Cipaglucosidase alfa (Pompe disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walk test
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	Analysis of Covariance
CSR	clinical study report
EMA	European Medicines Agency
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GSGC	Gait, Stairs, Gowers‘ manoeuvre, Chair
IAR	infusion-associated reaction
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
LOPD	late-onset Pompe disease
MD	mean difference
MMRM	mixed-effects model repeated measures
MMT	manual muscle function test
MRC	Medical Research Council
OR	Odds Ratio
PROMIS	Patient Reported Outcome Measurement Information System
QMT	quantitative muscle function test
RCT	randomized controlled trial
R-PAct	Rasch-built Pompe-specific Activity
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGIC	Subject's Global Impression of Change
SMD	standardized mean difference
SPC	Summary of Product Characteristics
TUG	Timed Up and Go
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cipaglucosidase (in combination with miglustat). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 August 2023.

Research question

The aim of this report is to assess the added benefit of cipaglucosidase alfa in combination with miglustat (hereinafter referred to as "cipaglucosidase alfa + miglustat") in comparison with alglucosidase alfa as appropriate comparator therapy (ACT) in adult patients with late-onset Pompe disease (LOPD) (acid α-glucosidase [GAA] deficiency).

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of cipaglucosidase alfa + miglustat

Therapeutic indication	**ACT**[a]
Adults with LOPD (GAA deficiency)	Alglucosidase alfa[b]
a. Presented is the ACT specified by the G-BA. b. If indicated, physiotherapy measures should be made available to patients in both arms of the study. GAA: acid α-glucosidase; G-BA: Federal Joint Committee; LOPD: late-onset Pompe disease	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

PROPEL study

The PROPEL study was used for the benefit assessment. The PROPEL study is a double-blind RCT on cipaglucosidase alfa in combination with miglustat versus alglucosidase alfa in combination with placebo in adult patients with LOPD.

To be included in the study, patients had to have a confirmed diagnosis of LOPD at screening by genotyping the coding gene of the acid α-glucosidase. At screening, all patients had to have a body weight of ≥ 40 kg and a seated forced vital capacity (FVC) ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III). Patients who

required invasive or non-invasive respiratory support for > 6 hours per day while awake were excluded from participation in the study. For inclusion in the study, the patient had to have two valid 6-minute walk tests (6MWT) as assessed by the investigator, with the distance travelled being ≥ 75 m and ≤ 90% of the predicted value for healthy adults (based on sex, age, height and weight). Patients could be treatment-naive or pretreated with enzyme replacement therapy (alglucosidase alfa).

A total of 125 patients were randomly assigned in a 2:1 ratio either to treatment with cipaglucosidase alfa + miglustat (N = 85) or to alglucosidase alfa + placebo (N = 40). Treatment with cipaglucosidase alfa in combination with miglustat in the intervention arm was in compliance with the recommendations of the Summary of Product Characteristics (SPC). Patients in the comparator arm received alglucosidase alfa according to the recommendations of the SPC, in combination with placebo. Treatment was continued for 52 weeks. The use of non-drug concomitant treatment (including physiotherapy and occupational therapy) was possible in both study arms.

Primary outcome of the PROPEL study was the change in the distance travelled in the 6MWT at Week 52 in comparison with baseline. Further patient-relevant outcomes were recorded in the categories of morbidity and side effects. Health-related quality of life outcomes were not recorded in the PROPEL study.

The final data cut-off of 15 December 2020 presented by the company took place at the time when the last patient had completed the study.

Risk of bias

For the Gait, Stairs, Gowers' manoeuvre, Chair (GSGC) total value, 15% vs. 18% of patients in the intervention arm vs. the comparator arm were not included in the analysis (covariance analysis [ANCOVA]); in addition, the last observation carried forward (LOCF) value at Week 52 was imputed for 15% vs. 13% of patients. For the outcome of motor function assessed using GSGC (ANCOVA), the risk of bias of the results is therefore rated as high.

The risk of bias for the results of all other outcomes was rated as low in each case.

Results

Mortality

all-cause mortality

No deaths occurred in either of the 2 treatment arms. There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Morbidity

Endurance (6MWT)

There was no statistically significant difference between treatment arms for the outcome "endurance (6MWT)". There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Motor function (GSGC)

For the outcome of motor function (GSGC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. However, the 95% CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Physical functioning (R-PAct, PROMIS Physical Function)

No suitable data are available for the outcome of physical functioning (Rasch-built Pompe-specific Activity [R-PAct], Patient Reported Outcome Measurement Information System [PROMIS] Physical Function). There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Fatigue (PROMIS fatigue), dyspnoea (PROMIS dyspnoea severity) and function of the upper extremities (PROMIS upper extremity)

No suitable data are available for the outcomes of fatigue (PROMIS Fatigue), dyspnoea (PROMIS Dyspnea Severity) and function of the upper extremities (PROMIS Upper Extremity). In each case, there is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

General physical well-being (Subject's Global Impression of Change [SGIC]), respiratory effort (SGIC), muscle strength (SGIC), muscle function (SGIC), activities of daily living (SGIC), muscle pain (SGIC)

There was no statistically significant difference between the treatment arms for the outcomes of general physical well-being, respiratory effort, muscle strength, muscle function, activities of daily living and muscle pain (each SGIC). In each case, there is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Ability to move (SGIC)

For the outcome of ability to move (SGIC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. There is an

indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa.

Energy level (SGIC)

For the outcome of energy level (SGIC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. There is an indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa.

Health status (EQ-5D VAS)

No statistically significant difference between treatment arms was found for the outcome of health status (EQ-5D visual analogue scale [VAS]). There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Health-related quality of life

Outcomes of the outcome category “health-related quality of life” were not recorded in the study. There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

There was no statistically significant difference between the treatment arms for the outcome "serious AEs (SAEs)". There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events (AEs)

There was no statistically significant difference between treatment arms for the outcome of discontinuation due to AEs. There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

Infusion-related reactions (AEs, SAEs)

No statistically significant difference between treatment arms was found for the outcome of infusion-related reactions (AEs and SAEs). There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug cipaglucosidase alfa + miglustat in comparison with the ACT is assessed as follows:

Overall, there were only positive effects for cipaglucosidase alfa + miglustat compared to alglucosidase alfa: For the outcomes “ability to move” and “energy level” recorded with the SGIC, there was an indication of an added benefit, with the extent being considerable or minor. Further patient-reported outcomes were recorded in the PROPEL study, for which, however, no suitable data were available for the present benefit assessment. This applies in particular to the recording of symptoms using several PROMIS instruments for the outcomes of physical functioning, fatigue, dyspnoea and function of the upper extremities. The PROMIS instrument on physical functioning, for example, records these symptoms using a total of 20 questions. The patient’s physical functioning was also recorded with the R-PAct using 18 questions, while the SGIC was only used to assess the ability to move using one single question. The PROMIS questionnaire on fatigue (short form: 8 questions) also reflects patient-reported aspects on the energy level, which are only represented by one question in the SGIC. An adequate assessment of the patient-reported symptoms is not possible without suitable analyses of the outcomes recorded using PROMIS and R-PAct. Outcomes on health-related quality of life were not recorded.

In summary, the added benefit of cipaglucosidase alfa + miglustat over the ACT alglucosidase alfa is not proven for adult patients with LOPD in this data constellation.

Table 3 presents a summary of the probability and extent of the added benefit of cipaglucosidase alfa + miglustat.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Cipaglucosidase alfa + miglustat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with LOPD (GAA deficiency)	Alglucosidase alfa[b]	Added benefit not proven[c]

a. Presented is the ACT specified by the G-BA.
b. If indicated, physiotherapy measures should be made available to patients in both arms of the study.
c. The PROPEL study included patients with seated FVC ≥ 30% who achieved ≥ 75 m and ≤ 90% of the predicted value for healthy adults in the 6MWT and did not require invasive or non-invasive respiratory support for > 6 hours per day while awake. It remains unclear whether the effects observed in the study are transferable to patients with severe impairment of lung function and endurance.

6MWT: 6-minute walk test; FVC: forced vital capacity; GAA: acid α-glucosidase; G-BA: Federal Joint Committee; LOPD: late-onset Pompe disease

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of cipaglucosidase alfa in combination with miglustat (hereinafter referred to as “cipaglucosidase alfa + miglustat”) in comparison with alglucosidase alfa as ACT in adult patients with LOPD (acid α-glucosidase [GAA] deficiency).

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cipaglucosidase alfa + miglustat

Therapeutic indication	**ACT**[a]
Adults with LOPD (GAA deficiency)	Alglucosidase alfa[b]
a. Presented is the ACT specified by the G-BA. b. If indicated, physiotherapy measures should be made available to patients in both arms of the study. GAA: acid α-glucosidase; G-BA: Federal Joint Committee; LOPD: late-onset Pompe disease	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving the added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on cipaglucosidase alfa (status: 16 May 2023)
- bibliographical literature search on cipaglucosidase alfa (last search on 16 May 2023)
- search in trial registries/trial results databases for studies on cipaglucosidase alfa (last search on 16 May 2023)
- search on the G-BA website for cipaglucosidase alfa (last search on 16 May 2023)

To check the completeness of the study pool:

- search in trial registries for studies on cipaglucosidase alfa (last search on 14 August 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ATB200-03 (PROPEL[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The PROPEL study was used for the benefit assessment. The study pool concurs with that of the company. The study is described in the following section.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROPEL	RCT, double-blind	Adults (≥ 18 years) with LOPD with ▪ confirmed diagnosis according to GAA genotyping at screening ▪ enzyme replacement therapy status ▫ naive[b] or ▫ pretreated[c]	Cipaglucosidase alfa + miglustat (N = 85) alglucosidase alfa + placebo (N = 40[d])	Screening: ≤ 30 days[e] treatment: 52 weeks[f] follow-up: 30 days	62 centres in: Argentina, Australia, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Netherlands, New Zealand, Poland, Slovenia, South Korea, Spain, Sweden, Taiwan, United Kingdom, USA 12/2018–12/2020	Primary: change in the distance travelled in the 6MWT at Week 52 in comparison with baseline secondary: mortality, morbidity, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Patient never received enzyme replacement therapy, neither as investigational preparation nor commercially available enzyme replacement therapy.
c. Defined as current standard enzyme replacement therapy (alglucosidase alfa) at the recommended dose and regimen (i.e. 20 mg/kg every 2 weeks) for ≥ 24 months.
d. 2 of the 40 patients randomized in the comparator arm received no dose of the study medication because genotyping did not confirm the diagnosis of Pompe disease; they were therefore excluded from all analyses by the company.
e. The screening visits took place over ≥ 2 days to allow repeated measurements of the 6MWT and the lung function (e.g. FVC).
f. Patients who missed visits due to COVID-19-related quarantine, travel restrictions and risk of infection could be included in the study for more than 12 months. Patients who had completed the study had the opportunity to participate in an open extension study and to receive cipaglucosidase alfa + miglustat.

6MWT: 6-minute walk test; AE: adverse event; FVC: forced vital capacity; GAA: acid α-glucosidase; LOPD: late-onset Pompe disease; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study	Intervention	Comparison
PROPEL	Cipaglucosidase alfa 20 mg/kg IV[a] every 2 weeks + miglustat orally[b], depending on weight: ▪ ≥ 40 to < 50 kg: 195 mg (3 capsules) ▪ ≥ 50 kg: 260 mg (4 capsules)	Alglucosidase alfa 20 mg/kg IV[a] every 2 weeks + placebo orally[b], depending on weight: ▪ ≥ 40 to < 50 kg: 3 capsules ▪ ≥ 50 kg: 4 capsules
	Permitted pretreatment ▪ enzyme replacement therapy (alglucosidase alfa) **non-permitted pretreatment** ▪ investigational preparation or pharmacological therapy for the treatment of Pompe disease (excluding alglucosidase alfa) within 30 days or 5 half-lives of therapy/treatment, whichever was longer, prior to Day 1 or expected to happen during the study ▪ within 30 days before Day 1: miglitol, miglustat, acarbose, voglibose ▪ gene therapy for the treatment of Pompe disease ▪ use of invasive or non-invasive respiratory support while awake for > 6 hours per day **concomitant treatment** ▪ use of non-drug therapies (including physiotherapy and occupational therapy) was possible	

a. As a 4-hour intravenous infusion; after 6 months of study participation it was possible to receive the study medication at home (with the exception of countries or centres in which the administration of alglucosidase alfa is reserved for hospital use), provided no infusion-related reactions occurred.
b. Ingestion 1 hour before the start of infusion with cipaglucosidase alfa or alglucosidase alfa.
IV: intravenous; RCT: randomized controlled trial

The PROPEL study is a double-blind RCT on cipaglucosidase alfa in combination with miglustat versus alglucosidase alfa in combination with placebo in adult patients with LOPD.

To be included in the study, patients had to have a confirmed diagnosis of LOPD at screening by genotyping the coding gene of the acid α-glucosidase. At screening, all patients had to have a body weight of ≥ 40 kg and a seated FVC ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III). Patients who required invasive or non-invasive respiratory support for > 6 hours per day while awake were excluded from participation in the study. For inclusion in the study, the patient had to have two valid 6MWT as assessed by the investigator, with the distance travelled being ≥ 75 m and ≤ 90% of the predicted value for healthy adults (based on sex, age, height and weight [8]). Patients could be treatment-naive or pretreated with an enzyme replacement therapy (alglucosidase alfa).

A total of 125 patients were randomly assigned in a 2:1 ratio either to treatment with cipaglucosidase alfa + miglustat (N = 85) or to alglucosidase alfa + placebo (N = 40). Randomization was stratified according to the distance travelled in the 6MWT at the start of

the study (75 to < 150 m vs. 150 to < 400 m vs. ≥ 400 m) and the enzyme replacement therapy status (naive vs. pre-treated).

Treatment with cipaglucosidase alfa in combination with miglustat in the intervention arm was in compliance with the recommendations of the SPC [9]. Patients in the comparator arm received alglucosidase alfa according to the recommendations of the SPC [10], in combination with placebo. Treatment was continued for 52 weeks. The use of non-drug concomitant treatment (including physiotherapy and occupational therapy) was possible in both study arms.

Primary outcome of the PROPEL study was the change in the distance travelled in the 6MWT at Week 52 in comparison with baseline. Further patient-relevant outcomes were recorded in the categories of morbidity and side effects. Health-related quality of life outcomes were not recorded in the PROPEL study.

The final data cut-off of 15 December 2020 presented by the company took place at the time when the last patient had completed the study.

Table 8 shows the characteristics of the patients in the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study characteristic category	**Cipaglucosidase alfa + miglustat N[a] = 85**	**Alglucosidase alfa + placebo N[a] = 38**
PROPEL		
Age [years], mean (SD)	48 (13)	45 (13)
Sex [f/m], %	58/42	47/53
Region, n (%)		
North/South America	26 (31[b])	15 (39[b])
Europe	43 (51[b])	12 (32[b])
Asia-Pacific	16 (19[b])	11 (29[b])
Age at diagnosis [years], mean (SD)	40 (14)	37 (15)
Enzyme replacement therapy status, n (%)		
Naive	20 (24)	8 (21)
Pretreated	65 (76[b])	30 (79)
Age at the first dose of an enzyme replacement therapy [years][c], mean (SD)	41 (13)	39 (15)
Duration of the enzyme replacement therapy [years][c], mean (SD)	7 (3)	7 (4)
Use of aids at the start of the study, n (%)	17 (20)	11 (29)
Medical history with falls, n (%)	44 (52)	17 (45)
Distance travelled in the 6MWT [metres][d], mean (SD)	358 (112)	350 (120)
Distance travelled in the 6MWT[d], n (%)		
≥ 75 to < 150 m	4 (5)	4 (11)
≥ 150 to < 400 m	55 (65)	22 (58)
≥ 400 m	26 (31)	12 (32)
Seated FVC [% of the predicted value][d], mean (SD)	71 (20)	70 (21)
Treatment discontinuation, n (%)	N D	N D
Study discontinuation, n (%)[e]	5 (6)	1 (3)

a. Number of analysed patients. For the intervention arm, this corresponds to the number of randomized patients. 2 of the 40 patients randomized in the comparator arm received no dose of the study medication because genotyping did not confirm the diagnosis of Pompe disease; they were therefore excluded from all analyses by the company. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Related to patients pre-treated with enzyme replacement therapy: intervention arm N = 65, comparator arm N = 30.
d. Mean of the last two values determined on or before the day of the first dose.
e. Reasons for study discontinuation in the intervention vs. the comparator arm were: withdrawal of consent (2 vs. 0), investigator's decision (1 vs. 0), COVID-19 pandemic (1 vs. 0), AEs (0 vs. 1), other (1 vs. 0).

6MWT: 6-minute walking test; AE: adverse event; COVID-19: coronavirus disease 2019; FVC: forced vital capacity; F: female; M: male; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are mostly comparable between the treatment arms. There is an imbalance between the treatment arms in terms of region: In the intervention arm, 51% of patients were included in Europe. In the comparator arm, in contrast, 32% of patients come from Europe.

At the start of the study, the mean age of the patients was 48 or 45 years, and their mean age at the time of diagnosis of Pompe disease was 40 or 37 years. The sex distribution within the study arms was almost balanced and sufficiently comparable between the study arms. Almost 80% of the patients were pretreated with enzyme replacement therapy.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
PROPEL	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the PROPEL study.

Transferability of the study results to the German health care context

The company stated that the transferability to the German healthcare context was assessed on the basis of the criteria of age, family origin, duration and severity of the disease (via distance travelled in the 6MWT and FVC). The company stated that the PROPEL study was conducted at 62 sites in 24 countries, including Germany, and shows a representative patient population for this rare disease. Therefore, the company assumed a good transferability of the study results to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - outcomes recorded by means of functional tests
    - physical endurance (recorded with the 6MWT)
    - motor function, recorded using the GSGC test
  - patient-reported outcomes
    - recorded using R-PAct
      - physical functioning
    - recorded using the PROMIS
      - physical functioning (PROMIS Physical Functioning)
      - fatigue (PROMIS Fatigue)
      - dyspnoea (PROMIS Dyspnea Severity)
      - function of the upper extremities (PROMIS Upper Extremity)
    - recorded using the SGIC
      - general physical well-being (SGIC)
      - respiratory effort (SGIC)
      - muscle strength (SGIC)
      - muscle function (SGIC)
      - ability to move (SGIC)
      - activities of daily living (SGIC)
      - energy level (SGIC)
      - muscle pain (SGIC)
    - recorded using the EQ-5D VAS
      - health status
- health-related quality of life

- Side effects
  - SAEs
  - discontinuation due to AEs
  - infusion-related reactions (AEs, SAEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study	Outcomes																					
	All-cause mortality[a]	**Endurance (6MWT)**	**Motor function (GSGC)**	**Physical functioning (R-PAct, PROMIS Physical Function)**	**Fatigue (PROMIS Fatigue)**	**Dyspnoea (PROMIS Dyspnea Severity)**	**Function of the upper extremities (PROMIS Upper Extremity)**	**General physical well-being (SGIC)**	**Respiratory effort (SGIC)**	**Muscle strength (SGIC)**	**Muscle function (SGIC)**	**Ability to move (SGIC)**	**Activities of daily living (SGIC)**	**Energy level (SGIC)**	**Muscle pain (SGIC)**	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**Serious adverse events (SAEs)**	**Discontinuation due to AEs**	**Infusion-related reactions[b] (AEs, SAEs)**	**Further specific AEs[c]**
PROPEL	Yes	Yes	Yes	No[d]	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	No

a. Deaths were recorded as AEs.
b. The "infusion-associated reactions (IARs)" recorded in the study were considered; for explanations see the following text.
c. No further specific AEs were identified based on the AEs occurring in the relevant study.
d. No suitable data available; see text below for explanation.
e. Outcome not recorded.

6MWT: 6-minute walk test; AE: adverse event; GSGC: Gait, Stairs, Gowers' manoeuvre, Chair; IAR: infusion-associated reaction; N: no; PROMIS: Patient Reported Outcome Measurement Information System; RCT: randomized controlled trial; R-PAct: Rasch-built Pompe-specific Activity; SAE: serious adverse event; SGIC: Subject's Global Impression of Change; VAS: visual analogue scale; Y: yes

Notes on the analyses presented by the company

Sensitivity analyses of the company

In the PROPEL study, 1 patient in the comparator arm was identified after database closure who may have been impaired in the 6MWT due to use of an investigational anabolic steroid (ostarine) prior to study inclusion and who reported having intentionally underperformed in the 6MWT and pulmonary function tests in order to gain entry to the study.

The company therefore conducted sensitivity analyses in which the results of this patient were excluded. For the patient-relevant outcomes for which corresponding sensitivity analyses are available (physical endurance [6MWT], motor function [GSGC], health status [EQ-5D VAS]), there are no differences in terms of significance and relevance between the results of the analysis with and without this patient. Furthermore, since only 1 patient is involved, the analyses for the population including this 1 patient are used for the present benefit assessment.

Responder analyses on morbidity outcomes presented by the company

Consideration of worsening in the responder analyses relevant for benefit assessment

In the dossier, the company presents responder analyses for the patient-relevant outcomes on morbidity for each an improvement and worsening and, in some cases, no change. According to the European consensus paper on enzyme replacement therapy in adults with Pompe disease [11], the aim of the treatment is to stabilise or improve in particular motor and respiratory function in the case of an overall progressive course of the disease. A patient who achieves this therapy goal therefore shows no worsening. With regard to the treatment goal in the present chronic, progressive disease and the patient population included in the study, worsening is considered a suitable operationalization in the present benefit assessment. Worsening means that the patient has not achieved the treatment goal of stabilisation or improvement.

Time of analysis at Week 52 relevant for the benefit assessment

In Module 4 A, the company describes that it considered the analysis period up to Week 52 for all responder analyses - with the exception of the outcomes collected using the SGIC. Thus, patients with worsening at (any) point in time during the course of the study are considered responders in the company's analyses. In the present therapeutic indication of a chronic, progressive disease, however, it is relevant to consider the outcomes as late as possible (i.e. in the PROPEL study at the end of the study at Week 52). However, responder analyses on worsening at the time of analysis at Week 52 are only available for the outcomes recorded with the SGIC. The available analyses at Week 52 are used for these outcomes. For all other patient-relevant outcomes on morbidity, however, the mixed-effects model with repeated

measures (MMRM) or ANCOVA analyses of the change at Week 52 compared to the start of the study presented by the company are used, provided that usable analyses are available.

Company's LOCF imputation in responder analyses

According to the company, missing values for the outcomes recorded using GSGC, R-PAct, PROMIS, SGIC and EQ-5D VAS were imputed using LOCF in the responder analyses. Based on the responses available for the various instruments per documentation time point, it can be assumed that there were patients for whom no survey was available at any documentation time point. LOCF imputation is not possible for these patients. However, according to the company, all patients were included in each of the responder analyses it presented. It is unclear how an imputation was made by the company for patients without any survey. For the motor function recorded with the GSGC and physical functioning recorded with R-PAct, it can be assumed that the proportion of these patients with unclear imputation is relevant (> 10% in each case), which leads to limited interpretability in the corresponding analyses - irrespective of other limitations described below. For the other outcomes, the proportion of patients with unclear imputation is at most low, so that this is of no consequence.

Note on included outcomes

Physical endurance recorded with the 6MWT

The loss of the ability to walk or physical endurance due to progressive muscle weakness is a common symptom in patients with Pompe disease. The 6MWT is a standardised and established instrument for determining the physical endurance (distance the patient can travel within 6 minutes [12]) and is considered relevant for the present assessment. In the PROPEL study, the 6MWT was performed at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation. The patient was instructed to walk (not run or jog) as far as possible on a flat surface for 6 minutes. The use of an aid (e.g. cane, walking aid or rollator) to perform the 6MWT was permitted. The patient then had to use the same walking aid for all subsequent tests.

Analysis used for the benefit assessment

For the outcome "physical endurance" recorded using the 6MWT, the company conducted responder analyses for the dossier (improvement, no change and worsening) for the analysis period up to Week 52, for which it applied the response criteria of either 6% (pre-specified) or 7% (specified post hoc) to the percentage change compared to baseline. Irrespective of the fact that responder analyses on the analysis period up to Week 52 are not relevant in the present therapeutic indication (see text section "Responder analyses on morbidity outcomes presented by the company"), the company does not present any information suitable for the derivation of the patient relevance of the response criteria presented by it in the present situation. The responder analyses on the 6MWT presented by the company were therefore not used for the present benefit assessment.

The company also presented an analysis of the change versus baseline for the outcome "physical endurance recorded with the 6MWT" at Week 52, using a MMRM (pre-specified). The MMRM contains the variable "visit", i.e. the planned visit is used for the modelling. This type of analysis can generally be biased by postponed surveys that are nevertheless assigned to the planned visit. The company did not address this issue in Module 4 A. However, detailed information on postponed surveys is available in the EPAR [13]. Even if some of these are clearly shifted surveys, their overall share can be rated as low.

Moreover, as part of the approval procedure for cipaglucosidase alfa, the European Medicines Agency (EMA) had requested an analysis for the 6MWT [13] in which the actual time point of documentation was used in the MMRM model instead of the planned visit. There is no relevant difference between the results of the two modellings. Even if a model that includes the actual survey time points is generally preferable, the MMRM analysis presented by the company in the dossier can be used for the benefit assessment in the present data situation.

Motor function

GSGC Test

The GSGC test combines the functional tests of gait (Gait [G]), stair climbing (Stairs [S]), Gower's manoeuvre (G) and rising from a chair (Chair [C]) [14]. In the PROPEL study, the performance of the 4 tests was qualitatively assessed by trained testing staff. In addition, the time taken by the patient to complete the individual tests was also measured. In the PROPEL study, the tests were performed at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation.

In the gait (G) test, the patient covers a distance of 10 metres. The qualitative assessment of the execution is based on a 7-point scale, where 1 stands for a "normal gait" and 7 for "wheelchair-dependent".

The Stair Climbing (S) Test is used to test the ability to climb stairs (4 steps). The qualitative assessment of performance is based on a 7-point scale, where 1 means that the patient was able to "climb stairs without assistance" and 7 stands for "unable to climb stairs".

During the Gower's manoeuvre, the patient must move from a lying position to a standing position. The qualitative assessment of performance is based on a 7-point scale, where 1 means that the test could be performed "normally" and 7 means that the patient was "unable to stand up".

The ability to get up from a chair is tested using the chair (C) test. The qualitative assessment of performance is based on a 6-point scale, where 1 means that the test could be performed "normally" and 6 means that it was "not possible" for the patient to stand up.

The GSGC test is an instrument used in the present therapeutic indication that provides a detailed picture of motor function by measuring 4 important motor performances (walking, stair climbing, Gower's manoeuvre, getting up from a chair) [14]. The instrument is therefore used in the present benefit assessment and the GSGC total value is considered. For the GSGC total score, the values from the qualitative assessment of the 4 individual tests are added together so that the GSGC total score can range from 4 (best value) to 27 (worst value). The time is not included in the total value and is shown as supplementary information.

However, there is uncertainty as to which patients were included in the analysis. According to the study design, a test should not be performed if it was not safe for the patient to perform it without an aid (e.g. cane). The reason should then be documented. However, the assessment in the gait (G) test, for example, also includes the assessment option that the patient can only walk with an aid. It is therefore unclear whether patients who were dependent on aids to complete the test were included in the analyses (for missing values, see Section I 4.2).

Timed Up and Go (TUG) test

The TUG test measures the time it takes a patient to stand up from a chair, walk 3 metres, turn around and walk back and then sit back down on the chair [15-17]. The TUG test was performed at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation. If it was not safe for the patient to perform it without an aid (e.g. cane), this test should not be carried out and the reason should be documented.

In the PROPEL study, motor function is assessed using the GSGC functional test (total score). The GSGC assesses several important motor functions on the basis of a qualitative assessment. The quantitative aspect (time in seconds) is not primarily relevant for the assessment of motor function, therefore the time required to complete the TUG test is presented as a supplementary information in the present benefit assessment.

Analysis used for the benefit assessment

For the outcome "motor function assessed by GSGC or TUG" (shown as supplementary information), the company presented analyses of the change at Week 52 compared to the start of the study using analysis of covariance (ANCOVA; pre-specified). In addition, the company conducted post hoc responder analyses (improvement and worsening) on the GSGC for the dossier for the analysis period up to Week 52, for which it used 15% of the scale range as the response criterion. However, these responder analyses on the GSGC for the analysis period up to week 52 are not relevant in the present therapeutic indication (see text section "Responder analyses on morbidity outcomes presented by the company"). In addition, the high proportion of patients with unclear imputation leads to limited interpretability of the

analyses (see text section "Responder analyses on morbidity outcomes presented by the company").

Therefore, for the outcome of motor function, the results from the analysis of the change at Week 52 compared to baseline by means of ANCOVA are used for the GSGC test and for the TUG test (presented as supplementary information). The estimated effect represents the difference in changes (compared to baseline) between the treatment groups at Week 52. If there was a statistically significant mean difference (MD) in the GSGC test, a standardized mean difference (SMD) was used to assess clinical relevance.

Physical functioning" (recorded using R-PAct)

The R-PAct is a patient-reported questionnaire based on an interval scale with Rasch analysis to measure the impact of Pompe disease on the patient's ability to perform activities of daily living and to quantify their social participation [18]. The R-PAct consists of 18 items, each with 3 response categories: 0 = "no", 1 = "yes, but with difficulty", 2 = "yes, without difficulty". The patients are asked about their current abilities, for example whether they are able to comb their hair, eat or exercise. In the PROPEL study, the R-PAct was recorded at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation. According to the publication on the development of the R-PAct [18], the answers are aggregated into an interval-scaled total score ranging from 0 to 100. Higher values stand for a better condition or better abilities.

The R-PAct was developed on the basis of the results of a survey of patients with Pompe disease and validated using Rasch analysis [18]. The R-PAct is considered validated in the present therapeutic indication and is used for the benefit assessment.

Analyses presented by the company are unsuitable for the benefit assessment

The company based its analyses on the raw values and did not transform the values. For example, it based its responder analyses for the R-PAct on 15% of the scale range of the raw values (5.4 points on a scale of 0 to 36) as a response criterion. The analyses of the change at Week 52 compared to baseline by means of ANCOVA (pre-specified) presented by the company are also based on the raw values. However, according to the publication on the development of the instrument [18], the answers are to be aggregated into an interval-scaled total score (0 to 100).

Irrespective of this - as described above (see text section "Responder analyses on morbidity outcomes presented by the company") - responder analyses at the time point of analysis at Week 52 are relevant instead of responder analyses for the analysis period up to Week 52. In addition, the high proportion of patients with unclear imputation leads to limited interpretability of the analyses (see text section "Responder analyses on morbidity outcomes presented by the company").

Overall, the analyses on the R-PAct presented by the company are therefore unsuitable for the present benefit assessment.

Irrespective of the lack of transformation of the values and the lack of suitability of the responder analyses presented, it is unclear for what proportion of the patient population of the PROPEL study conducted in 24 countries a validated version of the questionnaire was available in the relevant language. According to the publication on the R-PAct [18], a translation of the R-PAct questionnaire only exists from Dutch into English.

Morbidity outcomes recorded using the PROMIS

In the PROPEL study, physical functioning, fatigue, dyspnoea and function of the upper extremities were assessed via PROMIS. PROMIS is a valid, generic system consisting of domain-specific instruments for the self-reported and proxy-reported assessment of physical, mental, and social health. The following patient-reported short forms of the questionnaires were used in the PROPEL study: PROMIS Physical Function Short Form 20a (v2.0), PROMIS Fatigue Short Form 8a, PROMIS Dyspnea Severity Short Form 10a and PROMIS Upper Extremity Short Form 7a. Recording was performed at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation.

Consideration of the domains of physical functioning, fatigue, dyspnoea and function of the upper extremities is considered to be adequate with regard to the symptoms of patients with LOPD.

According to the respective PROMIS manuals (latest versions: [19-21]), the raw values are to be converted into T-scores. In doing so, the respective scale range can be taken from the PROMIS manuals. Two types of scoring are described for the PROMIS short forms: Firstly, a so-called "response scoring pattern", which can be calculated online via the HealthMeasures Scoring Service [22] and free of charge via tools. It uses the respective item-level parameters for each item and each answer. Alternatively, a manual conversion of the raw value into a T-Score is possible. For this purpose, PROMIS provides online conversion tables for all short forms. Both manual scoring using conversion tables and the use of the “Response Scoring Pattern” via the HealthMeasures Scoring Service utilize T-scoring. According to the PROMIS manuals, the use of the "Response Scoring Pattern" should be favoured, as it measures more accurately and deals better with missing values.

Analyses presented by the company are unsuitable for the benefit assessment

The company based its analyses on the raw values and did not transform the values. For example, it determined 15% of the scale range of the raw values as the response criterion for his responder analyses. The analyses of the change at Week 52 compared to baseline by means of ANCOVA (pre-specified) presented by the company are also based on the raw values.

However, according to the corresponding PROMIS manuals, the raw values are to be converted into T-scores (see above).

Irrespective of this - as described above (see text section "Responder analyses on morbidity outcomes presented by the company") - responder analyses at the time point of analysis at Week 52 are relevant instead of responder analyses for the analysis period up to Week 52.

Overall, the analyses presented by the company on physical functioning, fatigue, dyspnoea and function of the upper extremities assessed by PROMIS are not suitable for the present benefit assessment.

Morbidity outcomes recorded using the SGIC

The patient-reported SGIC on general physical well-being, respiratory effort, muscle strength, muscle function, ability to move, activities of daily living, energy levels and muscle pain was recorded in the PROPEL study. For this purpose, the patient was asked 8 individual questions by the investigator. For each of the 8 individual questions, the patient rates the overall change in their functional status compared to the start of the study medication on a 7-point scale (from "very much improved" to "very much worsened").

Analysis used for the benefit assessment

In the dossier, the company presented analyses on improvement, no change and worsening at Week 52 for each of the outcomes recorded using the SGIC. As described above, responder analyses on worsening at Week 52 are relevant in the present therapeutic indication (see text section "Responder analyses on morbidity outcomes presented by the company"). Worsening was predefined and included the statements: slightly worsened, severely worsened and very severely worsened, in each case compared to the start of study medication.

The responder analyses (worsening) at Week 52, in which missing values were replaced by means of LOCF, were used for the outcomes recorded using the SGIC. The company determined the relative risk (RR; including confidence interval and statistical test) using the Cochran-Mantel-Haenszel method, stratified by distance travelled in the 6MWT at baseline and enzyme replacement therapy status.

Health status, recorded using the EQ-5D VAS

In the PROPEL study, “health status” was recorded with the EQ-5D VAS [23]. The recording was based on a scale from 0 to 100, on which the patients answer the question about their current health status. A score of 0 indicates the worst and a score of 100 the best imaginable health status. The recording of the health status by means of a VAS is regarded as patient-relevant.

Analysis used for the benefit assessment

For the outcome “health status” recorded with the EQ-5D VAS, the company presented responder analyses specified post hoc (improvement and worsening) for the dossier for the analysis period up to Week 52, for which it used 15% of the respective scale range as the response criterion. However, these responder analyses for the analysis period up to week 52 are not relevant in the present therapeutic indication (see text section "Responder analyses on morbidity outcomes presented by the company").

Therefore, the results from the analysis of the change at Week 52 compared to baseline by means of ANCOVA (prespecified) were used for the outcome of health status recorded using EQ-5D VAS. The estimated effect represents the difference in changes (compared to baseline) between the treatment groups at Week 52. If there was a statistically significant MD, an SMD was used to assess clinical relevance.

Side effects

The analyses of AEs include events that can be attributed to side effects as well as to symptoms or late complications of the underlying disease, such as the Preferred Term (PT) muscular weakness, myalgia and pain of the musculoskeletal system. The company does not explain to what extent the events that occurred can be assigned to the outcome categories of morbidity or AEs. Since such events only occurred in the AEs presented as supplementary information, but not in the SAEs and discontinuations due to AEs used for the benefit assessment, this has no consequences for the present benefit assessment.

Infusion-related reactions

In the PROPEL study, infusion-related reactions were recorded as "infusion-associated reactions (IARs)". According to the study design, any symptom occurring during or within 2 hours after infusion should be documented as IAR unless there is an alternative obvious explanation (e.g. fall). Symptoms occurring between 2 and 96 hours after the infusion should be reported as IAR according to the investigator's opinion. The study protocol provided a predefined set of symptoms to be reported as infusion-related reactions. This list includes symptoms affecting the skin, eyes, nasopharynx, bronchopulmonary tissue and gastrointestinal tract and is considered an appropriate representation of infusion-related reactions for the present benefit assessment. The analyses at AE and SAE level presented by the company were used for the outcome "infusion-related reactions".

In the dossier, the company does not comment on whether the events underlying the outcome "infusion-related reactions" are also included in the analyses on AEs ("treatment-emergent AEs"; TEAEs). In the present situation, however, it can be assumed that symptoms that were recorded as infusion-related reactions in the PROPEL study were also included in the TEAE analyses.

Analysis used for the benefit assessment

The presented event analyses were used for the side effect outcomes. For this purpose, the company determined the RR using the Cochran-Mantel-Haenszel method (specified post hoc), stratified by the distance travelled in the 6MWT at baseline and enzyme replacement therapy status.

Further outcomes or instruments presented by the company to assess morbidity

Lung function

In Module 4 A, the company presents results on lung function measured by FVC. However, this outcome is not patient-relevant per se, as there is not necessarily a connection to the symptoms. The company did not conduct a validation as a surrogate outcome for a patient-relevant outcome. The presented results are therefore disregarded in the benefit assessment. However, outcomes on symptomatic lung function (e.g. shortness of breath) are relevant to patients. In the present benefit assessment, symptomatic lung function is considered via other outcomes (e.g. respiratory effort [SGIC], dyspnoea [PROMIS Dyspnea Severity]).

Manual muscle function test (MMT) and quantitative muscle function test (QMT)

In the dossier, the company presents results of the MMT and QMT in the outcome category of morbidity. Recording of the muscle function test was performed at screening and at Weeks 12, 26, 38 and 52 or at premature treatment discontinuation.

The MMT is a test for the qualitative assessment of the muscle function of various muscle groups [24,25]. In the PROPEL study, the muscle groups of the shoulder abductors, the shoulder adductors, the elbow extensors, the elbow flexors, the hip flexors, the hip abductors, the hip adductors, the knee extensors and the knee flexors were examined. The patient performed physical exercises and the investigator assessed the muscle function based on the muscle contractions that could be felt or observed. The assessment in the PROPEL study was carried out using the Medical Research Council (MRC) scale (0 to 5 points, with 5 indicating normal functioning and 0 indicating no muscle contraction).

The QMT is a test to assess the isometric (static) maximum strength of various muscle groups [26,27]. The patient is asked to push or pull with maximum force (measured in kg using a hand-held dynamometer) against a resistance exerted by the investigator. In the PROPEL study, the muscle groups of the shoulder abductors, the shoulder adductors, the elbow extensors, the elbow flexors, the hip flexors, the hip abductors, the hip adductors, the knee extensors and the knee flexors were examined.

The MMT is a subjective assessment of muscle function by the investigator, in which gravity and the resistance exerted by the person being examined are used as reference values. With the QMT, it is necessary to measure against an insurmountable resistance in order to

adequately determine the isometric maximum force. Both measurement instruments are unsuitable for representing any noticeable functional limitations for the patient. The results on MMT and QMT presented by the company were therefore excluded from the present benefit assessment. Rather, functional limitations are represented by other functional tests recorded in the PROPEL study (e.g. GSGC) and patient-reported outcomes (e.g. muscle strength [SGIC], muscle function [SGIC]).

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo

Study		Outcomes																					
	Study level	All-cause mortality[a]	Endurance (6MWT)	Motor function (GSGC)	Physical functioning (R-PAct, PROMIS Physical Function)	Fatigue (PROMIS Fatigue)	Dyspnoea (PROMIS Dyspnea Severity)	Function of the upper extremities (PROMIS Upper Extremity)	General physical well-being (SGIC)	Respiratory effort (SGIC)	Muscle strength (SGIC)	Muscle function (SGIC)	Ability to move (SGIC)	Activities of daily living (SGIC)	Energy level (SGIC)	Muscle pain (SGIC)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Infusion-related reactionsb (AEs, SAEs)	Further specific AEs[c]
PROPEL	Low	Low	Low	H[d]	–[e]	–[e]	–[e]	–[e]	Low	Low	Low	Low	Low	Low	Low	Low	Low	–[f]	Low	Low	Low	–

a. Deaths were recorded as AEs.
b. The "infusion-associated reactions (IARs)" recorded in the study were considered; for explanations see Section I 4.1 of the present dossier assessment.
c. No further specific AEs were identified based on the AEs occurring in the relevant study.
d. Due to the high proportion of patients not considered in the analysis or LOCF-imputed values.
e. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
f. Outcome not recorded.

6MWT: 6-minute walk test; AE: adverse event; GSGC: Gait, Stairs, Gower's manoeuvre, Chair; H: high; IAR: infusion-associated reaction; LOCF: last observation carried forward; L: low; N: no; PROMIS: Patient Reported Outcome Measurement Information System; RCT: randomized controlled trial; R-PAct: Rasch-built Pompe-specific Activity; SAE: serious adverse event; SGIC: Subject's Global Impression of Change; VAS: visual analogue scale

Risk of bias for the results of the relevant outcomes

For the morbidity outcomes, with the exception of the outcome "physical endurance" (6MWT; MMRM analysis without imputation of missing values), the company imputed missing values using LOCF in the ANCOVA or responder analyses. Missing values of a person were imputed by the last observed value of this person after the start of the study (post-baseline). The use of the LOCF method generally harbours the risk of biased results [28]. The underlying assumption that the value of the outcome remains unchanged from the time point of discontinuation is presumably not fulfilled, which can lead to significant bias (in both directions).

For the GSGC total value, 15% vs. 18% of patients in the intervention arm vs. the comparator arm were not included in the analysis (ANCOVA); moreover, the LOCF value at Week 52 was imputed for 15% vs. 13% of patients. For the outcome of motor function assessed using GSGC (ANCOVA), the risk of bias of the results is therefore rated as high.

The risk of bias for the results of all other outcomes was rated as low in each case.

I 4.3 Results

Table 12 and Table 13 summarize the results of the comparison of cipaglucosidase alfa + miglustat with alglucosidase alfa + placebo in adult patients with LOPD. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo (multipage table)

Study outcome category outcome	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
PROPEL					
Mortality[b]					
All-cause mortality[c]	85	0 (0)	38	0 (0)	–
Morbidity (at Week 52)					
Physical functioning					
R-PAct				No suitable data[d]	
PROMIS Physical Function				No suitable data[d]	
Fatigue (PROMIS Fatigue)				No suitable data[d]	
Dyspnoea (PROMIS Dyspnea Severity)				No suitable data[d]	
Function of the upper extremities (PROMIS Upper Extremity)				No suitable data[d]	
General physical well-being (SGIC; worsening[e])	85	15 (18)	38	11 (29)	0.65 [0.33; 1.26]; 0.199
Respiratory effort (SGIC; worsening[e])	85	7 (8)	38	4 (11)	0.79 [0.23; 2.75]; 0.715
Muscle strength (SGIC; worsening[e])	85	15 (18)	38	11 (29)	0.65 [0.34; 1.25]; 0.195
Muscle function (SGIC; worsening[e])	85	12 (14)	38	11 (29)	0.50 [0.25; 1.02]; 0.057
Ability to move (SGIC; worsening[e])	85	9 (11)	38	13 (34)	0.32 [0.15; 0.67]; 0.002
Activities of daily living (SGIC; worsening[e])	85	8 (9)	38	5 (13)	0.82 [0.28; 2.41]; 0.714
Energy level (SGIC; worsening[e])	85	9 (11)	38	9 (24)	0.40 [0.18; 0.88]; 0.023
Muscle pain (SGIC; worsening[e])	85	16 (19)	38	9 (24)	0.78 [0.37; 1.66]; 0.515
Side effects[b]					
AEs[f] (supplementary information)	85	81 (95)	38	37 (97)	–
SAEs	85	8 (9)	38	1 (3)	3.58 [0.50; 25.61]; 0.205

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo (multipage table)

Study outcome category outcome	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Discontinuation due to AEs	85	2 (2)	38	1 (3)	0.86 [0.09; 8.63]; 0.898
Infusion-related reactions (AEs)[g]	85	21 (25)	38	10 (26)	0.91 [0.48; 1.72]; 0.770
Infusion-related reactions (SAEs)	85	1 (1)	38	0 (0)	0.76 [0.16; 3.58]; 0.724

a. CMH method; stratified by distance travelled in the 6MWT at baseline and enzyme replacement therapy status; if 1 zero cell occurred in 1 stratum in the corresponding 2x2 table, a correction value of 0.5 was added to each of the cell frequencies of the stratum; outcomes recorded by SGIC: missing values were imputed with the last value collected after study start (post-baseline) (LOCF).
b. Events that occurred from the day of the 1st dose of study medication until 30 days after the last dose.
c. Deaths were recorded as AEs.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Defined as slightly worsened, severely worsened and very severely worsened compared to the start of study medication.
f. Includes events of the underlying illness.
g. In two patients in the intervention arm, events were recorded as infusion-related reactions that are not patient-relevant per se (laboratory parameters). However, it is unclear whether this is the only qualifying event in each case.

6MWT: 6-minute walk test; AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LOCF: last observation carried forward; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; PROMIS: Patient Reported Outcome Measurement Information System; RCT: randomized controlled trial; R-PAct: Rasch-built Pompe-specific Activity; RR: relative risk; SAE: serious adverse event; SGIC: Subject's Global Impression of Change; VAS: visual analogue scale

Table 13: Results (morbidity, continuous) – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo (multipage table)

Study outcome category outcome	Cipaglucosidase alfa + miglustat			Alglucosidase alfa + placebo			Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo
	N[a]	values at baseline mean (SD)	change at Week 52 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at Week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
PROPEL							
Morbidity							
Physical endurance							
6MWT [metres]	81	357.93 (111.84)	21.44 (5.75)[c]	37	350.14 (119.78)	16.11 (8.58)[c]	5.33 [-15.21; 25.88]; 0.608[c]
Motor function							
GSGC total value[d]	72	14.27 (5.04)	-0.56 (0.28)	31	13.97 (4.82)	0.74 (0.43)	-1.30 [-2.34; -0.26]; 0.015 SMD [95% CI] -0.51 [-0.94; -0.08]
Gait[e]	73	2.71 (1.09)	-0.09 (0.08)	35	2.67 (1.01)	0.12 (0.12)	-0.21 [-0.50; 0.08]
Climbing stairs[e]	67	3.63 (1.77)	-0.30 (0.14)	30	3.46 (1.84)	0.25 (0.21)	-0.55 [-1.06; -0.05]
Gower's manoeuvre[e]	63	4.41 (1.66)	0.12 (0.12)	27	4.52 (1.55)	0.10 (0.18)	0.01 [-0.42; 0.45]
Getting up from the chair[f]	73	3.84 (1.61)	-0.22 (0.12)	32	3.91 (1.54)	0.09 (0.19)	-0.31 [-0.76; 0.15]
Time [seconds] required to complete the individual GSGC tests[g] (presented as supplementary information)							
Gait [seconds]	*80*	*9.68 (7.63)*	*-0.60 (0.63)*	*36*	*9.53 (5.44)*	*1.96 (0.95)*	*-2.56 [-4.85; -0.27]*
Climbing stairs [seconds]	*78*	*13.95 (70.97)*	*-6.70 (0.85)*	*35*	*7.95 (9.67)*	*-3.64 (1.28)*	*-3.06 [-6.15; 0.04]*
Gower's manoeuvre [seconds]	*61*	*10.84 (7.45)*	*-0.35 (0.79)*	*26*	*15.30 (11.68)*	*-1.92 (1.25)*	*1.57 [-1.44; 4.58]*
Getting up from the chair [seconds]	*77*	*13.58 (86.05)*	*-7.50 (0.41)*	*33*	*4.42 (5.19)*	*-6.71 (0.63)*	*-0.80 [-2.305; 0.711]*
TUG [seconds] (presented as supplementary information)	*75*	*12.88 (10.14)*	*-0.40 (0.76)*	*32*	*11.37 (4.99)*	*0.03 (1.19)*	*-0.43 [-3.29; 2.42]; 0.763*
Health status (EQ-5D VAS)[h]	84	68.86 (18.25)	0.05 (1.54)	37	71.91 (15.20)	3.87 (2.36)	-3.82 [-9.51; 1.87]; 0.187

Table 13: Results (morbidity, continuous) – RCT, direct comparison: cipaglucosidase alfa + miglustat versus alglucosidase alfa + placebo (multipage table)

Study outcome category outcome	Cipaglucosidase alfa + miglustat			Alglucosidase alfa + placebo			Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo
	N[a]	values at baseline mean (SD)	change at Week 52 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at Week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers. b. Unless stated otherwise, mean and SE (change at Week 52 per treatment group) as well as MD, CI and p-value (group comparison): ANCOVA without repeated measurement modelling; adjusted for baseline value, enzyme replacement therapy status, sex, age, weight and height; the estimated effect represents the difference in changes (from baseline) between the treatment groups at Week 52. c. Mean and SE (change at Week 52 per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for baseline value, enzyme replacement therapy status, sex, age, weight and height; the estimated effect represents the difference in changes (from baseline) between the treatment groups at Week 52. d. Lower (decreasing) values indicate better motor function (scale range 4 to 27); negative effects (intervention minus comparator) indicate an advantage for the intervention. e. Lower (decreasing) values indicate better motor function (scale range 1 to 7); negative effects (intervention minus comparator) indicate an advantage for the intervention. f. Lower (decreasing) values indicate better motor function (scale range 1 to 6); negative effects (intervention minus comparator) indicate an advantage for the intervention. g. The time required is not included in the GSGC total score. h. Higher (increasing) values indicate better health status (scale range 0 to 100); positive effects (intervention minus control) indicate an advantage for the intervention. 6MWT: 6-minute walk test; ANCOVA: analysis of covariance; CI: confidence interval; GSGC: Gait, Stairs, Gower's manoeuvre, Chair; LOCF: last observation carried forward; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; TUG: Timed Up and Go; VAS: visual analogue scale						

On the basis of the available information and due to the high risk of bias, at most hints, for example of an added benefit, and for the other outcomes at most indications, for example of an added benefit, can be determined for the outcome "motor function" (assessed using GSGC).

Mortality

All-cause mortality

No deaths occurred in either of the 2 treatment arms. There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Morbidity

Endurance (6MWT)

There was no statistically significant difference between treatment arms for the outcome "endurance (6MWT)". There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Motor function (GSGC)

For the outcome of motor function (GSGC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. However, the 95% CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Physical functioning (R-PAct, PROMIS Physical Function)

No suitable data are available for the outcome of physical function (R-PAct, PROMIS Physical Function). There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Fatigue (PROMIS fatigue), dyspnoea (PROMIS dyspnoea severity) and function of the upper extremities (PROMIS upper extremity)

No suitable data are available for the outcomes of fatigue (PROMIS Fatigue), dyspnoea (PROMIS Dyspnea Severity) and function of the upper extremities (PROMIS Upper Extremity). In each case, there is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

General physical well-being (Subject's Global Impression of Change [SGIC]), respiratory effort (SGIC), muscle strength (SGIC), muscle function (SGIC), activities of daily living (SGIC), muscle pain (SGIC)

There was no statistically significant difference between the treatment arms for the outcomes of general physical well-being, respiratory effort, muscle strength, muscle function, activities of daily living and muscle pain (each SGIC). In each case, there is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Ability to move (SGIC)

For the outcome of ability to move (SGIC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. There is an indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa.

Energy level (SGIC)

For the outcome of energy level (SGIC), a statistically significant difference was found in favour of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa. There is an indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status (EQ-5D VAS)". There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Health-related quality of life

Outcomes of the outcome category “health-related quality of life” were not recorded in the study. There is no indication of an added benefit of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome “discontinuation due to AEs”. There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

Infusion-related reactions (AEs, SAEs)

No statistically significant difference between treatment arms was found for the outcome of infusion-related reactions (AEs and SAEs). There is no indication of greater or lesser harm from cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- Age (≥ 18 to < 35 years versus ≥ 35 to < 50 years versus ≥ 50 to < 65 years versus ≥ 65 years)
- Sex (female versus male)

- Distance travelled in the 6MWT at baseline (≥ 75 to < 150 m vs. ≥ 150 to < 400 m vs. ≥ 400 m)
- Enzyme replacement therapy status (naive vs. pretreated)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

The company presented the result of an interaction test for each outcome and each subgroup characteristic regardless of how many people were in the respective subgroups. In Module 4 A, the company describes that it presents the results of the associated subgroup analyses for a characteristic if the corresponding subgroups each comprise at least 10 patients. The described approach is appropriate. However, the company conducted no subgroup analyses for the characteristics of interest, i.e. age, distance travelled in the 6MWT at baseline as well as enzyme replacement therapy status, although there were at least 10 persons in each of the subgroups for the characteristics age and enzyme replacement therapy status. The subgroup results by enzyme replacement therapy status are not available as part of the subgroup analyses for the dossier, however, the company reports the results for enzyme replacement therapy-naive patients and enzyme replacement therapy-pretreated patients in its additional analyses. The subgroup analyses for the characteristic “age” are completely missing. Irrespective of this, the company provides no information on how it substantiates the age categories defined post hoc for the age characteristic (≥ 18 to < 35 years vs. ≥ 35 to < 50 years vs. ≥ 50 to < 65 years vs. ≥ 65 years) in terms of content.

Furthermore, for the outcome "physical endurance" (6MWT), the results of the interaction tests conducted by the company for the dossier differ from the results of interaction tests reported in the clinical study report (CSR). In Module 4 A, for example, the company states a p-value of 0.031 as the result of the interaction test for the characteristic "sex". The CSR, in contrast, reports a p-value of 0.448. However, it is unclear where these deviations come from, as the respective description of the model used does not reveal any differences. In addition, the subgroup results also differ slightly between Module 4 A or the additional analyses and the study report. However, this cannot be the reason for the strong deviations in the results of the interaction tests either. The Institute's calculation (based on the aggregated data) shows no statistically significant result ($p = 0.374$ or $p = 0.335$; Q-test in each case), both based on the subgroup results presented in Module 4 A and on the subgroup results provided in the CSR.

Furthermore, the company's approach in the case of binary data is unclear. Regardless of the data type, the company states that the interaction was tested by supplementing the corresponding term in the model. In the case of binary data, the company conducted the analysis in the overall population using the Cochran-Mantel-Haenszel method (stratified by

distance travelled in the 6MWT at baseline and enzyme replacement therapy status) for the RR, the odds ratio (OR) and the absolute risk reduction. Here, it is unclear which model the company used for the interaction test. It is possible that, in the case of binary data, by supplementing the corresponding term in the model, the company meant adding the corresponding subgroup characteristic in its calculation procedure, whereby, for example, the Breslow-Day test for homogeneity of the ORs can be performed in the SAS software [29]. However, a test regarding the RR would be necessary, as the results for RR and OR may differ.

Overall, the described uncertainties lead to the subgroup analyses of the company not being used for the present benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 14).

Determination of the outcome category for the outcomes “ability to move (SGIC)” and “energy level (SGIC)”

For the morbidity outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Morbidity

Ability to move (SGIC) and energy level (SGIC)

For the outcomes of ability to move (SGIC) and energy level (SGIC), there is insufficient information available to categorize the severity. These outcomes were therefore assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Table 14: Extent of added benefit at outcome level: cipaglucosidase alfa + miglustat vs. alglucosidase alfa (multipage table)

Outcome category **outcome**	**Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo** **event rate (%) or change at Week 52 (mean)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity (at Week 52)		
Physical endurance		
6MWT [metres]	21.44 vs. 16.11 MD: 5.33 [-15.21; 25.88] p = 0.608	Lesser/added benefit not proven
Motor function		
GSGC total value	-0.56 vs. 0.74 MD: -1.30 [-2.34; -0.26] p = 0.015 SMD: -0.51 [-0.94; -0.08][c]	Lesser/added benefit not proven
TUG [seconds]	-0.40 vs. 0.03 MD: -0.43 [-3.29; 2.42] p = 0.763	Lesser/added benefit not proven
Physical functioning		
R-PAct	No suitable data	Lesser/added benefit not proven
PROMIS Physical Function	No suitable data	Lesser/added benefit not proven
Fatigue (PROMIS Fatigue)	No suitable data	Lesser/added benefit not proven
Dyspnoea (PROMIS Dyspnea Severity)	No suitable data	Lesser/added benefit not proven
Function of the upper extremities (PROMIS Upper Extremity)	No suitable data	Lesser/added benefit not proven
General physical well-being (SGIC; worsening)	18% vs. 29% RR: 0.65 [0.33; 1.26] p = 0.199	Lesser/added benefit not proven
Respiratory effort (SGIC; worsening)	8 % vs. 11 % RR: 0.79 [0.23; 2.75] p = 0.715	Lesser/added benefit not proven
Muscle strength (SGIC; worsening)	18% vs. 29% RR: 0.65 [0.34; 1.25] p = 0.195	Lesser/added benefit not proven

Table 14: Extent of added benefit at outcome level: cipaglucosidase alfa + miglustat vs. alglucosidase alfa (multipage table)

Outcome category **outcome**	**Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo** **event rate (%) or change at Week 52 (mean)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Muscle function (SGIC; worsening)	14% vs. 29% RR: 0.50 [0.25; 1.02] p = 0.057	Lesser/added benefit not proven
Ability to move (SGIC; worsening)	11% vs. 34% RR: 0.32 [0.15; 0.67] p = 0.002 probability: indication	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit; extent: considerable
Activities of daily living (SGIC; worsening)	9% vs. 13% RR: 0.82 [0.28; 2.41] p = 0.714	Lesser/added benefit not proven
Energy level (SGIC; worsening)	11% vs. 24% RR: 0.40 [0.18; 0.88] p = 0.023 probability: indication	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit; extent: “minor”
Muscle pain (SGIC; worsening)	19% vs. 24% RR: 0.78 [0.37; 1.66] p = 0.515	Lesser/added benefit not proven
Health status (EQ-5D VAS)	0.05 vs. 3.87 MD: -3.82 [-9.51; 1.87] p = 0.187	Lesser/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	9% vs. 3% RR: 3.58 [0.50; 25.61] p = 0.205	Greater/lesser harm not proven
Discontinuation due to AEs	2% vs. 3% RR: 0.86 [0.09; 8.63] p = 0.898	Greater/lesser harm not proven
Infusion-related reactions (AEs)	25% vs. 26% RR: 0.91 [0.48; 1.72] p = 0.770	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: cipaglucosidase alfa + miglustat vs. alglucosidase alfa (multipage table)

Outcome category **outcome**	**Cipaglucosidase alfa + miglustat vs. alglucosidase alfa + placebo** **event rate (%) or change at Week 52 (mean)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Infusion-related reactions (SAEs)	1% vs. 0% RR: 0.76 [0.16; 3.58] p = 0.724	Greater/lesser harm not proven

a. Probability provided there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.

6MWT: 6-minute walk test; AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; GSGC: Gait, Stairs, Gower's manoeuvre, Chair; MD: mean difference; PROMIS: Patient Reported Outcome Measurement Information System; R-PAct: Rasch-built Pompe-specific Activity; RR: relative risk; SAE: serious adverse event; SGIC: Subject's Global Impression of Change; SMD: standardized mean difference; TUG: Timed Up and Go; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of cipaglucosidase alfa + miglustat in comparison with alglucosidase alfa

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ ability to move (SGIC), worsening: indication of an added benefit – extent: "considerable" ▪ energy level (SGIC): worsening: indication of an added benefit – extent: "minor"	–
Outcomes on health-related quality of life were not recorded.	
SGIC: Subject's Global Impression of Change	

Overall, there were only positive effects for cipaglucosidase alfa + miglustat compared to alglucosidase alfa: For the outcomes "ability to move" and "energy level" recorded with the SGIC, there was an indication of an added benefit, with the extent being considerable or minor. Further patient-reported outcomes were recorded in the PROPEL study, for which,

however, no suitable data were available for the present benefit assessment. This applies in particular to the recording of symptoms using several PROMIS instruments for the outcomes of physical functioning, fatigue, dyspnoea and function of the upper extremities. The PROMIS instrument on physical functioning, for example, records these symptoms using a total of 20 questions. The patient's physical functioning was also recorded with the R-PAct using 18 questions, while the SGIC was only used to assess the ability to move using one single question. The PROMIS questionnaire on fatigue (short form: 8 questions) also reflects patient-reported aspects on the energy level, which are only represented by one question in the SGIC. An adequate assessment of the patient-reported symptoms is not possible without suitable analyses of the outcomes recorded using PROMIS and R-PAct. Outcomes on health-related quality of life were not recorded.

In summary, the added benefit of cipaglucosidase alfa + miglustat over the ACT alglucosidase alfa is not proven for adult patients with LOPD in this data constellation.

Table 16 summarizes the result of the assessment of the added benefit of cipaglucosidase alfa + miglustat versus the ACT.

Table 16: Cipaglucosidase alfa + miglustat – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with LOPD (GAA deficiency)	Alglucosidase alfa[b]	Added benefit not proven[c]

a. Presented is the ACT specified by the G-BA.
b. If indicated, physiotherapy measures should be made available to patients in both arms of the study.
c. The PROPEL study included patients with seated FVC ≥ 30% who achieved ≥ 75 m and ≤ 90% of the predicted value for healthy adults in the 6MWT and did not require invasive or non-invasive respiratory support for > 6 hours per day while awake (see Section I 3.2). It remains unclear whether the effects observed in the study are transferable to patients with severe impairment of lung function and endurance.

6MWT: 6-minute walk test; FVC: forced vital capacity; GAA: acid α-glucosidase; G-BA: Federal Joint Committee; LOPD: late-onset Pompe disease

The above assessment deviates from the assessment by the company, which derived an indication of major added benefit of cipaglucosidase alfa + miglustat.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Amicus Therapeutics. A Phase 3 Double-Blind Randomized Study To Assess The Efficacy And Safety Of Intravenous ATB200 Co-Administered With Oral AT2221 In Adult Subjects With Late-Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo; study ATB200-03; Clinical Study Report [unpublished]. 2021.

4. Amicus Therapeutics. A Phase 3 Double-Blind Randomized Study To Assess The Efficacy And Safety Of Intravenous ATB200 Co-Administered With Oral AT2221 In Adult Subjects With Late-Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo; study ATB200-03; Zusatzanalysen [unpublished]. 2023.

5. Amicus Therapeutics. A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo [online]. [Accessed: 16.08.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000755-40.

6. Amicus Therapeutics. A Study Comparing ATB200/AT2221 With Alglucosidase/Placebo in Adult Subjects With Late-onset Pompe Disease (PROPEL) [online]. 2021 [Accessed: 16.08.2023]. URL: https://classic.clinicaltrials.gov/show/NCT03729362.

7. Schoser B, Roberts M, Byrne BJ et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial. Lancet Neurol 2021; 20(12): 1027-1037. https://doi.org/10.1016/S1474-4422(21)00331-8.

8. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998; 158(5 Pt 1): 1384-1387. https://doi.org/10.1164/ajrccm.158.5.9710086.

9. Amicus Therapeutics. Pombiliti 105 mg; Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 27.09.2023]. URL: https://www.fachinfo.de.

10. Sanofi. Myozyme [online]. 2023 [Accessed: 04.10.2023]. URL: https://www.fachinfo.de.

11. van der Ploeg AT, Kruijshaar ME, Toscano A et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. Eur J Neurol 2017; 24(6): 768-e731. https://doi.org/10.1111/ene.13285.

12. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117.

13. European Medicines Agency. Pombiliti; Assessment report [online]. 2022 [Accessed: 27.09.2023]. URL: https://www.ema.europa.eu/documents/assessment-report/pombiliti-epar-public-assessment-report_en.pdf.

14. Angelini C, Semplicini C, Ravaglia S et al. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. Muscle Nerve 2012; 45(6): 831-834. https://doi.org/10.1002/mus.23340.

15. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced walk test (SPWT), stair climb test (SCT), Six-Minute walk test (6MWT), chair stand test (CST), timed up & go (TUG), sock test, lift and carry test (LCT), and car task. Arthritis Care Res (Hoboken) 2011; 63(S11): S350-S370.

16. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999; 70(2): 113-119.

17. Christopher A, Kraft E, Olenick H et al. The reliability and validity of the Timed Up and Go as a clinical tool in individuals with and without disabilities across a lifespan: a systematic review. Disabil Rehabil 2021; 43(13): 1799-1813. https://doi.org/10.1080/09638288.2019.1682066.

18. van der Beek NA, Hagemans ML, van der Ploeg AT et al. The Rasch-built Pompe-specific activity (R-PAct) scale. Neuromuscul Disord 2013; 23(3): 256-264. https://doi.org/10.1016/j.nmd.2012.10.024.

19. PROMIS. Dyspnea Scoring Manual; A brief guide to scoring the PROMIS Dyspnea instruments [online]. 2021 [Accessed: 12.10.2023]. URL: https://www.healthmeasures.net/images/PROMIS/manuals/Scoring_Manuals_/PROMIS_Dyspnea_Scoring_Manual.pdf.

20. PROMIS. User Manual And Scoring Instructions; PROMIS Fatigue [online]. 2023 [Accessed: 12.10.2023]. URL: https://www.healthmeasures.net/images/PROMIS/manuals/Scoring_Manual_Only/PROMIS_Fatigue_User_Manual_and_Scoring_Instructions_02202023.pdf.

21. PROMIS. User Manual And Scoring Instructions; PROMIS Physical Function [online]. 2023 [Accessed: 12.10.2023]. URL: https://www.healthmeasures.net/images/PROMIS/manuals/Scoring_Manual_Only/PROMIS_Physical_Function_User_Manual_and_Scoring_Instructions_08Sept2023.pdf.

22. HealthMeasures. HealthMeasures Scoring Service powered by Assessment Center; An application to score PROMIS, NIH Toolbox, and Neuro-QoL instruments [online]. 2023 [Accessed: 27.09.2023]. URL: https://www.assessmentcenter.net/ac_scoringservice/.

23. EuroQoL Research Foundation. EQ-5D-3L user guide: basic information on how to use the EQ-5D-3L instrument [online]. 2018 [Accessed: 28.09.2023]. URL: https://euroqol.org/wp-content/uploads/2018/12/EQ-5D-3L-User-Guide_version-6.0.pdf.

24. Personius KE, Pandya S, King WM et al. Facioscapulohumeral dystrophy natural history study: standardization of testing procedures and reliability of measurements. Phys Ther 1994; 74(3): 253-263.

25. Montagnese F, Rastelli E, Khizanishvili N et al. Validation of Motor Outcome Measures in Myotonic Dystrophy Type 2. Front Neurol 2020; 11. https://doi.org/10.3389/fneur.2020.00306.

26. Hébert LJ, Remec J-F, Saulnier J et al. The use of muscle strength assessed with handheld dynamometers as a non-invasive biological marker in myotonic dystrophy type 1 patients: a multicenter study. BMC Musculoskelet Disord 2010; 11(1): 1-9.

27. Symonds T, Campbell P, Randall JA. A review of muscle- and performance-based assessment instruments in DM1. Muscle Nerve 2017; 56(1): 78-85. https://doi.org/10.1002/mus.25468.

28. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials 2016; 13(2): 161-168. https://doi.org/10.1177/1740774515602688.

29. SAS Institute. SAS/STAT 15.3 User's Guide; The FREQ Procedure [online]. 2023 [Accessed: 27.09.2023]. URL: https://documentation.sas.com/api/collections/pgmsascdc/9.4_3.5/docsets/statug/content/freq.pdf?locale=en#nameddest=statug_freq_toc.

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