

To: Oregon Health Authority
Drug Class Update with New Drug Evaluation: Drugs for Pompe Disease
Re: Pompe Disease: avalglucosidase alfa-ngpt (Nexviazyme®)
January 14, 2022

Dr. Engen,

We are responding to the Drug Class Update with New Drug Evaluation: Drugs for Pompe Disease letter in reference to the newly approved enzyme replacement therapy avalglucosidase alfa-ngpt.

Pompe disease is a rare, autosomal recessive genetic disorder caused by a deficiency of the lysosomal enzyme acid alfa glucosidase –which leads to accumulation of the substrate glycogen in muscle cells. Pompe disease occurs in an estimated 1 in every 40,000 births. Its primary symptoms are heart and skeletal muscle weakness, generally progressing to respiratory weakness and death from respiratory failure.

Infantile-onset Pompe disease (IOPD) usually presents with symptoms within the first months of life and has a rapidly progressive disease course, involving the cardiac, musculoskeletal and smooth muscle and it is usually fatal by 2 year of age.

Late-onset Pompe disease (LOPD) has a less rapid and more variable disease course involving the musculoskeletal and smooth muscle, where symptoms may begin anywhere from infancy to adulthood.

Lumizyme (alglucosidase alfa) was approved by the FDA in 2010 for treatment of patients with late (non-infantile) onset Pompe disease 8 years of age and older. Subsequently in 2014, the FDA expanded the approval of Lumizyme to treat Pompe Disease patients of all ages. It continues to be the only available approved treatment for Infantile-onset Pompe disease.

Nexviazyme (avalglucosidase alfa-ngpt) was approved by the FDA in August 2021 for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). The phase III trial titled “Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised multi-center trial” was published in *Lancet Neurology* on November 17 2021. (*Lancet Neurol.* 2021;20: 1012-26)

Please see below the responses to the conclusions included in the Drug Class Update with New Drug Evaluation: Drugs for Pompe Disease.

Conclusion #1:

The safety and efficacy of avalglucosidase alfa was assessed in one phase 3, randomized, double-blind multinational, multicenter non-inferiority (NI) trial in enzyme replacement therapy (ERT)-naïve late-onset Pompe disease (LOPD) patients aged 16 years and older.^{1,2} In the 49-week study, patients (n=100) were randomly allocated in a 1:1 ratio to either avalglucosidase alfa 20 mg/kg (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49).^{1,2} The study is unpublished so risk of bias could not be fully assessed.

Response to conclusion #1:

On November 17, 2021, the *Lancet Neurology* published the phase 3, randomized, double-blind multinational, multicenter trial in enzyme replacement therapy (ERT)-naïve late-onset Pompe disease (LOPD) patients aged 16 years and older by Dr. Diaz-Manera et al. titled “Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised multi-center trial” (*Lancet Neurol.* 2021;20: 1012-26)

The authors concluded that that this study provides evidence of clinically meaningful improvement with avalglucosidase alfa therapy over alglucosidase alfa in respiratory function, ambulation, and functional endurance, with no new safety signals reported. An open-label extended-treatment period is ongoing to further evaluate the long-term safety and efficacy of avalglucosidase alfa, with the aim for this therapy to become the new standard treatment in late-onset Pompe disease. (*Lancet Neurol.* 2021;20: 1012-26)

Conclusion #2:

The primary outcome was least square means (LSM) change in percent of predicted forced vital capacity (FVC) in the upright position from baseline to 49 weeks.^{1,2} The NI margin for the lower bound of the two-sided 95% confidence interval (CI) for the difference between the two treatment arms was set at -1.1%.¹ At 49 weeks, the estimated mean change from baseline in percent predicted FVC was higher in the avalglucosidase alfa arm (2.9%) versus alglucosidase alfa (0.5%) with an estimated treatment difference of 2.4% (95% CI -0.1 to 5.0; p=0.06) in favor of avalglucosidase alfa.^{1,2} The trial met noninferiority for the primary efficacy endpoint but did not achieve statistical superiority.¹

Response to conclusion #2:

In “Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised multi-center trial” (*Lancet Neurol.* 2021;20: 1012-26), Diaz-Manera et al. conclude that the observed improvement in upright FVC is clinically meaningful for several reasons. Respiratory morbidity and mortality, including respiratory failure and requirement for ventilatory support, is associated with severity of respiratory muscle weakness as assessed by upright FVC. A minimal clinical difference of 2–6% was established for a restrictive

respiratory disease and has been applied to other studies in late-onset Pompe disease.³⁰ The difference of 2-43% reported for upright FVC% predicted between the avalglucosidase alfa treatment group versus the alglucosidase alfa group is within this range and is clinically meaningful for patients with late-onset Pompe disease. Moreover, initiation of respiratory support results in reduced physical function with adverse effects on quality of life. Given the progressive nature of late-onset Pompe disease, improvement in respiratory muscle strength (MIP or MEP) and upright FVC would delay onset of respiratory failure and potentially decrease reliance on mechanical ventilatory support. Lastly, the observed correlation between improvements in upright FVC with several domains, including endurance, muscle strength, quality of life, and biomarkers (eg, hexose tetrasaccharide, a breakdown product of glycogen), further reinforces the clinical meaningfulness for the observed increase in upright FVC with avalglucosidase alfa.

In addition, a post hoc analysis based on the available data from The COMET phase 3 trial (NCT02782741) was presented by Dr. Kenneth Berger at the World Muscle Society in 2021 in order to define thresholds for FVC (expressed as % predicted), that reflect clinically important response (CIR) in LOPD using an anchor-based approach for both arms analyzed together and to estimate patient-relevant change in FVC % predicted using The Patient Global Impression of Change (PGIC) and to assess the differences in the prevalence of a clinically meaningful change in FVC during therapy with avalglucosidase alfa as compared with alglucosidase alfa. Cumulative distribution functions were generated to depict the percentage of patients experiencing a change from baseline greater than or equal to the value of different thresholds. Data suggest that an improvement between 1.7 and 4.1 units in FVC % predicted corresponds to a minimal patient relevant change. Studies in other diseases with restrictive respiratory impairment have reported a similar range of relevant change in FVC (2–6%). Empirical cumulative distribution function of the change in FVC % predicted indicates clear separation between treatment with avalglucosidase alfa and alglucosidase alfa at each level of change. A greater proportion of patients treated with avalglucosidase alfa demonstrated improvement in FVC at or above any of the clinically meaningful thresholds as compared to alglucosidase alfa. The authors concluded that these findings aid in the interpretation of clinically meaningful effect for the respiratory function from the LOPD patient perspective and show greater efficacy of avalglucosidase alfa in the COMET phase 3 trial.

Conclusion #3:

Clinically relevant secondary endpoints evaluated the estimated treatment difference of distance walked in the 6-minute walk test (6MWT) and health-related quality of life as measured by the 12-item short form health survey (SF-12).^{1,2} The estimated mean change from baseline to week 49 in the 6MWT was higher in the avalglucosidase alfa arm (32.2 meters) versus alglucosidase alfa (2.2 meters) with an estimated treatment difference of 30.0 meters (95% CI 1.3 to 58.7; p=0.04) in favor of avalglucosidase alfa.^{1,2} There were no statistically significant differences between groups in the SF-12 score at week 49 compared to baseline.¹

Response to conclusion #3:

As reported in the publication of the phase III trial “Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised multi-center trial” (*Lancet Neurol.* 2021;20: 1012-26), greater numerical improvements in mean changes from baseline to week 49 were observed (although the 95% CIs crossed 0) with avalglucosidase alfa compared with alglucosidase alfa in the prespecified secondary endpoints of respiratory muscle strength (MIP% predicted and MEP% predicted), lower extremity muscle strength (HHD), motor function (quick motor function test), and health-related quality of life (SF-12 PCS and SF-12 MCS; table 2, figure 3A, B; appendix pp 8–11). In figure 3 A and figure 3 B in the phase III trial publication “Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised multi-center trial” (*Lancet Neurol.* 2021;20: 1012-26) please see the Forest plots representing the differences between treatment groups in changes from baseline to week 49 in predefined study objectives (A) Least-squares mean (95% CI) differences for predefined objectives for efficacy, measuring respiratory muscle function, functional endurance, muscle strength, and motor function. (B) Least-squares mean (95% CI) differences for predefined objectives measuring health-related quality of life. 6MWT=6-min walk test. EQ-5D-5L=five-level EQ-5D. EQ-5D-VAS=EQ-5D visual analogue scale. FVC=forced vital capacity. HHD=hand-held dynamometry. GMFM-88=gross motor function measure-88. GSGC=Gait, Stair, Gower’s Maneuver, and Chair. MCS=mental component summary. MEP=maximum expiratory pressure. MIP=minimum expiratory pressure. PCS=physical component summary. PDIS=Pompe disease impact scale. PDSS=Pompe disease symptom scale. PGIC=patient global impression of change. QMFT=quick motor function test. R-Pact=Rasch-built Pompe-specific activity. SF-12=health-related quality of life 12-item short-form health survey. *Health-State Utility Values (5L) using UK tariff by treatment (crosswalk method). †Shortness of breath score included breathing and breathing while lying down; overall fatigue score included tiredness, fatigue, muscle weakness anywhere, muscle weakness in the lower body, and muscle weakness in the upper body; upper extremity weakness score included muscle weakness in the arms and muscle weakness in the hands; pain score included muscle aches and pain; and fatigue and pain score included the overall fatigue score, upper extremity weakness score, and pain score. ‡Mood score included anxiety, worry, and depression; difficulty performing activities score included walking difficulty, climbing difficulty, rising difficulty, bending over difficulty, and squatting down difficulty. (*Lancet Neurol.* 2021;20: 1012-26)

Figure 3 A:

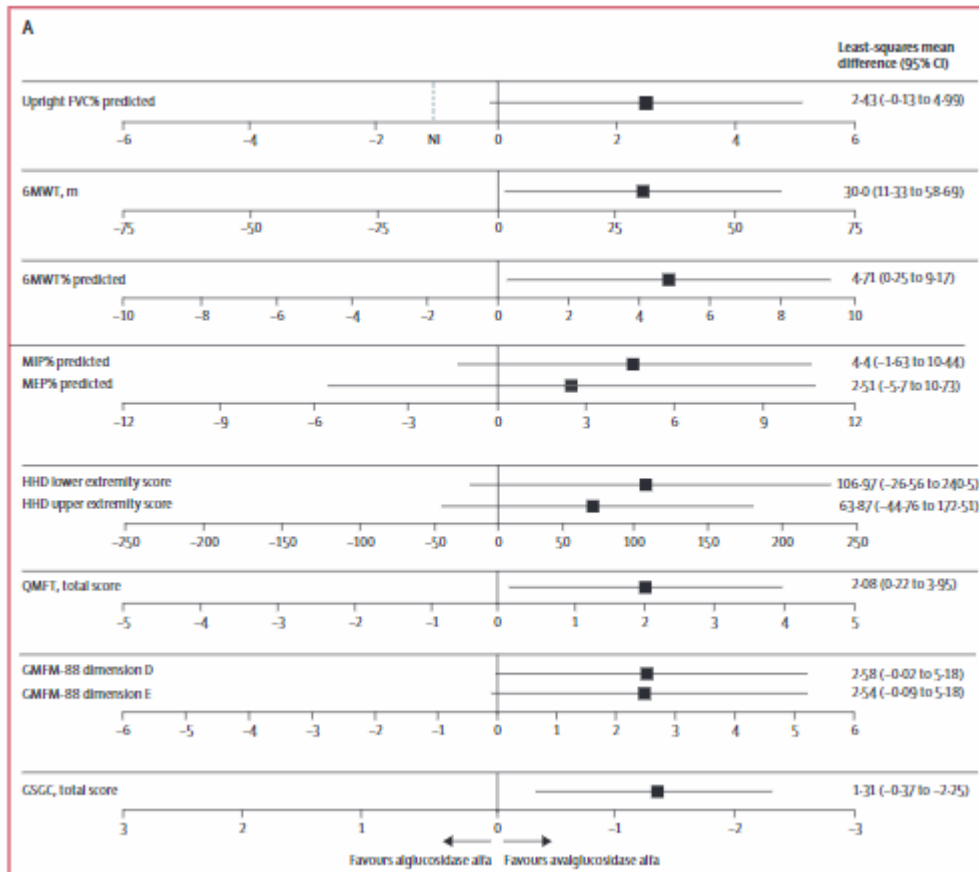
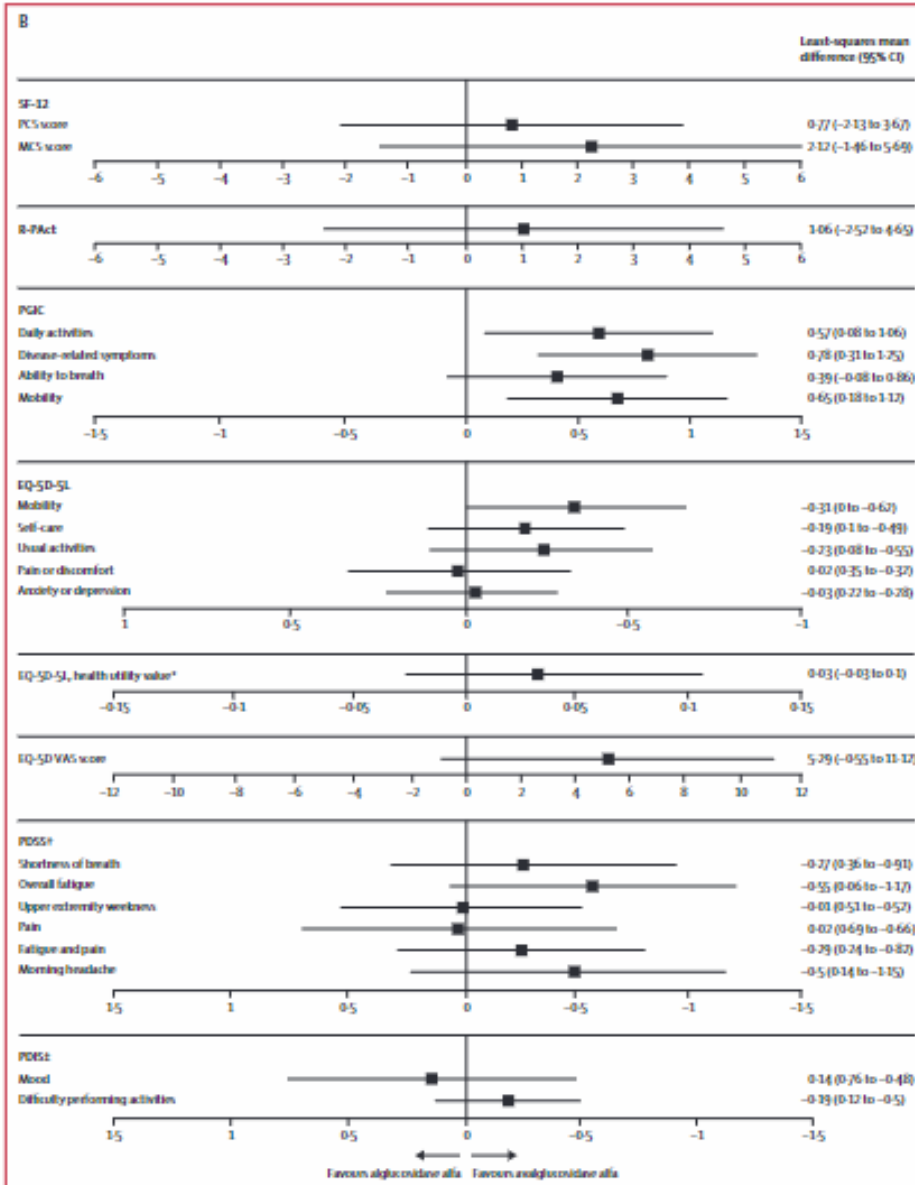


Figure 3 B:



Conclusion #4:

The most common adverse events that occurred during treatment over 49 weeks in the avalglucosidase and alglucosidase groups, respectively, were headache (22% vs. 33%), fatigue (18% vs. 14%), diarrhea (12% vs. 16%), nausea (12% vs. 14%), arthralgia (10% vs. 16%), dizziness (10% vs. 8%), and myalgia (10% vs. 14%).^{1,2}

Response to conclusion #4:

No response needed.

Conclusion #5:

FDA labeling has a black boxed warning (BBW) for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs) and risk of acute cardiorespiratory failure in susceptible patients.² More frequent monitoring of vital signs should be performed during infusion for susceptible patients.² If severe IAR occurs, therapy should be immediately discontinued and appropriate medical treatment initiated.² Those with higher risk for IARs include patients with:

- advanced Pompe disease*
- susceptibility to fluid volume overload*
- acute underlying respiratory illness*
- compromised cardiac or respiratory function necessitating fluid restriction.²*

Response to conclusion #5:

Both avalglucosidase alfa – ngpt and alglucosidase alfa have boxed warnings.

Conclusion #6:

There is low-quality evidence of no difference between alglucosidase alfa 20 mg/kg and 40 mg/kg in safety and effectiveness for the treatment of IOPD based on one systematic review.³

Response to conclusion #6:

Your comment is regarding alglucosidase alfa and does not apply to avalglucosidase alfa-ngpt since avalglucosidase alfa-ngpt is not approved for treatment for infantile-onset Pompe disease (IOPD). Our response below concerns alglucosidase alfa and not avalglucosidase alfa-ngpt.

Regarding the treatment alglucosidase alfa 20 mg/kg and 40 mg/kg and related safety and effectiveness for the treatment of IOPD, an additional observational cohort study published in 2022 in collaboration with the European Pompe Consortium in 124 patients with IOPD diagnosed between 1998 and 2019 of whom 116 were treated with ERT (median age at start of treatment 3·3 months [IQR 1·8–5·0, range 0·03–11·8]). During follow-up (mean duration 60·1 months [SD 57·3]; n=115), 36 (31%) of 116 patients died. 39 different ERT dosing regimens were applied. Among the 64 patients

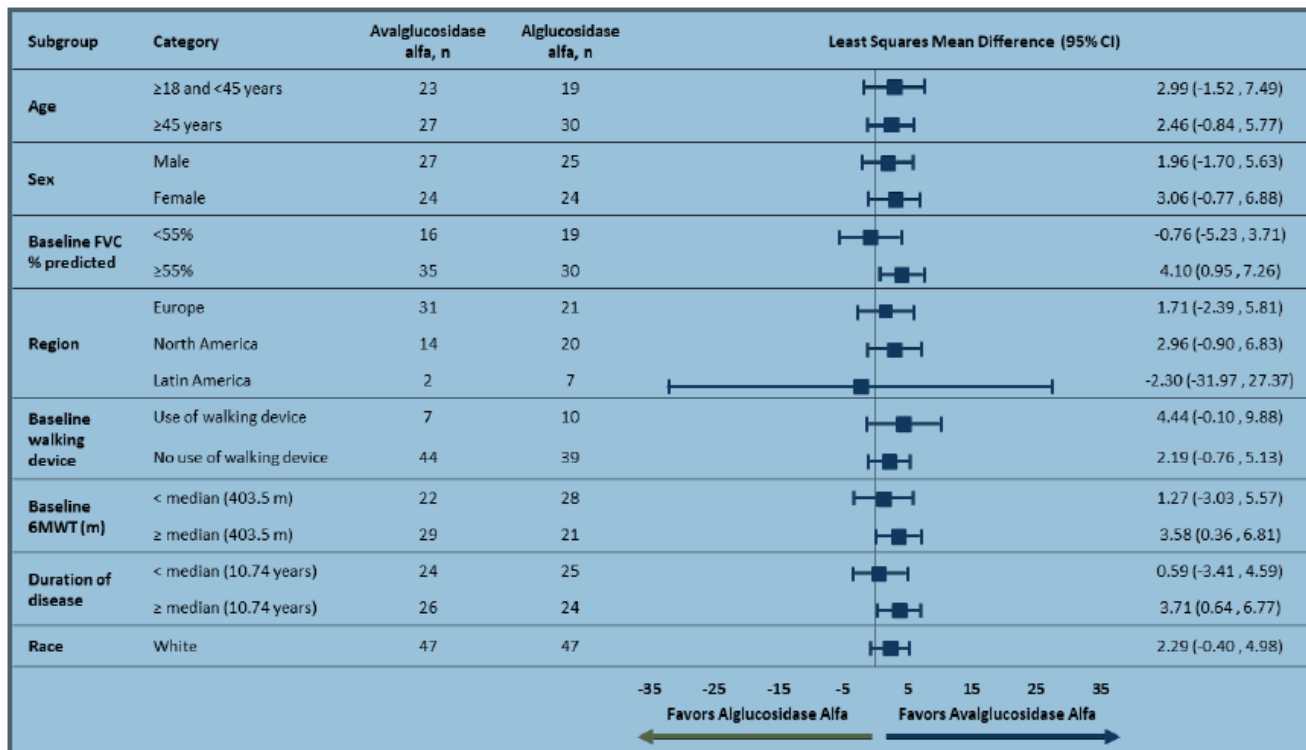
who remained on the same dosage, 16 (52%) of 31 patients on the standard dosage (20 mg/kg every other week), 12 (80%) of 15 patients on an intermediate dosage (20 mg/kg per week or 40 mg/kg every other week), and 16 (89%) of 18 patients on the high dosage (40 mg/kg per week) were alive at last follow-up. Survival was significantly improved in the high dosage group compared with the standard dosage group (hazard ratio [HR] 0.17 [95% CI 0.04–0.76], p=0.02). (Lancet Child Adolesc Health 2022; 6: 28–37)

Conclusion #7:

There is insufficient evidence to evaluate the use of avalglucosidase alfa in the treatment of specific subpopulations based on age, gender, race, ethnicity, comorbidities, disease duration or severity.

Response to conclusion #7:

From the Supplement to: Diaz-Manera J, Kishnani PS, Kushlaf H, et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial (*Lancet Neurol* 2021; **20**: 1012–26), please note the subgroup analyses for the primary outcome FVC% predicted and secondary outcome 6MWT based on subgroups of age, sex, baseline FVC % Predicted, geographical regions, baseline use of walking devices, baseline 6MWT, duration of disease and race.



6MWT=6-minute walk test; ALGLU=alglucosidase alfa; AVAL=avalglucosidase alfa; CI=confidence interval; FVC=forced vital capacity; LS=least squares; 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

Statement page 8 and page 9

The FDA reviewed data from the open-label extension trial where all remaining patients who had received alglucosidase alfa treatment were switched over to avalglucosidase alfa 20 mg/kg to continue treatment every other week until week 97.¹ There were 23/44 patients available for assessment of the primary outcome at the data cutoff point. The mean change in percent predicted FVC from week 49 to week 97 among the 23 patients was -0.1% (95% CI -3.2 to 2.8; p=0.92), which failed to show a statistically significant improvement.¹ There were 26/44 crossover patients available for assessment of the 6MWT during the same time period and the mean change in distance walked in 6MWT from week 49 to 97 among the 26 patients was 8.6 meters (95% CI -20.4 to 37.5; p=0.55), which also failed to show a statistically significant improvement.¹

There was no explanation as to why only about half the patients crossed over to avalglucosidase alfa in the open-label extension trial were available for outcome assessment. With details regarding trial methods absent until the full study is published it is not possible to ascertain to what extent sources of bias such as concealment of allocation and blinding could affect the validity of the results.

Response to statement page 8 and page 9

The number of patients who switched from alglucosidase alfa in PAP to avalglucosidase alfa in ETP as reported by the FDA is only partial since it is based on data cutoff of July 3, 2020. On July 30 2020, only a subset of patients enrolled in the COMET trial treated with alglucosidase alfa in PAP reached week 97. We caution from drawing conclusions from this partial, unpublished data on patients who switched from alglucosidase alfa in PAP to avalglucosidase alfa in ETP. An open-label extended-treatment period is ongoing to confirm the long-term safety and efficacy of avalglucosidase alfa.

Statement page 9-a

Although avalglucosidase alfa met criteria for non-inferiority compared to alglucosidase alfa, it is uncertain whether a 2.4% change in percent predicted FVC is clinically meaningful.

Response to statement page 9-a

A post hoc analysis based on the available data from The COMET phase 3 trial (NCT02782741) was presented by Dr. Kenneth Berger at the World Muscle Society in 2021 in order to define thresholds for FVC (expressed as % predicted), that reflects clinically important response (CIR) in LOPD using an

anchor-based approach for both arms analyzed together and to estimate patient-relevant change in FVC % predicted using The Patient Global Impression of Change (PGIC) and to assess the differences in the prevalence of a clinically meaningful change in FVC during therapy with avalglucosidase alfa as compared with alglucosidase alfa. Cumulative distribution functions were generated to depict the percentage of patients experiencing a change from baseline greater than or equal to the value of different thresholds.

Data suggest that an improvement between 1.7 and 4.1 units in FVC % predicted corresponds to a minimal patient relevant change.

Studies in other diseases with restrictive respiratory impairment have reported a similar range of relevant change in FVC (2–6%). Empirical cumulative distribution function of the change in FVC % predicted indicates clear separation between treatment with avalglucosidase alfa and alglucosidase alfa at each level of change. A greater proportion of patients treated with avalglucosidase alfa demonstrated improvement in FVC at or above any of the clinically meaningful thresholds as compared to alglucosidase alfa. The authors concluded that these findings aid in the interpretation of clinically meaningful effect for the respiratory function from the LOPD patient perspective and show greater efficacy of avalglucosidase alfa in the COMET phase 3 trial.

Statement page 9-b

It is also unclear why there was only a 0.5% change in percent predicted FVC in the alglucosidase alfa comparator given there was almost a 3% change vs placebo observed in previous trials.

Response to statement page 9-b

In the “Safety and Efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial”, the findings of the prespecified constancy assumption showed that the estimates of the effect of alglucosidase alfa compared with placebo from the predictive model were 2·87 for COMET and 3·02 for Late Onset Treatment Study (LOTS) phase III trial of alglucosidase alfa in late-onset Pompe disease. The difference in the effect of alglucosidase alfa calibrated to the LOTS and COMET trials was small (–0·15) compared with the non-inferiority margin (1·1% predicted). Based on this result, the constancy assumption was considered to hold. Direct comparison of these results to those of the LOTS trial is constrained by multiple differences. First, the COMET trial did not include a placebo group, precluding comparisons with untreated patients, which was the objective of LOTS. Second, participants randomly assigned to alglucosidase alfa in both trials differed across baseline characteristics. Baseline mean upright FVC% predicted and 6MWT were higher in COMET compared with in LOTS. Participants in COMET also had an older mean age at symptom onset, longer mean disease duration, and shorter median time from diagnosis to treatment compared with those in LOTS. Third, COMET included a broad geographical population from 55 sites across 20 countries compared with LOTS, which enrolled participants at seven sites in France, the Netherlands, and the USA. Although the number of participants with the

most common GAA variants, particularly with at least one IVS1 variant, was similar across both studies, COMET included more participants of Hispanic and Asian backgrounds enrolled at sites in Latin America and Asia-Pacific regions than did LOTS. The primary analysis period duration also differed between the trials (49 weeks in COMET vs 78 weeks in LOTS). Finally, in the 10 years between these trials, the standard of care for patients with late-onset Pompe disease, including physical therapy, pulmonary care, and nutrition, has substantially changed.

Statement on page 9-c

The small sample size and underrepresentation of minorities further limits the applicability of results to the general Oregon Medicaid population.

Response to statement on page 9-c

The COMET included a broad geographical population from 55 sites across 20 countries compared with the phase III study of alglucosidase alfa Late Onset Treatment Study (LOTS), which enrolled participants at seven sites in France, the Netherlands, and the USA. Although the number of participants with the most common GAA variants, particularly with at least one IVS1 variant, was similar across both studies, COMET included more participants of Hispanic and Asian backgrounds enrolled at sites in Latin America and Asia-Pacific regions than did LOTS.

In conclusion, based on the above data and to allow for appropriate management for individuals with Pompe, we request that Medicaid in the state of Oregon allows open access for commercially available treatments in the Pompe class, including Nexviazyme, avalglucosidase alfa-ngpt.

Thank you for your consideration.

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