24 June 2022
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EMADOC-1700519818-627695
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Nexviadyme (avalglucosidase alfa, recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan)
Treatment of glycogen storage disease type II (Pompe's disease)
EU/3/14/1251

Sponsor: Genzyme Europe B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance	Recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan
Other name	-
International Non-Proprietary Name	Avalglucosidase alfa
Tradename	Nexviadyme
Orphan condition	Treatment of glycogen storage disease type II (Pompe's disease)
Sponsor's details:	Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Genzyme Europe B.V.
COMP opinion	6 February 2014
EC decision	26 March 2014
EC registration number	EU/3/14/1251
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	M. Stain / A. Moreau
Applicant	Genzyme Europe B.V.
Application submission	11 September 2020
Procedure start	1 October 2020
Procedure number	EMA/H/C/0005501
Invented name	Nexviadyme
Proposed therapeutic indication	Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency). Further information on Nexviadyme can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Nexviadyme
CHMP opinion	11 November 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	A. Magrelli / C. Dop
Sponsor's report submission	25 November 2020
COMP discussion	13-15 July 2021
Adoption of list of questions (via written procedure)	27 July 2021
Oral explanation	7 December 2021
COMP opinion (adoption via written procedure)	20 December 2021

Appeal to the COMP opinion procedural history	
COMP rapporteur	E. J. Rook / I. Barisic
Appeal submission	21 March 2022
Appeal oral explanation	12 April 2022
COMP final opinion (adoption via written procedure)	26 April 2022

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

"The sponsor Genzyme Europe BV submitted on 17 September 2013 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan for treatment of glycogen storage disease type II (Pompe's disease) (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan was considered justified based on preclinical data in a valid model of the disease;
- the condition is chronically debilitating and life-threatening, in particular due to progressive weakness of muscles, respiratory and cardiac failure and limited survival;
- the condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting that the product improves the muscle function compared to the authorised treatment. The Committee considered that this could translate into a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan, as an orphan medicinal product for the orphan indication: treatment of glycogen storage disease type II (Pompe's disease)."

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Pompe disease is a rare autosomal recessive genetic disorder caused by pathogenic variants in both copies of acid alpha-glucosidase (GAA) gene, localized on the long arm of chromosome 17, leading to a partial or total deficiency of GAA, which induces glycogen storage. As a genetic disease, Pompe disease is present at birth and is progressive, regardless of when signs and symptoms become apparent. The broad clinical spectrum of the disease depends on the age of onset. All presentations have a varying degree of myopathy but differ with respect to time at symptom onset, organ involvement, and rate of progression, factors that are determined in part by the residual GAA activity. In general, age of onset appears to correlate with residual GAA level, which tends to correlate inversely with disease severity. Thus, in general, the earlier the onset, the lower the residual GAA level, and the more severe the prognosis. The condition has not changed in terms of classification or description since the initial orphan designation.

The approved therapeutic indication "Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency)" falls within the orphan designation of "treatment of glycogen storage disease type II (Pompe's disease).

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The infantile-onset Pompe disease (IOPD) typically present with signs within the first year of life. Accumulation of glycogen in the heart and skeletal muscle results in rapidly progressive cardiomyopathy and generalized muscle weakness with hypotonia. Motor development is often completely arrested –or if motor milestones are achieved, they are subsequently lost– and death from cardiac and/or respiratory failure occurs before most patients reach 1 year of age without treatment.

Late-onset Pompe disease patients (LOPD) manifest signs and symptoms of the disease anywhere from early childhood through the sixth decade of life and usually present with more slowly progressive myopathy, predominantly affecting the proximal muscles in the trunk and pelvic and shoulder girdles, and a variable degree of respiratory involvement. While the heart is typically spared, cardiomegaly has been reported to occur in up to 4% of patients with late-onset Pompe disease and other cardiac manifestations secondary to chronic respiratory failure have been observed. Whereas children and adults with late-onset Pompe disease usually display more gradual and variable rates of disease progression, the prognosis often remains unpredictable and poor without treatment.

Based on this clinical picture, Pompe disease is regarded a life-threatening and chronically debilitating condition. There have been no changes in the chronically debilitating or life-threatening nature of the condition since the designation stage.

Number of people affected or at risk

The highest literature-reported birth incidence combined with reported mortality rates and estimated the total maximum prevalence of Pompe disease is proposed to be 6.0 in 100,000 (or 0.6 in 10,000).

The literature-reported birth prevalence of Pompe disease ranges from about 0.06/100,000 in Finland up to a maximum of 11.6 per 100,000 in Austria. An outlier value of 22.08/100,000, related to a founder effect, was observed in French Guiana but should not be considered as representative of Europe or the US.

In agreement with other literature about the natural progression of the disease, Martiniuk et al. assigned average ages of death of 1, 15-20 and 45-60 years for infantile, juvenile and adult-onset phenotypes respectively.

There were approximately 5 million infants born in the EU28 (2017 Eurostats data) (29). Using the birth incidence rate of 11.6 per 100,000 results in 580 infants born with Pompe disease each year (5 million x 11.6/100,000). Of the 580 infants born with Pompe disease, 220 (38%) will have the infantile-onset form, 23 (4%) will have the juvenile-onset form, and 336 (58%) will have the adult-onset form of the disease (Martiniuk F, et al. 1998). Based on the natural history, while no treatment is available, the 220 infantile cases will die in one year. For simplicity of calculation, the sponsor assumed that of the juvenile cases born each year, each case will survive to 20 years of age. Similarly, the sponsor assumed that the 336 adult-onset cases survive to 60 years of age. Based on the maximum birth incidence of 11.6 per 100,000, the sponsor estimates that there are approximately 224 infantile-onset, 471 juvenile-onset, and 20,490 adult-onset individuals in the EU28 with mutations that could lead to Pompe disease.

The sponsor also provided a sensitivity analysis to determine the symptomatic prevalent population, by looking to estimates from analysis of the Pompe Registry to determine the age of symptom onset. The analysis confirmed that the condition is unlikely to exceed the proposed value of 0.6 in 10,000.

The sponsor did not notify about any significant prevalence differences across the globe. Therefore, the estimate provided for the EU 28 may be accepted as it is unlikely to differ from the post-Brexit appropriate EU-27 estimate.

The estimate is approximately in line with previous estimates. Due to uncertainly of the impact of existing treatment options on the true survival of patients, the prevalence may be also phrased as previously accepted as 'less than 1 in 10,000'.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Myozyme (alglucosidase alfa) 50 mg, powder for concentrate for solution for infusion, is currently the only available treatment for Pompe disease. It is approved in the European Union for long-term

enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The recommended dose regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks.

In Europe, consensus was reached based on expert opinion and supported by the literature on how the diagnosis of Pompe disease in adult patients should be confirmed, when treatment should be started, reasons for stopping treatment and the use of ERT during pregnancy (van der Ploeg A.T et al). Recommendations for diagnostic, treatment and follow-up have recently been published for paediatric patients with Pompe disease in Germany (Hahn A et al., 2020).

Significant benefit

An EMA Scientific Advice/Protocol Assistance meeting was held prior to the initiation of the phase 3 clinical trial (EFC14028) and phase 2 trial (ACT14132) in 2015 (EMEA/H/SA/3170/2/2015/PA/III) to obtain feedback on the overall development program for avalglucosidase alfa, including the clinical data results from the phase 1/2 Study TDR12857, and the planned phase 2 Study ACT14132 in IOPD patients and the planned phase 3 Study EFC14028 in LOPD patients, respectively. A follow-up Scientific Advice/ Protocol Assistance was sought in 2018 (EMEA/H/SA/3170/3/2018/PA/II) on questions related to clinical significance of the primary endpoint (change in %FVC) in the pivotal trial EFC14028, statistical analysis plans, and significant benefit related to orphan designation. The proposed development plan, as detailed and discussed in the protocol assistance requests, was supported by CHMP, in terms of the proposed studies, their design, endpoints, statistical analysis, targeted populations, and quantity of efficacy and safety data, to support an indication for use in Pompe disease. The comments made by CHMP during the protocol assistance requests have been taken into account by the applicant and the current data package addresses the received advice.

The Sponsor considers that the clinical development of avalglucosidase alfa and the results from the pivotal phase 3 trial EFC14028 meet the advice received from COMP on significant benefit.

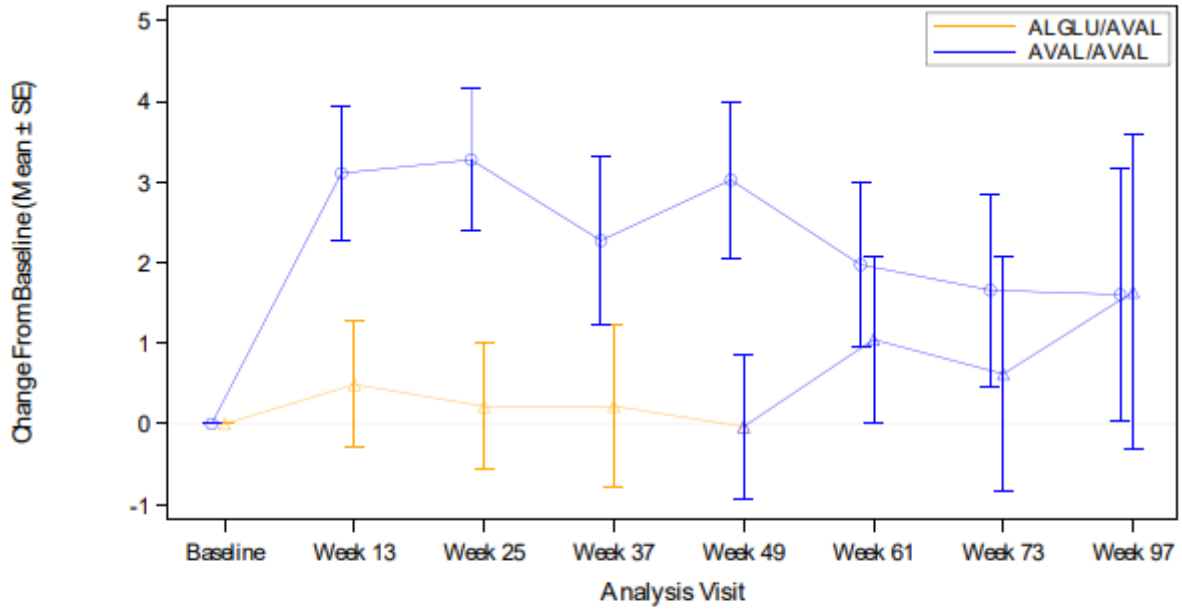
The avalglucosidase alfa clinical development program was designed to demonstrate improved therapeutic benefit, via reductions in burden of the disease in children and adults with Pompe disease, as compared with alglucosidase alfa.

The sponsor discussed several aspects in attempt to demonstrate significant benefit:

Efficacy

Change in FVC % predicted was the primary efficacy endpoint of study EFC14028 conducted in LOPD patients. At Week 49, the LS mean change from baseline (SE) was 2.89% (0.88) in the avalglucosidase alfa group and 0.46% (0.93) in the alglucosidase alfa group, demonstrating statistical noninferiority (LS mean difference +2.43% [95% CI: -0.13, 4.99]; p=0.0074) of avalglucosidase alfa versus standard of care in improving this key parameter of respiratory function in the mITT population throughout the PAP. Inferential testing of superiority of avalglucosidase alfa over alglucosidase alfa in FVC % predicted at Week 49 fell short of statistical significance (p=0.0626).

Figure 1. Plot of Mean (SE) change from baseline of FVC (% Predicted) - in upright position over time - in PAP - mITT population in study EFC14028



ALGLU/AVAL	49	47	45	44	43	35	29	21
AVAL/AVAL	51	51	51	51	49	41	36	24

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.

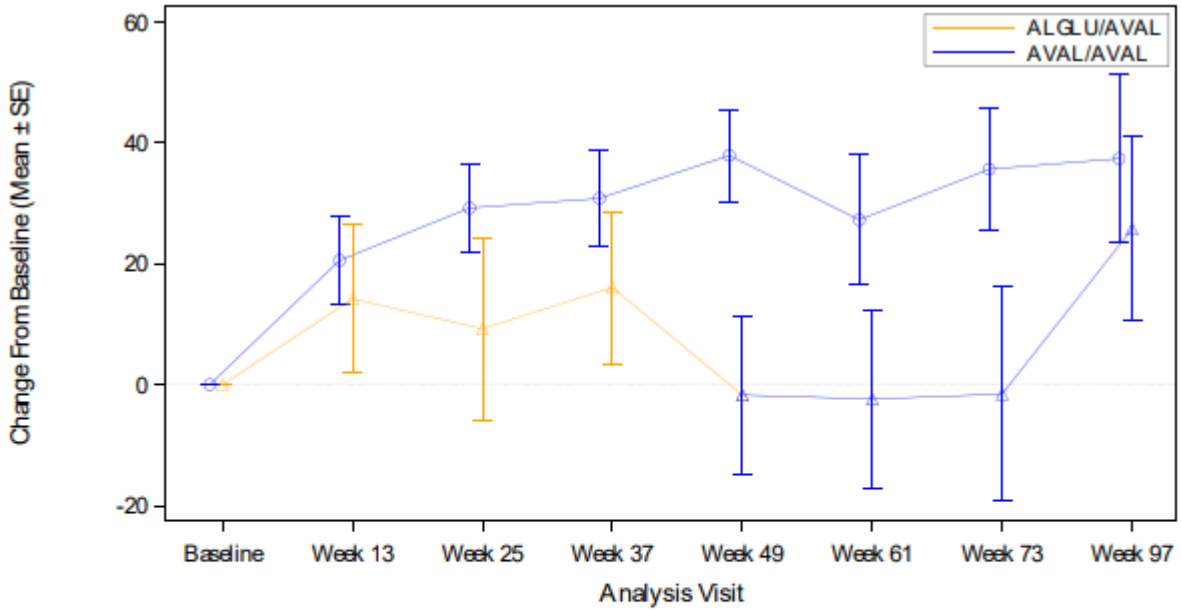
Source: 5.3.5.1 EFC14028 [16.2.6.1.1.50]

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

Change in 6MWT distance walked was the key secondary endpoint in study EFC14028. At Week 49 the LS mean change from baseline (SE) in distance walked was 32.21 (9.93) meters in the avalglucosidase alfa group and 2.19 (10.40) meters in the alglucosidase alfa group, demonstrating greater improvement in ambulatory function with avalglucosidase alfa as compared to alglucosidase alfa (LS mean difference +30.01 m [95% CI: 1.33, 58.69]; nominal p-value=0.0405). Estimates of change from baseline in percent predicted walk distance at Week 49 were also numerically greater with avalglucosidase alfa as compared with alglucosidase alfa: respectively (improvement of 5.02% [1.54%] as compared to 0.31% [1.62%]; nominal p value=0.0386). Gains in walk distance in patients dosed with avalglucosidase alfa throughout the study appeared to be sustained through Week 97 in this preliminary dataset (Figure 2).

It should be noted that some imbalance was present at baseline between the two arms: in the avalglucosidase alfa group the mean baseline distance was 399.3 m vs 378.1 m in the comparator arm, thus a difference of 21.2 m, indicating a better baseline performance in the avalglucosidase alfa arm. The difference between the median baseline distances was even greater (28.7 m). The observed change from baseline in avalglucosidase alfa was 32.21 m vs 2.19 m in the comparator, with a difference of 30.01 m. Therefore, the baseline imbalance had a magnitude very close to the observed improvement. It is not clear, thus, whether the poorer baseline performance observed in the comparator arm could have had any impact on the poorer outcome performance of the comparator.

Figure 2. Plot of Mean (SD) change from baseline of 6MWT (distance walked in meters) over time - in PAP and ETP - mITT population in study EFC14028



ALGLU/AVAL	49	47	45	45	43	36	29	22
AVAL/AVAL	51	51	49	50	48	42	38	24

Abbreviation: ALGLU: alglucosidase alfa; AVAL: avalglucosidase alfa; PAP: PAPNote: 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.

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.

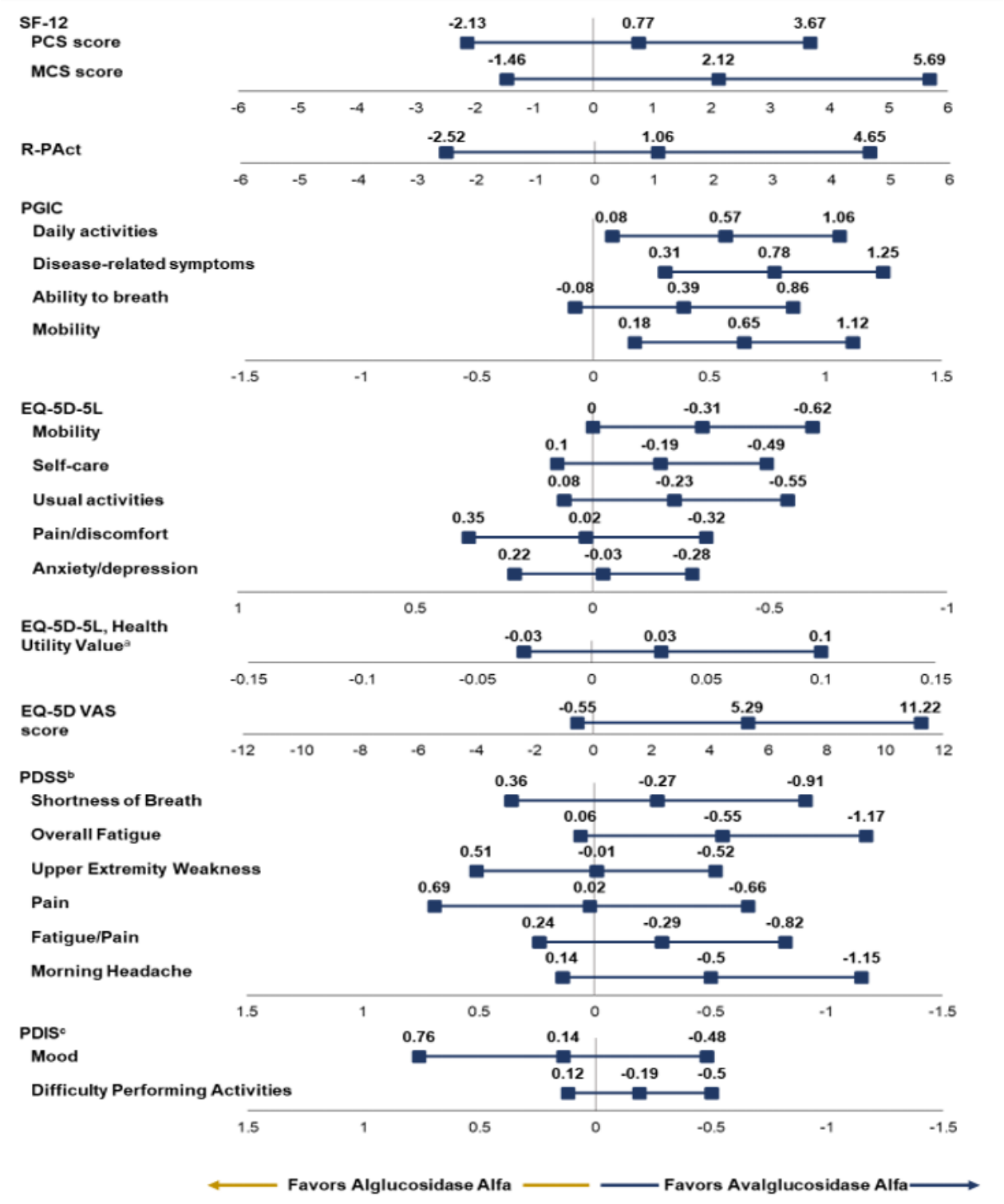
PGM=PRODOPS/GZ402666/EFC14028/CSR/REPORT/PGM/eff_meanchange_m_i_f.sas
OUT=REPORT/OUTPUT/eff_meanchange_m_i_6mwt_f_i.rtf (13JUL2020 11:17)

Avalglucosidase alfa demonstrated clinically meaningful and consistent improvement on other secondary endpoints of percent predicted Maximum inspiratory pressure (MIP) and Maximum expiratory pressure (MEP) [after exclusion of 4 patients with supraphysiologic baseline values], Hand held dynamometry (HHD) lower extremity strength, Quick motor function test (QMFT), and Medical outcomes study 12 items short form health survey (SF-12), and the observed benefit was greater compared to alglucosidase alfa (but in most cases not reaching statistical significance).

Of note, an inconsistency was found in the secondary endpoints data, which may be perceived as weakening the interpretability of the results. MIP appears to be conserved in the avalglucosidase alfa arm (i.e. it decreases less) whereas MEP shows higher improvement in the comparator arm. However, a post-hoc analysis excluding four patients with supra-physiological MIP and MEP values at baseline, which might have been a data entry error, were again more in favour of avalglucosidase.

Patient-reported outcomes (PDIS-Pompe Disease Impact Scale) were also collected and favoured avalglucosidase alfa compared to alglucosidase alfa. However, the results do not reach statistical significance in most subscores.

Figure 3. LS mean (95% CI) difference for changes from baseline on secondary and other efficacy outcomes measuring health-related quality of life



The sponsor performed also a post-hoc analysis which provides additional evidence of a beneficial effect of avalglucosidase alfa on FVC % predicted compared to alglucosidase alfa, based upon a larger dataset including the pivotal dataset for alglucosidase alfa (AGLU02704), which is important in a rare

disease in which large, controlled datasets are limited. The validity of this post-hoc analysis needs further discussion.

The sponsor claims also that avalglucosidase alfa demonstrated benefit in paediatric patients with IOPD previously treated with alglucosidase alfa and who presented with clinical decline or suboptimal response at doses greater than the alglucosidase alfa approved doses (ranging between 20 mg/kg qow and up to 42.6 mg/kg weekly). Avalglucosidase alfa 40 mg/kg qow demonstrated stabilization and, in some patients, improvement of parameters of motor function, respiratory function, cardiac function, eyelid position and health-related quality of life. This is not immediately obvious from the data submitted in the maintenance report. Depending on the outcome of the CHMP assessment the sponsor should be invited to further discuss this data. The heterogeneity of the population enrolled may be a contributing factor to the fact that treatment effects in IOPD seem at best comparable/non-inferior between alglucosidase and avalglucosidase.

SAFETY:

No additional safety or immunogenicity concerns were detected in studies with avalglucosidase. However, it was noted in the CHMP assessment report that the product may be of improved safety in cross reactive immunologic material (CRIM) positive patients. In such patients, lower risk of immunogenicity was observed. The sponsor does not discuss this aspect in the maintenance report, and generally, due to the low numbers of patients treated with avalglucosidase to date, arguments of improved safety should be treated with caution.

Overall, the best argument for clinically relevant advantage that the sponsor presented is the data on the 6MWT in LOPD patients. The significance of this endpoint in the context of other endpoints that trend positively in this patient population may be discussed. The sponsor would have to further discuss the data in IOPD to support the claim of improved efficacy.

4. COMP list of issues

Significant benefit

The sponsor is requested to further justify the significant benefit, with any arguments since the results from the pivotal study in adult LOPD naïve patients showed that avalglucosidase alfa is non-inferior to alglucosidase alfa at a 20 mg/kg dose and the data from the study in IOPD pre-treated patients did not show apparent difference between avalglucosidase alfa and alglucosidase alfa.

Comments on sponsor's response to the COMP list of issues

In the written responses and during the oral explanation the sponsor stated that a statistically significant effect should not be needed in support of the orphan significant benefit as this is not mandated by the regulation.

In this respect, it should be noted that, in the absence of conclusive evidence proving significant benefit at the time of the MA, the COMP is required to conclude that the designation criteria laid down in Article 3 of the regulation are no longer met and, therefore, recommend that the Commission remove the medicinal product concerned from the Community Register of orphan medicinal products (in this respect, see: Judgment of the General Court of 5 December 2018 in *BMS v Commission and EMA*, T-329/16, EU:T:2018:878, paragraph 86). This requirement is aligned with the fact that, for the purpose of maintenance of orphan designation, the comparative analysis between the new medicinal product and the reference product must establish not only that the new product provides a benefit to

patients but also that benefit is significant (by analogy, see: Judgment of the General Court of 16 May 2019 in *GMPO v Commission*, T-733/17, EU: T:2019:334, paragraph 39).

The sponsor made a claim for clinically relevant advantage in LOPD patients based on the primary and secondary endpoints from the EFC14028 pivotal Phase 3 study:

The primary endpoint was forced vital capacity (FVC) and the difference of 2.43% with lower boundary of 95% CI of -0.13 exceeded -1.1 (the predefined non-inferiority margin of 1.1) and thus met the predefined criteria for declaring success at the 5% level (p-value for non-inferiority =0.0074) and the primary study objective. However, upon testing for superiority, the endpoint missed formal statistical superiority (p=0.0626) for which a difference of 3.5% was targeted. The sponsor was of the opinion that any improvement in FVC observed with Nexviadyme is clinically meaningful from the patient's perspective. The applicant provided the following reason for missing statistical significance in the superiority test: "This was because the study was underpowered to detect the change, which is a known problem with rare diseases and small sample sizes and not driven by an absence of treatment difference." It was further clarified during the Oral Explanation on 7th December that the sponsor based this statement on a "retrospective/post-hoc" power calculation, meaning that the observed treatment effect was used instead of the previously anticipated treatment effect of 3.5 %. Hence, the statement of an underpowered study does not hold true, and it is apparent from the study protocol that the study was adequately powered for the anticipated predefined clinically relevant effect of 3.5 %. It rather shows a discrepancy between the anticipated and the observed treatment effect.

Post-hoc analyses were conducted, aiming at increasing sample size by pooling data (*n*=163) from COMET (Nexviadyme [n=51] or Myozyme [n=49]), NEO1/NEO-EXT phase 2 (Nexviadyme [n=3]) and the Myozyme historical phase 3: late-onset treatment study (LOTS) (Myozyme [n=60]). Regression analyses similar to the COMET pre-specified analysis using mixed model for repeated measures were performed post-hoc to compare COMET's primary endpoint. The results from the pooled analyses were consistent with those from COMET and favour improvement in FVC with Nexviadyme compared to Myozyme in treatment-naïve patients with LOPD.

In addition, the sponsor performed a post-hoc Bayesian posterior probability distribution using non-informative priors generated for the primary analysis of the primary endpoint in COMET. The sponsor found that the posterior probability for Nexviadyme being better than Myozyme is 97%. This analysis is very consistent with the unsuccessful analysis of superiority, as we would expect the result to be just less than 97.5%. There is 87% posterior probability that the difference between treatments is above 1% and 63% posterior probability that the difference is above 2%. Post-hoc analyses can be viewed as sensitivity analyses and a selection of favourable results has been presented. It is unclear to what extent unfavourable results exist as these have not been presented.

Finally, the sponsor discussed that the pre-specified subgroup analyses results were observed to be consistent regardless of gender, age and regions.

The COMP was of the opinion that the change in FVC of 2.4% was not substantial enough to outweigh the failed statistical analysis and the possibility that the data could be a chance finding.

Secondary endpoint 6-minute walk test (6MWT): The sponsor claimed that a clinically meaningful improvement in distance walked during the 6MWT was observed with Nexviadyme (LS mean change from baseline [SE] 32.21 [9.93]), and the benefit was greater compared to Myozyme (LS mean difference +30.01 [95% CI: 1.33, 58.69]; nominal p=0.0405). This corresponds to a LS mean (SE) relative improvement of 5.02 (1.54) in % predicted value (LS mean difference +4.71% [95% CI: 0.25, 9.17]; nominal p=0.0386. However, the superiority of Nexviadyme could not be formally claimed due to the multiplicity rules. The hierarchical testing procedure stopped with the failure to show

superiority for the primary endpoint and could not continue to the secondary endpoints that were outlined in section 11.4.2.3 of the study protocol.

The sponsor also addressed the concerns from the COMP about possible differences in the baseline characteristics of the two arms. It is agreed that small differences can be seen even in a randomised study and even more so in a study with small and heterogeneous patient population. Therefore, the COMP accepted the sponsor justification for the base line characteristics.

The COMP was of the opinion that the numerical difference of 30 meters was not clinically relevant and large enough to outweigh the failed statistical analysis and the possibility that the data could be a chance finding.

Other secondary, tertiary and exploratory endpoints: The sponsor measured respiratory function (maximum inspiratory and expiratory pressure), 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)). The trend towards better efficacy with Nexviadyme was noted by the COMP but again the magnitude of this difference was not large enough to be considered clinically relevant.

The sponsor also included several methods of measuring patient reported outcomes in the EFC14028 study: generic measures SF-12, Patient Global Impression of Change [PGIC], EQ-5D-5L and LOPD-specific measures Pompe Disease Symptom Scale [PDSS], Pompe Disease Impact Scale [PDIS] and Rasch-Built Pompe-Specific Activity [R-PAct]. The sponsor submitted forest plots which show that Nexviadyme was numerically better than Myozyme for all domains except pain. Also, the post-hoc responder analyses favoured Nexviadyme vs. Myozyme for all PROs. In order to strengthen the clinical relevance of these exploratory findings, the sponsor also submitted a recent publication (November 2021) from the International Pompe Association wherein it is described that due to the heterogeneity of the patient population not all outcomes are equally important to the patients.

The COMP was of the opinion that the trend towards better responses in patients treated with Nexviadyme as compared to Myozyme did not outweigh the failed statistical analysis and the possibility that the data could be a chance finding.

An argument for clinically relevant advantage was also made for the IOPD patients. Study ACT14132 included 22 patients with IOPD who demonstrated clinical decline or sub-optimal clinical response to Myozyme treatment at doses ranging between 20 mg/kg qow and 42.6 mg/kg weekly, representing patients with the highest unmet need.

Results of study ACT14132 show positive trends (stabilization or improvement) in secondary and tertiary efficacy outcomes with Nexviadyme. However, the COMP was of the opinion that due to its design and small size study ACT14132 could not deliver firm conclusions on Nexviadyme's efficacy in IOPD patients setting.

Finally, the sponsor also argues a clinically relevant advantage based on improved safety: The sponsor argues that there is a lower risk of immunogenicity observed with Nexviadyme than with Myozyme, based on antibody titres. However, there is no clear evidence that these higher titres change the safety for the patients. At this stage of development there is limited safety data available with Nexviadyme and the one available indicate towards a similar safety profile as Myozyme. Therefore, the safety argument is not accepted by the COMP in support of a significant benefit.

In conclusion, the efficacy and safety data provided by the sponsor do not demonstrate a clinically significant difference between Nexviadyme and Myozyme.

5. COMP position adopted on 20 December 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of glycogen storage disease type II (Pompe's disease) (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening, in particular due to progressive weakness of muscles, respiratory and cardiac failure and limited survival;
- in view of the fact that a satisfactory method for the treatment of the condition has been authorised in the European Union (Myozyme), the existence of significant benefit over the authorised method of treatment should be established at the stage of the granting of marketing authorisation;
- the sponsor's claim that Nexviadyme is of significant benefit to those affected by the orphan condition does not hold. Significant benefit over Myozyme was claimed on the grounds of a clinically relevant advantage. The sponsor presented data from a clinical study which showed that Nexviadyme was non-inferior to Myozyme but failed to show in a robust way that Nexviadyme was superior to Myozyme. Although the analyses of secondary and other endpoints trended towards a better effect with Nexviadyme as compared to Myozyme, the limitations of the study entailed that the data submitted did not allow the COMP to conclude that the claim for significant benefit of Nexviadyme over Myozyme has been appropriately demonstrated.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products has recommended that Nexviadyme, recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan, avalglucosidase alfa for treatment glycogen storage disease type II (Pompe's disease) (EU/3/14/1251) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 20 December 2021

Grounds for appeal

The sponsor presented detailed grounds for appeal on 21 March 2022.

Please refer to the sponsor's appeal documents in the case *Input from Industry* folder.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 12 April 2022.

Biostatics working party consultation on 8 April 2022

The Biostatistics Working Party (BSWP) was consulted.

In the context of the appeal procedure for this application, the BSWP was asked to provide its views on the following issues:

1) Do BSWP consider that the assumptions of the MMRM model are met, specifically normality of the residuals? (See Written Response to COMP document, Question 1). If not, would BSWP consider it more appropriate to rely on non-parametric methods instead?
2) Do the submitted non-parametric analyses provide additional evidence that would make BSWP more willing to consider relaxing the traditional 5% alpha level, mindful this is a superiority trial against an active comparator in an orphan condition? Or is the existence of such analyses irrelevant to this decision?

The BSWP discussed the questions from the COMP, in the light of the data and argumentation presented and their feedback is as follows:

1) There is agreement at BSWP that there is not a strong violation of the model assumptions, meaning that we don't have a problem with the MMRM. The MMRM is fairly robust against deviations from normality.
2) The type 1 error control should remain at study level; and here the MMRM was pre-specified which leads to a formally negative study result. The type 1 error control will not be preserved if we switch now to a different method, leading to difficulties in interpretation. It should be noted that decisions at an individual study level and regulatory decision-making should be distinguished. If the COMP is open to consider a positive outcome for decision-making, this should be based on the totality of evidence, rather than the change in statistical methods.

Comments on the grounds of appeal

Ground #1: COMET (EFC14028) new analysis: nonparametric equivalent to the pre-specified MMRM analysis

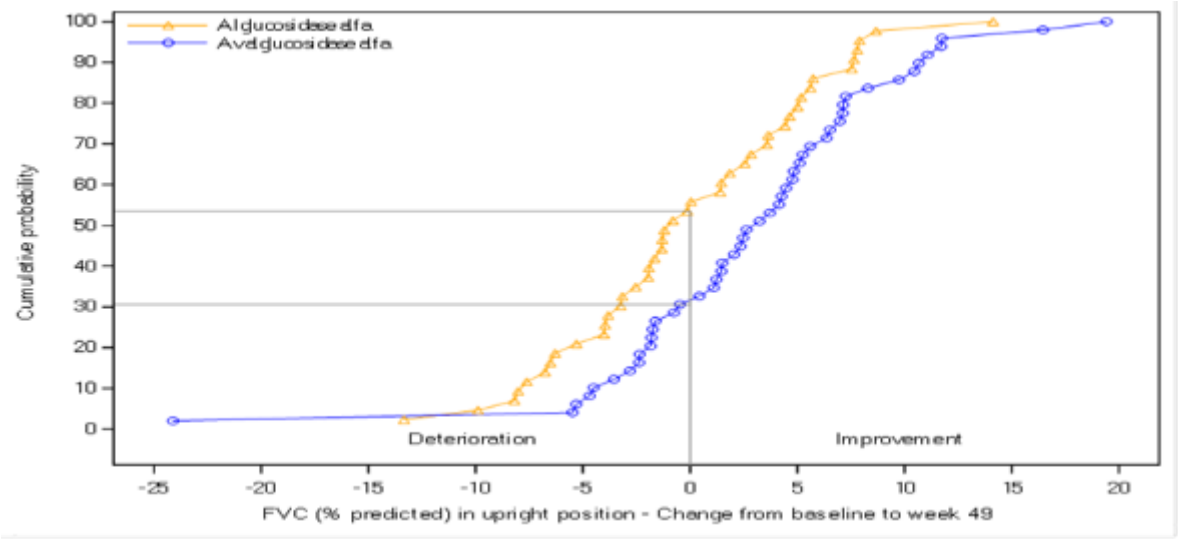
The sponsor submitted a nonparametric analysis (using rank Repeated-Measures ANCOVA) equivalent to the primary MMRM analysis.

When the observed changes from baseline to Week 49 in FVC % predicted are represented as a cumulative probability function, a clear right shift of the Nexviadyme curve compared to the Myozyme curve is observed (Figure 5). According to the sponsor figure 5 clearly shows the systematically greater benefit of Nexviadyme regardless the level of change from baseline. Approximately 70% of patients

improved their FVC (i.e., had a positive absolute change from baseline) with Nexviadyme versus 47% patients in the Myozyme group.

The plot in Figure 5 below shows that one patient from Nexviadyme had a relative low response comparing to the rest of patients in both treatment groups (depicted at the extreme left of the blue curve in Figure 1). The Sponsor considered that there was an outlier for the primary endpoint FVC (% predicted) in the Nexviadyme treatment arm, and therefore, this non-parametric method would be more robust than the pre-scheduled primary MRMM analyses included in the protocol. It was mentioned that the steep FVC (%Predicted) decline could have been confounded by concurrent diagnosis of asthma and COPD in this patient.

Figure 4. Plot of the cumulative probability function of change from baseline to week 49 in FVC (% Predicted) in upright position - in PAP - mITT population – COMET study



When removing this patient from the primary MMRM analysis, the estimated treatment difference changes from 2.43 to 2.93 and results in p-value of 0.0126 (Table 1).

In presence of an outlying patient in the Nexviadyme group, the Wald-type rank test was performed by incorporating the rank transform statistic of the rank repeated measures analysis of covariance model into GEE framework including all available data. This nonparametric test achieved a p-value of 0.0192 using all data including the outlier (Table 1). The p-value from this nonparametric test is close to the p-value of 0.0126 from the primary MMRM analysis after removing the outlying patient.

Table 1. FVC (% Predicted) change from Baseline at Week 49 - in upright position - mITT population - COMET study

	Statistics	**Nexviadyme (N=51)**	**Myozyme (N=49)**	**Difference**
Primary analysis: MMRM	LS mean	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			0.0626
MMRM excluding an outlying patient[#]	LS mean	3.41	0.43	2.98
	SE	0.81	0.84	1.17
	95% CI	1.81, 5.01	-1.24, 2.10	0.65; 5.30
	P-value			0.0126
Rank Repeated-Measures ANCOVA	n	49	43	
	median	3.2359	-0.8098	
	P-value*			0.0192

*P-values are based on Wald-type Rank Test from the rank repeated measures ANCOVA model includes the rank transformed change from baseline of FVC % predicted as a response and visit, treatment, visit and treatment interaction, the rank transformed baseline FVC % predicted, the rank transformed baseline age, and sex as fixed effects.
[#] This patient 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.

According to the sponsor, this further explains that the narrowly missed statistical superiority (p=0.0626) based on the pre-specified MMRM analysis is due to lower power in presence of an outlier, and not a chance finding.

In reply to the COMP's request, the sponsor also submitted an analysis of the residuals from the primary analysis of MMRM showing that data at Week 49 are approximately normal after removing one patient with outlying data. Furthermore, the results from an additional analysis using quantile regression showed superiority of Nexviadyme over Myozyme: a median improvement of 4.35% in FVC % predicted change from baseline at Week 49 with 95% CI of (1.68%, 7.02%) and p-value 0.0017.

COMP position on Ground #1

In examining the submitted primary MMRM analysis, the COMP questioned whether the one patient with the worst response in the Nexviadyme (AVAL) arm should indeed be considered, as per the company's proposal, as an outlier and therefore excluded from the analysis.

In this regard, the COMP noted that there is wide heterogeneity in the Pompe disease regarding symptoms and disease course.

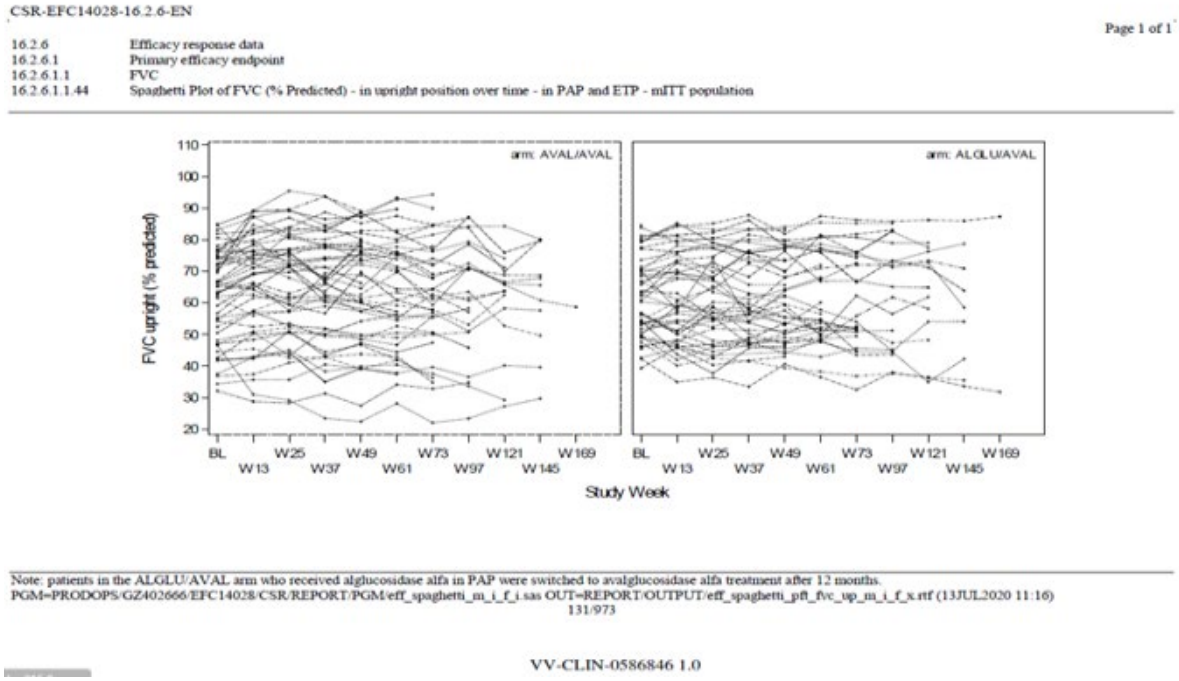
Further, the heterogeneity of the disease was also reflected in the COMET study, with participants showing heterogeneity regarding baseline disease severity and response. As a matter of fact, the supposedly outlier patient had complied with the inclusion/exclusion criteria of the COMET study.

In addition, Nexviadyme will be indicated also for the supposedly outlier patient with asthma and COPD.

Also, a decline of 25% within 49 weeks (as the one shown by the supposedly outlier patient) is not unexpected from a clinical point of view.

Actually, the spaghetti plots of the primary outcome FVC (% Predicted) in the COMET study (Figure 6) are illustrative of the heterogeneity of the study population in what regards the treatment response over time, given that it is actually not possible –on the basis of these plots– to identify the so-called outlier amongst the other study subjects.

Figure 5. Spaghetti plot of FVC (% Predicted) – in upright position over time – in PAP and ETP-mITT population (Source CSR-EFC14028)



In addition to the above, from a statistical point of view, the exclusion of the outlier is considered as a violation of the ITT principle since it was specified in the protocol that the mITT population will include all randomized patients who received at least 1 infusion.

Further to the above, the data from this specific patient should be considered as one of the influencers on the outcome, rather than as a true outlier. Thus, the post-hoc MMRM analyses excluding this patient are not considered justified.

In that respect, the COMP's position is aligned with the (non-binding) input of the BSWP, insofar as both bodies consider that there is no valid justification for the exclusion of the supposedly outlier patient.

Turning to the non-parametric analysis, the COMP took the position that this could only be seen as exploratory. Replacing the pre-specified MMRM analysis with a non-parametric analysis approach would not allow to maintain control over the type 1 error of the study.

On balance, the COMP concluded that the clinical trial COMET had failed to demonstrate that the primary endpoint showed superiority of Nexviadyme over Myozyme. Due to the limitations of the primary MMRM excluding an outlying patient and the non-parametric analyses, those analyses were not sufficient (albeit statistically significant) to establish the existence of significant benefit of Nexviadyme over Myozyme.

In that respect, it also bears noting that the BSWP and the COMP are aligned insofar as both bodies consider that the COMET trial had failed to establish formally the superiority of Nexviadyme over

Myozyme. According to the BSWP, the existence of a potential significant benefit could not simply be based on the primary analysis of the COMET study for FVC. The BSWP left expressly the final decision on the existence or non-existence of significant benefit (by reference to the totality of the evidence for regulatory decision-making) to COMP. For the reasons explained in this report, the COMP considered that the additional analyses (the totality of the evidence) were not sufficient for establishing the existence of significant benefit.

Ground #2: COMET (EFC14028) new analysis: Win ratio methodology

Data from the modified intent-to-treat (mITT) population of the COMET trial were analysed post-hoc with the win ratio approach to assess the overall effect of treatment on the primary (FVC % predicted) and key secondary (6MWT) endpoints of the trial, preserving the idea of a sequential comparison as in the original design of the study while gaining power by considering the endpoints jointly. The sponsor argued that the win ratio method has been applied as a post hoc analysis in the EMA approval of several medicinal products.

The approach to the win ratio analyses was pre-specified in a statistical analysis plan documenting the prioritization of endpoints and clinically meaningful thresholds for improvement and worsening to be used in the comparisons. Comparisons in the win ratio analyses were based on change from baseline (CFB) at 49 weeks and used thresholds for clinically meaningful improvement and worsening, selecting the middle value of the published range, for FVC % predicted (4%; range = 2-6%) and the 6MWT (39minutes; range = 24-54minutes). While stability or any improvement in respiratory function and mobility can be a meaningful positive outcome to patients with Pompe disease due to the disabling and progressive nature of the disease, conservative thresholds for improvement based on evidence from psychometric studies were selected for this analysis. The order of comparison, consistent with the primary and secondary endpoints in the COMET trial, was first change in FVC % predicted and second change in 6MWT.

Each patient's outcomes are classified as representing 1) meaningful improvement if patient's score improved by at least the threshold for improvement, 2) meaningful decline if a patient's score declined by more than the threshold for worsening, 3) neither meaningful improvement or decline (i.e., no meaningful change) if a patient's score did not meet the criteria for improvement or decline.

Results from analyses are summarized in the Table 2.

Table 2. Results for multiple imputation and data as observed win ratio analyses- COMET study

	Analyses with Multiple Imputation*						**Analysis of Data as Observed#**
Nexviadyme	**Pooled****	**1**	**2**	**3**	**4**	**5**	
Wins on FVCPP	1021	1035	1036	1036	989	1010	923
Losses on FVCPP	509	489	498	498	535	526	417
Wins on 6MWT	347	346	342	346	357	342	314
Losses on 6MWT	145	150	150	122	153	148	106
Total Wins	1368	1381	1378	1382	1346	1352	1237
Total Losses	654	639	648	620	688	674	523
Win Ratio	**2.10**	**2.16**	**2.13**	**2.23**	**1.96**	**2.01**	**2.37**
Lower bound of 95% CI	1.19	1.22	1.21	1.25	1.12	1.14	1.30
Upper bound of 95% CI	3.69	3.82	3.75	3.96	3.42	3.52	4.29
P-value (two-sided)	**0.011**	**0.008**	**0.009**	**0.006**	**0.019**	**0.015**	**0.005**

*One patient treated with Myozyme died due to a TESAE of acute myocardial infarction (unrelated) in the PAP. For this patient no imputations were made. **Pooled results were calculated as the average values across replications for number of wins and losses (rounded) and the win ratio. The confidence interval and p-value for the pooled win ratio are calculated based on the average of variances derived used to calculate p-values in the five replications. P-values are for testing for a null win-ratio of 1. # The Nexviadyme arm included 51 patients; 1 patient was missing CFB in both FVC % predicted and the 6MWT and did not contribute to analyses without imputation; 1 patient was only missing CFB in FVC % predicted and 2 were only missing 6MWT at week 49. These patients are compared based on their available observations and the conservative assumption is made that they are ties for comparisons of outcomes that were missing, even if the patient with data on those outcomes was improving. The Myozyme arm included 49 patients; five patients were missing CFB in both FVC % predicted and the 6MWT and did not contribute to analyses without imputation; 1 patient was only missing CFB in FVC % predicted and 1 was only missing 6MWT at week 49. These patients are compared based on their available observations and treated as ties for comparisons of outcomes that were missing.

The sponsor claimed that analyses with imputation yielded a win-ratio of 2.10 (p = 0.011; 95% CI: 1.19 – 3.69); that is, patients on Nexviadyme were more than twice as likely as those receiving Myozyme to have a more favourable outcome on FVC % predicted or the 6MWT at week 49. Results of the as-observed analyses (without imputation) produced consistent results that are less precise (i.e., slightly wider confidence intervals): 2.37 (95% CI: 1.30 – 4.29; p = 0.005). Furthermore, an estimated win ratio greater than 2 is observed from the results on FVC alone.

In reply to the COMP's request, the sponsor provided an analysis where subjects with missing data were considered losses, regardless of any improvements beforehand. This was implemented by assuming that patients with missing FVC % predicted or 6MWT at week 49 had a "meaningful decline" on the missing measure(s), regardless of any prior improvements. This imputation was also applied for the patient in the Myozyme arm who died prior to week 49. Pairwise comparisons were carried out as per the original analyses and yielded a win ratio of 2.47 (95% CI: 1.42-4.31). According to the sponsor, the increase in the win ratio is explained by missing observations being more common in the Myozyme arm; imputing these as a decline increases the number of wins for the Nexviadyme arm. An alternate approach was also considered where patients who had missing data on FVC % predicted or 6MWT were treated as having lost in pairwise comparisons with patients with non-missing values and treated as a tie if the other patient was also missing the measure being compared. This implies missingness is treated as a worse outcome than "meaningful decline" and is a departure from the original framework of the analyses which assumed three categories of responses. Nevertheless, results were consistent with those noted above with a win ratio of 2.43 (95% CI: 1.40-4.22).

COMP position on Ground #2

The COMP agreed with the sponsor that the win ratio approach has been accepted in the past during the evaluation of medicinal products. However, this approach has been accepted in duly justified cases, such as clinical trials investigating both mortality and a clinically relevant outcome such as hospital admission for heart failure. The idea behind a win ratio approach, in such case, would be that a drug which improves mortality might have difficulty showing improved relevant secondary outcomes such as hospital admission rates simply because more and perhaps sicker surviving patients are at risk for hospital admission due to the lower mortality rate. However, this is not applicable in this particular case with the use of FVC and 6MWT, where there is no competition between the endpoints and where the use of the win ratio method seems to be intended to simply increase power by combining endpoints. The COMP considers that the win ratio approach in this case is not a method justified on clinical grounds (COMP's position would also be aligned with the way in which the originators of the win ratio approach in cardiovascular medicine have conceptualized this new approach; see: 'Analysing composite endpoints with varying severity, and to account for the relative priority of components', Redfors, Eur Heart J 2020 41:4391-9.).

The COMP considered that the win ratio analyses are rather considered exploratory than confirmatory evidence, particularly since the pre-specified primary analyses of this confirmatory trial failed to demonstrate superiority. Indeed, the CHMP took into consideration win ratio analyses for other products including an orphan one, but in that case the primary analyses were met. Although the chosen cut-off points for a clinically relevant effect are indeed conservative, the analyses seem data-driven since they were not pre-specified in the protocol submitted to COMP by the sponsor.

Therefore, and in line with the conclusion of the ground # 1, the COMP concluded that claims of superiority of Nexviadyme based on secondary, sensitivity or post-hoc analyses as the win ratio analyses were not sufficiently compelling from a methodological point of view and also not justified on clinical grounds; and they could therefore not establish the claim of significant benefit of Nexviadyme over Myozyme.

Ground #3: Additional support for the clinical relevance of Nexviadyme effects on respiratory function and mobility - time to event simulation analysis

The sponsor conducted a simulation study to predict the percentage of patients on Nexviadyme and Myozyme who would require future ventilation (non-invasive and invasive) or a wheelchair and the average time to requiring ventilation or wheelchair.

When simulated over a lifetime horizon (i.e., until the set of patient profiles all die), the estimated cumulative percentage of patients on Myozyme needing a non-invasive ventilation was 69.4%, the percentage needing invasive ventilation was 36.4%, and the percentage needing a wheelchair was 58.1%. The estimated percentages were lower in patients using Nexviadyme over a lifetime horizon: Percentages in this group were 55.6%, 23.3% and 38.0%, for non-invasive ventilation, invasive ventilation, and wheelchair use, respectively.

In Myozyme patients, the average estimated time to usage of non-invasive ventilation was 17.4 years, 30.7 years for use of invasive ventilation, and 19.6 years for use of a wheelchair. The length of time was increased in Nexviadyme patients: the average times were 22.0, 36.3, and 26.0 years for non-invasive ventilation, invasive ventilation, and wheelchair use, respectively.

According to the sponsor, these analyses confirm the finding that Nexviadyme prevents the need for assisted ventilation and wheelchair use. This supports the overall clinical relevance of the effects of Nexviadyme in LOPD patients.

COMP position on Ground #3

The COMP concluded that it is very difficult to accept the results of the simulation study since it seems very problematic to assess the validity of a model that predicts events over a time horizon exceeding 15 years over the observed data of Nexviadyme. The large extrapolation to future time without support from long-term (observational) data for both products was considered to be speculative and cannot be accepted.

On balance, this study was at best exploratory and could not possibly be considered to be conclusive evidence for the purpose of establishing the claim of significant benefit of Nexviadyme over Myozyme.

Ground #4: Analysis of PRO outcomes

The sponsor claimed that Pompe Disease Symptom Scale (PDSS), Pompe Disease Impact Scale (PDIS) and Rasch-Built Pompe-Specific Activity Scale (R-PAct) measure symptoms and functional limitations that are important to PD patients and are critical manifestations of the underlying pathophysiology of the condition. Responder analysis and cumulative distribution functions for PDS, PDIS and R-PAct were presented by the sponsor. According to the sponsor, the results extend the findings from the analyses of the exploratory endpoints based on these measures to further illustrate the clinical relevance of the effect of Nexviadyme on the patient experience. Across the analyses, patients receiving Nexviadyme were more likely to experience meaningful improvements in symptoms and physical functioning than patients on Myozyme in the COMET study. Patients receiving Nexviadyme were also more likely to report switching from being unable to complete basic mobility-related activities (e.g., bend over to pick something up, walk at a rapid rate) than patients receiving Myozyme.

COMP position on Ground #4

The responder analysis in the PRO endpoints seems problematic. There seems to be an imbalance at baseline of potential prognostic factors, not in favour of Myozyme (e.g. median predicted FVC; 65.5 vs 60.8%, median 6MWT 415.7m vs 387.0 m, use of a walking device 13.7% vs 20.4%) which could have biased the outcomes. In addition, from the cumulative distribution curves, it seems that the distribution for Nexviadyme is consistently broader than that for Myozyme. Thus, it seems that the higher responder rates presented for Nexviadyme would be counterbalanced by higher deteriorator rates for Nexviadyme as well. In general, the application of a cut-off to a continuous variable leads to loss of power and a selective view.

Further to the above, the COMP took the view that this analysis could not suffice for establishing the existence of the claimed significant benefit of Nexviadyme over Myozyme.

Ground #5: Clinically relevant benefit in IOPD patients declining on Myozyme

The sponsor presented a recent data analysis performed on 15 February 2022 for study ACT14132 (Mini-COMET). In this analysis, the 22 patients enrolled in the study have reached at least 2 years of treatment with Nexviadyme, including 20 patients who received the highest dose of 40 mg/kg qow, and 18 who have been treated for at least 3 years. Updated data on biomarkers are also available from the review performed by the Data Monitoring Committee (DMC).

Review of functional outcome data is available up to Week 145 for the majority of these patients and demonstrates sustained increase in motor skills as measured by the Pompe-specific Quick Motor Function Test (QMFT), with 14 patients continuing to improve in motor function and only two exhibiting a decline in QMFT scores more than 3 points on a 0-64 scale.

According to the sponsor, all efficacy biomarkers continue to improve, consistent with a sustained reduction in muscle damage. In addition, the quantity of improvers and degree of improvement in motor function exceeded the quantity and degree of decline, with 14 patients continuing to improve in motor function, only 2 patients exhibiting a decline in quick motor function test (QMFT) scores more than 3 points on a 0-64 scale, and 8 patients exceeding a 3-point change.

As part of the ACT14132 study, sites were requested to provide functional outcome data to document clinical decline to meet inclusion criteria. Three patients from a single site had available Gross Motor Function Measure 88 (GMFM-88), a performance based clinical outcome assessment utilized in the study thus providing opportunity for long term comparison of patient motor function using a standardized measure.

When three individual young patients are observed over time, either with retrospective data or with attention to functional changes, improvements in function observed on Nexviadyme are appreciated for a variety of baseline ages and functional levels after motor decline on Myozyme. These individual trajectories illustrate patient cases that have been positively impacted by Nexviadyme and are not limited to a certain age or functional level. The sponsor argued that Nexviadyme showed a substantial and clinically relevant positive impact on functional abilities of a wide range of patients that have suboptimal response or experience decline on standard of care.

COMP position on Ground #5

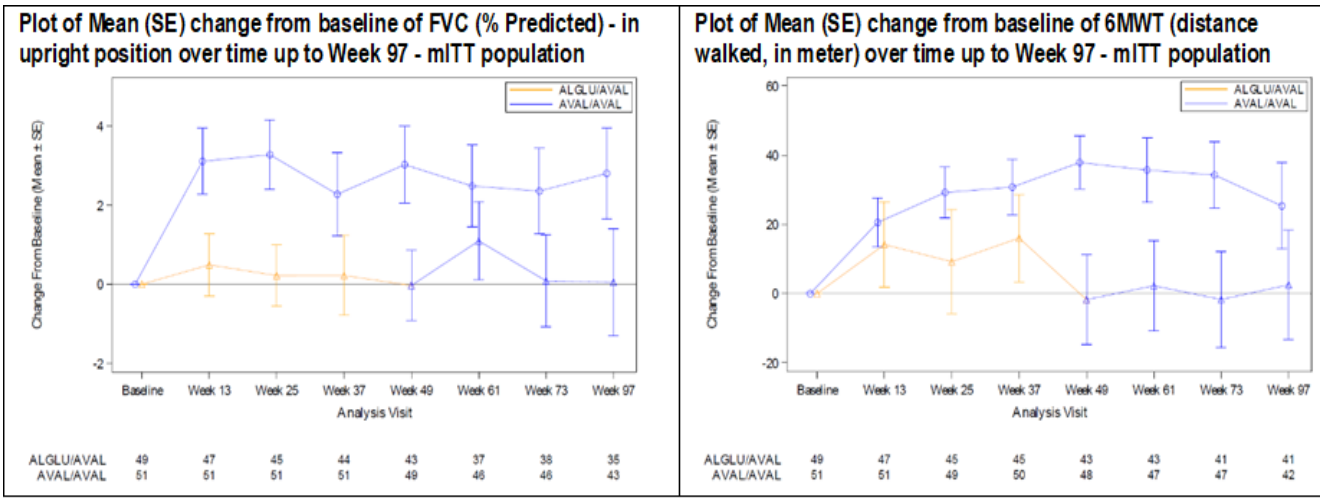
The COMP considered that, based the recent data analyses (cut-off date 15 February 2022) for study ACT14132 of the 22 patients, the long-term QMFT outcomes of the 3 cohorts in the Mini-COMET study (IOPD), there is no clear difference in response in patients depending on whether they were treated with high or low dose Nexviadyme up to 145 weeks, or depending on whether they continued Myozyme in the first 25 weeks.

The Sponsor discussed the improvement in 6MWT in 3 children after switching to Nexviadyme in cohort 3a, that was not achieved with prior treatment with Myozyme in the first 25 weeks. However, the observation time was longer for Nexviadyme. Moreover, the other motor domains did not improve in these children It is further noted that the motor outcomes like the 6MWT could also be influenced by the development of the young children (aged 1-3 years) that were also included, reaching motor milestones with aging.

The COMP concluded that the updated long-term data with a more recent cut-off (15 February 2022) are of exploratory or descriptive nature. Due to the design, the small sample size, and the descriptive nature of the results in secondary and tertiary efficacy outcomes, this study does not allow to deliver conclusions on Nexviadyme efficacy in this setting.

Moreover, the study in LOPD patients (COMET) did not demonstrate a clear benefit of switching to Nexviadyme in patients with what could be considered as a modest response to previous Myozyme treatment (lower than reported before for other trials).

Figure 6. Plot of Mean (SE) change from baseline of FVC (% Predicted) – in upright position over time up to week 97 mITT population and Plot of Mean (SE) change from baseline of 6MWT (distance walked, in meter) over time up to week 97 mITT population



Altogether, in neither the LOPD nor the IOPD population has it been robustly demonstrated that switching to Nexviadyme improves outcomes in inadequate responders to Myozyme.

For completeness, it also bears noting that a claim suggesting that reduced burden of treatment (on the basis of less frequent administration) would amount to better efficacy cannot be accepted. The existence of better efficacy needs to be shown on the basis of appropriate conclusive evidence and cannot be presumed on the basis of a less frequent regime of administration. Moreover, according the SmPC of both Nexviadyme and Myozyme, the posology is similar for both products (i.e. intravenous infusion every two weeks).

Ground #6: Survey in Pompe disease patients declining on Myozyme

A qualitative survey of patients receiving Nexviadyme through several European early access programs (N=21) was conducted to explore the real-world impact of treatment on IOPD and LOPD symptoms and functioning. Patients had been using Nexviadyme for an average of approximately 6 months at the time of the survey. According to the sponsor, the results highlighted several areas of meaningful improvement for the majority of IOPD and LOPD patients who were previously declining on Myozyme. Fifteen (15; 71.4%) respondents reported improvements in at least one functional area. Improvements in muscle strength were most often reported. These improvements had a positive impact on mobility and activities of daily living. Additionally, improvement in respiratory function and less fatigue were also often reported. Patients also reported improvements related to their treatment; treatment with Nexviadyme was better tolerated than Myozyme in several instances. Most patients and caregivers indicated that the improvements were "very" or "extremely" important. Two patients reported negative changes following initiation of Nexviadyme, but it is not clear if these changes were maintained over time or if they outweighed positive changes that were also experienced. The sponsor argued that these preliminary survey data support the real-world effectiveness of Nexviadyme treatment in patients who were previously declining on Myozyme.

COMP position on Ground #6

The COMP concluded that although the preliminary data from the ongoing survey showed positive effects of Nexviadyme on disease complications and patient daily functioning for the majority of IOPD and LOPD patients who were previously declining on Myozyme, this data is hampered by the fact that

this was a small sample size and there was no control data (consequently, blinding, which is an important trial design element to prevent bias, was not possible). There were no systematic and objective measurements of muscle strength or respiratory function. In addition, with only 21 of the 30 patients completing the survey the proportion of non-completing patients impacts the conclusions that one could draw. Therefore, this data cannot be considered reliable in order to support the claim for superiority of Nexviazyme over Myozyme.

Ground #7: Nexviadyme is of significant benefit based on improved safety compared to Myozyme

The sponsor argued that Nexviadyme provides a clinically meaningful, improved safety benefit because of its lower immunogenicity.

Decreased immunogenicity and thus, improved immunogenicity and tolerability of Nexviadyme versus Myozyme is due to additional glycans having a shielding effect for ADA binding.

- A comprehensive assessment of immunogenicity using data from Pompe disease patients treated with Nexviadyme in clinical studies demonstrated Nexviadyme has an improved immunogenicity profile relative to Myozyme. This is evidenced by the observation that fewer patients receiving Nexviadyme have clinically relevant ADA titers and a lower incidence of NAb.
- Patients receiving Nexviadyme had 4-fold lower ADA titers, and fewer patients had high ADA titers (≥12800), including those with HSAT (high sustained antibody titers; ≥51200 after 6 months of treatment). Titer levels >12800 have been established to be clinically relevant. In addition, the incidence of NAb was reduced by approximately 40% with Nexviadyme.
- The additional synthetic glycans constitute the only structural difference between Nexviadyme and Myozyme. The glycoengineering process used to develop Nexviadyme results in a more extensively glycosylated molecule, with glycosylation contributing to decreased immunogenicity by likely shielding known immunogenic epitopes, while maintaining the native conformation of the protein.

Clinically meaningful changes in safety, related to decreased immunogenicity

- Nexviadyme was better tolerated as compared to Myozyme in the 49-week blinded comparative period of the COMET (EFC14028) study as shown by lower frequencies of TEAEs, SAEs, and protocol-defined infusion associated reactions (IARs) with Nexviadyme. Overall, a lower incidence of IARs and hypersensitivity reactions was observed in the ADA-positive Nexviadyme arm compared to the ADA-positive Myozyme arm which was particularly evident in patients with persistent ADA.
- Analyses of change from baseline to at week 49 in respiratory function including FVC (% predicted), MIP (% predicted), and MEP (% predicted) assessed in the upright position, as well as 6MWT (distance walked and % predicted) was performed by treatment emergent ADA, ADA titers, and neutralizing ADA in the naïve patient population in Study COMET (EFC14028). There was no association shown between the ADA titers and the evaluated clinical efficacy parameters for Nexviadyme.
- Immune mediated reactions have occurred during clinical studies and have been reported during the post marketing safety experience for Myozyme. Such reactions have not been observed to date with Nexviadyme despite more than 8 years of exposure since the start of the Phase 1/ 2 TDR12857 study in LOPD patients.

COMP position on Ground #7

The COMP considered that no firm conclusions could be drawn on an improved safety profile of Nexviadyme as compared to Myozyme, because of the low numbers of exposed patients (in EFC14028 49 and 51 LOPD naïve patients were randomized to Myozyme and Nexviadyme respectively). In addition, no long-term comparative data are available after the end of PAP (49 weeks duration) since all patients previously randomized to Myozyme were switched to Nexviadyme.

Finally, regarding the claim that fewer patients treated with Nexviadyme had clinically relevant high ADA titers as compared to Myozyme, the COMP considered the limitations of the low number of ADA positive patients in each peak titer categories and the confounding influence of previous exposure to Myozyme in the 22 IOPD patients in study ACT14132.

During the oral hearing a patient representative emphasised the unmet medical need. The patient representative highlighted the clinical importance of patients reported outcome/QoL parameters reported in the survey and the finding that Nexviadyme prevents the need for wheelchair use. The COMP agreed with the need for alternative treatments. However, the survey provided by the sponsor cannot justify the significant benefit because of the limitations reported above in connection with the patient survey; and, in any event, it was noted that the COMET study failed to demonstrate the superiority of Nexviadyme over Myozyme in the primary endpoint of FVC. The assumption that Nexviadyme could prevent the need of a wheelchair was based on simulations, and not confirmed by long-term observational data, and therefore not supported by the COMP.

On balance, the COMP identified significant limitations in the data submitted by the company as part of its detailed grounds of appeal. In view of those limitations, the data (whether taken in isolation or in combination and in their totality) cannot be considered to be conclusive evidence for the purpose of establishing the existence of significant benefit of Nexviadyme over Myozyme. In view of their limitations, the additional analyses could not be sufficient to overcome the formal failure of the COMET study to show in a robust manner the superiority of Nexviadyme over Myozyme.

7. COMP final position on review of criteria for orphan designation adopted on 26 April 2022

Based on the assessment of the detailed grounds for appeal and the explanations presented by the sponsor during the oral explanation, the COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of Pompe disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening, in particular due to progressive weakness of muscles, respiratory and cardiac failure and limited survival;
- in the context of the first opinion, the significant benefit over Myozyme was claimed on the grounds of a clinically relevant advantage. The sponsor presented data from a clinical study which showed that Nexviadyme was non-inferior to Myozyme but failed to show that Nexviadyme was superior to Myozyme. Although the analyses of secondary and other endpoints trended towards a better effect with Nexviadyme as compared to Myozyme, the limitations of the study entailed that the data submitted did not allow the COMP to conclude that the claim for significant benefit of Nexviadyme over Myozyme has been appropriately demonstrated;
- in the context of the appeal, the sponsor presented additional evidence and/or arguments to the COMP to further substantiate the claims of clinically relevant advantage;
- the COMP considered that the additional post hoc analyses are rather considered exploratory than confirmatory evidence, particularly since the pre-specified primary analyses of this confirmatory trial failed to demonstrate superiority. This equally applies to the non-parametric and the win-ratio analyses;
- the additional time to event simulations were considered too uncertain as these entail a prediction of response multiple years over the actual observation time in the studies;
- the preliminary survey data, the updated analyses on the patient reported outcomes and the updated efficacy data on the supportive study on switching from previous Myozyme to Nexviadyme, were not considered sufficient to establish the significant benefit of Nexviadyme over Myozyme due to the underlying methodological uncertainties and the limited data provide;
- due to the limitations of the study, the safety analysis could not demonstrate a clinically relevant advantage of Nexviadyme over Myozyme;
- therefore, the COMP considered that the submitted evidence and/or arguments in the context of the appeal did not suffice to establish that Nexviadyme provides a significant benefit over Myozyme.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The COMP recommends that Nexviadyme, recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan, avalglucosidase alfa for treatment glycogen storage disease type II (Pompe's disease) (EU/3/14/1251) is removed from the Community Register of Orphan Medicinal Products.