20 March 2023
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EMADOC-360526170-1359200
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Pombiliti (Recombinant human acid alpha-glucosidase)
Treatment of glycogen storage disease type II (Pompe's disease)
EU/3/18/2000

Sponsor: Amicus Therapeutics Europe Limited

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 acid alpha-glucosidase
Other names	Pombiliti, Recombinant human acid alpha-glucosidase
International Non-Proprietary Name	Cipaglucosidase alfa
Tradename	Pombiliti
Orphan condition	Treatment of glycogen storage disease type II (Pompe's disease)
Sponsor's details:	Amicus Therapeutics Europe Limited Block 1 Blanchardstown Corporate Park Ballycoolen Road Blanchardstown Dublin 15 D15 AKK1 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Amicus Therapeutics UK Ltd
COMP opinion	15 February 2018
EC decision	21 March 2018
EC registration number	EU/3/18/2000
Post-designation procedural history	
Transfer of sponsorship	Transfer from Amicus Therapeutics UK Ltd, to Amicus Therapeutics Europe Limited – EC decision of 25 March 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Alexandre Moreau
Applicant	Amicus Therapeutics Europe Limited
Application submission	05 November 2021
Procedure start	25 November 2021
Procedure number	EMA/H/C/005703/0000
Invented name	Pombiliti
Proposed therapeutic indication	Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α glucosidase [GAA] deficiency). Further information on Pombiliti can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Pombiliti
CHMP opinion	15 December 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Cécile Dop / Elisabeth Johanne Rook
Sponsor's report submission	20 July 2022

Oral explanation (cancelled by sponsor)	18 January 2023
COMP opinion	19 January 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant human acid alpha-glucosidase when used in combination with miglustat was considered justified based on non-clinical data in a valid in-vivo model of the condition showing improved muscle function as well as preliminary clinical data showing improvement of motor function in patients with the condition;
- the condition is life-threatening and chronically debilitating due to accumulation of glycogen in muscle and nerve cells leading to progressive skeletal myopathy, cardiomyopathy, and respiratory insufficiency, leading to death within two years of birth in the infantile forms, and in the fourth decade of life in forms with later onset;
- the condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human acid alpha-glucosidase when used in combination with miglustat will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid model of the condition showing better responses on muscle function compared to Myozyme, currently authorised for the condition. In addition to that, the sponsor has provided preliminary clinical data indicating improvement in motor function in patients treated with the product used in combination with miglustat after switching from the currently authorised enzyme replacement therapy. The Committee considered that this constitutes a clinically relevant advantage.

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 (also known as acid maltase deficiency or glycogen storage disease type II) 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.

Pompe disease is considered to be a continuous spectrum of phenotypes, with the clinically most severe, rapidly progressive phenotype being the classic infantile-onset Pompe disease (IOPD) and the less severe, more slowly progressive phenotypes being late-onset Pompe disease (LOPD) (Güngör,

Reuser 2013). 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.

The condition has not changed in terms of classification or description since the initial orphan designation.

The approved therapeutic indication "Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α glucosidase [GAA] deficiency)" falls within the scope of the designated orphan condition "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 sponsor has adequately outlined the chronically debilitating and life-threatening nature of the disease.

The 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.

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 as 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 sponsor proposed a prevalence of 0.37 in 10,000 persons, for the total orphan condition which includes both LOPD and IOPD. The sponsor states that with the implementation of newborn screening programs and the use of dried blood spot analysis for determination of the presence of acid alpha-glucosidase activity using enzyme analysis, the incidence (birth prevalence) of Pompe disease is becoming increasingly well characterised in many countries in the EU.

The sponsor summarises eight studies on incidence in Europe published between 2006 and 2021 in which the incidence ranges from 1 in 40,000 to 1 in 600,000.

The infantile form has an apparent higher incidence among people from African and Asian decent, whereas the late-onset adult form has a higher incidence in The Netherlands. A study in The Netherlands reported a combined frequency of IOPD and LOPD as 1 in 40,000 births with the incidence of the infantile onset form as 1 in 138,000 (Ausems, Verbiest et al. 1999). The combined global incidence of all forms of Pompe disease is estimated to be 1 in 40,000 (0.25 per 10,000) live births (Ausems, Verbiest et al.1999; Martiniuk, Chen et al.1998; Hirschhorn, Reuser et al. 2001).

The sponsor concluded on an estimated birth incidence in the EU of 0.37 per 10,000 births, based on the literature and as it is similar to the global incidence rate of 1 in 40,000 (0.25 per 10,000 persons). The sponsor then seemed to extrapolate the incidence to the prevalence and states that the estimated point prevalence for Pompe disease (all forms) in the EU is based on a global incidence rate (0.37 per 10,000, as described above), including accrual of additional patients in the EU on an annual basis based on assumptions for increasing survival and duration of survival for enzyme replacement therapy (ERT)-treated patients with the availability of an approved ERT product for treatment of Pompe disease (all forms) in the EU beginning in 2006.

The COMP considered that it was not clear why the duration of the disease has not been taken into consideration for the purpose of estimating the prevalence. The sponsor also referred to EMA/452415/2012 Rev. 11, 16 December 2014 which is marked as "no longer valid" and should not be used as a reference for the purpose of estimating prevalence.

Based on updated survival estimates for Pompe disease provided by the sponsor, of the estimated 151 infants born with Pompe disease in the EU, approximately 57 (38%) will have the infantile-onset form, 6 (4%) will have the juvenile-onset form, and 88 (58%) will have the adult-onset form of the disease (Martiniuk, Chen et al. 1998) with assigned average ages of death of 1, 15-20 and 45-60 years for infantile, juvenile, and adult-onset phenotypes, respectively. Based on these survival estimates, the 57 infantile cases will die in one year. For simplicity of calculation, the sponsor assumed that the 6 juvenile cases born each year will survive to 20 years of age. Similarly, the sponsor assumed that the 88 adult-onset cases survive to 60 years of age. However, the sponsor did not provide a prevalence estimate based on the duration of the disease and they claimed a prevalence of 0.12 per 10,000 which is considered underestimated.

In conclusion, the COMP considered that, in view of the uncertainties about birth prevalence and the effect of available treatments, the prevalence should be rounded to "less than 1 per 10,000" (as opposed to 0.12). Altogether, the criteria that the condition is rare are met.

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

The sponsor correctly identified the two approved ERT in the EU:

Table 1. Existing methods

Trade Name	Member State Approval	Marketing Authorisation Holder	Authorised Indication
Myozyme (alglucosidase alfa)	Centralised (EU/1/06/333)	Genzyme Europe B.V.	Myozyme is indicated for long-term enzyme-replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid-α-glucosidase deficiency). In patients with late-onset Pompe disease, the evidence of efficacy is limited.
Nexviadyme (avalglucosidase alfa)	Centralised (EU/1/21/1579)	Genzyme Europe B.V.	Nexviazyme is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency) including adult and paediatric patients.

Abbreviation: EU = European Union

Both Myozyme and Nexviadyme are considered satisfactory treatments for the target patient population of Pombiliti, although it is noted that substantial morbidity and mortality persists even with ERT treatment (Schoser, Bilder et al. 2017).

Significant benefit

Cipaglucosidase alfa was developed to be a more potent ERT compared to the first approved ERT, alglucosidase alfa (Myozyme). The aim was to enhance the glycan structure, using an at least 10-fold higher bis M6P-bearing N-glycans than alglucosidase alfa. This specialised glycosylation was envisaged to lead to substantially higher binding to the cell surface receptor, CI-MPR, resulting in enhanced uptake of the exogenous ERT by the target muscle cells and intracellular trafficking to the lysosomes, the site of glycogen accumulation in affected tissues. However, the CHMP concluded that not superiority, but non-inferiority of efficacy was demonstrated versus alglucosidase alfa.

The sponsor is aiming to use cipaglucosidase alfa together with miglustat. Miglustat functions as a GAA stabiliser in the near neutral pH of the blood to significantly reduce inactivation of enzyme activity and ensure that cipaglucosidase alfa delivered to lysosomes is active. Miglustat alone has no direct effect on glycogen reduction in Pompe disease. The combination of cipaglucosidase alfa and miglustat was intended to provide improved skeletal muscle targeting, with greater tolerability, reduced immunogenicity, and potentially improve efficacy in order to address the limitations of the existing standard of care.

Protocol assistance was sought by the sponsor in 2020 but did not contain a question on the significant benefit.

- Significant benefit over newly approved alglucosidase alfa (Myozyme):

The sponsor bases the justification of significant benefit on data from Study ATB200-03 (PROPEL study). This was a double-blind, randomised, multicentre study of cipaglucosidase alfa/miglustat in adult subjects with LOPD who had received ERT with alglucosidase alfa (ERT-experienced) or who had never received ERT (ERT-naïve) compared with alglucosidase alfa/placebo. The aim of the study was to demonstrate superiority of the combination. The primary endpoint was change in 6MWD (6-minute

walk distance) measured in meters from baseline to week 52. The test was performed at screenings 1 and 2 and at weeks 12, 26, 38, and 52.

The ITT (intention to treat) study population (ERT-experienced and ERT-naïve) treated with cipaglucosidase alfa in combination with miglustat therapy had a mean improvement in walk distance from baseline of 20.0 meters as compared to those treated with alglucosidase alfa/placebo with a mean improvement of 8.3 meters, resulting in a difference mean change from baseline of 11.7 meters (95% CI [-1.0, 24.4]; p = 0.07). However, statistically significant superiority of cipaglucosidase alfa in combination with miglustat was not demonstrated for this primary efficacy endpoint.

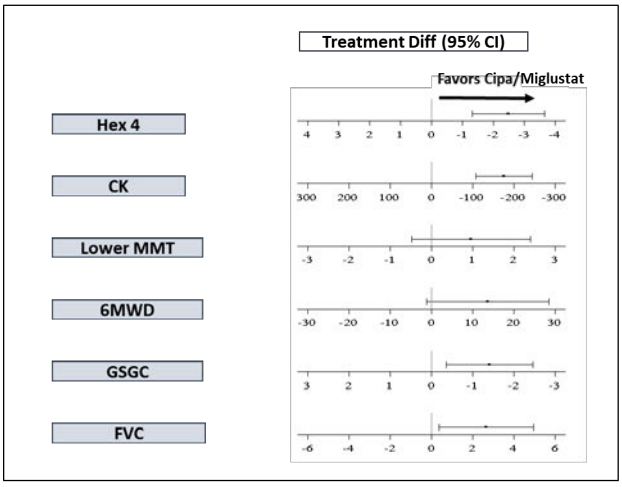
Even when excluding one outlying subject the study failed the primary endpoint test based on the pre-specified MMRM analysis. The estimated mean treatment difference (95%CI) excluding the outlying subject is 14.2 (-2.6, 31.0) meters with two-sided p-value of 0.096.

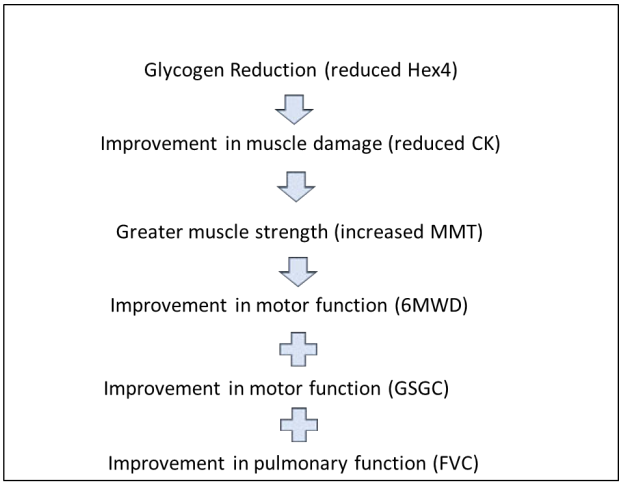
Although the study failed to meet its primary endpoint, and (key) secondary endpoints could not be formally tested according to the pre-defined hierarchy of statistical tests, the sponsor claims that the significant benefit should be based on the totality of the data and argues a clinically relevant advantage over alglucosidase alfa (Myozyme) based on efficacy as follows:

On the first key secondary endpoint, % predicted forced vital capacity (FVC), cipaglucosidase alfa/miglustat showed a nominally statistically significant (p = 0.023) and clinically meaningful difference for superiority versus alglucosidase alfa in the overall population. Cipaglucosidase alfa/miglustat significantly slowed the rate of respiratory decline in subjects after 52 weeks. Progressive respiratory muscle weakness is a major cause of morbidity and mortality in LOPD even after ERT treatment has been ongoing for some time (Boentert, Prigent et al. 2016). Furthermore, % predicted FVC was the primary endpoint in pivotal clinical studies of alglucosidase alfa and avalglucosidase alfa, and the observed treatment difference for this endpoint was similar in those studies to that observed between cipaglucosidase alfa/miglustat and alglucosidase alfa in the ATB200-03 study (van der Ploeg, Clemens et al. 2010; Diaz-Manera, Kishnani et al. 2021).

As the majority of prespecified secondary efficacy endpoints of interest, when informally tested, favoured cipaglucosidase alfa/miglustat over alglucosidase alfa (see Figure 1 and Table 2), the sponsor is of the opinion that cipaglucosidase alfa/miglustat showed improved outcomes in important Pompe disease domains compared to the approved therapy, alglucosidase alfa.

Figure 1. Change from Baseline at Week 52 in Primary and Key Secondary Endpoints for the ITT Population Excluding Subject 4005-2511 (Outlier) – Study ATB200-03





Abbreviations: 6MWD = 6-minute walk distance; ATB200 = cipaglucosidase alfa; CI = confidence interval; CK = creatine kinase; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and rising from a Chair test; Hex4 = hexose tetrasaccharide; ITT = intent-to-treat; MMT = manual muscle test
Source: Forest Plot NAS Q107.1.1

Table 2. Summary of All Endpoints for the ITT Population Excluding Subject 4005-2511 (Outlier) – Study ATB200-03

Category	Endpoint	Endpoint Hierarchy	Overall Subjects				
			Cipaglucosidase alfa/miglustat		Alglucosidase alfa/placebo		2-sided P value
			BL Mean	CFBL Week 52 LOCF Mean (95%CI)	BL Mean	CFBL Week 52 LOCF Mean (95%CI)	
Motor Function	6MWD	Primary	357.93	20.79 (11.56, 30.01)	350.95	7.24 (-6.19, 20.67)	0.071
	6MWD week 26	Key Secondary	357.93	17.44 (9.80, 25.08)	350.95	9.19 (-0.20, 18.59)	0.195
	GSGC	Key Secondary	14.51	-0.53 (-1.13, 0.06)	14.50	0.77 (0.09, 1.44)	**0.009**
	% Predicted 6MWD	Secondary	57.82	4.07 (2.56, 5.59)	56.03	1.58 (-0.42, 3.58)	0.077
	10m walk (time in sec)	Secondary	9.68	-0.53 (-1.81, 0.76)	9.58	1.90 (-0.17, 3.96)	**0.025**
	4 stair climb (time in sec)	Secondary	14.09	-8.46 (-24.26, 7.34)	8.22	0.32 (-1.66, 2.29)	**0.050**
	Gowers' (time in sec)	Secondary	10.84	-0.26 (-1.74, 1.22)	19.82	-2.19 (-5.04, 0.66)	0.305
	Chair test (time in sec)	Secondary	13.58	-10.17 (-29.40, 9.06)	4.52	-0.50 (-1.92, 0.92)	0.290
	TUG (time in sec)	Secondary	12.88	-0.30 (-2.24, 1.65)	12.77	-0.13 (-1.11, 0.85)	0.748
Pulmonary Function	FVC (Sitting, % predicted)	First Key Secondary	70.74	-0.93 (-2.29, 0.42)	69.68	-3.95 (-5.58, -2.32)	**0.023**
	FVC (Supine, % predicted)	Secondary	54.78	-0.24 (-1.46, 0.99)	55.09	-3.00 (-4.67, -1.33)	**0.009**
	SVC (Sitting, % predicted)	Secondary	69.94	-2.32 (-4.25, -0.38)	68.59	-5.86 (-8.83, -2.90)	0.125
	MIP (% predicted)	Secondary	61.79	2.06 (-2.11, 6.23)	59.90	-2.70 (-8.32, 2.92)	0.278
	MEP (% predicted)	Secondary	70.72	0.62 (-4.14, 5.38)	65.08	-1.59 (-5.86, 2.67)	0.617
Muscle Strength	Lower MMT	Key Secondary	27.96	1.56 (0.72, 2.40)	27.65	0.88 (-0.02, 1.78)	0.191
	Upper MMT	Secondary	34.30	1.51 (0.76, 2.25)	34.70	0.68 (-0.51, 1.86)	0.117
	Overall MMT	Secondary	62.25	3.07 (1.66, 4.48)	62.35	1.41 (-0.12, 2.94)	0.059
	QMT total	Secondary	165.83	6.86 (-5.31, 19.04)	158.8	8.20 (-2.38, 18.77)	0.751
QOL	PROMIS-Physical	Key Secondary	66.86	1.94 (0.31, 3.57)	67.97	0.19 (-3.42, 3.80)	0.276
	PROMIS-Fatigue	Key Secondary	22.26	-2.02 (-3.26, -0.77)	21.08	-1.67 (-3.88, 0.54)	0.970
Biomarker	CK	Secondary	447.0	-130.5 (-180.4, -80.7)	527.8	60.2 (7.0, 113.3)	**<0.001**
	HEX4	Secondary	4.61	-1.88 (-2.40, -1.36)	6.92	1.22 (-0.26, 2.70)	**<0.001**

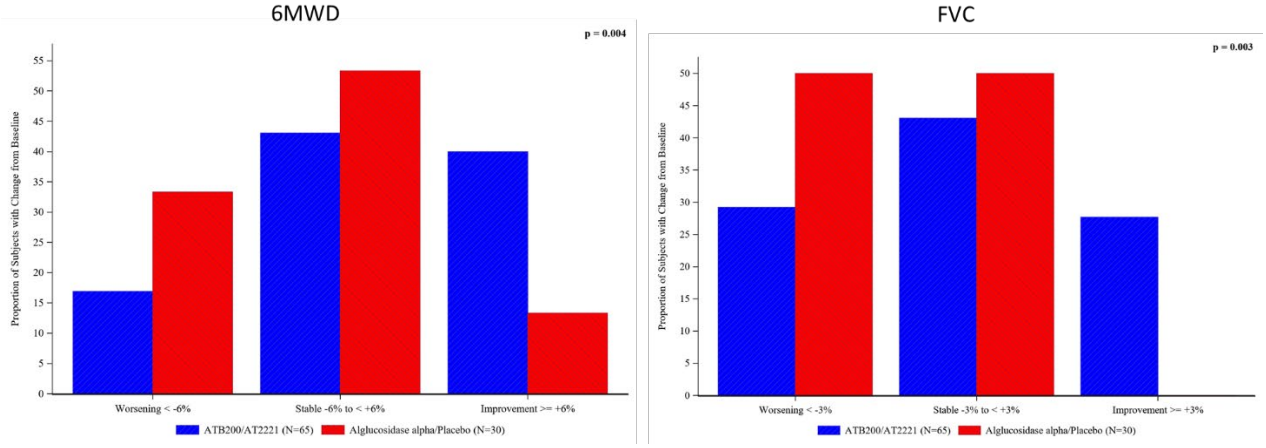
Abbreviations: 6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; ATB200 = cipaglucosidase alfa; BL = baseline; CFBL = change from baseline; CI = confidence interval; CK = creatine kinase; CSR = clinical study report; ERT = enzyme replacement therapy; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and rising from a Chair test; Hex4 = hexose tetrasaccharide; ITT = intent-to-treat; LOCF = last observation carried forward; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; MMT = manual muscle testing; PROMIS = Patient-Reported Outcomes Measurement Information System; QMT = quantitative muscle testing; QOL = quality of life; SVC = slow vital capacity; TUG = timed up and go
Note: Blue font = CFBL improved; red font = CFBL worsened.
Note: Green shading indicates treatment group favoured.
Note: P-values are nominal and based on ANCOVA except for 6MWD, which is based on nonparametric randomisation-based ANCOVA.
Note: Based on LOCF means
Note: Bold p-values indicate the superiority test of the specified endpoint (eg, 6MWD) in that specified population (eg, overall or ERT-experienced) was nominally significant.
Source: ATB200-03 CSR, Table 14.2.2.1.1.b1, Table 14.2.2.4.1.b1, Table 14.2.1.1.1.b1, Table 14.2.8.1.1.b1, Table 14.2.9.1.b1, Table 14.2.1.1.2.b1, Table 14.2.9.2.b1, Table 14.2.3.1.1.b1, Table 14.2.3.1.4.b1, Table 14.2.13.1.b1, Table 14.2.4.1.1.b1, Table 14.2.10.1.b1, Table 14.2.6.1.1.b1, Table 14.2.7.1.1.b1, Table 14.4.1.1.b1, and Table 14.4.1.2.b1

- Efficacy in ERT-experienced patients

Enzyme replacement therapy-experienced patients differ from ERT-naïve patients in the extent of long-term muscle damage. Enzyme replacement therapy -naïve patients are usually in a less-advanced stage of their disease; therefore, muscle damage is not yet significant. The sponsor thinks this is supported by the baseline characteristics of ERT-experienced versus ERT-naïve subjects in the ATB200-03 study. For example, the mean baseline 6MWD in the ERT-experienced group was 343.0 meters compared to 397.8 meters in the ERT-naïve group. Similarly, the mean baseline % predicted FVC in the ERT-experienced group was 67.7% compared to 80.0% in the ERT-naïve group (ATB200-03 CSR). The greater extent of long-term tissue damage in ERT-experienced compared to ERT-naïve patients provides a scientific rationale for greater sensitivity in detecting treatment benefit in the ERT-experienced population and necessitates a mechanistically improved and more potent rhGAA to manifest improvement in this population.

As shown by patient-level responder analyses, more than 3 times as many ERT-experienced subjects on cipaglucosidase alfa/miglustat showed clinically meaningful improvement of > 6% for 6MWD versus alglucosidase alfa (approximately 40% versus 13%), and approximately 28% of ERT-experienced subjects on cipaglucosidase alfa/miglustat versus 0 subjects on alglucosidase alfa showed clinically meaningful improvement of > 3% for FVC. Additionally, only about half as many subjects on cipaglucosidase alfa/miglustat demonstrated clinically meaningful worsening of > 6% for 6MWD versus alglucosidase alfa (17% versus 33%) or clinically meaningful worsening of FVC > 3% (29% versus 50%) (ATB200-03 CSR).

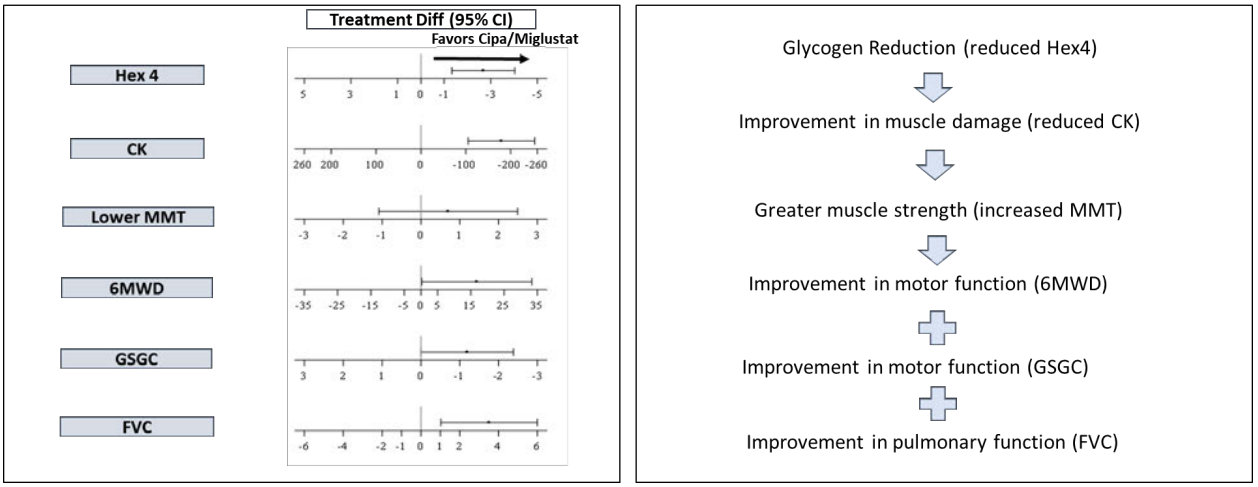
Figure 2. Proportion of Subjects with Change from Baseline at Week 52 in 6MWD and % Predicted FVC Grouped by Consolidated Ranges (ERT-experienced Subjects)



Abbreviations: 6MWD = 6-minute walk distance; ATB200 = cipaglucosidase alfa; AT2221 = miglustat; ERT = enzyme replacement therapy; FVC = forced vital capacity

According to the sponsor, the initial improvement imparted by cipaglucosidase alfa's glycan structures and better uptake into muscles is manifested in the ERT-experienced population initially as a reduction in Hex4, a biomarker of glycogen storage, followed by subsequent reductions in creatine kinase, a biomarker of muscle damage, and improvements in measures of muscle strength (lower manual muscle testing [MMT]), motor function (6MWD, Gait, Stairs, Gowers' manoeuvre, and rising from a Chair test [GSGC]), and pulmonary function (FVC) (Figure 3 (Figure 6 from sponsor)). In fact, according to the sponsor the majority of primary and secondary endpoints showed improvement and directionally favoured cipaglucosidase alfa/miglustat over alglucosidase alfa/placebo.

Figure 3. Change from Baseline at Week 52 in Primary and Key Secondary Endpoints for ERT-experienced Subjects Excluding Subject 4005-2511 (Outlier) – Study ATB200-03



Abbreviations: 6MWD = 6-minute walk distance; ATB200 = cipaglucosidase alfa; CI = confidence interval; CK = creatine kinase; ERT = enzyme replacement therapy; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and rising from a Chair test; Hex4 = hexose tetrasaccharide; MMT = manual muscle testing, NAS
Source: Forest Plot NAS Q156.1.2

The sponsor specifically discusses the ERT-experienced patients but not the ERT-naïve ones however the COMP cannot draw final conclusions regarding a subgroup, as the study failed to meet its endpoint for the total ITT (intention to treat) study population.

It is noted that the nominal effect sizes of the clinical effects of cipaglucosidase alfa in combination with miglustat tended to be larger for multiple pharmacodynamic (Hexose tetrasaccharide, and creatine kinase) and secondary clinical endpoints (Gait, Stairs, Gowers' maneuver, and rising from a Chair test, and sitting forced vital capacity) in ERT-experienced adult LOPD study patients in the pivotal study ATB200-03. However, for the purpose of the significant benefit it would also be important to also have the data on the ERT-naïve LOPD patients.

The individual contribution of cipaglucosidase alfa on the overall efficacy observed with cipaglucosidase alfa/miglustat versus alglucosidase alfa is discussed by the sponsor but is of less interest for the significant benefit conclusion as there is no data supporting that cipaglucosidase alfa monotherapy has a better effect than alglucosidase alfa.

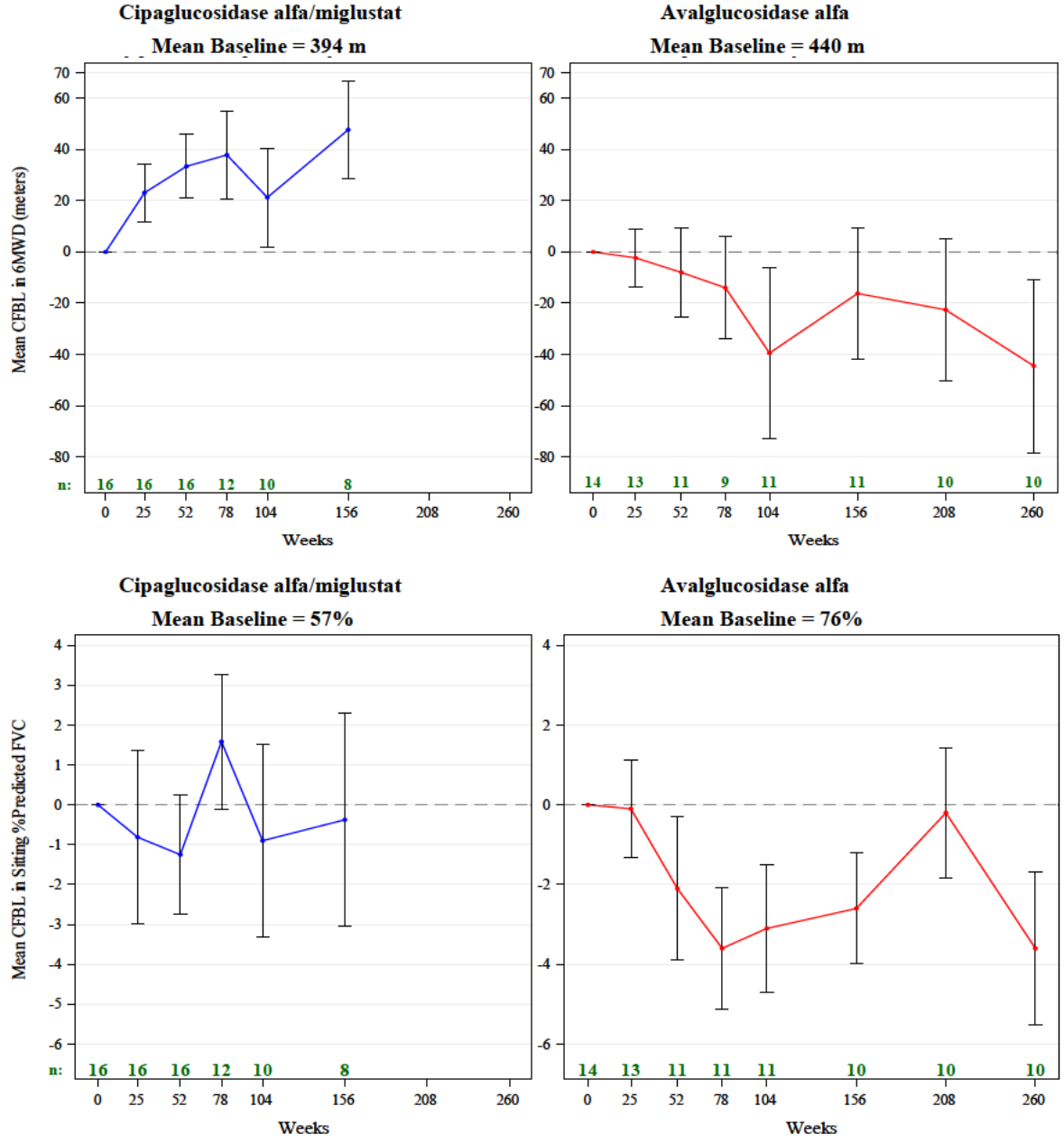
- Significant benefit over newly approved avalglucosidase alfa (Nexviadyme):

There are no clinical study data available that directly compare cipaglucosidase alfa/miglustat versus avalglucosidase alfa. The sponsor is using the Phase 1/2 avalglucosidase alfa study to compare with as that is the only study in which the long-term ERT-experienced adults were included. The sponsor has conducted a comparison of the long-term clinical data (6MWD and % predicted FVC) based on the data observed in the respective Phase 1/2 studies. Additionally, the sponsor has conducted a network meta-regression (NMR) analysis for 6MWD and % predicted FVC including all available Phase 1/2 and Phase 3 data across the different ERT development programs.

Side-by-side comparison:

Results from the respective Phase 1/2 studies are shown as change from baseline.

Figure 4. Long-term Effect of Cipaglucosidase Alfa/Miglustat Compared with Avalglucosidase Alfa on Change from Baseline for 6MWD and % Predicted FVC (Sitting) in ERT-experienced Subjects



Abbreviations: 6MWD = 6-minute walk distance; CFBL = change from baseline; ERT = enzyme replacement therapy; FVC = forced vital capacity
Note: Some of the cipaglucosidase alfa/miglustat-treated ERT-experienced subjects received single doses of 5, 10, and 20 mg/kg cipaglucosidase alfa alone, followed by 3 doses of 20 mg/kg + 130 mg miglustat over the first 12 weeks before transitioning long-term to the final dose of 20 mg/kg cipaglucosidase alfa/miglustat.
Note: Some of the avalglucosidase alfa-treated subjects received 5 or 10 mg/kg for 26 weeks before transitioning long-term to the final dose of 20 mg/kg.
Source: ad hoc Figure 1.2 and Figure 1.4; Dimachkie, Barohn et al. 2022

Network meta-analysis of 6MWD and FVC

The studies incorporated into the network analysis include:

1) Three Phase 3 randomised controlled trials:

- LOTS (alglucosidase alfa versus placebo) (van der Ploeg, Clemens et al. 2010)
- COMET (avalglucosidase alfa versus alglucosidase alfa) (Diaz-Manera, Kishnani et al. 2021)
- ATB200-03 (PROPEL) (cipaglucosidase alfa/miglustat versus alglucosidase alfa)

2) Two single arm Phase 1/2 trials:

- NEO-1/-EXT (avalglucosidase alfa) (CDER 2021; Schoser, Barohn et al. 2019; Dimachkie, Barohn et al. 2022)
- ATB200-02 (cipaglucosidase alfa/miglustat)

3) Three Phase 3 open-label extension (OLE) trials:

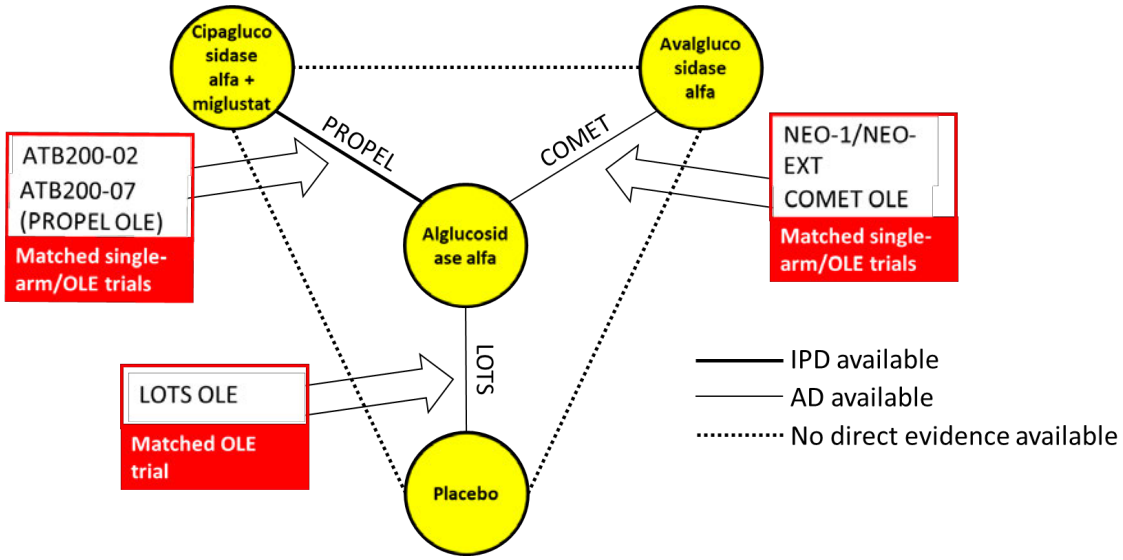
- LOTS OLE (alglucosidase alfa) (van der Ploeg, Barohn et al. 2012)
- COMET OLE (avalglucosidase alfa) (CDER 2021)
- ATB200-07 (PROPEL OLE) (cipaglucosidase alfa/miglustat)

The Bayesian multi-level network meta-regression (ML-NMR) method was applied to the combination of patient level data (PROPEL trial) and aggregate data (LOTS, LOTS OLE, NEO1/-EXT, COMET, ATB200-02, and PROPEL OLE) extracted for the 2 endpoints: 6MWD (m) and sitting FVC (% predicted) change from baseline over time. Part of the evidence informing treatment efficacy especially in ERT-experienced subjects is coming from single arm studies (ATB200-02, NEO-1/-EXT, COMET, and PROPEL OLE studies). To be able to include this evidence into a comparative setting of a network, the single arms were matched to appropriate comparator arms of the randomised controlled trials based on prior ERT duration being similar.

The network includes cipaglucosidase alfa/miglustat as the reference treatment and the following 2 treatments as the comparator treatments to cipaglucosidase alfa/miglustat:

- Alglucosidase alfa with both ERT-experienced and ERT-naïve subjects
- Avalglucosidase alfa with both ERT-experienced and ERT-naïve subjects

Figure 5. Network for 6MWD and FVC (% Predicted)



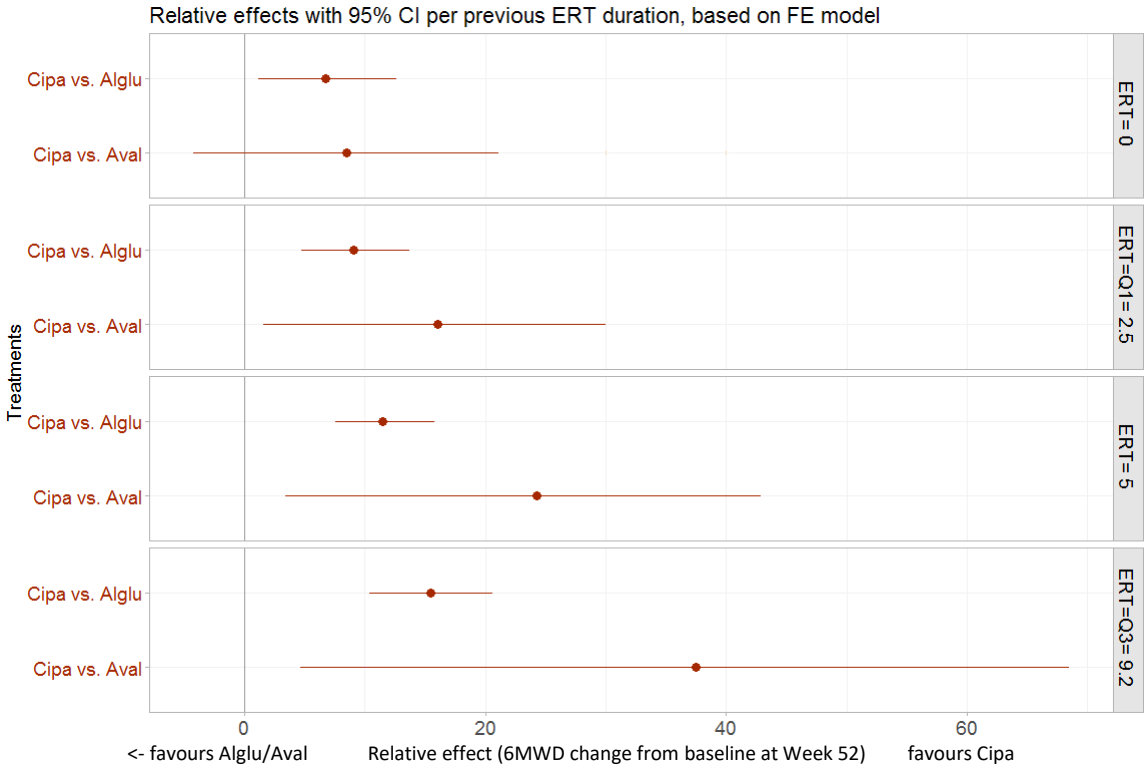
Abbreviations: AD = aggregate data; IPD = individual patient-level data; OLE = open-label extension

For the main analysis, cipaglucosidase alfa/miglustat was chosen as the reference treatment, and covariates were set to match the mean baseline values of the PROPEL trial (Scenario 1). An additional scenario was defined by setting covariates to match the mean baseline values of the COMET trial (Scenario 2). In each scenario, the following are shown:

- Forest plot (relative effects with its 95% CI) for the comparisons
  - Cipaglucosidase alfa/miglustat versus alglucosidase alfa
  - Cipaglucosidase alfa/miglustat versus avalglucosidase alfa
- Estimation table of relative effects with its 95% CI and p-value

The sponsor claimed that based on these results, it is clear that cipaglucosidase alfa/miglustat shows a statistically significant favourable effect versus alglucosidase alfa and avalglucosidase alfa on both 6MWD and FVC in either 1 or both of the scenarios evaluated, and results are consistent across various baseline parameters. E.g. Figure 6 and Table 3 show the relative effects for 6MWD change from baseline at Week 52 with previous ERT duration equal to 0, 2.5 (25% quartile), 5, and 9.2 (75% quartile) years under the FE model with other covariates set as in the base case scenario for PROPEL. This sensitivity analysis shows that the significant favourable effect on 6MWD for cipaglucosidase alfa versus both alglucosidase alfa and avalglucosidase alfa in ERT-experienced subjects increases in magnitude as the duration of previous ERT-experience at baseline increases.

Figure 6. 6MWD Change from Baseline at Week 52 by ERT Duration (Effects ML-NMR Model)



Abbreviations: 6MWD = 6-minute walk distance; Alglu = alglucosidase alfa; Aval = avalglucosidase alfa; CI = confidence interval; Cipa = cipaglucosidase alfa/miglustat; ERT = enzyme replacement therapy; FE = fixed effects; ML-NMR = multi-level network meta-regression

Table 3. Impact of Previous ERT Duration on Relative Effects for 6MWD Change from Baseline at Week 52 (Fixed Effects ML-NMR Model)

Scenario	Treatment	Relative Effect	P-value
ERT = 0	Cipaglucosidase alfa/miglustat versus alglucosidase alfa	6.819 (1.143, 12.614)	0.020
	Cipaglucosidase alfa/miglustat versus avalglucosidase alfa	8.32 (-4.261, 21.081)	0.200
ERT = Q1 = 2.5	Cipaglucosidase alfa/miglustat versus alglucosidase alfa	9.177 (4.728, 13.698)	< 0.001
	Cipaglucosidase alfa/miglustat versus avalglucosidase alfa	16.223 (1.533, 29.989)	0.025
ERT = 5	Cipaglucosidase alfa/miglustat versus alglucosidase alfa	11.535 (7.597, 15.815)	< 0.001
	Cipaglucosidase alfa/miglustat versus avalglucosidase alfa	24.126 (3.408, 42.903)	0.017

Table 4. Impact of Previous ERT Duration on Relative Effects for 6MWD Change from Baseline at Week 52 (Fixed Effects ML-NMR Model) (Continued)

Scenario	Treatment	Relative Effect	P-value
ERT =Q3 = 9.2	Cipaglucosidase alfa/miglustat versus alglucosidase alfa	15.497 (10.389, 20.614)	< 0.001
	Cipaglucosidase alfa/miglustat versus avalglucosidase alfa	37.402 (4.663, 68.458)	0.021

Abbreviations: 6MWD = 6-minute walk distance; ERT = enzyme replacement therapy; ML-NMR = multi-level network meta-regression

However, the COMP considered that there are several aspects of the ML-NMR that needs further clarification:

- The methodology needs further clarification, a detailed description of the methodology would be needed as section 3.3.2.2.2 of the sponsor's report is quite general.
- From section 3.3.2.2.3 it should be clarified how a mix of IPD and aggregate data were used in the network meta-analyses (NMA) and how they incorporate the OLE trials. These seem to be follow-up studies of the same patients that were used in preceding trials, and if so, were they counted as independent patients/studies, or was a longitudinal/repeated measures approach taken? The time point(s) used should also be elaborated on.
- The term "matched" that is used in Section 3.3.2.2.4 should be explained and what it means in the context of the NMA. In line with the previous point, it needs to be clarified whether some patients were included multiple times in the NMA, first as part of the PROPEL OLE trial, and thereafter as part of the matched control arm for trials ATB200-02 or PROPEL OLE, and how this dependency was handled in the NMR. Additionally, information needs to be provided on the matching methodology. Furthermore, diagnostics on the matching including baseline descriptions of the resulting control arm and the comparability with the SATs need to be provided (see Table 7 in the Sponsor report for matched studies).

- Figure 5 (9 in the sponsor's report) indicates a longitudinal approach, which however, leave the question how the OLE was incorporated: If the focus is on the week 52 outcome, and the trial duration is 78 weeks for LOTS and an additional 26 weeks for LOTS OLE, which additional benefit would LOTS OLE add to the analysis?
- Furthermore, it is unclear how missing data was handled. The statistical approaches to handle missing data need to be explained in detail. Additionally, the percentages of missing data and how it affects the results should be elaborated on.
- Section 3.3.2.2.5 presents a Baseline table with the most important variables. There are some differences across trials (see e.g. 6MWD differs by >100m for NEO-1 vs. LOTS) or within trials (see e.g. %Male within LOTS, 20% difference). What are the implications for the NMA?
- The choices of fixed and random effects in the analyses and reported results in Section 3.3.2.2.6 need further justification.
- The sponsor should present a side-by-side comparison of the direct evidence and the NMA results for the respective direct comparison (e.g. comparing the NMA predicted effect estimates for avalglucosidase alfa versus alglucosidase alfa with the respective results from COMET, and similar for all other RCTs) and explain any differences.
- The calculation of relative effects needs to be elaborated. In particular, the dependency of the relative effects on the scenario should be further explained (see for the 6MWD treatment effect e.g. the Base case scenario of 26.478 vs. the COMET trial scenario 10.818).
- What are the underlying assumptions of the NMA? The sponsor needs to explain and elaborate on e.g., consistency, transitivity, and homogeneity for this trial. Which tests and approaches have been taken to investigate potential violations of the assumptions? Were all assumptions met, or were violations observed?
- Can the sponsor show in a convincing way that the results of the NMA are robust? In particular, the sponsor is requested to provide the results of a NMA
    - that is only based on PROPEL, COMET and LOTS without including supporting studies (e.g. ATB200-2 etc.);
    - that excludes LOTS and LOTS OLE, with and without the supporting studies (ATB200-02, etc.).

According to the COMP, a network meta-regression analysis in the ERT-experienced subgroup of adult LOPD patients may provide supportive evidence on the clinical efficacy of cipaglucosidase alfa in combination with miglustat relative to other enzyme replacement therapies such as alglucosidase alfa, or avalglucosidase alfa. However, the indirect treatment comparisons in such an analysis which is limited to the ERT-experienced LOPD subgroup do not allow definitive conclusions on the clinical effects of cipaglucosidase alfa only relative to other enzyme replacement therapies in adult LOPD patients in general.

As it is not agreed with the sponsor that they have demonstrated superiority of cipaglucosidase alfa/miglustat to alglucosidase alfa in the ERT-experienced population, and avalglucosidase alfa is non-inferior to alglucosidase alfa, it follows by analogy that there cannot be an advantage over avalglucosidase alfa either, the COMP concluded that the results from the indirect comparisons cannot compensate for the results derived from the pivotal clinical trial results.

Prior to assessing the sponsor's responses to the COMP's list of issues on the claim of significant benefit, it bears recalling that, in the absence of conclusive evidence proving significant benefit at the time of marketing authorisation, 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).

In their written responses, the sponsor further argued that the evidence observed in Study ATB200-03 across multiple endpoints, the comparison of long-term Phase 1/2 study data, as well as the indirect comparisons derived from an NMR analysis, all demonstrate that cipaglucosidase alfa/miglustat offers significant clinical benefit versus approved therapy. According to the sponsor, even though the Study ATB200-03 narrowly missed demonstrating statistical significance for its primary endpoint (6MWD), the data still showed relevant improvements across secondary endpoints such as muscle strength, pulmonary and motor function, and patient reported outcomes (PROs).

The COMP was of the opinion that the improvements across muscle strength, pulmonary and motor function, and PROs in patients treated with Pombiliti as compared to Myozyme did not outweigh the failed statistical analysis of the primary endpoint. Since Study ATB200-03 (the pivotal Phase 3 study) failed to meet its primary endpoint for the total intention-to-treat study population, no confirmatory conclusions can be drawn regarding the secondary endpoints according to the (sponsor's own) pre-defined statistical testing hierarchy. According to the sponsor's own pre-defined statistical testing hierarchy: to control the overall alpha level, hierarchical testing was planned with an ordering of the secondary endpoints to be tested sequentially after the primary efficacy endpoint was tested statistically significant. In this case, the primary efficacy endpoint did not test statistically significant; and, therefore, the sequential testing of the secondary endpoints does not return confirmatory results. (Only for completeness, the COMP would also to note that the 2002 "Points to consider on multiplicity issues in clinical trials" (CPMP/EWP/908/99) of the Committee for Proprietary Medicinal Products/EMA and the draft 2017 CHMP/EMA "Guideline on multiplicity issues in clinical trials" (EMA/CHMP/44762/2017) both consider that sequential testing of (hierarchically ranked) secondary endpoints may not be relied upon for establishing a claim when the primary endpoint has failed.)

In its responses, the sponsor also presented the outcomes on the primary and key secondary endpoints for the small number of ERT-naïve subjects. In the ERT-naïve population (n = 27), subjects in both treatment groups showed improvement in 6MWD at Week 52. The mean (SD) change in 6MWD from baseline to Week 52 showed a mean improvement of 33.4 (48.70) meters for the cipaglucosidase alfa/miglustat group compared to 38.3 (29.32) meters for the alglucosidase alfa/placebo group. The mean (SD) change in sitting % predicted FVC from baseline to Week 52 were -4.1% (6.53%) for the cipaglucosidase alfa/miglustat group and -3.6% (4.71%) for the alglucosidase alfa/placebo group.

Analyses of 6MWD and % predicted FVC were performed for the ERT-naïve population using the MMRM model with actual time point of assessments, excluding the outlier Subject 4005-2511. For change from baseline to Week 52 in 6MWD, there was an estimated mean improvement of 28.5 m (95% CI 12.4, 44.7) in the 20 ERT-naïve subjects who received cipaglucosidase alfa/miglustat. In the alglucosidase alfa/placebo control group (n = 7) mean improvement was 52.7 m (95% CI 23.3, 82.3). For the first key secondary endpoint of % predicted FVC, the estimated mean difference compared to

baseline observed during the first year of treatment was -5.2 (95% CI -7.5, -2.9) in the cipaglucosidase alfa/miglustat group and -2.4 (95% CI -6.7, 1.8) in the alglucosidase alfa/placebo group.

The sponsor argued that while the values for 6MWD and % predicted FVC favour alglucosidase alfa/placebo, the difference is not statistically significant as this group is small and prone to variability.

According to the sponsor, one potential explanation for the observed difference in outcomes between the ERT-naïve and ERT-experienced patients is that these two groups differ in the extent of long-term muscle damage. ERT-naïve patients are usually in a less-advanced stage of their disease; therefore, muscle damage is not yet significant, and there may be less room for improvement. The greater extent of long-term tissue damage in ERT-experienced compared to ERT-naïve patients provides a scientific rationale for greater sensitivity in detecting treatment benefit in the ERT-experienced population. Furthermore, the sponsor referred to the CHMP conclusion that extrapolation of the benefit in the generally more severe and difficult to treat ERT-experienced LOPD to ERT-naïve patients is considered justified, primarily since there is no biologically plausible argument that the expected benefit would be less in ERT-naïve LOPD patients.

The COMP concluded that in contrast with the ERT experienced population, the clinical efficacy was less clear in the treatment naïve patients with an observed clinically relevant improvement in 6MWD and a change in sitting % predicted FVC suggestive of a deterioration under cipaglucosidase alfa/miglustat co-administration. In any event, the submitted results for ERT-naïve population cannot establish the existence of a clinically relevant advantage of cipaglucosidase alfa/miglustat over alglucosidase alfa as the results for the former appeared to be worse.

Finally, in its responses, the sponsor addressed the concerns mentioned above regarding the ML-NMR analysis. However, notwithstanding the sponsor's responses, the COMP considered that major uncertainties regarding the ML-NMR remain. The ML-NMR has severe limitations that strongly limit the weight of the evidence derived from the results. In particular:

- As the matched control arms to the single arm trials or open label extensions, the alglucosidase alfa arm from PROPEL and of COMET were included multiple times in the ML-NMR without adequate statistical adjustment for re-using the same patients. This results in an underestimation of the uncertainty by the statistical model of an unknown magnitude.
- For COMET OLE, LOTS OLE and PROPEL OLE, the placebo patients switching to active treatment were re-baselined; namely, the measurement at the beginning of the open label extension was assumed to be a new baseline measurement and the ensuing measurements (following the new baseline measurement) were counted as new measurements from week 0. These switching arms were subsequently included in the ML-NMR as separate, independent studies with the duration of the extension presented as the study duration. In turn, these patients were included twice in the ML-NMR (once as part of COMET, LOTS and PROPEL, and again as part of the OLEs) without accounting statistically for the independence. This approach can lead to an underestimation of the uncertainty by the statistical model of an unknown magnitude.
- The final model specifications, in particular the fixed and random effects of the ML-NMR, were a data-driven model based on the deviance information criterion. The lack of pre-specification (i.e. absence of a hypothesis or assumptions about fixed or random effects) adds to the uncertainty of the conclusions.
- The robustness of the ML-NMR is further questioned by the large discrepancy of direct evidence and indirect evidence derived from the ML-NMR for the comparisons of Avalglucosidase alfa vs

Alglucosidase alfa in table 1 of the responses to the COMP list of issues (p10/170). The direct evidence (from the COMET trial) is different in magnitude and treatment effect direction to the indirect comparison in the COMET scenario, which is not sufficiently solved by the sponsor's response.

- The implications of massive Baseline imbalances (e.g. %male or 6MWD) remain unclear. The sponsor simply states that the relevant covariables are incorporated in the model and thus are accounted for.

Due to those limitations, the COMP considered that the ML-NMR analysis does not conclusively demonstrate the existence of the claimed significant benefit of cipaglucosidase alfa/miglustat over alglucosidase alfa.

Based on the above, the COMP concluded that the sponsor did not demonstrate superiority of cipaglucosidase alfa/miglustat to alglucosidase alfa for the treatment of adults with late-onset Pompe disease as the pivotal study missed demonstrating statistical significance for its primary endpoint. The major uncertainties regarding the indirect comparison do not allow to conclude on a benefit of cipaglucosidase alfa/miglustat over alglucosidase alfa. Furthermore, given that avalglucosidase alfa is non-inferior to alglucosidase alfa, it follows that there cannot be an advantage of cipaglucosidase alfa over avalglucosidase alfa either as the results from the indirect comparisons, taking into account also the major uncertainties regarding the ML-NMR analysis, cannot compensate for the results derived from the pivotal clinical trial results.

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

4. COMP position adopted on 19 January 2023

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;
- satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Pombiliti, and the assumption that Pombiliti may be of potential significant benefit to those affected by the orphan condition does not hold. Significant benefit over Myozyme and Nexviadyme was claimed on the ground of a clinically relevant advantage;
- the sponsor presented data from a clinical study which failed to show in a robust way that Pombiliti was superior to Myozyme. Although the analyses of secondary and other endpoints trended towards a better effect with Pombiliti as compared to Myozyme, the limitations of this clinical study entailed that the data submitted did not allow the COMP to conclude that the claim for significant benefit of Pombiliti over Myozyme has been appropriately demonstrated;
- in addition, uncertainties regarding the network meta-analysis did not allow to conclude that Pombiliti has an advantage over Nexviadyme. Given that Nexviadyme is non-inferior to Myozyme,

it follows that the submitted data also do not allow COMP to conclude that Pombiliti has a clinically relevant advantage over Nexviadyme.

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 Pombiliti, recombinant human acid alpha-glucosidase, cipaglucosidase alfa for treatment of glycogen storage disease type II (Pompe's disease) (EU/3/18/2000) is removed from the Community Register of Orphan Medicinal Products.