) in Annex I on line extensions:

"replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different"

Both conditions must be demonstrated by the applicant for the extension approval and cannot be presumed. Conversely, there can also not be a presumption that a biological active substance that has a different molecular structure does not qualify as a NAS. In addition, any change in the active substance that is more than "slight" will be sufficient to support a NAS finding under Indent 1. The Applicant concludes that the submitted discussion clearly demonstrates that there are important differences in molecular structure between avalglucosidase alfa and alglucosidase alfa and that they cannot be considered merely "slight".

### 5.1.2. Ground #2: criterion under indent 3

**Ground #2: Based on the review of the available data, the CHMP considers that avalglucosidase alfa in comparison to alglucosidase alfa previously authorised as a medicinal product in the European Union is not to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.**

The Applicant argues that as outlined above, the differences in molecular structure have a clinical function and demonstrated a meaningful impact on immunogenicity of Nexviadyme in LOPD patients in the EFC14028 trial, as well as on clinical outcomes in IOPD patients who showed incomplete clinical response to Myozyme.

In the following sections, the Applicant summarizes protocol-prespecified as well as post-hoc analyses of the available clinical data including long-term outcome data in LOPD demonstrating sustained and durable benefits.

The Applicant considers that, although Nexviadyme narrowly missed statistical significance for superiority in the primary endpoint of the pivotal study EFC14028 (COMET), the totality of data provides sufficient indications that there is a significant difference in safety and/or efficacy with Nexviadyme treatment as compared to Myozyme. The increased potency of Nexviadyme was demonstrated clinically by consistent, substantial and relevant improvements on meaningful efficacy outcome measures for Pompe patients, as well as by a more favorable safety and immunogenicity profile of Nexviadyme compared to Myozyme. Thus, also on that basis alone Nexviadyme could qualify as a NAS.

Overall, the applicant position is that Nexviadyme demonstrated clinically meaningful differences in LOPD.

### *5.1.2.1. Primary endpoint- forced expiratory volume (FVC)*

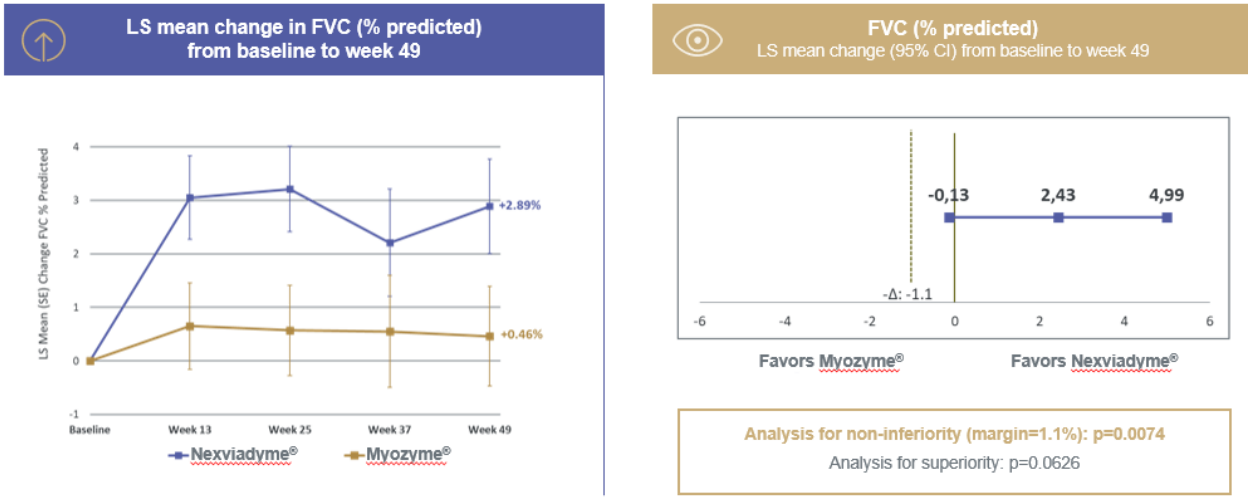
#### *5.1.2.1.1.* Main Analysis- Primary Endpoint (FVC)

EFC14028 is a pivotal Phase 3 head-to-head study comparing avalglucosidase alfa (Nexviadyme) to alglucosidase alfa (Myozyme) in LOPD patients. In agreement with the Regulatory Agencies, the study EFC14028 was set up to primarily demonstrate non-inferiority (NI) on the primary endpoint of %predicted FVC, then further test for superiority once NI has been demonstrated.

Forced vital capacity (FVC) is a respiratory outcome variable that is readily obtainable in the clinical setting and commonly reported in studies pertaining to LOPD patients. FVC decline was observed to be associated with an increased incidence of respiratory complications and death. In LOPD, a patient-level data meta-analysis has demonstrated that FVC is associated with numerous outcome measures and the progression in FVC is associated with changes in exercise tolerance, peripheral muscle strength and health-related quality of life. Improvement in FVC is positively associated with a variety of other LOPD measures and outcomes across multiple domains including endurance (6MWT), skeletal muscle strength and patient-reported outcomes (SF-36) (Lachmann and Schoser, 2013). Therefore, FVC is the appropriate choice as a primary endpoint to measure the clinical difference between Nexviadyme and Myozyme.

In the mITT population, the LS mean change (SE) from baseline to Week 49 in % predicted FVC was 2.89 (0.88) in the Nexviadyme group and 0.46 (0.93) in the Myozyme group. The difference of 2.43 with lower boundary of 95% CI of -0.13 exceeded -1.1 (the predefined NI margin of 1.1) and thus achieved statistical NI (p=0.0074) and the primary study objective). Upon further testing for superiority, the endpoint barely missed formal statistical superiority (p=0.0626), while the observed effect is numerically greater and clinically meaningful (Figure 25).

*Figure 22 - Nexviadyme® demonstrated a clinically meaningful improvement in % predicted FVC*




CI, confidence interval; FVC, forced vital capacity; LS, least squares; SE, standard error.
The nominal p-values for pre-specified sensitivity analyses for superiority ranged between 0.0174 and 0.1377; p=0.0174 for the non-parametric Wilcoxon-Mann-Whitney test

In a large study in patients with another restrictive respiratory disease, idiopathic pulmonary fibrosis (IPF), the minimal clinically important difference (MCID) of FVC was defined as 2 to 6% (equivalent to a 3 to 9% relative change) and it was concluded that changes from baseline in % predicted FVC reflected changes in

global health status (du Bois et al, 2011). In the majority of studies of alglucosidase alfa treatment, patients who had a change in FVC within or above the MCID range that was established for IPF, also reported a noticeable perceived improvement (Lachmann and Schoser, 2013).

In Pompe disease, impaired FVC is associated with an increased incidence of respiratory complications and death. A patient-level data meta-analysis has demonstrated that FVC is associated with numerous LOPD outcome measures and the progression in FCV is a respiratory outcome variable that is readily obtainable in the clinical setting and commonly reported in studies pertaining to LOPD patients. Improvement in FVC is positively associated with a variety of other LOPD measures and outcomes across multiple domains including endurance (6MWT), skeletal muscle strength and patient-reported outcomes (SF-36) (Berger et al, 2019).

That was also observed in study EFC14028 as the improvement in FVC is associated with clinically meaningful improvement in other parameters of respiratory function, ambulation, motor function and health-related quality of life (HRQoL). The improvement in FVC observed with Nexviadyme is therefore clinically meaningful from the patient's perspective, and the difference compared with Myozyme is also clinically meaningful and very close to the pre-specified 5% significance level for statistical superiority.

#### 5.1.2.1.2. Subgroup analysis - primary endpoint (FVC)

Pre-specified subgroup analyses results were observed to be consistent regardless of gender, age and regions (Figure 26). Consistent improvements were also observed in the global population of mainly adult patients and the 2 pediatric patients with LOPD included in the study (Table 33). This demonstrates the robustness of the improvement observed along the spectrum of clinical presentations, despite the variability inherent to the disease.

*Figure 23 - Forest Plot of FVC (% Predicted) - in upright position change from baseline at Week 49 for subgroup analyses - mITT population*

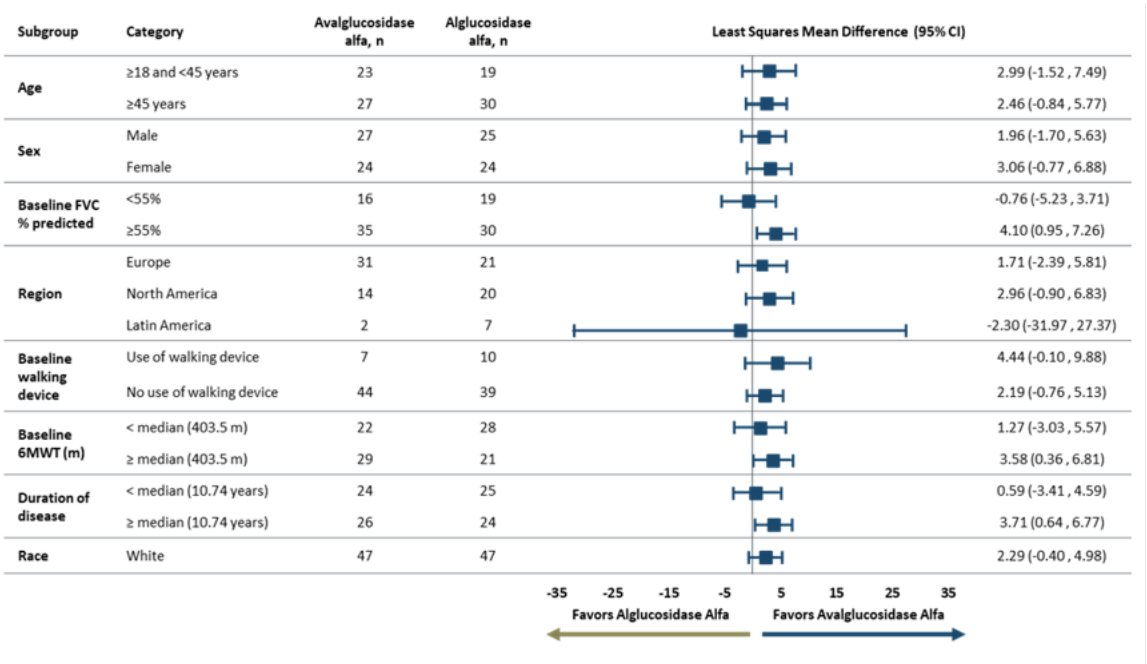


*Table 28 - FVC (% Predicted) - in upright position in Nexviadyme arm – full populations and pediatric patients*

| Patient ID | Age (year) | Baseline | Week 25 | | Week 49 | |
|---|---|---|---|---|---|---|
| | | Observed value | Observed value | % change from baseline | Observed value | % change from baseline |
| All (N=51) Mean (SD) | 16 to 78 | 62.55 (14.39) | 65.82 (16.52) | +3.27 (6.30) | 65.49 (17.42) | +3.02 (6.83) |
| Patient 1 | | 84.79 | 89.01 | +4.22 | 87.42 | +2.63 |
| Patient 2 | | 82.72 | 84.51 | +1.79 | NA | NA |

#### 5.1.2.1.3. Prespecified sensitivity analysis- primary endpoint (FVC)

Pre-specified per protocol and sensitivity analyses were conducted, as detailed in the statistical analysis plan (SAP). A summary of results is shown in Table 34 and demonstrates the robustness of the results which are consistent irrespective of the analysis approach. The nominal p-values for superiority ranged between 0.0174 and 0.1377; it was below 5% in the non-parametric Wilcoxon-Mann-Whitney test. The small p-values illustrate the low probability for a false positive claim of superiority.

Greater values of change from baseline in FVC (% predicted) were observed in the Nexviadyme group PP population during the PAP. Similarly, to the mITT population, statistical superiority was narrowly missed at the 5% significance level (nominal p=0.0555; 95% CI: -0.06, 5.44).

Five patients in the alglucosidase alfa group dropped out of the PAP due to treatment-related reasons. The FVC (% predicted) was analyzed in completers and dropouts and when compared there appeared to be no impact on the robustness of the results.

A tipping point analysis of FVC (% predicted) for sensitivity analysis with respect to missing at random assumption in the PAP was done. A shift of -16 (16% reduction in FVC % predicted) in the avalglucosidase alfa group and a shift of 2 (2% increase in FVC % predicted) in the alglucosidase alfa group to overturn significance indicated a robust result for primary NI analysis.

Further sensitivity analyses were conducted including FVC (% predicted) in the PAP (mITT population) with respect to constancy assumption with results of the pivotal trial for the registration of Myozyme (AGLU02704/LOTS trial) and estimates and hypothesis tests of change from baseline at Week 49 using different statistical approaches.

*Table 29 - FVC (% Predicted) - in upright position change from baseline to Week 49: per protocol and sensitivity analyses*

| | | Nexviadyme (Avalglucosidase alfa) | Myozyme (Alglucosidase alfa) | Difference |
|---|---|---|---|---|
| per-protocol population | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N = 46<br>2.87 (0.93)<br>1.02, 4.73 | N=39<br>0.19 (1.02)<br>-1.83, 2.21 | 2.69 (1.20)<br>-0.06, 5.44<br>0.0076<br>0.0555 |
| per-protocol population with additional 6 patients* | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N=48<br>2.76 (0.91)<br>0.95, 4.56 | N=43<br>0.24 (0.96)<br>-1.67, 2.14 | 2.52 (1.32)<br>-0.11, 5.16<br>0.0075<br>0.0601 |
| Wilcoxon-Mann-Whitney[a] (mITT population) | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N=51 | N=49 | 2.93 (1.18)<br>0.61, 5.25<br>0.0009<br>0.0174 |
| MMRM model 5[b] (mITT population) | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N=51<br>2.89 (0.89)<br>1.13, 4.65 | N=47<br>0.45 (0.93)<br>-1.40, 2.30 | 2.44 (1.29)<br>-0.12, 5.01<br>0.0073<br>0.0619 |
| Linear mixed effects[c]** (mITT population) | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N=51<br>2.10 (0.88)<br>0.36, 3.85 | N=49<br>0.19 (0.93)<br>-1.66, 2.03 | 1.92 (1.28)<br>-0.63, 4.46<br>0.0295<br>0.1377 |
| Analysis of Covariance[d] (mITT population) | Estimate (SE)<br>95% CI<br>p-value for non-inferiority<br>p-value for superiority | N=51<br>2.68 (0.88)<br>0.92, 4.43 | N=47<br>0.50 (0.92)<br>-1.33, 2.32 | 2.18 (1.28)<br>-0.36, 4.72<br>0.0120<br>0.0918 |

*A post-hoc assessment suggested that 6 patients (2 in avalglucosidase alfa group and 4 in alglucosidase alfa group) have been excluded from the per-protocol population due to very conservative Sanofi's procedures.

[a] Wilcoxon-Mann-Whitney model: missing FVC (% predicted) at week 49 is imputed by baseline or last assessment in PAP for the subject, whichever is worse.

[b] MMRM model 5 includes baseline FVC (% predicted, as continuous), sex, age (in years, at baseline), treatment group, visit, interaction term between treatment group and visit, and interaction term of baseline FVC by visit.

[c] Linear mixed effects model includes fixed effects of age (as continuous variables), gender, treatment, time (in years) and the treatment * time interaction; as well as subject specific random intercept and random slope.

[d] An analysis of covariance including baseline FVC, age, gender, treatment group as covariates will be performed for the endpoint of change from baseline in FVC % predicted at Week 49.

For the patients who are known to start alternative treatment prior to Week 49, the last value prior to initiation of an alternative treatment will be used in the analysis.

For other patients who prematurely discontinued prior to Week 49 but with unknown alternative treatment information, their last value prior to dropout will be used in the analysis.

** updated compared to initial study report to follow the SAP specification for this model

### *5.1.2.2. Secondary and exploratory efficacy endpoints*

Pompe disease is a multisystemic disease affecting pulmonary function, ambulation, motor function and, ultimately, HRQoL. Nexviadyme provided greater benefit compared to Myozyme on the vast majority of secondary and exploratory endpoints in study EFC14028.

#### 5.1.2.2.1. Main analysis- secondary endpoint (6MWT)

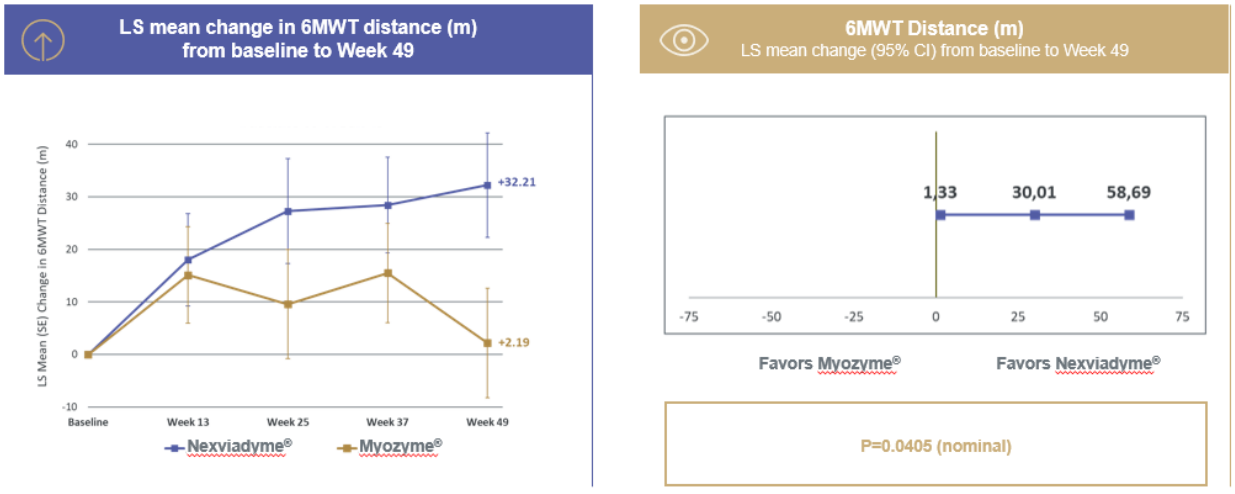
The main secondary endpoint was the ambulation measure of distance walked (in meters) during 6-minute walk test (6MWT).

In mITT population LS mean change (SE) in 6MWT (distance walked in meters) from baseline to Week 49 was 32.21 (9.93) in the Nexviadyme group, which was clinically meaningful, and 2.19 (10.40) in the Myozyme group; the difference was 30.01 (nominal p=0.0405), showing an improvement with Nexviadyme, compared to Myozyme (Figure 27).

Based on studies in chronic diseases other than LOPD that had aimed to relate changes in the 6-minute walk test (6MWT) to changes in patient perception, the MCID in 6MWT was defined as 24 to 54 m (Lachmann and Schoser, 2013).

Approximately 70% of patients improved their FVC and more than 80% improved their 6MWT (i.e., had a positive absolute change from baseline) with Nexviadyme compared to less than 50% with Myozyme, and approximately twice as many patients had improvements above predefined clinically meaningful thresholds.

*Figure 24 - Nexviadyme® demonstrated a clinically meaningful improvement in distance walked during the 6MWT*



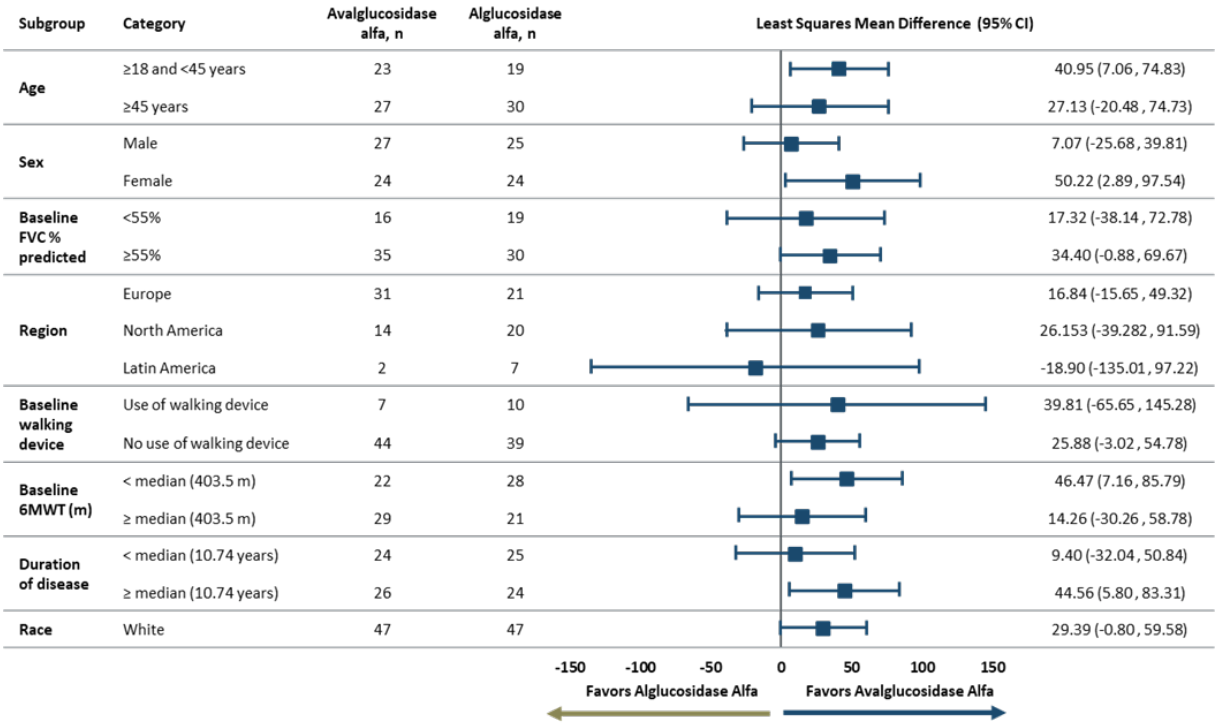

6MWT, 6-minute walk test; CI, confidence interval; LS, least squares; SE, standard error.

#### 5.1.2.2.2. Pre-specified subgroups analyses- secondary endpoint (6MWT)

Pre-specified subgroups analyses results were observed to be consistent regardless of gender, age and regions (Figure 28). Consistent improvements are also observed in the global population of mainly adult patients and the 2 pediatric patients with LOPD included in the study (Table 35). This demonstrates the

robustness of the improvement observed along the spectrum of clinical presentations, in spite of the variability inherent to the disease.

*Figure 25 - Forest Plot of 6MWT (distance walked, in meter) - change from baseline at Week 49 for subgroup analyses - mITT population*




6MWT=6-minute walk test; ALGLU=alglucosidase alfa; AVAL=avalglucosidase alfa; CI=confidence interval; FVC=forced vital capacity; LS=least square; mITT=modified intent-to-treat
Duration of Pompe disease is calculated as time from the onset of first symptoms of Pompe disease to the first study drug infusion dose.

*Table 30 - 6MWT (distance walked in meters) in avalglucosidase alfa arm – full populations and pediatric patients*

| Patient ID | Age (year) | Baseline | Week 25 | | Week 49 | |
|---|---|---|---|---|---|---|
| | | Observed value | Observed value | Change from baseline | Observed value | Change from baseline |
| All (N=51)<br>Mean (SD) | 16 to 78 | 399.30 (110.93) | 428.01 (101.07) | +29.19 (51.56) | 441.31 (109.77) | +37.86 (52.81) |
| Patient 1 | | 602 | 619 | +17 | 636 | +34 |
| Patient 2 | | 444 | 463.14 | +19.14 | NA | NA |

NA: data not yet available since the subject was included in August 2020

#### 5.1.2.2.3. Other secondary endpoints and exploratory endpoints

##### 5.1.2.2.3.1. Respiratory function

Clinically meaningful improvements in maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were also observed with avalglucosidase alfa, numerically greater than results observed with alglucosidase alfa (Table 36). This confirms the consistent improvement in all parameters of respiratory function with avalglucosidase alfa.

*Table 31 - Primary and secondary endpoint results for avalglucosidase alfa and alglucosidase alfa*

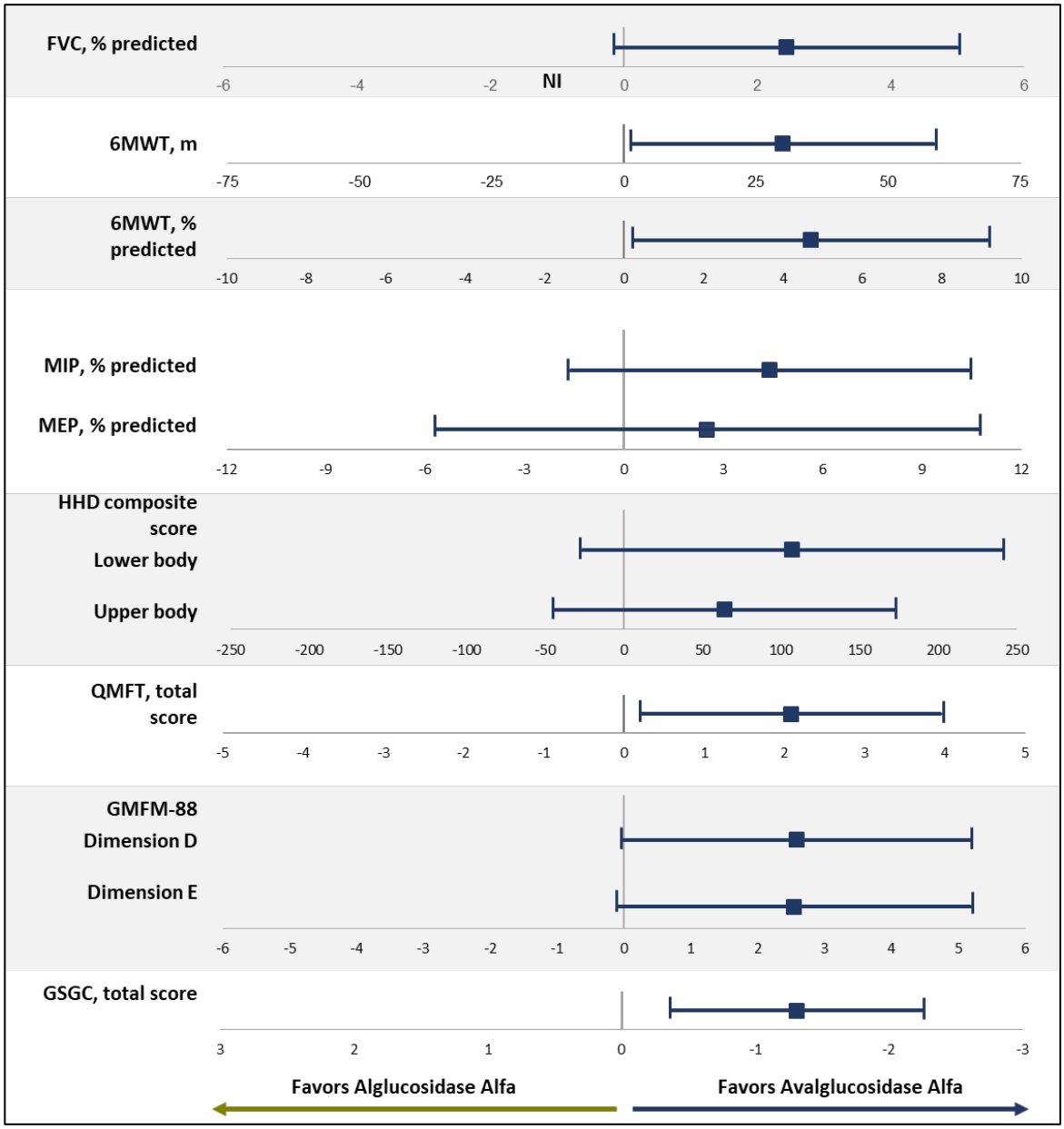
| LS mean (SE) change from Baseline to Week 49 | Avalglucosidase alfa N=51 | Alglucosidase alfa N=49 | LS Mean Difference (95% CI) N=100 | Nominal p-value for superiority |
|---|---|---|---|---|
| FVC (% predicted) | 2.89 (0.88) | 0.46 (0.93) | 2.43 (-0.13, 4.99) | 0.0626 |
| 6MWT (distance) | 32.21 (9.93) | 2.19 (10.40) | 30.01 (1.33, 58.69) | 0.0405 |
| MIP (% predicted)[a] | 8.70 (2.09) | 4.29 (2.19) | 4.40 (-1.63, 10.44) | 0.1505 |
| MEP (% predicted)[a] | 10.89 (2.84) | 8.38 (2.96) | 2.51 (-5.70, 10.73) | 0.5449 |
| HHD Composite Score | 260.69 (46.07) | 153.72 (48.54) | 106.97 (-26.56, 240.50) | 0.1150 |
| QMFT Total Score | 3.98 (0.63) | 1.89 (0.69) | 2.08 (0.22, 3.95) | 0.0288 |
| SF-12 - PCS | 2.37 (0.99) | 1.60 (1.07) | 0.77 (-2.13, 3.67) | 0.5996 |
| SF-12 - MCS | 2.88 (1.22) | 0.76 (1.32) | 2.12 (-1.46, 5.69) | 0.2427 |

[a] Post-hoc sensitivity analysis excluding 4 patients with supraphysiologic baseline MIP and MEP values (200 $cmH_2O$ at baseline were noted after DBL).

##### 5.1.2.2.3.2. Motor function

Clinically meaningful improvement in motor function evaluated by the lower extremity muscle strength (composite score) by hand-held dynamometry (HHD) and the global score quick motor function test (QMFT) are also observed (Table 36), as well as in the upper extremity muscle strength (composite score) by HHD and in the GMFM-88 Dimension D and Dimension E (Figure 29). The improvement in QMFT is of particular relevance since this is a reliable and valid test specific to Pompe disease. This test correlates strongly with proximal muscle strength, shows significant differences between patient groups with different disease severities, and measures the ability to perform everyday movements that are particularly difficult for patients with Pompe disease (van Capelle et al, 2012). A clinically meaningful improvement was observed (LS mean change from baseline [SE] 3.98 [0.63]), and the benefit was greater compared to alglucosidase alfa (LS mean difference +2.08 [95% CI: 0.22, 3.95]; nominal p=0.0288, performed without multiplicity adjustment). Even if the superiority of avalglucosidase alfa cannot be formally claimed due to the strict control of multiplicity, the estimate, the 95% CI and the nominal p-value below the commonly agreed threshold for statistical significance ($p<0.05$) confirm the greater benefit observed with avalglucosidase alfa.

*Figure 26 - LS mean (95% CI) differences for changes from baseline on the primary, secondary, and other efficacy outcomes measuring respiratory muscle function, functional endurance, muscle strength, and motor function.*




### 5.1.2.2.3.3. Health-related quality of life and patient-reported outcomes

Pompe disease has a substantial humanistic burden and the association of LOPD with the many measures of clinical, functional, social and emotional well-being that comprise the humanistic burden is reasonably well documented, confirming the impact of LOPD on the everyday life of patients and their caregivers. Clinical progression of disease is strongly associated with greater humanistic burden and reduced HRQoL (Schoser et

al, 2017). The improvement observed in the validated 12-item short form survey (SF-12) for both the physical component summary (PCS) and the mental component summary (MCS) is therefore very important for patients since it illustrates reduction in the disease-related burden (Table 36). Consistent improvement in other parameters evaluating HRQoL (Figure 30) certifies the robustness of the data and the global improvement in the disease-related burden as perceived and reported by the patients.

The EuroQol 5-dimension 5-level (EQ-5D-5L) is a multi-attribute utility measure of health-related quality of life, showing overall better outcomes with avalglucosidase alfa compared to alglucosidase alfa (Figure 30). Overall, greater mean (SD) EQ-5D-5L changes from baseline to Week 49 were observed in the avalglucosidase alfa group for mobility (-0.50 [0.89] in the avalglucosidase alfa group and -0.14 [0.68] in the alglucosidase alfa group), usual activities (-0.34 [0.89] in the avalglucosidase alfa group and 0.00 [0.73] in the alglucosidase alfa group). Similarly, EQ-5D VAS mean (SD) scores were greater (8.80 [15.01] in the avalglucosidase alfa group than in the alglucosidase alfa group (-0.33 [16.13]). Avalglucosidase alfa group scores in comparison to the alglucosidase alfa group with lower scores indicating less burden. Little change and differences between treatment groups were observed in self-care, pain/discomfort, anxiety/depression scores. Using Wilcoxon Mann Whitney test at the nominal level, mean changes from baseline to Week 49 were greater with avalglucosidase alfa, as compared to alglucosidase alfa, for mobility and usual activities, which are the most relevant domains in LOPD, as well as for EQ-5D VAS. This supports an additional therapeutic benefit of avalglucosidase alfa over the current standard of care on the treatment relevant aspects of LOPD.

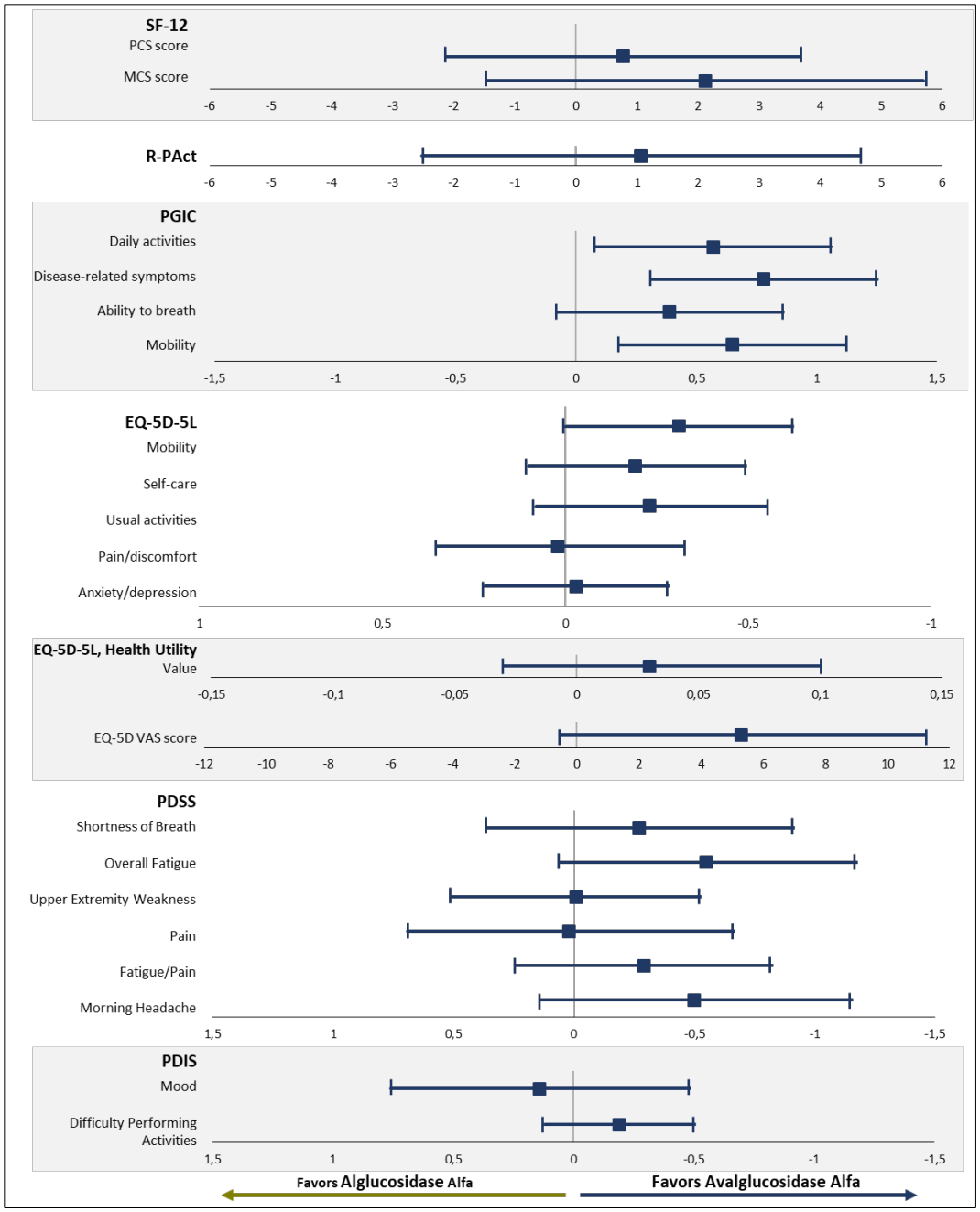
The Pompe disease symptom scale (PDSS) measures severity of breathing difficulties, fatigue and tiredness, muscle weakness and ache, pain, and headache from the patient's perspective. In general, median change from baseline to Week 49 for all the PDSS domains and the total symptom score were numerically better with avalglucosidase alfa as compared to alglucosidase alfa.

The Pompe disease impact scale (PDIS) captures the impact of the disease on mood and mobility-related physical activities. The PDIS includes negative mood score and Difficulty Physical Activity Score (DPAS) which includes difficulty performing activity. Median changes from baseline to Week 49 for the DPAS domain of the PDIS was significantly better (-0.62 vs. -0.07, nominal p=0.0296) with avalglucosidase alfa as compared to alglucosidase alfa (Figure 30).

The PGIC is a 7-point verbal scale designed specifically to assess patients' perception of changes following treatment (i.e., "feeling better" or "feeling worse") with the options "very much improved", "much improved", "minimally improved", "no change", "minimally worsened", "much worsened", and "very much worsened" (Perrot and Lantéri-Minet, 2019). Improvement of several dimensions (daily activities, disease-related symptoms, ability to breath, mobility) was observed with avalglucosidase alfa, with the lower bound of the 95% CI above or close to 0 (Figure 30). The PGIC (ability to breathe) anchor-based improvements were categorized as "somewhat to moderately better" (definition 1), "somewhat to a great deal better" (definition 2) and "moderately to a great deal better" (definition 3) at week 49. Changes from baseline to Week 49 in % predicted FVC were computed for the three anchor definitions and compared to the "no change" PGIC category. There was minimal change in FVC in subjects that reported "no change" in their PGIC. In contrast, FVC increased in ascending order of magnitude for the three PGIC improvement definitions (FVC % predicted median [IQR] of 1.7 [-2.1-5.4]; 2.1 [-2.1-6.0]; and 4.1 [-2.1-7.6], respectively). Data suggest that an improvement of 1.7 % or greater in % predicted FVC corresponds to minimal patient relevant change and as shown above, a greater proportion of patients treated with avalglucosidase alfa improved at or above the threshold compared with alglucosidase alfa (Table 36). This supports the greater benefit of avalglucosidase alfa on the respiratory function from the perspective of patients with LOPD.

Overall, avalglucosidase alfa has demonstrated greater improvements compared with alglucosidase alfa in several generic and disease-related measures of HRQoL, including in novel measures of the severity and impact of Pompe disease on the patient experience. This is clinically meaningful since it represents benefits in motility and in the ability to perform daily activities, and ultimately an improvement in patient's quality of life and a substantial reduction of the burden of the disease.

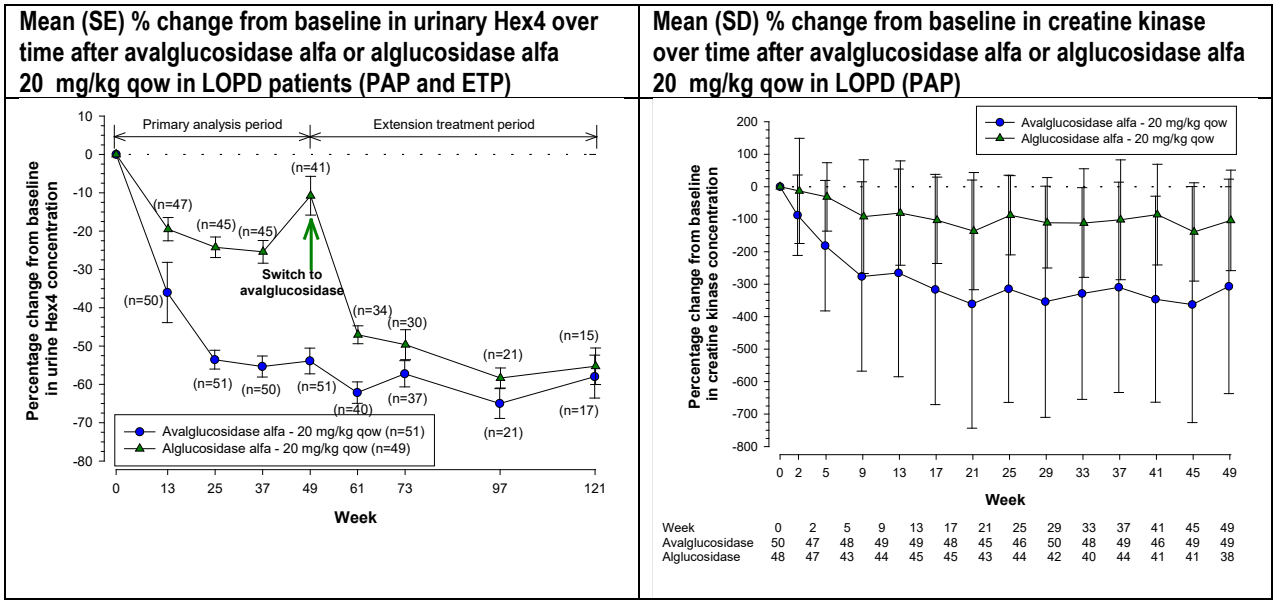
*Figure 27 - LS mean (95% CI) difference for changes from baseline on secondary and other efficacy outcomes measuring health-related quality of life*



#### 5.1.2.2.3.4. Efficacy biomarkers

Efficacy biomarkers (urinary Hex4 and creatine kinase) decreased to a greater extent with avalglucosidase alfa as compared with alglucosidase alfa at Week 49 (Figure 31). This is clinically meaningful since an improvement in biomarkers was shown to positively correlate with clinical outcomes (Manwaring et al, 2012, Young et al, 2012). Of note, a further decrease in Hex4 was observed in patients switching from alglucosidase alfa to avalglucosidase alfa.

*Figure 28 - Change from baseline in efficacy biomarkers*




### *5.1.2.3. Responder Analysis*

#### 5.1.2.3.1. Prespecified Responder Analyses- primary endpoint (% predicted FVC)

Pre-specified responder analyses were conducted as per study plans. Overall, approximately twice as many patients had an improvement above a given value, whatever the threshold, in the avalglucosidase alfa group compared to alglucosidase alfa (Table 37). More than half of the patients (26/51) in the avalglucosidase alfa group had a relative increase of 5% or more, 27.5% (14/51) a relative increase of 10% or more and approximately 20% (10/51) a relative increase of 15% or more. This is clinically meaningful for patients since these thresholds are above the MCID for IPF (Lachmann and Schoser, 2013), and since a natural progressive decline is generally observed with age and disease progression.

*Table 32 - FVC (% Predicted) - in upright position: pre-specified responder analysis - in PAP - mITT population*

| Parameter | Statistics | Avalglucosidase alfa (N=51) | Alglucosidase Alfa (N=49) |
|---|---|---|---|
| Responder defined as having a relative increase from baseline of 5% or more at Week 49 | | | |
| Yes | n (%) | 26 (51.0) | 14 (28.6) |
| Odds ratio from logistic regression | Estimate | 2.52 | |
| | 95% CI | 1.08, 5.86 | |
| | P value | 0.032 | |
| Responder defined as having a relative increase from baseline of 10% or more at Week 49 | | | |
| Yes | n (%) | 14 (27.5) | 8 (16.3) |
| Odds ratio from logistic regression | Estimate | 1.78 | |
| | 95% CI | 0.65, 4.86 | |
| | P value | 0.264 | |
| Responder defined as having a relative increase from baseline of 15% or more at Week 49 | | | |
| Yes | n (%) | 10 (19.6) | 3 (6.1) |
| Odds ratio from logistic regression | Estimate | 3.47 | |
| | 95% CI | 0.86, 13.98 | |
| | P value | 0.080 | |

#### 5.1.2.3.2. Post-hoc Responder Analyses- primary endpoint (% predicted FVC)

To further evaluate the benefit of improving respiratory function from a patient perspective, a post-hoc responder analysis was conducted in study EFC14028 to assess the absolute changes in % predicted FVC in relation to PROs. Patient-relevant absolute change in % predicted FVC of 1.7%, 2% and 4 % were estimated based on the Patient Global Impression of Change (PGIC) - Ability to Breathe - rated on a 7-point Likert scale, used as an anchor.

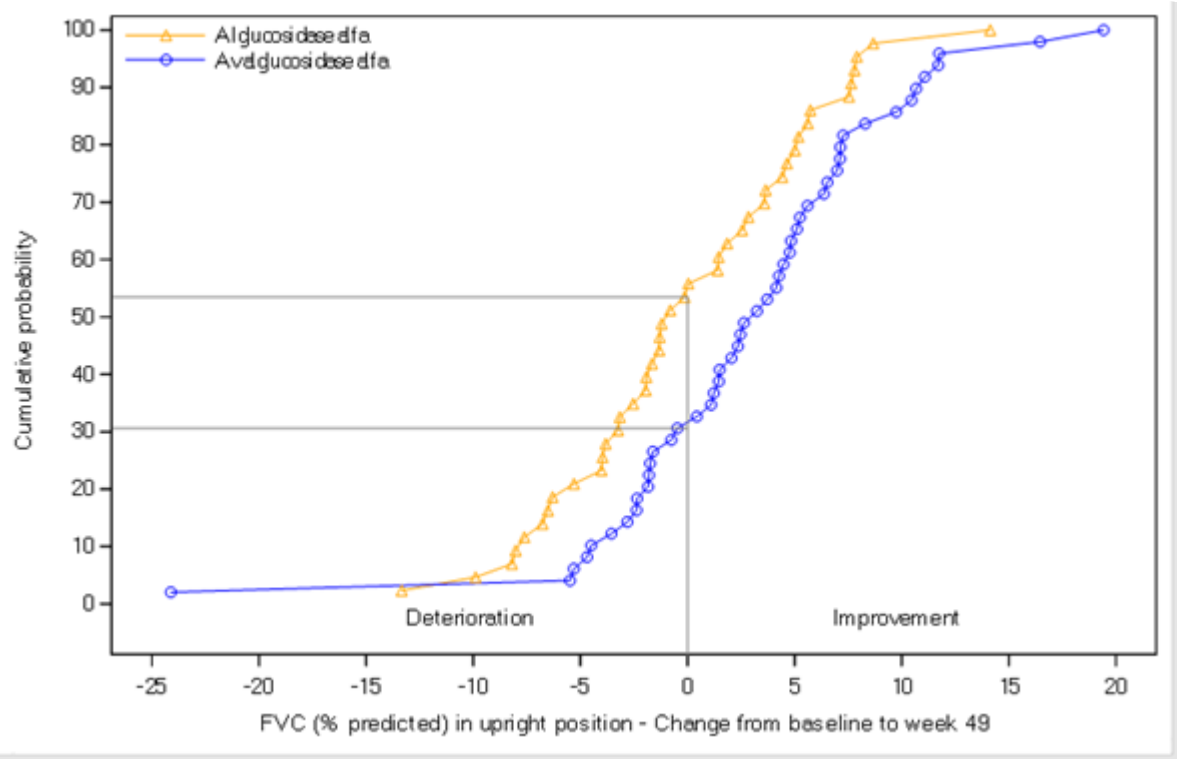
Data suggest that an absolute improvement of at least 1.7 % in % predicted FVC corresponds to minimal patient relevant change and a greater proportion of patients treated with avalglucosidase alfa improved at or above the threshold compared with alglucosidase alfa (Table 38).

*Table 33 - FVC (% Predicted) - in upright position: post-hoc responder analysis - in PAP - mITT population*

| Parameter | Statistics | Avalglucosidase alfa (N=51) | Alglucosidase Alfa (N=49) |
|---|---|---|---|
| Responder defined as having an absolute increase from baseline of 1.7% or more at Week 49 | | | |
| Yes | n (%) | 29 (56.9) | 17 (34.7) |
| Odds ratio from logistic regression | Estimate | 2.31 | |
| | 95% CI | 1.01, 5.27 | |
| | p-value | 0.046 | |
| Responder defined as having an absolute increase from baseline of 2% or more at Week 49 | | | |
| Yes | n (%) | 29 (56.9) | 16 (32.7) |
| Odds ratio from logistic regression | Estimate | 2.56 | |
| | 95% CI | 1.12, 5.85 | |
| | p-value | 0.026 | |
| Responder defined as having an absolute increase from baseline of 4% or more at Week 49 | | | |
| Yes | n (%) | 23 (45.1) | 12 (24.5) |
| Odds ratio from logistic regression | Estimate | 2.43 | |
| | 95% CI | 1.02, 5.78 | |
| | p-value | 0.045 | |

When the observed changes from baseline to Week 49 in % predicted FVC are represented as a cumulative probability function, a clear right shift of the avalglucosidase alfa curve compared to the alglucosidase alfa curve is observed (Figure 32). The figure clearly shows the numerically greater benefit of avalglucosidase alfa whatever the level of change from baseline. Approximately 70% of patients improved their FVC (i.e., had a positive absolute change from baseline) with avalglucosidase alfa. Since the natural progression of the disease shows gradual decline, any improvement of pulmonary function can be considered a positive response to the therapy (Stepien et al, 2016). In the alglucosidase alfa group more than half of the patients had a deterioration of FVC (i.e., had a negative absolute change from baseline).

*Figure 29 - Plot of the cumulative probability function of change from baseline to week 49 in FVC (% Predicted) in upright position - in PAP - mITT population*




Overall, approximately twice as many patients had an improvement above a given value, whatever the threshold, in the avalglucosidase alfa group compared to alglucosidase alfa.

#### 5.1.2.3.3. Prespecified Responder Analysis- main secondary endpoint (6 MWT)

In the pre-specified responder analyses (Table 39), a greater number of patients receiving avalglucosidase alfa than patients receiving alglucosidase alfa showed an increase from baseline exceeding the pre-defined clinically meaningful thresholds of 27.5, 30, 37 and 54 meters based on what is perceived as a MCID by patients with LOPD or other chronic diseases affecting ambulation (Lachmann and Schoser, 2013).

*Table 34 - 6MWT (distance walked, in meter): responder analysis - in PAP - mITT population*

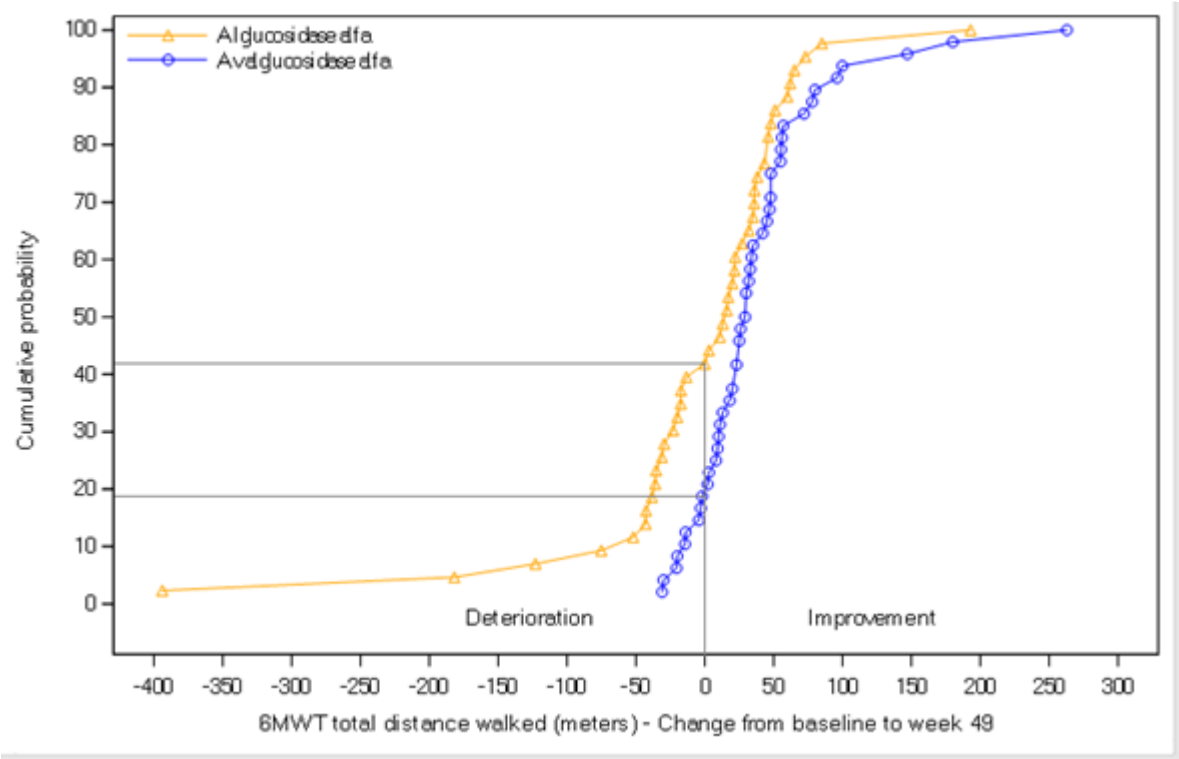
| Parameter | Statistics | Avalglucosidase alfa (N=51) | Alglucosidase Alfa (N=49) |
|---|---|---|---|
| Responder defined as having a change from baseline at week 49 in 6MWT distance of >=27.5 meters | | | |
| Yes | n (%) | 25 (49.0) | 16 (32.7) |
| Odds ratio from logistic regression | Estimate | 1.90 | |
| | 95% CI | 0.81, 4.45 | |
| | P value | 0.141 | |
| Responder defined as having a change from baseline at week 49 in 6MWT distance of >=30 meters | | | |
| Yes | n (%) | 24 (47.1) | 16 (32.7) |
| Odds ratio from logistic regression | Estimate | 1.76 | |
| | 95% CI | 0.75, 4.15 | |
| | P value | 0.195 | |
| Responder defined as having a change from baseline at week 49 in 6MWT distance of >=37 meters | | | |
| Yes | n (%) | 18 (35.3) | 12 (24.5) |
| Odds ratio from logistic regression | Estimate | 1.53 | |
| | 95% CI | 0.63, 3.74 | |
| | P value | 0.352 | |
| Responder defined as having a change from baseline at week 49 in 6MWT distance of >=54 meters | | | |
| Yes | n (%) | 12 (23.5) | 6 (12.2) |
| Odds ratio from logistic regression | Estimate | 2.09 | |
| | 95% CI | 0.70, 6.25 | |
| | P value | 0.188 | |

Note: Patients without week 49 value will be considered as non-responders;
If a subject had a change from baseline at week 49 in 6MET distance >=54 meters, s/he will be included in responders of >=27.5, >=30, >=37 and >=54 meter; if a subject has a change >=37 meters, s/he will be included in responders of >=30 and >=37 meters.
Logistic regression models adjust for baseline 6MWT distance, age (in years, at baseline), and gender.

#### 5.1.2.3.4. Post-hoc Responder Analyses- main secondary endpoint (6 MWT)

When the observed changes from baseline to Week 49 in 6MWT are represented as a cumulative probability function, a right shift of the avalglucosidase alfa curve compared to the alglucosidase alfa curve is observed (Figure 33). The figure clearly shows the greater benefit of avalglucosidase alfa whatever the level of change from baseline. More than 80% of patients improved their 6MWT (i.e., had a positive absolute change from baseline) with avalglucosidase alfa, which is clinically meaningful since any improvement in motility can be considered as positive response to the therapy taking into account the natural progression of the disease with gradual decline (Stepien et al, 2016). In the alglucosidase alfa group more than 40% of the patients had a deterioration of 6MWT (i.e., had a negative absolute change from baseline).

*Figure 30 - Plot of the cumulative probability function of change from baseline to week 49 in 6MWT total distance walked (meters) - in PAP - mITT population*




### *5.1.2.4. Post-hoc analyses aiming at increasing the precision and the power*

In consideration of the challenges with statistically powering a comparative trial in a rare disease, post-hoc analyses were conducted, aiming at increasing the precision and the power. While post-hoc analyses are not a typical consideration in the evaluation of a new therapy, the EMA guideline on Clinical Trials in Small Populations specifically mentions that meta-analyses of good-quality randomized controlled clinical trials that all show consistent results is the highest tier in the hierarchy of levels of evidence, and as such may provide important evidence of avalglucosidase alfa's meaningful clinical improvement over alglucosidase alfa. In these post-hoc analyses the treatment effect estimate remains similar to that of study EFC14028, providing reassurance that these post-hoc analyses are not biased. When pooling the 51 patients randomized to receive avalglucosidase alfa in study EFC14028 and the 3 treatment-naïve patients who received avalglucosidase alfa 20 mg/kg qow in study TDR12857/LTS13769 and adjusting for main baseline characteristics, the results are not different from the primary analysis (LS mean difference: 2.27%; 95% CI: -0.30; 4.85) due to the small number of additional patients. In the 2 other analyses described below, the result reaches nominal statistical significance since the confidence interval no longer includes 0, supporting the hypothesis that an effect exists but was not formally demonstrated due to a lack of precision and power:

- By pooling the 49 patients randomized to alglucosidase alfa in study EFC14028 and the 60 treatment-naïve patients who received alglucosidase alfa 20 mg/kg qow in the historical study ALGLU02704/LOTS, the sample size of the alglucosidase alfa arm was more than doubled. After adjusting for differences in baseline characteristics between the 2 studies, the difference (95% CI) in % predicted FVC between avalglucosidase alfa and alglucosidase alfa at Week 49/Week 52 was 2.41 (0.18; 4.64).

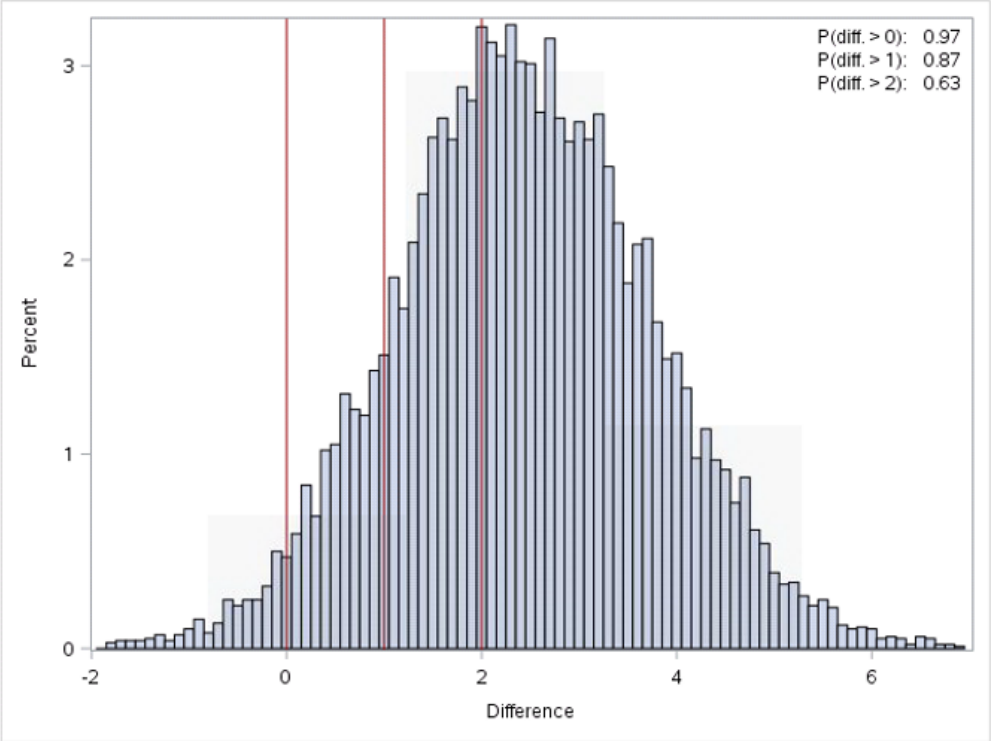
- To increase the precision and reduce the variance, a sensitivity post-hoc analysis was conducted after excluding an extreme outlying patient in the avalglucosidase alfa group. This patient, depicted at the extreme left of the blue curve in Figure 32, had a low baseline value and an atypical trajectory of respiratory function testing and the largest worsening at every visit in the context of concomitant poorly controlled asthma and chronic obstructive pulmonary disease and corresponding treatment. After excluding this patient, the variance decreased from 1.29 to 1.17 and the difference (95% CI) in % predicted FVC between avalglucosidase alfa and alglucosidase alfa at Week 49 was 2.98 (0.65; 5.30). While excluding an outlying patient can be considered arbitrary and debatable, this highlights the impact a single patient can have on the overall result in the context of a rare disease with high heterogeneity and variability. It may be hypothesized that the avalglucosidase alfa effect estimate in study EFC14028 is underestimated owing to this outlying patient.

#### 5.1.2.4.1. Post-hoc Bayesian analysis

The p-value approach focuses on the probability of incorrectly rejecting the null hypothesis of no difference between the drugs (dichotomize the decision based on a false positive rate of 0.05). Since the p-value (0.0626) is slightly above the pre-specified threshold, the null hypothesis of no difference in 49-week change from baseline in % predicted FVC between avalglucosidase alfa and alglucosidase alfa could not be rejected. However, this does not imply that equivalence was demonstrated, especially considering that the study was not sufficiently powered for superiority. We propose a Bayesian interpretation of the trial results based on posterior probability distributions and credibility intervals.

A post-hoc Bayesian posterior probability distribution using non-informative priors was generated for the primary analysis of the primary endpoint in study EFC14028. The posterior mean (SD) is 2.44% (1.30%) and the 95% credible interval is (-0.07%, 5.02%) based on 10000 draws. The posterior probability for avalglucosidase alfa being better than alglucosidase alfa is 97%. There is 87% posterior probability that the difference between treatments is above 1% and 63% posterior probability that the difference is above 2% (Figure 34).

*Figure 31 - Posterior distribution of difference between avalglucosidase alfa and alglucosidase alfa in % predicted FVC change from baseline at Week 49*




aval. = avalglucosidase alfa; alglu.= alglucosidase alfa; diff.= difference; pred. = predicted

#### 5.1.2.4.2. Post-hoc sensitivity analyses

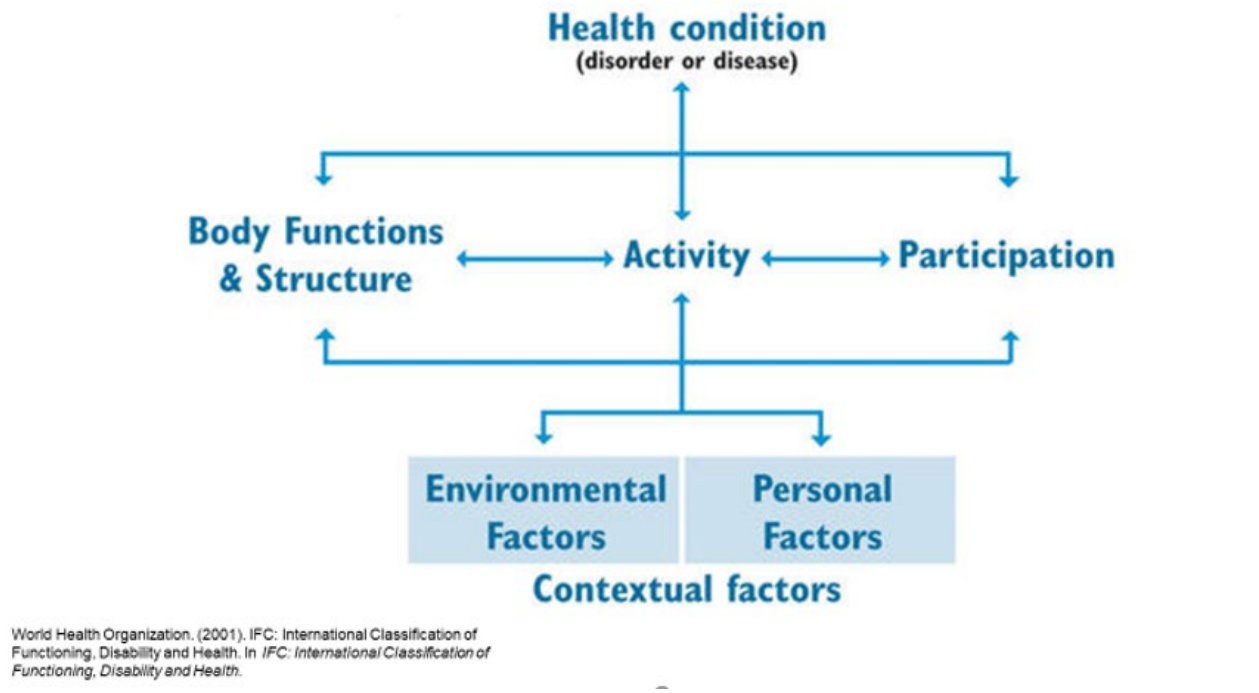
The 6 patients who were initially excluded from the PP population were reincluded in the PP for a post-hoc sensitivity analysis. This post-hoc analysis showed that the difference in % predicted FVC at Week 49 was still in favor of avalglucosidase alfa and did not change the PP conclusion (LS mean change of 2.52 and 2.69 with and without additional 6 patients, respectively).

Finally, another post-hoc sensitivity analysis was conducted by removing 4 patients who were excluded due to implausible MIP/MEP values of 200 mmHg at baseline. The results of these analyses were very similar to that including the 4 patients.

### *5.1.2.5. International Classification of Functioning, Disability, and Health (ICF)*

Clinical outcome assessments have been utilized in Nexviadyme clinical trials in order to capture relevant changes in how patients feel, function, and participate in their daily lives. The International Classification of Functioning, Disability, and Health (ICF) is a framework used to conceptualize functioning as an interaction between body function (physiological functions of body systems), activities (execution of a task or action by an individual), and participation in activities that are meaningful, such as community, work, and socialization (WHO 2001). Environmental and personal factors also impact how a health condition presents for an individual, though these are not focused on in clinical trial research. The ICF Model is helpful in understanding the impact of changes in body function and structure, activity, and quality of life as measured in clinical outcome assessments in the COMET study.

*Figure 32 - The International Classification of Functioning, Disability and Health (ICF)*




#### 5.1.2.5.1. Body Function and Structure

Muscle strength measured by handheld dynamometry

Muscle strength was measured in the EFC14028 (COMET) study by handheld dynamometry. Isometric measurement of peak force in Newtons was measured by trained assessors with standardized patient positions, dynamometer placement, and assessor verbal instructions. Observed and estimated changes in muscle force generation at Week 49 of the PAP were previously reported in the CSR and are summarized in Table 40 and Table 41.

The primary analyses for PAP are based on MMRM presented Table 40. The primary MMRM analyses captured greater positive change in the Nexviadyme group on the Lower Extremity Composite Score and Upper Extremity Composite scores. The same pattern is observed in the Lower Extremity percent predicted and Upper Extremity Scores percent predicted, which controls for changes in muscle strength attributed to patient factors such as age, gender, height, and weight. Ten of 14 lower extremity muscle groups had greater strength changes in the Nexviadyme group. The largest difference between lower extremity muscle groups was observed in Knee Flexion, with the Nexviadyme group having 21.14 Newton greater increase on the left and 10.88 Newton greater increase on the right compared to the Myozyme group. Additionally, 12 of 14 upper extremity muscle groups had greater strength changes observed in the Nexviadyme group; the two muscle groups that favored the Myozyme group had small differences between groups of less than one Newton.

Results in Table 41 are based on descriptive statistics by visit in PAP and ETP with p-values from Wilcoxon-Mann-Whitney without adjustment for baseline scores and other factors such as age and gender. Greater positive change was observed in the Nexviadyme group on both the Lower Extremity Composite Score and Upper Extremity Composite Score (nominal p=0.0439 for the Upper Extremity Composite score). The same pattern is observed in the Lower Extremity and Upper Extremity Scores of percent predicted, which controls

for changes in muscle strength attributed to patient factors, such as age, gender, height and weight. Patients in the Nexviadyme group had a 3.09%-predicted greater gain in muscle strength for the lower extremity composite score and 3.69%-predicted greater gain in the upper extremity composite score (Table 40)

Considering observed changes at Week 49 in individual muscle groups, majority of muscle groups tested had numerical greater positive change in the Nexviadyme group, though nominal p>0.05 Table 41. Ten of 12 lower extremity muscle groups had greater percent predicted strength changes in the Nexviadyme group; the two muscle groups which favored the Myozyme group had small differences of less than 1 percent predicted point. In upper extremity muscles, all muscle groups had numerically greater change in percent predicted muscle strength in the Nexviadyme group.

*Table 35 - Changes in muscle force and muscle force percent prediction- mITT population - Estimates and Hypothesis Tests of Change from Baseline to Week 49*

| | Avalglucosidase Alfa | Alglucosidase Alfa | Difference | nominal *p* -value |
|---|---|---|---|---|
| **Lower Extremity Muscle Groups** | | | | |
| *Composite Scores* | | | | |
| Lower Extremity Composite Score | 260.69 | 153.72 | 106.97 | 0.115 |
| Lower Extremity Summary score, % predi | 6.97 | 4.78 | 2.18 | 0.2681 |
| *Individual Muscle Groups Change in Force (Newtons)* | | | | |
| Hip Flexion, Right | 22.25 | 12.31 | 9.94 | 0.171 |
| Hip Flexion, Left | 17.25 | 13.65 | 3.59 | 0.6515 |
| Hip Extension, Right | 12.7 | 9.71 | 3 | 0.7823 |
| Hip Extension, Left | 10.62 | 1.64 | 8.98 | 0.3511 |
| Hip Abduction, Right | 12.07 | 11.65 | 0.42 | 0.9485 |
| Hip Abduction, Left | 20.93 | 12.81 | 8.12 | 0.2557 |
| Knee Flexion, Right | 22.62 | 11.74 | 10.88 | 0.0935 |
| Knee Flexion, Left | 25.87 | 4.74 | 21.14 | 0.003 |
| Knee Extension, Right | 19.87 | 23.86 | -4 | 0.7306 |
| Knee Extension, Left | 32.53 | 15.26 | 17.26 | 0.1102 |
| Ankle Dorsiflexion, Right | 20.08 | 21.49 | -1.41 | 0.8708 |
| Ankle Dorsiflexion, Left | 26.52 | 21.54 | 4.98 | 0.5535 |
| Ankle Plantarflexion, Right | 24.63 | 28.22 | -3.59 | 0.7897 |
| Ankle Plantarflexion, Left | 34.06 | 36.73 | -2.67 | 0.8579 |
| **Upper Extremity Muscle Groups** | | | | |
| *Composite Scores* | | | | |
| Upper Extremity Composite Score | 173.54 | 109.67 | 63.87 | 0.2455 |
| Upper Extremity Summary score, % pred | 5.35 | 3.96 | 1.39 | 0.5316 |
| *Individual Muscle Groups Change in Force (Newtons; grip strength units: lbs)* | | | | |
| Shoulder Flexion, Right | 15.83 | 14.23 | 1.6 | 0.8298 |
| Shoulder Flexion, Left | 14.08 | 12.32 | 1.76 | 0.7835 |
| Shoulder Extension, Right | 12.11 | 7.28 | 4.83 | 0.38 |
| Shoulder Extension, Left | 14.02 | 15.01 | -0.99 | 0.8646 |
| Shoulder Abduction, Right | 10.32 | 10.51 | -0.2 | 0.9746 |
| Shoulder Abduction, Left | 14.3 | 9.04 | 5.26 | 0.4456 |
| Shoulder Adduction, Right | 14.25 | 9.26 | 4.99 | 0.4746 |
| Shoulder Adduction, Left | 15.99 | 5.63 | 10.36 | 0.0934 |
| Elbow Flexion, Right | 15.71 | 13.17 | 2.54 | 0.7427 |
| Elbow Flexion, Left | 19.84 | 8.61 | 11.23 | 0.0951 |
| Elbow Extension, Right | 7.94 | 5.35 | 2.59 | 0.6392 |
| Elbow Extension, Left | 14.16 | 7.41 | 6.75 | 0.258 |
| Grip Strength, Right | 3.53 | 0 | 3.53 | 0.2644 |
| Grip Strength, Left | 1.75 | -1.57 | 3.33 | 0.2931 |

CSR tables 16.2.6.2.4.1 and 16.2.6.3.4.1

*Table 36 - Changes in muscle force and muscle force percent prediction- mITT population - Observed Mean Change from Baseline to Week 49*

| | Avalglucosidase Alfa | Alglucosidase Alfa | Difference | nominal *p* -value |
|---|---|---|---|---|
| **Lower Extremity Muscle Groups** | | | | |
| *Composite Scores* | | | | |
| Lower Extremity Composite Score | 275.41 | 145.77 | 129.64 | 0.1911 |
| Lower Extremity Summary score, % predi | 7.57 | 4.48 | 3.09 | 0.2104 |
| *Individual Muscle Groups, % predicted* | | | | |
| Hip Flexion, Right | 4.5 | 2.28 | 2.22 | 0.2052 |
| Hip Flexion, Left | 3.91 | 3.48 | 0.43 | 0.393 |
| Hip Extension, Right | 4.16 | 3.15 | 1.01 | 0.9754 |
| Hip Extension, Left | 3.63 | -0.03 | 3.66 | 0.3683 |
| Hip Abduction, Right | 4.68 | 3.71 | 0.97 | 0.7793 |
| Hip Abduction, Left | 7.69 | 4.33 | 3.36 | 0.5387 |
| Knee Flexion, Right | 12.26 | 6.22 | 6.04 | 0.149 |
| Knee Flexion, Left | 12.87 | 1.56 | 11.31 | 0.006 |
| Knee Extension, Right | 5.96 | 6.92 | -0.96 | 0.8447 |
| Knee Extension, Left | 6.92 | 4.1 | 2.82 | 0.2075 |
| Ankle Dorsiflexion, Right | 9.56 | 9.92 | -0.36 | 0.7348 |
| Ankle Dorsiflexion, Left | 12.85 | 9.46 | 3.39 | 0.3382 |
| Ankle Plantarflexion, Right | nd | nd | nd | nd |
| Ankle Plantarflexion, Left | nd | nd | nd | nd |
| **Upper Extremity Muscle Groups** | | | | |
| *Composite Scores* | | | | |
| Upper Extremity Composite Score | 211.03 | 93.76 | 117.27 | 0.0439 |
| Upper Extremity Summary score, % pred | 7.35 | 3.66 | 3.69 | 0.173 |
| *Individual Muscle Groups, % predicted* | | | | |
| Shoulder Flexion, Right | 8.91 | 8.87 | 0.04 | 0.5671 |
| Shoulder Flexion, Left | 10.29 | 6.55 | 3.74 | 0.227 |
| Shoulder Extension, Right | 4.65 | 3.08 | 1.57 | 0.3899 |
| Shoulder Extension, Left | 6.73 | 6.42 | 0.31 | 0.4696 |
| Shoulder Abduction, Right | 6.55 | 3.89 | 2.66 | 0.4059 |
| Shoulder Abduction, Left | 6.85 | 2.97 | 3.88 | 0.3512 |
| Shoulder Adduction, Right | nd | nd | nd | nd |
| Shoulder Adduction, Left | nd | nd | nd | nd |
| Elbow Flexion, Right | 8.19 | 6.04 | 2.15 | 0.254 |
| Elbow Flexion, Left | 13.57 | 4.05 | 9.52 | 0.0628 |
| Elbow Extension, Right | 4 | 1.49 | 2.51 | 0.4618 |
| Elbow Extension, Left | 10.4 | 3.11 | 7.29 | 0.0472 |
| Grip Strength, Right | 6.58 | 1.66 | 4.92 | 0.4693 |
| Grip Strength, Left | 4.79 | -1.98 | 6.77 | 0.1514 |

CSR Outputs 16.2.6.2.4.4, 16.2.6.2.4.5, 16.2.6.3.4.6, 16.2.6.3.4.8

The pattern of greater numerical change in muscle force generation in the Nexviadyme group is hypothesized as the result of improved glycogen clearance and improved skeletal muscle function via improved muscle preservation. The consistent improvement in percent predicted muscle strength in the majority of muscle groups with Nexviadyme indicates improved ability of the muscle to generate force as measured by a handheld dynamometer.

Muscle strength to perform FVC, MIP, and MEP

In addition to the skeletal muscle groups measured with handheld dynamometry, muscle force generation contributed to the outcomes of FVC, MIP, and MEP (Figure 23). These respiratory measures rely on neuromuscular coordination and strength of the diaphragm, abdominal, and other accessory muscles to generate force required to expand and contract the chest wall. Direct measurement of these muscle groups is not feasible with handheld dynamometry, but changes in the respiratory measures can indicate improved muscle function and force generation. At Week 49, the Nexviadyme group appreciated greater improvements in FVC % predicted and MIP % predicted compared to the Myozyme group.

#### 5.1.2.5.2. Activity Changes

Functional strength as measured by the 6 Minute Walk Test (6MWT) Quick Motor Function Test (QMFT), Gross Motor Function Measure (GMFM-88), and Gait, Stairs, Gower's, Chair (GSGC)

Changes in muscle force generation contribute to a patient's ability to use muscle strength to complete functional activities such as walking, stair navigation, balance, and transitions. These activities, among others, are captured in the functional outcome assessments in the COMET study of the secondary endpoints 6MWT, QMFT, as well as tertiary endpoints GMFM, and GSGC, as evaluated by a trained assessor.

Changes observed and estimated in these functional outcome assessments at Week 49 of the COMET study are summarized in Table 42 and Table 43. All measures had an observed difference between groups favoring the Nexviadyme group. Nominal $p<0.05$, was reported in all with the exception of the GMFM Dimension D ($p=0.0613$). Table 43 highlights estimates and nominal p-values for secondary outcomes of 6MWT and QMFT; all difference between groups show nominal $p<0.05$.

*Table 37 - Changes in functional outcome assessment scores - mITT population -Observed mean values Baseline to Week 49*

| Functional Outcome Metric | Nexviadyme | Myozyme | Difference | Nominal p-value |
|---|---|---|---|---|
| 6MWT Distance Walked[a] | 37.86 | -1.73 | 39.59 | 0.0211 |
| 6MWT Percent Predicted[b] | 5.8 | -0.4 | 6.2 | 0.0157 |
| QMFT Total Score[c] | 4.41 | 1.77 | 2.64 | 0.02 |
| GMFM_Dimension D (Standing) Score[d] | 4.29 | 1.77 | 2.52 | 0.0613 |
| GMFM_Dimension E (Walking/Running/Jumping) Score[d] | 5.33 | 2.81 | 2.52 | 0.0475 |
| GMFM_Dimension D and E Score[d] | 4.81 | 2.29 | 2.52 | 0.018 |

| | | | | |
|---|---|---|---|---|
| GSGC Score* (negative change indicates functional improvement)[e] | -1.57 | -0.38 | -1.19 | 0.0205 |

a EFC14028 CSR output 16.2.6.2.2.17
b EFC14028 CSR output 16.2.6.2.2.40
c EFC14028 CSR output 16.2.6.2.5.2
d EFC14028 CSR output 16.2.6.3.2.1
e EFC14028 CSR output 16.2.6.3.1.1

*Table 38 - Changes in functional outcome assessment scores - mITT population - Estimates and p-value- Baseline to Week 49*

| Functional Outcome Metric | Nexviadyme | Myozyme | Difference | Nominal p-value |
|---|---|---|---|---|
| 6MWT Distance Walked[a] | 32.21 | 2.19 | 30.01 | 0.0405 |
| 6MWT Percent Predicted[a] | 5.02 | 0.31 | 4.71 | 0.0386 |
| QMFT Total Score[b] | 3.98 | 1.89 | 2.08 | 0.0288 |

a EFC14028 CSR output 16.2.6.2.2.1
b EFC14028 CSR output 16.2.6.2.5.1

#### 5.1.2.5.3. Patient report of Global Impression of Change and Quality of Life

Pompe disease has a substantial humanistic burden and the association of LOPD with measures of clinical, functional, social and emotional well-being is reasonably well documented, confirming the impact of LOPD on the everyday life of patients and their caregivers. Clinical progression of disease is strongly associated with greater humanistic burden and reduced health-related quality of life.

In EFC14028 COMET study, in addition to greater positive change in muscle strength and ability to perform functional activities, the change in patients' impressions of their overall health and well-being illuminates the impact of therapies on daily lives and ability to participate more fully in work, community, and socialization. The EQ-5D-5L Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0-100) visual analog scale. Patients in the avalglucosidase alfa group had a mean 8.8-point increase in rating at Week 49 compared to a mean change of -0.33 in the alglucosidase alfa group (nominal p=0.0043) (Table 44). The greater positive change in perceived health aligns with improved muscle strength, respiratory measures, and ability to perform functional activities appreciated in the avalglucosidase alfa group.

*Table 39 - Changes in functional outcome assessment scores- mITT population Estimates and p-value- Baseline to Week 49*

| EQ-5D-5L | Avalglucosidase Alfa | Alglucosidase Alfa | Difference | Nominal p-value |
|---|---|---|---|---|
| EQ-5D VAS Score | 8.8 | -0.33 | 9.13 | 0.0043 |

EFC14028 CSR output 16.2.6.3.5.1

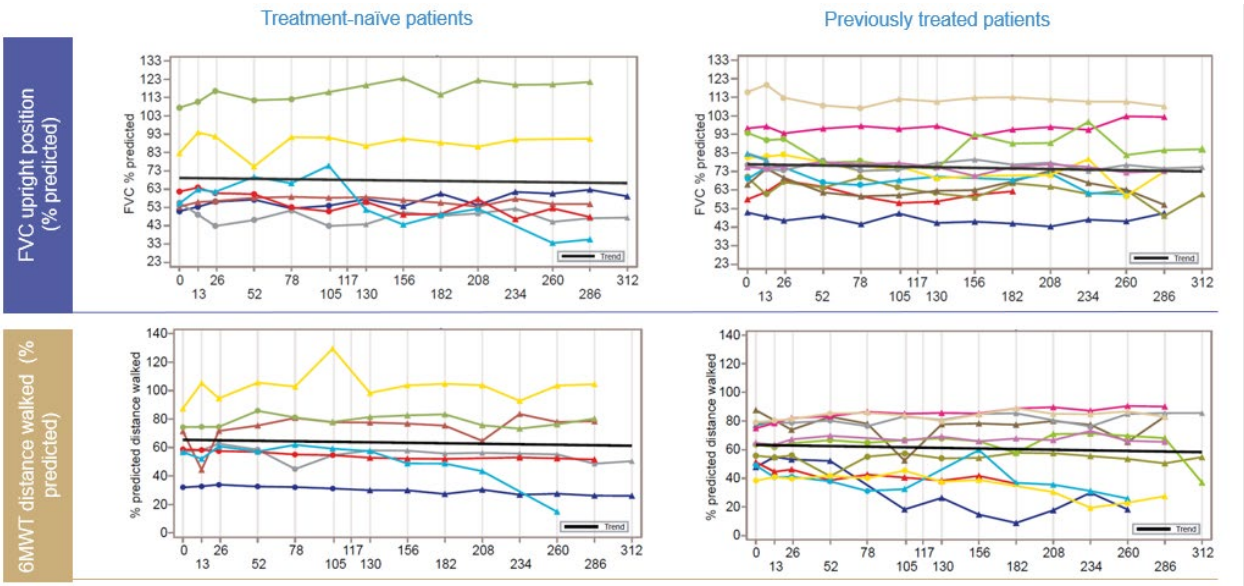
Greater improvement of PGIC several dimensions (daily activities, disease-related symptoms, ability to breath, mobility) was also observed with avalglucosidase alfa than in alglucosidase alfa (Section 0).

### *5.1.2.6. Long-term efficacy data*

#### 5.1.2.6.1. Long Term Safety Extension Study LTS13769

Recent studies showed that the effect of Myozyme seems to peak at 2 to 3 years of treatment and is followed by a plateau or a secondary decline after 3 to 5 years (Schoser et al, 2017, Gutschmidt et al, 2021, Semplicini et al, 2020). In study LTS13769, the maintained long-term effect of avalglucosidase alfa on respiratory function and ambulation in patients with LOPD was shown up to 6 years (Figure 36). Despite the natural decline of the disease over time with age and occurrence of intercurrent medical events in some patients, stabilization was observed Nexviadyme in pulmonary and motor function among both naive and switch group patients, indicating a sustained benefit compared to the natural history of Pompe disease.

*Figure 33 – Nexviadyme Long Term Safety Extension Study LTS13769 - 6 Years Follow up*




#### 5.1.2.6.2. Long term data in COMET- EFC14028 Study

Due to roll-out enrollment, 2-year data were available in approximately half of the patients randomized to Nexviadyme at the time of initial submission. An additional analysis was performed after the last subject completed Week 97 visit. Overall, the effect observed in PAP was maintained over time in patients treated with Nexviadyme for most primary, secondary and exploratory endpoints of respiratory function, ambulation, motor function and health-related quality of life, as well as in patient-reported outcomes measuring the burden of the disease as perceived by the patients.

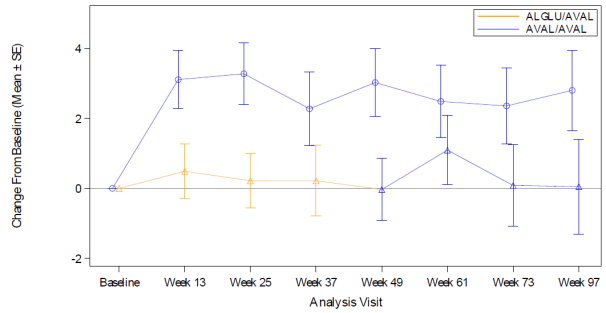
In patients initially treated with Nexviadyme during PAP, maintenance of effect on % predicted FVC was observed, as well as the maintenance or continuous improvement of effect in other parameters of MIP and MEP (Figure 37). MIP and MEP are respiratory pressure measurements that require recruitment and utilization of skeletal muscles of respiration, such as the diaphragm, intercostals, and abdominals, and positive change was observed to be maintained in the Nexviadyme group at Week 97.

The effects of Nexviadyme on 6MWT is sustained up to at least 2 years (Figure 37). The initial improvement in most motor function endpoints with Nexviadyme is maintained over time. The increased force generated

by lower extremity muscle groups contributed to improved motor function scores, as indicated by higher scores on the QMFT, which were maintained through Week 97. The improvement in QMFT is of particular relevance since this is a reliable and valid test specific to Pompe disease. This test correlates strongly with proximal muscle strength, shows significant differences between patient groups with different disease severities, and measures the ability to utilize increased strength for functional mobility and perform everyday movements that are particularly difficult for Pompe disease patients (van Capelle et al, 2012).

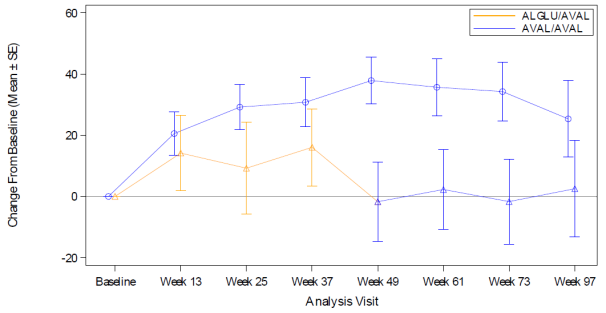
*Figure 34 - Nexviadyme Long-Term Efficacy in EFC1408 COMET Study: Respiratory, ambulatory and Motor Function- up to W97*

**Plot of Mean (SE) change from baseline of FVC (% Predicted) - in upright position over time up to Week 97 - mITT population**



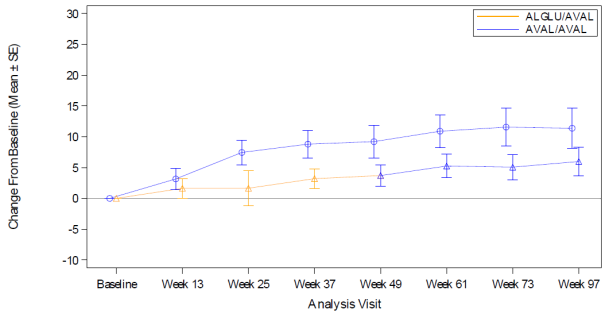

| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 49 | 47 | 45 | 44 | 43 | 37 | 38 | 35 |
| AVAL/AVAL | 51 | 51 | 51 | 51 | 49 | 46 | 46 | 43 |

**Plot of Mean (SE) change from baseline of 6MWT (distance walked, in meter) over time up to Week 97 - mITT population**



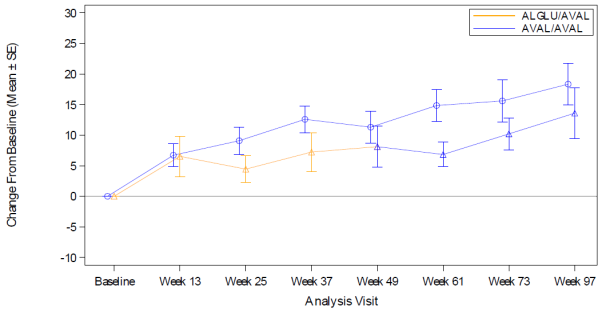

| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 49 | 47 | 45 | 45 | 43 | 43 | 41 | 41 |
| AVAL/AVAL | 51 | 51 | 49 | 50 | 48 | 47 | 47 | 42 |

**Plot of Mean (SE) change from baseline of MIP (% predicted) - in upright position over time to Week 97 - mITT population**



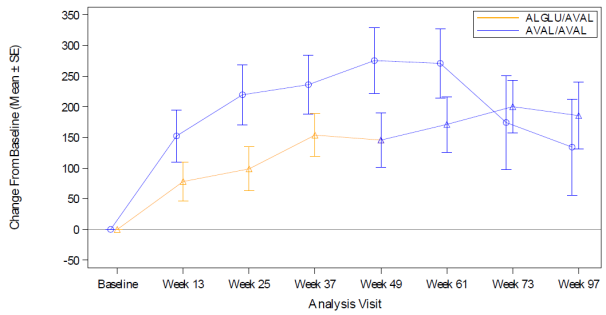

| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 47 | 43 | 43 | 42 | 41 | 33 | 36 | 33 |
| AVAL/AVAL | 48 | 46 | 48 | 48 | 46 | 43 | 43 | 40 |

**Plot of Mean (SE) change from baseline of MEP (% predicted) - in upright position over time to Week 97 - mITT population**



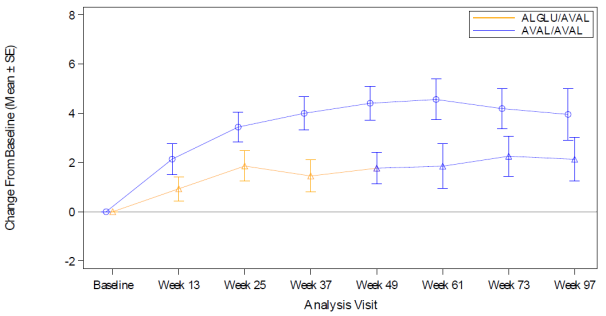

| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 47 | 43 | 43 | 42 | 41 | 33 | 36 | 33 |
| AVAL/AVAL | 48 | 46 | 48 | 48 | 46 | 43 | 43 | 40 |

**Plot of Mean (SE) change from baseline of HHD (lower - composite score) over time up to Week 97 - mITT population**




| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 46 | 44 | 41 | 42 | 40 | 41 | 39 | 40 |
| AVAL/AVAL | 50 | 49 | 47 | 47 | 46 | 44 | 42 | 40 |

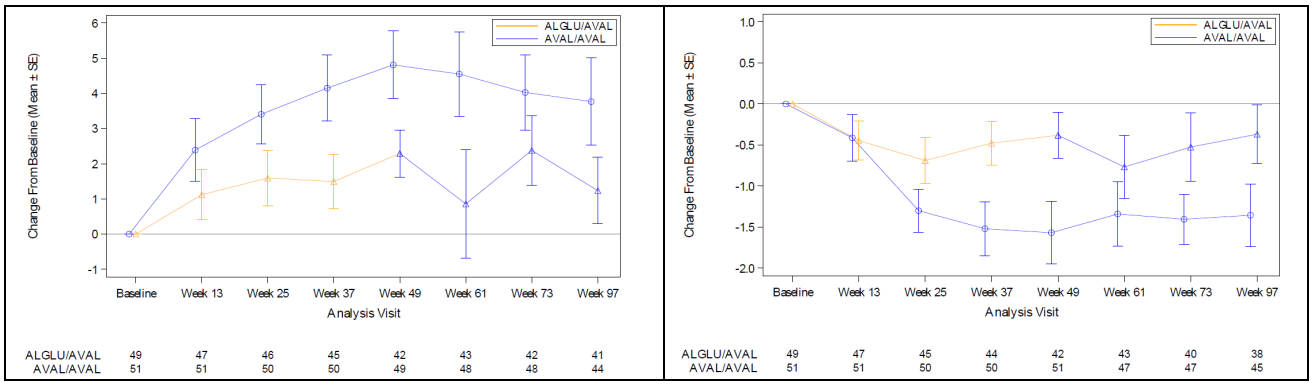
**Plot of Mean (SE) change from baseline of QMFT score over time up to Week 97 - mITT population**




| | Baseline | Week 13 | Week 25 | Week 37 | Week 49 | Week 61 | Week 73 | Week 97 |
|---|---|---|---|---|---|---|---|---|
| ALGLU/AVAL | 46 | 44 | 42 | 42 | 39 | 40 | 39 | 38 |
| AVAL/AVAL | 51 | 51 | 50 | 49 | 49 | 48 | 47 | 44 |

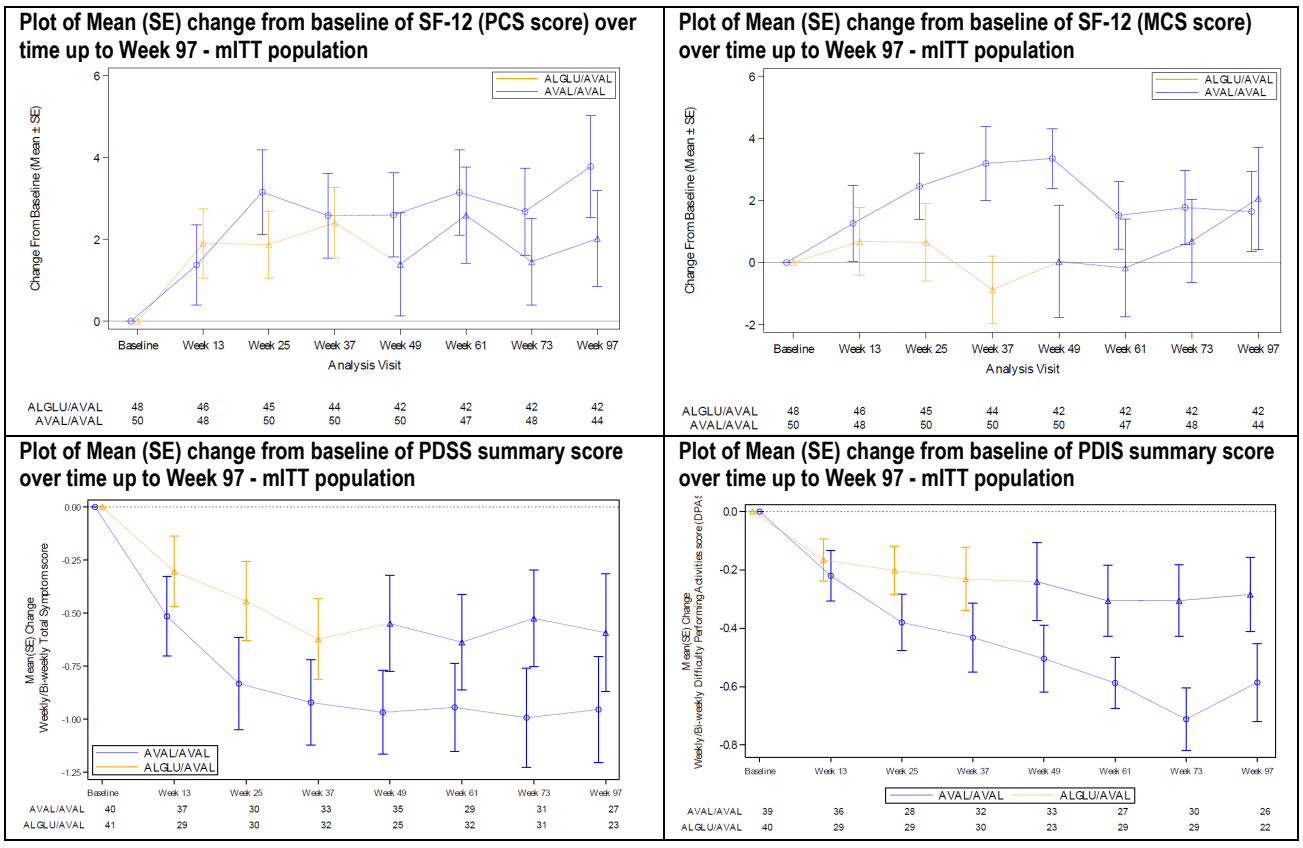
**GMFM-88 Total score for dimension D and dimension E**

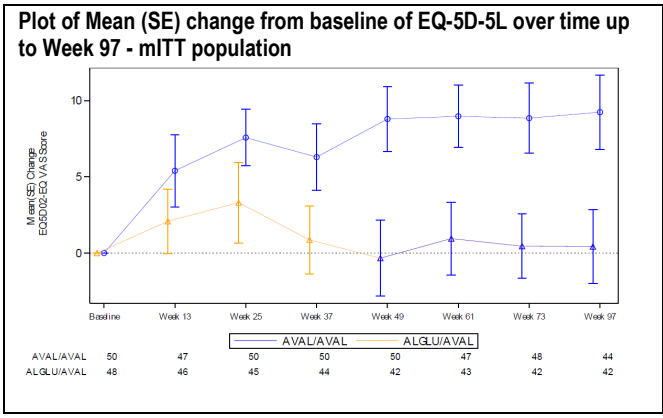
**GSGC Total Score**

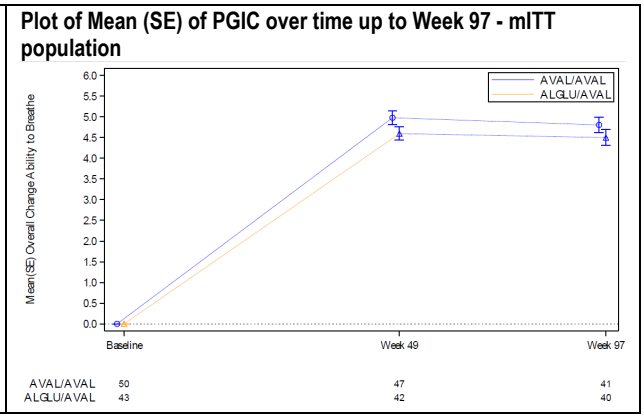



The beneficial effect on secondary outcomes of health-related quality of life (HRQoL) and on exploratory patient-reported outcomes evaluating the ability to perform daily activities (Figure 38) was also maintained or continued to improve up to at least Week 97, indicating the sustained benefit for patients in reducing the burden of the disease as perceived by the patients and fulfilling unmet clinical needs.

*Figure 35 - Nexviadyme Long Term Treatment Effect COMET Study- Up to W97 HRQoL Assessments*






Patients on Myozyme who switched to Nexviadyme experienced a maintenance or improvement in all endpoints after the switch. Similar to the nonclinical results in mouse models, the molecular structural differences of Nexviadyme versus Myozyme translated to improved muscle function in patients, as measured by increased muscle strength (force generated) and ability to utilize increased strength for functional mobility as measured on the QMFT and measures of breathing capabilities (MIP and MEP).

This is clinically meaningful in the context of a multi-systemic chronic disease and taking into account the natural decline in these parameters with age and progressing disease. In study EFC14028, data at Week 97 have recently been made available and the efficacy was maintained up to at least 2 years for outcomes of respiratory function, ambulation, motor function and health-related quality of live, as well as patient-related outcomes measuring the burden of the disease.

### *5.1.2.7. Safety data*

#### 5.1.2.7.1. Safety events overview

From a safety perspective, avalglucosidase alfa was better tolerated as compared to alglucosidase alfa in the 49-week blinded comparative period of the trial as demonstrated by lower frequencies of TEAEs, SAEs, and protocol-defined infusion associated reactions (IARs) with avalglucosidase alfa (Table 45). One patient treated with alglucosidase alfa died and 4 patients withdrew due to AEs in the alglucosidase alfa arm (including 2 patients with IARs), compared to none in the avalglucosidase alfa arm in the comparative period. Median exposure to study drug was comparable with 11.53 months for avalglucosidase alfa and 11.50 months for alglucosidase alfa, respectively. Overall, 44 patients switched from alglucosidase alfa to avalglucosidase alfa in the extension treatment period.

*Table 40 - EFC14028 - Safety overview during the comparative primary analysis period*

| | Avalglucosidase alfa N=51 | Alglucosidase alfa N=49 |
|---|---|---|
| TEAEs | 44 (86.3) | 45 (91.8) |
| TEAEs Potentially Related to Treatment | 23 (45.1) | 24 (49.0) |
| Serious TEAEs | 8 (15.7) | 12 (24.5) |
| Serious TEAEs Potentially Related to Treatment | 1 (2.0) | 3 (6.1) |
| Severe TEAEs | 6 (11.8) | 7 (14.3) |
| TEAEs Leading to Study Withdrawal | 0 | 4 (8.2) |
| TEAEs Leading to Death | 0 | 1 (2.0) |
| IARs (protocol-defined)* | 13 (25.5) | 16 (32.7) |

IAR=infusion-associated reaction; PAP=primary analysis period; TEAE=treatment-emergent adverse event.

*Note*: Numbers reported are the number (%) of participants with at least 1 TEAE in each category.

*Defined as an adverse event that occurred during either the infusion or observation period following the infusion, related or possible related to the investigational treatment.

An IAR was defined in the protocol as adverse events (AE) that occurred during either the infusion or the observation period following the infusion which was deemed to be related or possibly related to the study medication. At the discretion of the Investigator, AEs occurring after completion of the post infusion observation period that were assessed as related could also be considered IARs. The most frequently reported protocol-defined IARs by preferred MedDRA term in more than 2 patients in the avalglucosidase alfa group were pruritus (7.8%) and urticaria (5.9%) and in the alglucosidase alfa group were nausea (8.2%), pruritus (8.2%), and flushing (6.1%). Most IARs in the avalglucosidase alfa group were mild and moderate and occurred during infusion and up to 24 hours after the end of the infusion. Protocol-defined severe IARs were reported in no patients in the avalglucosidase alfa group and in 2 patients (6 events) in the alglucosidase alfa group in the comparative period.

Standard MedDRA query criteria were used to identify TEAEs that were potentially associated with symptoms of hypersensitivity/anaphylactic and immune-mediated reactions. During the primary analysis period, 12 (23.5%) patients in the avalglucosidase alfa group and 15 [30.6%] patients in the alglucosidase alfa group reported treatment-emergent hypersensitivity events by SMQ. The most common events were pruritus (4 [7.8%] patients and 5 events in the avalglucosidase alfa group and 4 [8.2%] patients and 9 events in the alglucosidase alfa group) and erythema (3 [5.9%] patients and 4 events in the avalglucosidase alfa group and 3 [6.1%] patients and 7 events in the alglucosidase alfa group).

During the comparative period, 12 (23.5%) patients in the avalglucosidase alfa group and 15 (30.6%) patients in the alglucosidase alfa group reported treatment-emergent immune-mediated reactions by SMQ. The most common events were arthralgia (5 [9.8%] patients and 6 events in the avalglucosidase alfa group and 8 [16.3%] patients and 10 events in the alglucosidase alfa group) and myalgia (5 [9.8%] patients and 15 events in the avalglucosidase alfa group and 7 [14.3%] patients and 12 events in the alglucosidase alfa group). Immune complex-mediated syndromes may result in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, haematuria, proteinuria, papular rash, purpura-like eruptions, necrotizing skin lesions, arthritis, serositis, vasculitis, flu like symptoms with fever, myalgia, arthralgia, rash and serum sickness. During the study some patients receiving avalglucosidase alfa reported such TEAEs; arthralgia (15), myalgia (9), and lymphadenopathy (2), however, none of them had events consistent with immune-mediated reactions. There were no reports of glomerulonephritis, necrotizing skin lesions or

proteinuria. All events were mild, resolved in a few days with no change of treatment with study drug, and skin or renal biopsies were not performed. A few cases were associated with influenza, but with the exception of one participant, start and stop dates differed from the events of arthralgia or myalgia.

No comparative data are available after the end of PAP since all patients previously randomized to alglucosidase alfa were switched to avalglucosidase alfa. The favorable safety and immunogenicity profile of avalglucosidase alfa is maintained overall including in patients treated for up to 5.5 years, and no difference was observed between patients initially treated with avalglucosidase alfa and patients switching from alglucosidase alfa after PAP at the first interim analysis of the ETP (Table 46) and again after another 48 weeks of treatment (Table 47). At the first interim analysis, patients in the avalglucosidase alfa group had been treated for an additional median of 10.58 months and patients in the previous alglucosidase alfa group had been treated with avalglucosidase alfa for an additional median of 10.46 months. After another 48 weeks of treatment with avalglucosidase alfa, the additional median exposure in the ETP was 21.16 and 19.32 months. The additional treatment of about one year did not alter the EAIR per 100 patient years much for any of the different categories of TEAEs analysed.

*Table 41 - Overview of treatment-emergent adverse events in avalglucosidase alfa treatment - overall - safety population - 48 weeks of extended treatment period*

| Number of patients with events (%)<br>Patient years at risk<br>EAIR per 100 patient years | Group 1: Subjects received avalglucosidase alfa in both PAP and ETP<br>Events in PAP and ETP (N=51) | Group 1: Subjects received avalglucosidase alfa in both PAP and ETP<br>Events in ETP (N=51) | Group 2: Subjects received alglucosidase alfa in PAP and avalglucosidase alfa in ETP (N=44)<br>Events in avalglucosidase alfa treatment | Group 3: Subjects who received avalglucosidase alfa in either PAP or ETP (N=95)<br>Events in avalglucosidase alfa treatment | Group 4: Pediatric Subjects who received avalglucosidase alfa in either PAP or ETP (N=1)<br>Events in avalglucosidase alfa treatment |
|---|---|---|---|---|---|
| TEAEs | 48 (94.1) | 40 (78.4) | 35 (79.5) | 83 (87.4) | 1 (100) |
| | 19.1 | 12.9 | 9.3 | 28.4 | 0.9 |
| | 251.8 | 310.2 | 375.1 | 292.3 | 112.4 |
| TEAEs potentially related to Study Treatment | 25 (49.0) | 9 (17.6) | 19 (43.2) | 44 (46.3) | 0 |
| | 57.8 | 46.7 | 27.0 | 84.8 | 1.3 |
| | 43.3 | 19.3 | 70.4 | 51.9 | 0.0 |
| Serious TEAEs | 13 (25.5) | 8 (15.7) | 5 (11.4) | 18 (18.9) | 0 |
| | 84.5 | 47.2 | 41.1 | 125.6 | 1.3 |
| | 15.4 | 17.0 | 12.2 | 14.3 | 0.0 |
| Serious TEAEs potentially related to Study Treatment | 3 (5.9) | 2 (3.9) | 0 | 3 (3.2) | 0 |
| | 98.0 | 51.7 | 46.4 | 144.4 | 1.3 |
| | 3.1 | 3.9 | 0.0 | 2.1 | 0.0 |
| Severe TEAEs | 10 (19.6) | 8 (15.7) | 5 (11.4) | 15 (15.8) | 0 |
| | 89.1 | 45.9 | 42.0 | 131.1 | 1.3 |
| | 11.2 | 17.4 | 11.9 | 11.4 | 0.0 |
| TEAEs leading to permanent treatment discontinuation | 2 (3.9) | 2 (3.9) | 0 | 2 (2.1) | 0 |
| | 102.6 | 53.4 | 46.4 | 149.0 | 1.3 |
| | 2.0 | 3.7 | 0.0 | 1.3 | 0.0 |
| TEAEs leading to death | 0 | 0 | 1 (2.3) | 1 (1.1) | 0 |
| | 102.7 | 53.5 | 46.4 | 149.1 | 1.3 |
| | 0.0 | 0.0 | 2.2 | 0.7 | 0.0 |
| Protocol-defined IARs | 16 (31.4) | 6 (11.8) | 15 (34.1) | 31 (32.6) | 0 |
| | 77.1 | 48.8 | 32.9 | 110.1 | 1.3 |
| | 20.7 | 12.3 | 45.6 | 28.2 | 0.0 |

TEAE: treatment-emergent adverse event; IAR: infusion associated reaction

The exposure adjusted incidence rate (EAIR) will be calculated as 100 times number of patients with the specific TEAEs divided by patient years.

The patient year is calculated as time from first treatment infusion to the time of first event; for patients without event, it is calculated as time from first treatment infusion to the last administration + 4 weeks (28 days).

Events in PAP and ETP: include adverse events that developed, worsen or became serious on or after the 1st infusion of avalglucosidase alfa in PAP, and up to 28 days after the last infusion of avalglucosidase alfa in ETP.

Events in ETP: include adverse events that developed, worsen or became serious on or after the 1st infusion of study drug in ETP and up to 28 days after last infusion in ETP.

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*Table 42 - Overview of treatment-emergent adverse events in avalglucosidase alfa treatment - overall - safety population - 97 weeks of extended treatment period*

| | Group 1: Subjects received avalglucosidase alfa in both PAP and ETP | | All (N=96) Group 2: Subjects received alglucosidase alfa in PAP and avalglucosidase alfa in ETP (N=44) | Group 3: Subjects who received avalglucosidase alfa in either PAP or ETP (N=96) | Group 4: Pediatric Subjects who received avalglucosidase alfa in either PAP or ETP (N=2) |
|---|---|---|---|---|---|
| **Number of patients with events (%)<br>Patient years at risk<br>EAIR per 100 patient years** | **Events in PAP and ETP (N=51)** | **Events in ETP (N=51)** | **Events in avalglucosidase alfa treatment** | **Events in avalglucosidase alfa treatment** | **Events in avalglucosidase alfa treatment** |
| TEAEs | 50 (98.0) | 49 (96.1) | 42 (95.5) | 92 (95.8) | 1 (50.0) |
| | 19.8 | 15.5 | 11.1 | 31.4 | 1.5 |
| | 252.6 | 315.8 | 380.0 | 292.8 | 68.1 |
| TEAEs potentially related to Study Treatment | 29 (56.9) | 15 (29.4) | 25 (56.8) | 54 (56.3) | 0 |
| | 75.3 | 78.7 | 45.7 | 121.6 | 2.8 |
| | 38.5 | 19.1 | 54.7 | 44.4 | 0 |
| Serious TEAEs | 17 (33.3) | 12 (23.5) | 10 (22.7) | 27 (28.1) | 0 |
| | 112.6 | 79.8 | 71.5 | 184.7 | 2.8 |
| | 15.1 | 15.0 | 14.0 | 14.6 | 0 |
| Serious TEAEs potentially related to Study Treatment | 4 (7.8) | 3 (5.9) | 2 (4.5) | 6 (6.3) | 0 |
| | 137.3 | 92.0 | 81.5 | 219.4 | 2.8 |
| | 2.9 | 3.3 | 2.5 | 2.7 | 0 |
| Severe TEAEs | 11 (21.6) | 9 (17.6) | 9 (20.5) | 20 (20.8) | 0 |
| | 122.8 | 81.3 | 72.6 | 196.0 | 2.8 |
| | 9.0 | 11.1 | 12.4 | 10.2 | 0 |
| TEAEs leading to permanent treatment discontinuation | 2 (3.9) | 2 (3.9) | 3 (6.8) | 5 (5.2) | 0 |
| | 144.4 | 95.3 | 81.5 | 226.5 | 2.8 |
| | 1.4 | 2.1 | 3.7 | 2.2 | 0 |
| TEAEs leading to death | 0 | 0 | 1 (2.3) | 1 (1.0) | 0 |
| | 144.6 | 95.4 | 81.6 | 226.7 | 2.8 |
| | 0 | 0 | 1.2 | 0.4 | 0 |
| Protocol-defined IARs | 20 (39.2) | 10 (19.6) | 21 (47.7) | 41 (42.7) | 0 |
| | 105.2 | 84.9 | 53.7 | 159.5 | 2.8 |
| | 19.0 | 11.8 | 39.1 | 25.7 | 0 |

The second interim analysis included an analysis of the immune responses in patients who experienced IARs. The analysis presents the total number of IARs, the number of symptoms at each IAR, the number of infusions when the IARs were experienced, the time in the study along with the ADA titers for each of the 2 treatment groups.

In summary, the applicant supports that Nexviadyme provides a wide body of consistent evidence showing meaningful and better effect than Myozyme in LOPD patients, on respiratory and motor function, as well as HrQoL. While statistical significance for superiority is not seen on the predefined primary endpoint, treatment outcomes with Nexviadyme are consistently more favorable than with Myozyme treatment, i.e. allowing patients to function at a better level and with improved quality of life; there is no result that clearly favors Myozyme. In addition:

i) Long-term data also provides evidence of long-term benefit,
ii) There is a clinically relevant benefit with Nexviadyme in IOPD patients who clinically stabilize or improve after starting treatment with Nexviadyme when they declined or did not respond well with Myozyme
iii) The safety and immunogenicity profile of Nexviadyme is improved as compared to that of Myozyme.

Therefore, the applicant maintains that, based on the totality of the clinical data, Nexviadyme provides a better solution for patients in the long-term treatment of Pompe disease than Myozyme and qualifies as a NAS under Indent 3.

### *5.1.2.8. Methods and statistical Discussion*

Pompe disease is a rare disease, the incidence of all types amounts to approximately 1:40 000; the incidence of LOPD is approximately 1:60 000 while the most severe form of IOPD alone affects about 1 in 140 000 newborns (Leslie and Bailey, 2007). The challenges of conducting a clinical trial in conditions with small and very small populations is acknowledged by the EMA Guideline on clinical trials in small populations (CHMP/EWP/83561/2005), indicating that less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results. The guidance highlights the importance of controls and comparator groups, controlled studies with low statistical power in case of an important treatment effect may be preferable to no controlled studies even though the interpretation will be less clear compared to typically sized phase 3 trials. The guidance also concludes that in situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment may accept different approaches if they ensure that the patients' interests are protected. One important point in this EMA Guideline that supports orphan drug development is that "*although p<0.05 is a common but arbitrary threshold for 'statistical significance', no such value is adequate to confirm that a treatment effect truly does exist. In almost all cases, confidence intervals of estimates of the treatment effect are much more informative than P-values. … This will always have to be judged in a case-by-case basis*". The guidance also indicates that, "*for a given size of treatment effect, a larger sample size and/or a smaller variance will result in narrower confidence intervals (CI) and more extreme levels of statistical significance*".

Several publications also advocate that superiority should not entirely be ruled out when p is slightly above 0.05 since p-values alone cannot ensure that a decision is correct or incorrect (Pocock and Ware, 2009, Wasserstein and Lazar, 2016, Moher et al, 2010). Particularly when assessing a treatment for a rare disease, many contextual factors should be considered to derive scientific inferences. The Consolidated Standards of Reporting Trials (CONSORT) statement also encourages the use of confidence intervals and states that "*Authors should particularly avoid the common error of interpreting a non-significant result as indicating equivalence of interventions*" (Moher et al, 2010).

The development strategy for avalglucosidase alfa and the design of the studies to support the MAA were discussed and agreed with CHMP. The strategy and design also follow the FDA's recommendation made at the end-of-phase 2 meeting for EFC14028 study design: "*In addition, instead of directly demonstrating superiority, we suggest you consider a non-inferiority (NI) design. We understand that Pompe is a rare disease, and recruiting a sufficient number of patients for an NI study with 95%-95% rule can be challenging. Therefore you can consider lowering the percentage for the determination of the margin (e.g., 85%).*" In spite of the recognized challenges and limitations of developing a drug in the setting of a rare disease, a robust clinical development plan was conducted to evaluate avalglucosidase alfa in 147 patients (123 adults and 24 pediatric patients) with either LOPD (treatment-naïve or previously treated with alglucosidase alfa) or IOPD. As recommended, a controlled trial was conducted for both LOPD (study EFC14028) and IOPD (study ACT14132). The 2 studies follow the guideline recommendation to provide "*relatively small amounts of high-quality evidence (for example, small randomized trials)*". To our knowledge, study EFC14028 is the first occurrence of an active-controlled study in the population of newly diagnosed patients with Pompe disease, and study ACT14132 is the first occurrence of an active controlled study in any treatment in patients with IOPD.

The pre-defined primary statistical objective of the study was to demonstrate non-inferiority for % predicted FVC, as agreed with regulatory agencies, since recruiting a sufficient number of patients for superiority testing would be challenging due to the rarity of Pompe disease. In the EFC14028 study superiority testing

was powered at a larger effect size, based on prior AGLU02704-LOTS and TDR12857 studies. A common standard deviation (SD) of 5.1% and a true treatment difference of 3.6% were assumed to have more than 85% power to demonstrate superiority of avalglucosidase alfa to alglucosidase alfa. A total sample size of 96 (1:1 randomization ratio) was pre-specified in order to provide approximately 80% power to demonstrate the non-inferiority of avalglucosidase alfa versus alglucosidase alfa, assuming the true difference (avalglucosidase alfa – alglucosidase alfa) is 2.0% predicted. A statistical power of ≥80% is usually considered adequate in small clinical studies (Kianifard, Islam, 2010). In the EFC14028 modified intent-to-treat (mITT) population, the LS mean change (standard error [SE]) from baseline to Week 49 in % predicted FVC was 2.89 (0.88) in the avalglucosidase alfa group, and the difference compared with alglucosidase alfa was 2.43 (95% CI: -0.13, 4.99). The lower boundary of 95% CI was -0.13, exceeding -1.1 (the predefined NI margin of 1.1) and thus achieving the primary study objective of statistical non-inferiority (p=0.0074). However, the p-value for superiority (p=0.0626) was slightly above the pre-specified 5% level of significance and the lower bound of the 95% CI was just below 0, thus statistical superiority was not formally demonstrated.

Study EFC14028 was not sufficiently powered to demonstrate superiority in % predicted FVC. With regard to the power calculation at the time of the study design, as compared to the assumptions made at the end of the trial's PAP, since a smaller treatment difference (2.43%) and a larger standard deviation (6.83%) were observed in study EFC14028, a greater number of patients (evaluated to approximately 2- to 3-fold) would have been required to ensure >80% power to formally demonstrate superiority. With regard to reaching statistical significance, based on the treatment difference observed during the trial's PAP, a few more patients (approximately 10 more patients) would have provided statistically significant results in study EFC14028. Including more patients in a reasonable timeframe is challenging in the context of a rare disease, especially in a population of treatment-naïve patients with great variability at baseline. The EMA guideline recognizes that "*Applications for marketing authorisations in small populations will be judged against the same standards as for other products, although limitations on patient recruitment will be taken into account*". The minimal detectable difference is 2.51% for the primary endpoint based on a sample of 100 patients with 1:1 ratio and a common standard deviation of 6.35%. Several sensitivity and post-hoc analyses aiming to increase sample size and/or reduce variability are presented in the efficacy section, some of them reached a p-value <0.05.

A less conservative approach might have been selected to evaluate superiority, such as statistical significance at 10 % level or a 1-sided test but would have been at higher risk of false positive results. Although statistical superiority was not formally achieved, the results are robust as shown in the efficacy section by the consistent positive effects observed in various pre-specified and post-hoc sensitivity analyses and in the vast majority of clinical outcomes. Therefore, the Applicant maintains that avalglucosidase alfa demonstrated a clinically meaningful improvement in % predicted FVC (LS mean change from baseline [SE] +2.89% [0.88]), and that the observed benefit was clearly greater compared to alglucosidase alfa (LS mean difference [SE] +2.43% [1.29]; 95% CI: -0.13, 4.99). The p-value for superiority (p=0.0626) was very close to the common agreed threshold for statistical significance (p<0.05) and the lower end of the 95% CI was very close to 0, making it unlikely that there is no difference between avalglucosidase alfa and alglucosidase alfa. Although the p-value did not reach 0.05 for the main analysis of % predicted FVC, the evidence in favor of a greater effect of avalglucosidase alfa in general is strengthened by the data on all trial outcomes, some even achieving p <0.05 nominally.

## *5.2. Report from the AHEG*

**FINAL AD HOC EXPERT GROUP ANSWERS ON NEXVIADYME (AVALGLUCOSIDASE ALFA)**

**1) The development of avalglucosidase alfa was aimed at creating a form of alglucosidase alfa with enhanced cellular uptake and thereby a potentially more pronounced therapeutic effect. To achieve this, several copies of bis-mannose-6-phosphate (M6P) was conjugated to oxidized sialic acid residues on alglucosidase alfa. Please discuss the potential relevance of increased cellular uptake based on eg. external support from literature or other scientific sources.**

The experts agreed that the presence and amount of M6P moieties are pivotal for the enzyme replacement therapy (ERT) to improve cellular uptake and lysosomal targeting, even if the enzyme is the same protein. Cellular uptake and lysosomal targeting are important steps to allow the therapeutic effect to take place (1,2,3,4,5,6,7,8,9,10,11,12,13,14).

It was also explained that the absence of correlation between tissue glycogen depletion and glycosylation is expected since the enzyme binding to the receptor occurred in 1:1 ratio through the mannose 6-phosphate moieties and an optimal cellular uptake could be reached with 1-1.5 M6P, continuous increase in M6P is not expected to have a more pronounced therapeutic effect. It was further noted that dose comparison between Myozyme and Nexviadyme may not be suitable since the M6P content for Myozyme is lower compared to Nexviadyme and appeared to have fallen over time, possibly as low as 0.8-0.9 [1](15,16,17,18,19). This change was viewed as impacting on the biological effect of Myozyme with around one third of the ingredient, being possibly therapeutically active.

From a patient perspective it was commented that most patients decline on Myozyme and considered the suboptimal cellular uptake of Myozyme as questionable. At the same time, the patient representative was reassured to hear from all the experts that Nexviadyme could address the issue.

The experts also discussed the correlation between the enzyme activity and the disease progression in patients with Pompe. The experts agreed that there was a good correlation, as seen in clinical practice with differences in disease progression for IOPD and LOPD patients. However, the experts mentioned that other modifying factors can contribute to the clinical progression in addition to the enzyme activity in Pompe patients, and thus a dosage adjustment according to patients' characteristics is theoretically warranted but impossible to implement in reality . Whereas there is clear positive dose-response with ERT, there are limitations in increasing the dosage treatment most possible related to safety concerns. An expert indicated that there is no literature evidence about when a maximum level of enzyme activity can be reached, although 8 weeks could be a reasonable time to consider.

Post-meeting note: a list of literature references has been provided to support answers to question 1.

**2) Please discuss if the results of the pivotal phase 3 study can provide support for a meaningful clinical impact of the structural modification of Nexviadyme (avalglucosidase alfa) compared to Myozyme (alglucosidase alfa).**

[1] Upon further evaluation of this information, the Agency concluded that there are no indications that the potency of Myozyme would have decreased over time.

Based on the pivotal study EFC14028 results, the experts agreed that Nexviadyme is non inferior to Myozyme (non inferiority margin= 1.1%, p=0.0074 on the Force Vital Capacity (FVC)% predicted change from baseline). The experts agreed that the FVC % predicted change from baseline, as a primary endpoint was relevant, since the effect on the diaphragm muscle was seen as clinically important in Pompe disease, particularly as a prognostic factor for patients' improvement, since respiratory failure is the main life-threatening complication of Pompe disease.

The experts considered that the superiority of Nexviadyme over Myozyme cannot be concluded based on the primary endpoint results from study EFC14028 as it failed to show superiority from a statistical viewpoint (p=0.0626). As regards the respiratory outcome and the importance of statistical significance, one expert reminded that in the LOTS trial (14), FVC reached statistical significance compared to the untreated group (in which FVC continued to decline; and indeed, in the COMET trial also, the group treated with Myozyme only stabilizes), but actually only a stabilization occurred; on the contrary, in the COMET trial, while statistical significance was nearly missed (p=0.0626), a clinically meaningful improvement in respiratory function is observed. The improvement of other respiratory outcome measures (ie maximal inspiratory pressure) also supports an appreciable clinical impact on respiratory function from the expert's view.

Nevertheless, the majority of experts were of the view that clinically meaningful improvements were reached in clinical endpoints for the respiration, mobility, functional scores such as R-PACT and GSGC score, motor function and quality of life (QoL) in patients with LOPD; moreover, for most of these measures, the lower limit of the confidence intervals were above zero, suggesting a low or null proportion of non-responders, that is another important point to consider since a proportion of patients treated with Myozyme showed a poor response already from the beginning. Specifically, a clinically meaningful change in 6MWT has been reported ranging from 14-57 meters in different studies conducted in pulmonary disorders (20,21). Whereas there is a lack of evidence with regard to other chronic myopathies, some experts expressed the view that due to the poor regeneration potential of damaged muscles, it would be expected to observe less clinical differences in 6MWT in Pompe disease. As such, the observed difference of 30 meters between Nexviadyme and Myozyme treatments was considered clinically meaningful in the studied population.

One expert commented that the pivotal study was not powered to show superiority, due to the small size of the population (around 50 patients per group) and considered that the efficacy results for the primary and secondary endpoints, altogether were sufficiently convincing that Nexviadyme was superior to Myozyme from a clinical perspective. In addition, this expert mentioned that a notable difference in glycogen clearance on the diaphragm muscle was observed in non-clinical experiments in mice with 76% vs 16% for Nexviadyme and Myozyme, respectively and that the presented efficacy biomarkers (urinary Hex4 and Creatine Kinase) also indicated better results for Nexviadyme as compared to Myozyme. An additional expert also agreed that there was sufficient evidence to conclude that Nexviadyme was superior to Myozyme, based on the view expressed for question 1.

But there were as well other experts expressing a different view considering that study ECF14028 failed to statistically show superiority on the primary endpoint and that therefore it was not possible to draw conclusions on meaningful clinical improvement of Nexviadyme over Myozyme for the secondary endpoints.

The experts noted the comparative results were available until week 49 and that long term efficacy of Nexviadyme remains to be seen. Nevertheless, the experts commented that in general, ERT has shown functional improvement that subsequently stabilized to a plateau followed after this, by a decline over the years. This can be partly explained by the expected physiological decline with age and probable secondary factors. Such observations support a better efficacy of ERT when an earlier start of treatment is done, and

this has been documented in patients diagnosed throughout newborn screening versus those clinically diagnosed later on. However, it also raises the problem with the use of ERT in the long term for these patients, when secondary effects (e.g autophagia; mitochondrial dysfunction) occur and cannot be mitigated by the ERT. In those circumstances, some experts were of the view that even small clinical improvements in ERT treated patients can have greater impact on QoL for patients. This view was shared by both patient representatives.

With regard to the safety, no firm conclusions could be drawn on an improved safety profile of Nexviadyme as compared to Myozyme, in the absence of further comparative long term data. One expert observed that safety has never been a major concern for Myozyme also, at least for adults, and that it may be difficult to demonstrate improved safety in a small population and compare with a product that was already known to be generally safe in clinical practice. In addition, some experts commented that glycosylation can play a role in protecting from anti-drug antibodies (ADA) development and were convinced on an improved immunogenicity profile, since lesser patients with high ADA titers (>51,200) and infusion reactions were reported in the Nexviadyme group (5.8% vs 20.4% and 25.5-32-7% vs 29.4-40.8%, respectively) as compared the Myozyme group. One expert commented to not agree with this statement since the comparative data did not contain any statistical results and only a few patients could be included in these short term analyses.

The experts also noted that there was a lack of efficacy and safety data in IOPD patients and expressed the view that comparative data on immunogenicity would have been relevant to collect in this population where a more pronounced immunological effect is expected.

Both patient representatives emphasised the clinical importance of patients reported outcome/QoL parameters. In particular, a call was made to collect information on the effect on fatigue.

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## *5.3. Overall conclusion on grounds for re-examination*

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the AHEG.

**CHMP position on Ground #1**

*Scope*

The Applicant requests a re-examination of the claim for new active substance (NAS) status for avalglucosidase alfa, the active substance in the final product Nexviadyme.

This part of the assessment report evaluates the Applicant's claim to the first indent of the definition of NAS: "a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union". The first indent addresses the active substance structure only without considering evidence on the potential clinical implications of its structure or part of the structure.

*Background*

Currently, Myozyme (alglucosidase alfa; not an orphan medicinal product anymore (since 2016)), is the only approved enzyme replacement therapy and is the current standard of care for Pompe disease. Alglucosidase alfa is targeted to the lysosome of cardiac and skeletal muscle by the cation independent mannose-6-phosphate receptor (CIMPR). Alglucosidase alfa has extremely low levels of bis-M6P- N-linked glycans, the bivalent ligand required for high affinity binding to the CIMPR.

The molecular structures of avalglucosidase alfa (Nexviadyme) and alglucosidase alfa are described in sufficient detail in the dossier of the original procedure and specific features highlighted in the grounds for re-examination. In the manufacturing process of avalglucosidase alfa, alglucosidase alfa is expressed and further purified and processed to be conjugated with several copies of a synthetic glycan (bisM6P). This glycan, and the linker, is specifically selected to optimize the target receptor binding properties of the molecule and is conjugated to all seven N-glycosylation sites on alglucosidase alfa. Consequently, a molecule of avalglucosidase alfa contains seven copies of bisM6P. Each bisM6P is conjugated to a sialic acid on the alglucosidase alfa, via a linker. The natural post-translational process for alglucosidase alfa results in two sites observed to potentially present phosphorylated mannose type glycans.

In their re-examination request, the Applicant refers to the variation regulation, the EMA guideline on similar biological medicinal products (CHMP/437/04 Rev 1), the orphan regulation, the WHO INN, and the ATC code to elaborate their case further.

*Established practice*

It has been consistent CHMP practice to apply the first indent verbatim, as follows:

An active substance that is not previously authorised in a medicinal product for human use in the European Union and that is from a structural point of view not related to any other authorised substances should be considered as a NAS. Such substance is considered to be new in itself (i.e. first indent) when the administration of the applied active substance would not expose patients to the same therapeutic moiety as already authorised active substance(s) in the European Union[2]. Cases where active substances are structurally related and where the administration of the applied active substance does expose patients to the same therapeutic moiety, fall under the third indent.

*Assessment of NAS claim for Nexviadyme based on first indent*

If the biological active substance is structurally related to an already approved active substance(s) in the EU, it should first be assessed whether it shares the same therapeutic moiety at the site of the biological activity as the already approved active substance. If the answer is in the negative, then the active substance is a NAS in itself (indent 1). On the contrary, if the answer is in the affirmative, the candidate active substance may only be granted NAS status if it differs significantly in properties with regard to safety and/or efficacy (indent 3, discussed below). This principle has been used consistently in previous NAS assessments for biologicals. In addition, the same principle is in analogy to the criteria set out in the reflection paper on the determination of NAS status for chemical active substances.

For qualification as a NAS, the main molecular entity should be demonstrated to be more than slightly different from the basic structural element(s) contained in a medicinal product authorised in the EU (that is, at the EU level or national level). The main molecular entity is considered to be the basic structural element(s) without added functional structures.

[2] This principle, with slightly different/targeted wording is laid down in https://www.ema.europa.eu/en/chemical-structure-properties-criteria-be-considered-evaluation-new-active-substance-nas-status

For proteins, the amino acid sequence is considered as the basic structural element. Proteins containing differences in the amino acid sequence would normally be considered NAS. Importantly, changes introduced in the basic structural element should not be trivial (for example a conservative mutation of an amino acid only) in order to be sufficiently substantial to warrant a conclusion of NAS.

Where a molecular structure with the same basic structural element is produced but has additional post-translational modifications, such a structure would normally be considered as known active substance unless it can be shown that these modifications have a clinical impact in terms of safety or efficacy (such impact would be evaluated under indent 3). Where additional molecular structures are chemically attached as part of the downstream manufacturing process, that is covalently bound, with or without a linker to the basic structural element and such structures are not present in the authorised product, or located at different positions within this basic structural element, the whole molecule would normally be considered as known active substance, unless it can be shown that these modifications have a clinical impact in terms of safety or efficacy (such impact would be evaluated under indent 3).

The amino acid sequences of alglucosidase alfa and avalglucosidase alfa are the same. The synthetic glycans conjugated to the amino acid backbone are not considered part of the basic structural element. Therefore, the therapeutic moiety that the patient is exposed to, is the same, and a first indent NAS claim cannot be granted.

This conclusion is consistent with the previous CHMP positions on Rekovelle and Zinbryta. In both cases the NAS claim under indent 1 was not accepted (same aminoacid sequences to authorised products) and the applicants were asked to demonstrate that the difference in glycosylation had an impact on safety and/or efficacy (i.e. under indent 3).

It is also noted that increased in vitro target receptor affinity and increased cellular uptake is demonstrated for avalglucosidase alfa in comparison to alglucosidase alfa. The impact of the difference in increased binding to soluble CIMPR, in terms of translation to a clinical effect is unknown. The same limitation applies to the increased cellular uptake observed in Pompe fibroblast cells and proteolytic processing to the most active form as shown by Western blot. However, these results fall outside the assessment under indent 1 and will therefore be further elaborated under indent 3.

*Assessment of claims based on other documents*

In general, it is noted that NAS for biologicals is only defined in the NtA. Consequently, claims cannot be defended by applicants on the basis of other documents which a) have a different scope and b) do not define or further elaborate on how to support a NAS claim.

Therefore, references to the variation regulation and the guideline on similar biological products are considered not appropriate in this context as they do not provide guidance on how NAS claims should be supported.

The CHMP noted that the variation regulation acknowledges that active substances may be variable and that minor differences, if properly justified by the applicant do not block approval of a "replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different".

The guideline on similar biological products, states verbatim *'Intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach.'* In other words, an applicant must either claim that an active substance is similar (in which case it can be a biosimilar) or that it is different (where glyco-optimisation, with claimed different safety and/or efficacy, is given as an example only). If

similarity is claimed, then the applicant should prove that observed variability is slight and not clinically relevant. If differences/newness is claimed, then the applicant should prove that the observed variability is clinically relevant.

The principal molecular structural features (PMSF) considerations, as provided in orphan legislation, are not applicable for NAS assessment since it does not deal with market exclusivity.

INN assignment does not substantiate NAS status based on the NtA, as the criteria for INN assignment and NAS status are not the same. The INN is assigned by WHO and this takes place in advance of the evaluation of a MAA and it is based on a more limited data package. Therefore, the existence of a distinct INN can only be considered supportive and not pivotal to claim NAS status.

Likewise, the criteria applied by WHO for the assignment of the ATC code are not the same as the criteria for the NAS.

For the reasons mentioned above (the conclusion regarding molecular structure and the assessment of the different points raised by the Applicant), avalglucosidase alfa is not considered to qualify as a new active substance under indent 1 of the NAS definition. Any potential impact to clinical efficacy or safety is assessed under the claim to indent 3. As noted above, this conclusion is consistent with the previous CHMP positions on Rekovelle and Zinbryta.

**CHMP position on Ground #2**

At the applicant request, the AHEG was convened and the CHMP requested their view on the meaningful clinical impact of the structural modification of Nexviadyme (see 5.2).

*Non-clinical considerations*

Zhu et al. (2009) compared a single concentration of avalglucosidase alfa (20 mg/kg) with rhGAA (20 and 100 mg/kg) in a murine model for Pompe disease. During functional evaluation avalglucosidase alfa appeared to be more effective in young animals with increased potency, whereas in elderly animals 40 mg/kg avalglucosidase alfa is deemed to be equipotent to rhGAA dosed at 40 and 100 mg/kg. A stringent dose-dependency for efficacy of avalglucosidase alfa is not shown, so that potency is hard to be evaluated.

Since the glycosylation of avalglucosidase alfa is claimed to be responsible for efficacy, various glycan conjugates have been investigated in study 09-3981. It is clear, that there is no stringent correlation between incrementing avalglucosidase alfa glycosylation and tissue glycogen depletion in triceps, quadriceps, psoas and diaphragm. Importantly, avalglucosidase alfa conjugates were significantly less effective than alglucosidase in reducing glycogen in skeletal muscles in this study. Thus, again a consistent effect on efficacy is not documented. In the line of the latter observations there is no increase in glycogen depletion upon incrementing the dose from 12 to 20 mg/kg avalglucosidase alfa in triceps, psoas and diaphragm (study 10-00587). Conversely, rhGAA increments efficacy upon switching from 60 to 100 mg/kg. Thus, it is completely unclear why an increased potency of avalglucosidase alfa does not translate into an increased efficacy consistently.The CHMP noted the comment from the AHEG that the absence of correlation between tissue glycogen depletion and glycosylation is expected since the enzyme binding to the receptor occurred in 1:1 ratio through the mannose 6-phosphate moieties and an optimal cellular uptake could be reached with 1-1.5 M6P, continuous increase in M6P is not expected to have a more pronounced therapeutic effect. Subsequently the applicant argued and though the ratio of enzyme to CIMPR binding is 1:1, there is a dose

responsive increase in CIMPR binding, cell uptake and glycogen clearance with increasing levels of M6P. From the applicant's point of view cell uptake increases with increasing glycan content with a plateau following the conjugation of more than 3 glycans. This is based on the submitted non-clinical data in Pompe mice in which the conjugation of at least 3 glycans were needed to see maximal glycogen clearance following 4-weekly doses (Study 09-3981). Since alglucosidase alfa contains, on average, 1 M6P, the applicant considered that these data demonstrate that at least 7 M6P (from 3 bisM6P glycans and 1 M6P present on alglucosidase alfa) are required for maximal pharmacodynamic effect, not 1-1.5 M6P.

Acknowledging the different AHEG and applicant views with regards to the optimal M6P content required for a maximal therapeutic effect, the CHMP was of the opinion that from a preclinical perspective, results point towards an improved efficacy of avalglucosidase alfa, since the M6P content for Myozyme is lower compared to Nexviadyme. Avalglucosidase alfa showed an improved potency in terms of tissue glycogen reduction compared to rhGAA which varies between 3-7 fold. However, due to variability in efficacy between different tissues, and also an apparent plateau effect at higher doses of avalglucosidase alfa, overall superiority of avalglucosidase alfa could not be concluded based on non-clinical PD studies.

In preclinical experiments there is no indication of improved safety of avalglucosidase alfa over rhGAA. Results on immunogenicity that had been collected in most of the preclinical studies are inconclusive; thus, immunogenicity is higher for avalglucosidase alfa compared to rhGAA in studies 07-1948 and 10-00587. The avalglucosidase alfa conjugates to various glycans, in contrast, resulted in less anti-drug antibody titres (study 09-3981) than rhGAA.

In conclusion, the preclinical database on avalglucosidase alfa does not allow to support the NAS claim.

*Clinical efficacy considerations*

The EMA guideline on clinical trials in small populations (CHMP/EWP/83561/2005) highlights that most indications in rare diseases follow the usual methodological requirements. More importantly, it states that deviations from expected standards should be pre-planned and fully justified. The guideline also specifies that any justification for deviations from generally accepted rules should be done prospectively (i.e. in the study protocol), and that an orphan drug status is not sufficient justification in itself. The use of less conventional methods was not pre-specified and prospectively justified. Claims of superiority of avalglucosidase alfa based on secondary, sensitivity or post-hoc analyses were therefore not agreed from a methodological point of view.

Several post-hoc analyses to support the clinical efficacy data in patients with LOPD were conducted:

- Responder analyses have been performed with thresholds based on PGIC Ability to Breathe used as an anchor. The results appear to be consistent with pre-specified analyses.
- An analysis is provided where treatment-naïve patients from historical study ALGLU02704/LOTS who received alglucosidase alfa 20 mg/kg qow are pooled with patients randomized to alglucosidase alfa in study EFC14028. Baseline characteristics are said to be adjusted for, but no information is provided on the statistical methods used to perform these analyses. More generally, it should be noted that there are clear limitations associated with the use of external control data, as the presence of bias is likely and difficult to quantify.

- Another analysis is provided where treatment-naïve patients who received avalglucosidase alfa 20 mg/kg qow in study TDR12857/LTS13769 are pooled with patients randomised to avalglucosidase alfa in EFC14028. Similar limitations apply.
- A sensitivity analysis has been performed when excluding the largest worsening in the avalglucosidase alfa group, considered to be an outlier. As acknowledged by the Applicant, removing a single (and the smallest) value from the avalglucosidase alfa group is debatable, and a potential under- or over-estimation cannot be concluded based on this analysis.
- The Bayesian analysis is used by the Applicant to provide probabilistic statements on the parameter of interest (mean treatment difference in %predicted FVC). This is helpful for interpretation purposes, however it does not actually provide new information compared to the original frequentist analysis (the posterior distribution being essentially the same as the likelihood in the absence of an informative prior).
- Cumulative probability functions are also provided to visualise the endpoint distribution

These analyses provided an estimate of treatment effect consistent with the primary analysis estimate and other pre-specified analysis results. However, they are not pre-planned and some of them are potentially biased or do not bring additional information.

Regarding the long-term efficacy of alglucosidase alfa, a decline in respiratory and motor function was observed after 2-3 years of treatment. However, this is based on retrospective observations. Furthermore, an update of the 97-week (2 years) data from the pivotal study did not appear to show a continuous improvement of the avalglucosidase effect on 6MWT and FCV but rather a stabilisation.

Considering the uncertainties of the 2-year data for avalglucosidade alfa and the fact that the long-term efficacy data of alglucosidase alfa after 2-3 years of treatment are based on observational studies, it is difficult to conclude on a difference in long-term efficacy of avalglucosidase compared to alglucosidase. Additional six-year data from long term extension study were also presented and only confirmed that effect on FVC and 6MWT could be sustained but comparison to alglucosidase is limited and no new conclusions could be drawn from these data.

Post-hoc ANCOVA analyses were also performed on the trial to further assess efficacy endpoints in patients with IOPD (Study ACT14132/Mini-COMET), and updated long-term data were provided on a more recent cut-off (30th April 2021). These analyses are of exploratory or descriptive nature.

Due to the design, the small size, and the descriptive nature of the results in secondary and tertiary efficacy outcomes, this study does not allow to deliver conclusions on avalglucosidase alfa efficacy in this setting.

Taken together, these additional analyses, while showing consistency with previously submitted results, do not provide sufficient evidence to change the conclusions on avalglucosidase alfa efficacy compared to alglucosidase alfa.

The majority of the AHEG experts were of the view that clinically meaningful improvements were reached in clinical endpoints for the respiration, mobility, functional scores such as R-PACT and GSGC score, motor function and quality of life (QoL) in patients with LOPD; moreover, for most of these measures, the lower limit of the confidence intervals were above zero, suggesting a low or null proportion of non-responders. Nevertheless, the demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in the primary endpoint % predicted FVC at Week 49 was missed at the required significance level, and the CHMP therefore remains of the opinion

that all subsequent statistical tests for the secondary endpoints in the pre-specified hierarchy could not formally be carried out. under adequate experiment wise type-1-error control.

*Clinical safety considerations*

Alteration or masking of epitopes by the additional bisM6P-hexamannose glycans added to the N-linked glycan structures already present in alglucosidase alfa is hypothesized, which could disrupt epitopes in the molecule or cause increased steric interference of ADA binding. At this stage, the relevant and direct impact of the chemical modifications (glycosylation) of the molecular structure on the safety of avalglucosidase alfa versus alglucosidase alfa in IOPD and LOPD patients, notably regarding their immunology profile, cannot be established considering the main following limitations hampering data robustness:

- low number of exposed patients;
- need of long-term comparative safety data (EFC14028 PAP duration was 49 weeks with 49 LOPD naïve patients randomized to alglucosidase alfa and 51 naïve LOPD patients to avalglucosidase alfa);
- low number of ADA positive patients in each peak titer categories in study EFC14028; confounding influence of previous exposure to alglucosidase alfa in the 22 IOPD patients in study ACT14132, all experienced (PAP duration of 6 months, 16 patients randomized to avalglucosidase alfa and 6 to alglucosidase alfa);
- confusing definition and assessment of AE relationship to treatment.

The CHMP noted that no firm conclusions could be drawn on an improved safety profile of Nexviadyme as compared to Myozyme by the AHEG, in the absence of further comparative long term data.

In view of the provided efficacy and safety data, no clinically significant difference could be demonstrated.

Therefore, the CHMP maintains it view that avalglucosidase alfa in comparison to alglucosidase alfa previously authorised as a medicinal product in the European Union is not to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

## *5.4. Risk Management Plan*

### 5.4.1. Safety concerns

| | |
|---|---|
| Important identified risk | Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies |
| Important potential risks | Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies) |
| | Medication error in home infusion setting |
| | Immune complex related reactions |
| Missing information | Use in pregnant and lactating women |
| | Use in patients with renal or hepatic insufficiency |

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

## 5.4.2. Pharmacovigilance plan

| Study status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| Not applicable | | | | |
| Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| Not applicable | | | | |
| Category 3 - Required additional pharmacovigilance activities | | | | |
| LTS13769<br>Ongoing | Evaluate long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies".<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q4 2022 |
| EFC14028 (COMET)<br>Ongoing | Primary objective is 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.<br>Secondary objectives are to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies"<br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br>"Medication error in home infusion setting".<br>"Immune complex related reactions". | Report submission | Q1 2025 |

| | | | | |
|---|---|---|---|---|
| | (QMFT), and health-related quality of life (SF-12).<br><br>The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including adverse events of special interest and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with neutralizing antibodies in ADA-positive patients) are evaluated 1 week following the 1st infusion in ETP, then monthly through Week 73, then every 12 weeks up to the end of the follow-up. | | | |
| ACT14132 (Mini-COMET)<br><br>Ongoing | Primary objective is to evaluate the safety profile of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa. | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies".<br><br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br><br>"Medication error in home infusion setting".<br><br>"Immune complex related reactions". | Report submission | Q4 2025 |
| EFC14462<br><br>Planned | Primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment.<br><br>Secondary objectives are to determine the effect of avalglucosidase alfa treatment on survival and invasive ventilator-free | "Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies"<br><br>"Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)".<br><br>"Medication error in home infusion setting". | Report submission | Q2 2027 |

| | | | | |
|---|---|---|---|---|
| | survival at 12 and 18 months of age, as well the change in LVM-Z score; AIMS score; body length, body weight, and head circumference Z scores; and urinary Hex4 at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa. | "Immune complex related reactions". | | |
| DIREGC07005 (Pompe Disease Registry)<br>Planned | The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression, and management of Pompe disease including patients treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency. | "Use in patients with renal or hepatic insufficiency" | Start of data collection<br>End of data collection<br>Final cumulative report submission | Q3 2021<br>Q4 2031<br>Q3 2032 |
| AGLU03506 (Pompe Disease Pregnancy Sub-registry)<br>Planned | The primary objective of this Sub-registry is to track pregnancy outcomes, including complications and infant growth, in all women with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERT with alglucosidase alfa or avalglucosidase alfa.<br>This Sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated. | "Use in pregnant and lactating women" | Start of data collection<br>End of data collection<br>Final cumulative report submission | Q3 2021<br>Q4 2031<br>Q3 2032 |
| Post-Authorization Safety Study | This study aims at gathering more comprehensive safety information on | "Infusion associated reactions including hypersensitivity and anaphylactic reactions, | Final protocol | Q1 or Q2 2022 |

| | | | | |
|---|---|---|---|---|
| Planned | avalglucosidase alfa in a structured way to further characterize the important identified risk of infusion associated reactions, including hypersensitivity and anaphylactic reactions, and the important potential risk of medication error in the setting of clinical/ hospital and home infusion. | with or without development of IgG and IgE antibodies"<br>"Medication errors in home infusion setting" | Final report submission | Q2 2028 |

6MWT: 6-Minute Walk Test; ADA: Anti Drug Antibody; AIMS: Alberta Infant Motor Scale; ETP: Extended Treatment Period; ERT: Enzyme Replacement Therapy; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LVM-Z: Left Ventricular Mass Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure; PK: Pharmacokinetic; Q: Quarter; QMFT: Quick Motor Function Test; SF-12: 12 Item Short Form Health Survey.

## 5.4.3. Risk minimisation measures

| Safety concern | Risk minimization measures |
|---|---|
| Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies | **Routine risk minimization measures**:<br>Labeled in sections 4.4 and 4.8 of SmPC.<br>Labeled in section 2 of PL.<br>Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of adverse reactions are included in SmPC section 4.2.<br>Instructions to mitigate the infusion associated reactions are included in SmPC section 4.4.<br>How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 4.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (HCP guide for immunosurveillance service and Home infusion guide). |
| Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies) | **Routine risk minimization measures**:<br>Labeled in sections 4.4 and 4.8 of SmPC.<br>Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in section 4.4 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (HCP guide for immunosurveillance service). |
| Medication error in home infusion setting | **Routine risk minimization measures**:<br>Labeled in sections 4.2 and 6.6 of SmPC.<br>Labeled in sections 3 and 5 of PL. |

| Safety concern | Risk minimization measures |
|---|---|
| | Decision criteria to have a patient move to home are included in SmPC section 4.2, as well as the description of home infusion infrastructure, resources, and procedures.<br>The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in SmPC section 6.6.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>Educational materials (Home infusion guide). |
| Immune complex related reactions | **Routine risk minimization measures**:<br>Not applicable<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |
| Use in pregnant and lactating women | **Routine risk minimization measures**:<br>Labeled in section 4.6 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |
| Use in patients with renal or hepatic insufficiency | **Routine risk minimization measures** Labeled in sections 4.2 and 5.2 of SmPC.<br>Prescription only medicine.<br>**Additional risk minimization measures**:<br>None |

### 5.4.4. Conclusion

The CHMP considered that the risk management plan version 1.3 is acceptable.

## *5.5. Pharmacovigilance*

### 5.5.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 5.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in

the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *5.6. Product information*

### 5.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 5.6.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reason: vial label does not have the space necessary to display all required information in a suitable and readable font size.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

### 5.6.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nexviadyme (avalglucosidase alfa) is included in the additional monitoring list as it is a biological product, which will be authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 6. Benefit-risk balance following re-examination

## *6.1. Therapeutic Context*

### 6.1.1. Disease or condition

Avalglucosidase alfa is intended for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA). Defects in both alleles of the gene for GAA, located on chromosome 17q25, result in reduced or absent enzyme activity, leading to progressive intralysosomal accumulation of undegraded glycogen. The

resulting damage to affected cells produces a range of symptoms that characterize Pompe disease, including metabolic myopathy leading to neuromuscular dysfunction and ultimately death.

Currently, over 500 mutations of GAA, including missense, nonsense, splicing defect, and frameshift mutations, have been found. According to the variety of mutations, clinical presentation of Pompe disease is heterogeneous in timing, severity, and ranges of symptoms observed. The disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. The phenotypes range from a rapidly progressive infantile-onset form (IOPD) characterized by virtually complete absence (less than 1%) of acid alpha-glucosidase (GAA)-activity to a more slowly progressive late-onset form (LOPD).

Infantile-onset Pompe disease (IOPD), which represents up to one third of the cases, becomes manifest in the first months of life. Affected patients present with creatinine kinase elevations, hypertrophic cardiomyopathy (HCM), failure to thrive, muscular hypotonia and axial muscle weakness. IOPD is rapidly progressive, and the majority of untreated subjects die within the first year of life due to a combination of ventilatory and cardiac failure without achieving any motor milestones such as turning, sitting, or standing. Survival beyond the age of 18 months is exceptional.

The majority of patients with Pompe disease present after infancy with late-onset Pompe disease (LOPD), which takes a more variable course. In untreated patients, undegraded glycogen accumulates in diaphragm and respiratory muscles, and respiratory function declines over time, leading to dependence to external ventilation and, ultimately, to respiratory failure which is the most common cause of death regardless of age of disease onset. Glycogen also accumulates in skeletal muscles, and motor function declines over time, leading to problems with activities of daily living, reduced mobility, and eventually dependence on wheelchair. Quality of life is usually severely affected by the burden of the disease.

The estimated global incidence of Pompe disease is 1:40 000, with variations in incidence reported between different ethnic groups and clinical forms. Avalglucosidase alfa gained Orphan designation in 2014 with an estimated number of affected patients below 1/10,000 people in the EU, equivalent to around 51,000 people.

### 6.1.2. Available therapies and unmet medical need

Development and approval of ERT has profoundly changed the natural course of the disease, revealing new phenotypes in patients with classical IOPD who survive with ERT, and considerably extending productivity and quality of life for patients with LOPD. However, it is recognized that the progressive decline in muscle function in patients with Pompe disease is not completely abrogated with alglucosidase alfa ERT.

Studies in LOPD patients suggest that some patients on alglucosidase alfa continue to exhibit some decline in respiratory function, albeit at a slower pace than prior to treatment. Responses to treatment in LOPD patients vary and there might be room for improvement in individual patients, but overall there is not a huge unmet medical need in this population.

With respect to IOPD patients, literature data (Chien et al, 2015) indicate that some patients treated with Myozyme exhibit declines in motor function and mobility starting at 18-24 months of age, despite an initial decrease in CK levels. The reasons for the variable efficacy of ERT and the progression of disease with time are manifold and only imperfectly understood. Known factors include age at start of therapy and pre-treatment muscle pathology, CRIM-status and antibody titers, distribution of type I and II fibers, and altered autophagy (Kishnani et al., 2012).

Although ERT has substantially improved the prognosis of IOPD, mortality is still considerable, and decline of motor function over time is frequent in long-term survivors. Thus, further efforts are necessary to improve the outcome of children affected by this most severe form of Pompe disease, indicating an unmet medical need in IOPD patients deteriorating on the available ERT.

### 6.1.3. Main clinical studies

Study EFC14028 (COMET) in LOPD population

The main evidence of efficacy comes from a single phase III multicenter, randomized, double-blind study comparing avalglucosidase alfa (n=51) to alglucosidase alfa (n=49) in treatment-naïve LOPD patients from 3 years of age. The study comprises a primary analysis period (49 weeks) followed by an extended treatment period. The primary objective of study EFC14028 was to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by forced vital capacity (FVC)% predicted in the upright position, as compared to alglucosidase alfa.

The primary statistical objective was to test the non-inferiority (NI) of avalglucosidase alfa versus alglucosidase alfa at 5% level of significance. The non-inferiority (NI) of avalglucosidase alfa to alglucosidase alfa was to be investigated first before progressing to investigation of superiority.

Secondary objectives were to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT, key secondary endpoint), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health related quality of life (SF-12).

Study ACT14132 (Mini-COMET) in IOPD population

Additional evidence of efficacy comes from a multicenter, multistage phase II, open-label, ascending dose cohort study in 22 patients under 18 years of age with IOPD, who were previously treated (treatment-experienced) with alglucosidase alfa for at least 6 months. The study comprises a primary analysis period (week 25) followed by an extended treatment period. The primary objective of the ACT14132 study was the assessment of safety and tolerability of administering avalglucosidase alfa. The secondary objectives were characterization of the pharmacokinetic profile of avalglucosidase alfa and evaluation of the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. Efficacy endpoints in ACT14132 included motor function (evaluated through functional and clinical outcome assessments and 6-minute walk test [6MWT]), respiratory function (evaluated through pulmonary functional testing [PFT] and ventilator use questionnaire), quality of life, pain, cardiac function (echocardiography) and eyelid position measurements.

## *6.2. Favourable effects*

LOPD population

- The main evidence of efficacy and safety is based on a randomized, double-blind, active controlled study including 100 patients. The active comparator was alglucosidase alfa, an approved medicinal product of established therapeutic value, and currently the standard of care.
- The primary objective of the Phase 3 study EFC14028 was met by demonstrating non-inferiority of respiratory function as measured by % predicted FVC as compared to alglucosidase alfa at week 49. In the

mITT population, the LS mean change from baseline to Week 49 in % predicted FVC was 2.89 in the avalglucosidase alfa group and 0.46 in the alglucosidase alfa group. The difference in mean change (from baseline to Week 49) of 2.43 with lower boundary of 95% CI of -0.13 exceeded the predefined NI margin of -1.1 and thus achieved statistical significance (95% CI: -0.13, 4.99; p=0.0074)

- Results of a pre-planned sensitivity analysis of the primary efficacy endpoint done in the PP population support the non-inferiority conclusion: LS mean difference FVC% predicted at week 49 was 2.69 (95% CI: -0.06, 5.44; p=0.0076).
- The LS mean difference in distance walked in meters in the 6MWT (key secondary endpoint) was 30.01 (95% CI:1.33, 58.69).
- Subgroup analyses for study EFC14028 (primary efficacy endpoint, % predicted FVC), performed by age group (<18 years, ≥18 years to <45 years, ≥45 years old), gender, baseline FVC groups (<55%, and ≥ 55%), region, baseline walking device use, baseline 6MWT distance, duration of disease at baseline, and race indicate consistency of results across subgroups.

IOPD population

The descriptive results of study ACT14132 show positive trends (stabilization or improvement) in secondary and tertiary efficacy outcomes with avalglucosidase. During the primary analysis period (PAP), Gross Motor Function Measure-88 (GMFM-88) mean scores increased modestly from baseline to Week 25 in all four treatment groups (Cohort 1: 2.62, Cohort 2: 3.54, Cohort 3: AVAL: 4.20, AGLU: 6.82)

Home infusion

- As of 31 May 2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Few non-serious events was reported at the first administration at home (eyelid edema and flushing), which was treated appropriately and resolved at the same day. Current data do not indicate an increased risk of IARs or medication errors with home infusion in adults. No medication error occurred in the setting of home infusion.

## *6.3. Uncertainties and limitations about favourable effects*

LOPD population

- The pivotal trial was performed in adult LOPD patients, only two subjects were below the age of 18 years and included a 9 years old patient that was enrolled after the study cut-off date of 10 March 2020. Evidence for efficacy and safety of avalglucosidase in the paediatric population is limited to 22 previously treated IOPD patients > 6 months of age in the open-label phase 2 study (ACT14132).
- Demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in % predicted FVC at Week 49 was missed in Study EFC14028 at the 5% significance level (p= 0.0626). Since superiority could not be demonstrated for the primary endpoint, all subsequently planned statistical superiority tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate control of the experimentwise type-1-error.
- Despite some of the investigated efficacy parameters showed a positive trend for better outcome with avalglucosidase alfa; many of these endpoints were correlated and are measured in the same patients. Further significance testing was also hampered by the lack of demonstration of superiority in study EFC14028.

- The overall performance of alglucosidase alfa (i.e. LS mean change from baseline to Week 49 in FVC %: 0.46, in 6MWT: 2.19 meters) was notably poorer than in the registration trial for alglucosidase alfa (ALGLU02704/LOTS). In the LOTS trial the estimated change in FVC, expressed as a percentage of each patient's predicted value, was an increase of 1.2 percentage points at week 78 (1.73 at week 49) for the patients who received alglucosidase alfa. Furthermore, patients in the LOTS trial had a mean increase of 25.1 m on the 6-minute walk test by week 78. It is however acknowlegded that the results observed in the alglucosidase alfa group in Study EFC14028 are likely influenced by a randomized population different to the one randomized in Study AGLU02704.
- Data on long-term efficacy are limited. Extended treatment periods of the clinical trials are still ongoing. At the cut-off date of 19 March 2020, 91 patients were enrolled in the ongoing ETP; efficacy data at 97 weeks were available for 24 patients who had since study start continuously received avalglucosidase alfa and for 21 patients who switched from alglucosidase alfa to avalglucosidase alfa treatment after 49 weeks. After Week 49, FVC slightly decreased in patients continuing with avalglucosidase alfa.

IOPD population

- There is lack of data in treatment-naive IOPD patients under the age of 6 months.
- No formal dose-response studies have been performed. The 20 mg/kg dose was selected based on the clinical experience with alglucosidase alfa and results from non-clinical studies and the safety and exploratory efficacy results from the ascending dose phase 1 study TDR12857.
- The investigation in IOPD patients is limited to a pre-treated population in study ACT14132 (Mini-COMET), including 22 patients (Cohort 1 (n=6): 20 mg/kg AVAL, Cohort 2 (n=5): 40 mg/kg AVAL, Cohort 3 (n=11): 5 patients 40 mg/kg AVAL and 6 patients AGLU at various doses). The primary objective of the ACT14132 study was the assessment of safety and tolerability of avalglucosidase alfa. The secondary objectives were characterization of the pharmacokinetic profile and the evaluation of the preliminary efficacy of avalglucosidase alfa in comparison to alglucosidase alfa. The highest improvement was seen in Cohort 3, in the alglucosidase alfa group. Consistently to the results of the GMFM-88, the greatest degree of change in the Quick motor function test (QMFT)–total score was observed in the alglucosidase alfa group (5.17 vs. 4.25 in the AVAL group of Cohort 3). Due to its design and small size the study cannot deliver firm conclusions on avalglucosidase´s efficacy and safety in this setting. Moreover, the proposed higher starting dose in IOPD patients (40 mg/kg) has not been demonstrated to be more suitable than the 20 mg/kg dose proposed in LOPD patients.
- IOPD patients with higher anti-alglucosidase alfa antibody titers (≥1:25600) have been excluded from clinical studies.

Home infusion

- Home infusion is an established practice for some other ERTs. However limited data are available for avalglucosidase alfa and have been supplemented by the clinical experience with alglucosidase alfa. For IOPD patients, no data on home infusion are available. The risks related to home infusion is reflected in the RMP as important potential risk and will be reported in the PSURs.

## 6.4. Unfavourable effects

LOPD and IOPD populations

- In the ETS period of study ACT14132, only one patient, who received 20 mg/kg avalglucosidase alfa, developed a transient ADA response, whereas in the cohort, who received 40 mg/kg, 5 out of 10 patients (50%) developed a treatment emergent ADA response.
- 50% of adult and 30% of paediatric patients reported TEAEs potentially related to avalglucosidase treatment.
- IARs were reported by 26.1% of all patients studied, mostly 0-2 hours after infusion started.
- Anaphylactic reactions were reported by 8 patients, 4 naïve and 4 experienced patients.
- Six of the 60 patients experiencing hypersensitivity had hypersensitivity events that were considered by the Investigator to be severe, a TESAE, or both.
- AVAL IAR events in %: ADA peak titer ≥12 800 (53.8%, 7 of 13 patients) compared to patients with ADA titer 1600-6400 (17.2%, 5 of 29 patients), ADA low response titer 100-800 (7.1%, 1 of 14 patients), and patients who were ADA negative (33.3%, 1 of 3 patients).
- AVAL Hypersensitivity events in %: ADA titers: 100-800 peak titer (14.3%), 1600-6400 peak titer (27.6%) and ≥12 800 peak titer (30.8%)

## 6.5. Uncertainties and limitations about unfavourable effects

IOPD population

- The proposed higher starting dose of 40 mg/kg in IOPD patients is mainly based on recent publications of clinical experience in IOPD patients receiving alglucosidase alfa doses greater or at higher frequency than the label dose of 20 mg/kg qow (Chien, 2015, J Pediatr; Case, 2015, Neuromusc Disord). So far there are only very limited data with 40mg/kg avalglucosidase alfa from study ACT14132 (in total 10 patients in the PAP received the 40 mg/kg dose; cut-off date 30 April: during ETP all but 2 patients switched to the 40 mg/kg AVAL resulting in 20 patients currently treated with the highest dose of 40 mg/kg).
- So far, there are no data on avalglucosidase alfa in an ERT treatment naïve IOPD population. Treatment-experienced IOPD and LOPD patients appear to have some degree of attenuation of immunologic response, possibly due to development of immunologic tolerance given the shared protein structure of aval- and alglucosidase.
- Patients at high-risk for experiencing a severe allergic reaction to avalglucosidase alfa (i.e. patients who had previously severe anaphylactic reaction to alglucosidase alfa and/or a history of high sustained IgG antibody titers to alglucosidase alfa) were excluded from the phase 2 study in IOPD patients.

Paediatric LOPD and IOPD populations

- The number of paediatric patients is very limited: In total, 24 paediatric patients were treated with avalglucosidase alfa, 22 IOPD patients, and 2 paediatric/juvenile LOPD patients.

## 6.6. Effects Table

Effects Table for avalglucosidase alfa in the long-term use as an Enzyme replacement therapy (ERT) for the treatment of patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

| Effect | Short Description | Unit | AVAL | ALGLU | AVAL vs ALGLU | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | | |
| FVC | Mean change in FVC from baseline to week 49 | % | 2.89 | 0.46 | 2.43 | 95%CI (-0.13;4.99; p (NI)=0,0074, p (superiority)=0.0626 | EFC14028 |
| 6MWT | Mean change in distance walked in meters | m | 32.21 | 2.19 | 30.01 | Superiority tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate control of the experimentwise type-1-error, since statistical superiority was missed for the primary endpoint. | EFC14028 |
| | | | | | | | |
| **Unfavourable Effects** | | **unit** | **20mg/kg AVAL** | **40mg/kg AVAL** | | | |
| ADA | Proportion of patients developing ADA | % (n) | 16.7% (1/6) | 50% (5/10) | | A dosing regimen of 40 mg/kg qow might be associated with a higher risk for ADA-mediated IARs and hypersensitivity events. | ETS period of study ACT14132 |

## 6.7. Benefit-risk assessment and discussion

### 6.7.1. Importance of favourable and unfavourable effects

Despite some uncertainties regarding effect size and less severely affected studied population, efficacy of avalglucosidase alfa could be convincingly demonstrated in the phase 3 study in LOPD patients by showing non-inferiority in % predicted FVC compared to alglucosidase alfa. Although some of the investigated efficacy parameters showed a positive trend for better outcome with avalglucosidase alfa, many of these endpoints are correlated and are measured in the same patients. Most importantly, however, demonstration of superiority of avalglucosidase alfa over alglucosidase alfa in the primary endpoint % predicted FVC at Week 49 was missed at the required significance level. Accordingly, all subsequently conducted statistical tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate experimentwise type-

1-error control. Hence, any reference in the discussion of trial outcome for these endpoints indicating an advantage of avalglucosidase alfa over alglucosidase alfa is not permissible and a conclusion of demonstrated superiority is not possible.

Additional evidence for the paediatric population solely comes from phase 3 study EFC14028 and the phase 2 study ACT14132 in previously treated IOPD patient > 6 months. However, due to its design and small size of study ACT14132 , the study cannot deliver firm conclusions on avalglucosidase´s efficacy and safety in this setting at the proposed starting dose of 40 mg/kg. In particular, only one patient, who received 20 mg/kg avalglucosidase alfa, developed a transient ADA response, whereas in the cohort, who received 40 mg/kg, 5 out of 10 patients (50%) developed a treatment emergent ADA response.

Long term data are limited. Ongoing clinical studies and the extension of the applicant existing Pompe disease and Pompe disease Pregnancy sub registries to further characterise the efficacy (especially in the paediatric population) and safety of avalglucosidase alfa are thus part of the additional pharmacovigilance activities. In addition, a further study is planned in IOPD patients ⩽6 months naïve to previous treatment with alglucosidase alfa (approximately 16 males and females) and is expected as post-authorisation commitment.

## 6.7.2. Balance of benefits and risks

The proposed indication includes paediatric IOPD and LOPD patients, in first and second line of treatment. Results from the pivotal study in adult LOPD naïve patients showed that avalglucosidase is non-inferior to alglucosidase alfa at a 20 mg/kg dose with an acceptable safety profile. Extrapolation from adult to paediatric **LOPD and IOPD patients** is considered acceptable, since the pathophysiology of the disease, the mechanism of action, and the pharmacokinetic profile of enzyme replacement therapy (ERT) for Pompe Disease are comparable across the whole disease spectrum.

In IOPD patients, the results of study ACT14132 show positive trends in secondary and tertiary efficacy outcomes with avalglucosidase. However, subgroups of patients receiving different concentrations of avalglucosidase alfa in study ACT14132 were very small and clinical response varies greatly between patients. Moreover, beneficial effects are not consistently in favour of patients initially treated with avalglucosidase alfa 40 mg/kg and a clear dose response relationship could not be demonstrated. Thus, a higher starting dose was not recommended by the CHMP. However, for IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week can be considered in the absence of safety concerns.

Overall, based on the submitted data, a positive benefit risk can be concluded for the LOPD and IOPD populations with recommended dose of 20 mg/kg for LOPD and a starting dose of 20 mg/kg with possible increase to 40 mg/kg in IOPD.

## 6.7.3. Additional considerations on the benefit-risk balance

Not applicable

# 7. Recommendations following re-examination

***Outcome***

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the benefit-risk balance of Nexviadyme is favourable in the following indication(s):

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Additional risk minimisation measures**

Prior to the launch of Nexviadyme in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority. The educational

program is aimed at increasing the awareness about the immunosurveillance service and to support the correct and safe administration of the product in the home setting.

The MAH shall ensure that in each member state where Nexviadyme is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense and administer Nexviadyme are provided with the following educational package to be disseminated through professional bodies:

- Healthcare professionals (HCPs) guide for immunosurveillance service and
- Home infusion guide for HCPs

Guide for healthcare professionals for Immunosurveillance Service shall include the following key elements:

- Testing recommendations:
  - Baseline serum sample collection prior to the first infusion is strongly encouraged.
  - Immunoglobulin G (IgG) antibody titers should be regularly monitored and IgG anti-drug antibody (ADA) testing should be considered if patients do not respond to therapy.
  - Treated patients may be tested for inhibitory antibodies if they experience a decrease in clinical benefit despite continued treatment with Nexviadyme.
  - Adverse-event-driven immunologic testing, including IgG and Immunoglobulin E (IgE) ADA, should be considered for patients at risk for allergic reaction or previous anaphylactic reaction to Myozyme (alglucosidase alfa).
  - Adverse-event-driven immunologic testing should also be considered in patients who experience moderate/severe or recurrent infusion associated reactions (IARs) suggestive of hypersensitivity reactions, anaphylactic reactions.
- Testing practicalities of the testing service and contact details
  - Description of the testing services: available tests, indication for testing, sample type, Frequency of testing, collection time
  - Procedure for testing: diagram summarizing main steps for HCP requesting Specialty testing services

The Home Infusion guide for HCPs which will serve as training document to HCPs who will perform the infusion at home shall contain the following key elements:

- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.
- Details on the preparation and administration of Nexviadyme, including all the steps of preparation, reconstitution, dilution and administration
- Medical evaluation of the patient prior to administration of the infusion at home
- Information on signs and symptoms related to infusion associated reactions and recommended actions for the management of the ADRs when symptoms occur.

***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that avalglucosidase alfa is not to be qualified as a new active substance in itself.

Based on the review of the available data, the CHMP considers that avalglucosidase alfa in comparison to alglucosidase alfa  previously authorised as a medicinal product in the European Union is not to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.