Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Olipudase Alfa (acid sphingomyelinase deficiency (ASMD) type A/B or B)

of 16 March 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of

the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient olipudase alfa on 1 October 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 September 2022.

Olipudase alfa for the treatment of acid sphingomyelinase deficiency (ASMD) type A/B or B is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 02 January 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G22-33) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of olipudase alfa.

[1] General Methods, version 6.1 of 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Olipudase alfa (Xenpozyme) according to the product information

Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

Therapeutic indication of the resolution (resolution of 16 March 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of olipudase alfa is assessed as follows:

a) Adults with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the assessment of the additional benefit of olipudase alfa for adult patients with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, the pivotal, multicentre, randomised, double-blind, placebo-controlled phase II/III ASCEND study was submitted by the pharmaceutical company.

The ASCEND study was conducted to investigate the efficacy and safety of olipudase alfa in adults with a documented diagnosis of ASMD type B. A total of 36 people were assigned to treatment with olipudase alfa or placebo in a 1:1 ratio. The study is divided into the randomised, controlled, double-blind treatment phase and a still ongoing single-arm, open-label extension phase, in which patients in the placebo arm also received treatment with olipudase alfa. The data cut-off from 15.03.2021 is used for the benefit assessment. The results of the 52-week controlled, double-blind treatment phase are available.

According to the study protocol and module 4 of the benefit dossier, adults with a clinical diagnosis of ASMD type B were enrolled in the ASCEND study. The pharmaceutical company stated in the written statement procedure that adults with ASMD type A/B and B were enrolled in the ASCEND study.

The enrolled patients had to have a spleen volume ≥ 6 MN (multiple of the normal). Subjects who had already received a partial splenectomy were required to have a residual spleen volume of ≥ 6 MN.

Mortality

There were no deaths in the ASCEND study.

Morbidity

Diffusion capacity of the lung for carbon monoxide (DL_{CO})

The diffusion capacity of the lung for carbon monoxide (DL_{CO}) is a lung function test to detect changes in the function of the alveolar membrane.

The endpoint of percentage change in diffusion capacity of the lung for carbon monoxide (DL_{CO}) was collected as the primary endpoint at week 52 in the ASCEND study.

For the endpoint of percentage change in DL_{CO}, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo.

The pharmaceutical company additionally submitted a prespecified responder analysis for the ASCEND study. Responders are those who achieved an improvement in DL_{CO} by ≥ 15% at week 52. In the intervention arm of the ASCEND study, 5 out of 18 subjects showed an improvement in DL_{CO} by ≥ 15%. In the control arm, no subject achieved an improvement in DL_{CO} by ≥ 15%.

DL_{CO} is considered a surrogate endpoint. The results of this endpoint are only presented additionally for adults with ASMD due to insufficient surrogate validation.

Spleen volume

Spleen volume was assessed in the ASCEND study using magnetic resonance imaging (MRI). The endpoint percentage change in spleen volume was collected as the primary endpoint at week 52 in the ASCEND study.

For the endpoint of percentage change in spleen volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo.

The pharmaceutical company additionally submitted a prespecified responder analysis for the ASCEND study. Responders are those who achieved a reduction in spleen size ≥ 30% at week 52. In the intervention arm of the ASCEND study, 17 of 18 subjects showed a reduction in spleen size ≥ 30%. In the control arm, no subject achieved a reduction in spleen size ≥ 30%.

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms and improvement in the quality of life for the patient is considered to be patient-relevant.

However, no improvement in symptomatology or quality of life was shown for olipudase alfa.

Regardless of this, a prolonged reduction of the pathologically increased spleen volume is patient-relevant in the present therapeutic indication due to the risk of splenic rupture and the risk of splenectomy with the associated risks of the occurrence of post-splenectomy complications (especially immune incompetence or the occurrence of severe bacterial infections).

However, due to the lack of improvement in symptomatology and quality of life, the advantage shown for the endpoint of spleen volume is not quantifiable in its extent.

Liver volume

Liver volume was assessed in the ASCEND study using magnetic resonance imaging (MRI). For the endpoint of percentage change in liver volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo at week 52.

A long-lasting reduction of the pathologically elevated liver volume combined with a noticeable decrease of impairing disease symptoms and improvement in the quality of life for the patient is considered to be patient-relevant. However, no improvement in symptomatology or quality of life was shown for olipudase alfa. Even though a reduction in liver volume could be shown in the study, it still remains unclear to what extent the reduction in liver volume achieved during therapy with olipudase alfa is relevant for the patients. The results of this endpoint are therefore only presented additionally.

Fatigue: Brief Fatigue Inventory (BFI)

Fatigue was assessed in the ASCEND study using the Brief Fatigue Inventory (BFI) item 3 (most severe fatigue). Fatigue is considered a patient-relevant endpoint.

For the endpoint of fatigue, collected using BFI item 3, no statistically significant difference was detected between the treatment arms at week 52.

Pain: Brief Pain Inventory – Short Form (BPI-SF)

Pain was assessed in the ASCEND study using the BPI-SF questionnaire. Evaluations were submitted by the pharmaceutical company for item 3 of the BPI-SF as well as for the two summated scales "pain intensity" and "impairment due to pain".

For item 3 ("worst pain"), there was no statistically significant difference between the treatment arms in the mean change from baseline to week 52.

The results for the change in the summated scales of the BPI-SF "pain intensity" and "impairment due to pain" were not used for the benefit assessment due to the low return rates (< 70%).

Health status: EQ-5D-5L-VAS (visual analogue scale of the European Quality of Life Questionnaire – 5 Dimensions)

The health status was assessed in the ASCEND study using the visual analogue scale (VAS) of the EQ-5D questionnaire. Here, higher values indicate a better health status.

For the EQ-5D-5L-VAS, no statistically significant difference was found between the treatment arms in the ASCEND study.

Patient Global Impression of Symptom Severity (PGIS)/ Patient Global Impression of Change (PGIC)

Symptoms were recorded in the ASCEND study using PGIC and PGIS. In the PGIC[2], patients give a self-assessment of the improvement or deterioration of their symptoms on a seven-point scale from 1 (very big improvement) to 4 (no change) to 7 (very big deterioration). The scores were then converted into values from 3 (very big improvement), 0 (no change), to -3 (very big deterioration).

In the PGIS[3], the severity of symptoms was recorded using a five-point scale from 0 (no symptoms) to 4 (very severe symptoms).

Similar symptoms are collected for the endpoints of PGIC and PGIS. The PGIS is assessed both at baseline and at week 52. The endpoint of PGIC, in contrast, asks for the retrospective assessment of the change of the current state to the initial state.

In the ASCEND study, the change in health status was recorded using PGIC over a very long recall interval (week 52 compared to baseline). Due to the long recall interval, a risk of bias (so-called recall bias) of the results in both study arms cannot be excluded. The PGIC is used for the benefit assessment despite remaining uncertainties.
For the PGIC, there was no statistically significant difference between the treatment arms for the symptoms "abdominal disorders", "physical pain", "fatigue" and "ability to perform daily activities". For the "breathlessness" symptom of PGIC, a statistically significant advantage of olipudase alfa over placebo was shown for the change from baseline to week 52, the clinical relevance of which remains unclear.

For the PGIS, no statistically significant difference was found between the treatment arms for the symptoms "abdominal disorders", "physical pain", "fatigue" and "shortness of breath" respectively.

FACIT-Dyspnoea-SF

Dyspnoea was assessed in the ASCEND study using Functional Assessment of Chronic Illness Therapy - Dyspnoea - 10-item Short Form (FACIT-Dyspnoea-SF). The FACIT-Dyspnoea-SF is a patient-reported questionnaire with 10 questions each on the severity of dyspnoea and associated limitations in functioning.

The results for the change in the domain "severity of dyspnoea" of the FACIT-Dyspnoea-SF from baseline to week 52 are not used for the benefit assessment due to too low return rates

[2] PGIC: Please choose the response below that best describes the overall change in the severity of your shortness of breath since you started taking the study medication. (Check one response: very much better; moderately better; a little better; no change; a little worse; moderately worse; very much worse).

[3] PGIS: Please choose the response below that best describes your shortness of breath over the past week. (Check one response: none; mild; moderate; severe; very severe).

of 61.1% in the placebo arm. The domain "functional impairment due to dyspnoea" was not considered by the pharmaceutical company for the benefit assessment.

Quality of life

Short Form 36 Health Survey (SF-36)

In the ASCEND study, health-related quality of life was assessed using the Short Form-36 Health Survey (SF-36).

In the ASCEND study, there was no statistically significant difference between the treatment arms for either the mental component score (MCS) or the physical component score (PCS).

Side effects

In the ASCEND study, there was no statistically significant difference between olipudase alfa and the control arm for the endpoints of SAEs and severe adverse events.

In the ASCEND study, no subject discontinued treatment due to AEs. This results in no statistically significant difference between the treatment groups for the endpoint of therapy discontinuations due to AEs.

At the level of SOC (system organ class) and PT (preferred term), there were no statistically significant differences between the treatment groups in each case.

In the overall assessment, there are no advantages or disadvantages of olipudase alfa over placebo in the side effects category.

Overall assessment

For the assessment of the additional benefit of olipudase alfa for adults with non-CNS manifestations of ASMD with type A/B or B, the pivotal, multicentre, randomised, double-blind, placebo-controlled phase II/III ASCEND study was submitted by the pharmaceutical company.

The ASCEND study produced results on mortality, morbidity, quality of life and side effects.

There were no deaths in the ASCEND study.

For the endpoints of the morbidity category fatigue (BFI), pain (BPI-SF), health status (EQ-5D-5L-VAS) and PGIS, there was no statistically significant difference between the treatment groups.

For the endpoint of PGIC, a statistically significant advantage of olipudase alfa over placebo was shown for the “shortness of breath" symptom, the clinical relevance of which is unclear. For the PGIC, there was no statistically significant difference between the treatment arms for the symptoms "abdominal disorders", "physical pain", "fatigue" and "ability to perform daily activities".

For the endpoint of percentage change in spleen volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo, the extent of which is not quantifiable.

In the quality of life category, no statistically significant difference was found between the treatment groups for the endpoint SF-36.

In the overall assessment, there are no advantages or disadvantages of olipudase alfa in the side effects category.

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

Significance of the evidence

For the ASCEND RCT presented, the risk of bias at study level is assessed as low. However, the significance of the results is limited by the small number of patients enrolled in the study.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

b) Children and adolescents with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

Justification:

For the assessment of the additional benefit of olipudase alfa for children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, the pharmaceutical company presented the pivotal, multicentre, single-arm phase I/II ASCEND-Peds study to investigate the efficacy and safety of olipudase alfa in paediatric patients aged < 18 years with non-neuronopathic ASMD.

After the 64-week treatment phase, eligible patients were able to participate in the ongoing long-term LTS13632 study. The data cut-off at week 64 was used for the benefit assessment.

Adolescents (12 to < 18 years; N = 4), children (6 to < 12 years; N = 9) and infants (<6 years; N = 7) with ASMD type A/B or type B were enrolled in the study; all participants (N = 20) completed the study. It remains unclear what the percentages are in the respective ASMD types.

The enrolled patients had to have a spleen volume ≥ 5 MN (multiple of the normal). Subjects who had already received a partial splenectomy were required to have a residual spleen volume of ≥ 5 MN.

Mortality

There were no deaths in the ASCEND-Peds study.

Morbidity

Diffusion capacity of the lung for carbon monoxide (DL_{CO})

The diffusion capacity of the lung for carbon monoxide (DL_{CO}) is a lung function test to detect changes in the function of the alveolar membrane.

DL_{CO} is considered a surrogate endpoint. Based on the study submitted by the pharmaceutical company, it cannot be concluded that the DL_{CO} is a valid surrogate parameter for patient-relevant endpoints.

The results of this endpoint are only presented additionally due to the insufficient surrogate validation.

The endpoint percentage change in diffusion capacity of the lung for carbon monoxide (DL_{CO}) was collected at week 52 in the ASCEND-Peds study. In the single-arm ASCEND-Peds study, an improvement from baseline to week 52 was observed for the endpoint of percentage change in (DL_{CO}).

However, the certainty of the results and their interpretability are very limited due to the open-label study design without a control group; therefore, no statements on the additional benefit of olipudase alfa can be derived.

Spleen volume

Spleen volume was assessed in the ASCEND-Peds study using magnetic resonance imaging (MRI). The endpoint of percentage change in spleen volume was collected at week 52 in the ASCEND-Peds study.

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms and improvement of the quality of life for the patient is considered to be patient-relevant.

In the single-arm ASCEND-Peds study, an improvement from baseline to week 52 was observed for the endpoint of percentage change in spleen volume.

Regardless of this, a prolonged reduction of the pathologically increased spleen volume is patient-relevant in the present therapeutic indication due to the risk of splenic rupture and the risk of splenectomy with the associated risks of the occurrence of post-splenectomy complications (especially immune incompetence or the occurrence of severe bacterial infections).

Overall, the data presented can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in direct comparison to the natural course of the disease.

Taken together, the administration of olipudase alfa presently shows a relevant reduction in the spleen volume at week 52 compared to baseline, but the extent of which is non-quantifiable.

Liver volume

A long-lasting reduction of the pathologically elevated liver volume combined with a noticeable decrease of impairing disease symptoms and improvement in the quality of life for the patient is considered to be patient-relevant.

The endpoint of percentage change in liver volume was collected at week 52 in the ASCEND-Peds study.

Even though a reduction in liver volume could be shown in the study, it still remains unclear to what extent the reduction in liver volume achieved during therapy with olipudase alfa is relevant for the patients. The results of this endpoint are therefore only presented additionally.

In the single-arm ASCEND-Peds study, an improvement from baseline to week 52 was observed for the endpoint of percentage change in liver volume. However, the certainty of the results and their interpretability are very limited due to the open-label study design without a control group; therefore, no statements on the additional benefit of olipudase alfa can be derived.

Fatigue: PedsQL Multidimensional Fatigue Scale

Fatigue was assessed in the ASCEND-Peds study using the PedsQL Multidimensional Fatigue Scale. Fatigue is considered a patient-relevant endpoint.

The PedsQL-Fatigue is part of the PedsQL and was only used in the ASCEND-Peds study . For the PedsQL-Fatigue, there are different scales for different age groups (5-7, 8-12, 13-18 and 18-25 years). For 2 to 4-year-olds, there is a version that is filled in by the parents. If the patients were not able to fill in the questionnaire themselves, a questionnaire was used for parents, caregivers or carers to fill in. Reliability and validity of the Peds-QL are confirmed in validation studies. These are also available for the single scale "Multidimensional Fatigue Scale" of the Peds-QL, which is used for the multidimensional assessment of fatigue. Fatigue is considered a patient-relevant endpoint.

Self-assessment, if possible, is preferred over external assessment. The self-assessment version is therefore considered for the present age group of 5 years and older. For the age group of 2-4 years, the proxy-reported version by parents is used.

For the total score of the PedsQL Multidimensional Fatigue Scale, a reduction in fatigue from baseline was observed in the ASCEND-Peds study for both the patient-reported version (5-18 years) and the parent-reported version (2-4 years). However, the certainty of the results and their interpretability are very limited due to the open-label study design without a control group; therefore, no statements on the additional benefit of olipudase alfa can be derived.

Pain: PedsQL Paediatric Pain Questionnaire

PedsQL Paediatric Pain Questionnaire was used in the ASCEND-Peds study to assess pain.

The questionnaire consists of 3 items ("current pain"; "worst pain"; "location of pain"). The first two items are given on a VAS from 0 to 100 mm and evaluated individually. Higher values indicate more severe pain. For persons aged 5 to 18 years, there is a self-reported version and a parent-reported version. Self-assessment, if possible, is preferred over external assessment. The self-assessment version is therefore considered for the present age group of 5 years and older. In the ASCEND-Peds study, only the items "current pain" and "worst pain" were asked. Based on the visual validity, the instrument is considered appropriate to measure pain intensity.

For the PedsQL Paediatric Pain Questionnaire, the ASCEND-Peds study showed a reduction in pain for the item "current pain" compared to baseline. For the item "worst pain" there was no improvement compared to baseline. However, the certainty of the results and their interpretability are very limited due to the open-label study design without a control group; therefore, no statements on the additional benefit of olipudase alfa can be derived.

Body height (z score)

The anthropometric parameter of body height is assessed as a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disturbances. Data adjusted for age and sex (z scores) are preferred over absolute values. Body height was recorded as standing height for subjects > 2 years and lying length for subjects ≤ 2 years, and age and sex-adjusted z scores were calculated. The z scores reflect the number of standard deviations (SD) of each score from the normal mean scores, standardised by age and sex. The data were presented as SD values above or below the age-specific reference (≙ 0). It is not clear from the study documents which reference population the z scores refer to.

In the single-arm ASCEND-Peds study, an increase in age-related body height (z score) at week 52 was observed in the intraindividual comparison to baseline.

Patients in the present therapeutic indication usually have a reduced body height in the natural course of the disease compared to the normal population.

While the values at baseline predominantly indicate a below-average physical development of the children compared to the normal population, at the end of the ASCEND-Peds study the anthropometric values have approached the reference population of age-matched children of the normal population.

Overall, the data presented can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in direct comparison to the natural course of the disease.

Taken together, the administration of olipudase alfa showed a relevant increase in body height at week 52 compared to baseline, but the extent of which is non-quantifiable.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

Health-related quality of life was assessed in the ASCEND-Peds study using PedsQL. The PedsQL is a generic instrument for measuring health-related quality of life. The PedsQL for 5 to 18-year-olds consists of 23 items that are divided into four domains (physical, emotional, social and academic skills). For the 2 to 4-year-olds, the questionnaire to be completed by the parents includes 21 items with the same domains. The scores are then transformed on a scale of 0 to 100, higher scores indicating a better quality of life. The age-appropriate as well as self and proxy-reported versions for the age groups 2 to 4 years and 5 to 18 years were used, whereby the version for the age group 2 to 4 years was exclusively proxy-reported. The proxy report was done by the parents/carers. It is not clear from the study documents to which reference period the questionnaire refers.

In the ASCEND-Peds study, an improvement in quality of life was observed at week 52 compared to baseline for the patient-reported version (5-18 years) for both the total score and the physical health and psychosocial health domains. For the parent-reported version (2-4 years), an improvement in quality of life was shown for the physical health domain at week 52 compared to baseline.

However, due to the lack of a control group, no valid interpretation and assessment of the results for this endpoint can be derived. Overall, no statement on the additional benefit can be made for the quality of life.

Side effects

In the ASCEND-Peds study, SAEs occurred in 5 out of 20 patients (25%). Severe adverse events were recorded for 3 out of 20 patients (15%).

In the ASCEND-Peds study, no subject discontinued treatment due to AEs.

In the overall analysis of the results on the side effects, no statement can be made on the extent of the additional benefit due to the lack of a control group.

Overall assessment

For the assessment of the additional benefit of olipudase alfa for children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, the pivotal, multicentre, single-arm phase I/II ASCEND-Peds study was submitted by the pharmaceutical company.

The ASCEND-Peds study produced results on mortality, morbidity, quality of life and side effects.

For the present assessment, no control group is available for comparative assessment.

There were no deaths in the ASCEND-Peds study.

In the single-arm ASCEND-Peds study, an increase in age-related body height (z score) at week 52 was observed in the intraindividual comparison to baseline. While the values at baseline predominantly indicate a below-average physical development of the children compared to the normal population, at the end of the ASCEND-Peds study the anthropometric values have approached the reference population of age-matched children of the normal population.

A prolonged reduction of the pathologically increased spleen volume is patient-relevant in the present therapeutic indication due to the risk of splenectomy and the risk of splenic rupture.

The administration of olipudase alfa shows a relevant reduction in spleen volume at week 52 compared to baseline.

Overall, the presented data on body height and spleen volume can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in direct comparison to the natural course of the disease.

In the ASCEND-Peds study, endpoints were also collected to examine symptomatology using the PedsQL Multidimensional Fatigue Scale and PedsQL Paediatric Pain Questionnaire. Health-related quality of life was assessed with the PedsQL measurement instrument suitable for the paediatric patient population. In the present assessment, however, no valid statements can be derived on these endpoints due to the lack of a control group and the open-label study design .

With regard to the results on side effects, severe and serious adverse events occurred in part during treatment with olipudase alfa. No subject discontinued treatment due to AEs. No valid statements can be derived since there is no comparison with a control group.

In the overall assessment, a non-quantifiable additional benefit is identified for olipudase alfa for the treatment of children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, because the scientific data does not allow quantification.

Significance of the evidence

The ASCEND-Peds study is a single-arm study so that a comparative assessment is not possible.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Xenpozyme with the active ingredient olipudase alfa. Xenpozyme has been approved as an orphan drug as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in children, adolescents and adults with type A/B or type B.

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

For the assessment of the additional benefit of olipudase alfa for adults with non-CNS manifestations of ASMD with type A/B or B, the pivotal, multicentre, randomised, double-blind, placebo-controlled phase II/III ASCEND study was submitted by the pharmaceutical company.

The ASCEND study produced results on mortality, morbidity, quality of life and side effects.

There were no deaths in the ASCEND study.

For the endpoints of the morbidity category fatigue (BFI), pain (BPI-SF), health status (EQ-5D-5L-VAS) and PGIS, there was no statistically significant difference between the treatment groups.

For the endpoint of PGIC, a statistically significant advantage of olipudase alfa over placebo was shown for the “shortness of breath" symptom, the clinical relevance of which is unclear. For the PGIC, there was no statistically significant difference between the treatment arms for the symptoms "abdominal disorders", "physical pain", "fatigue" and "ability to perform daily activities".

For the endpoint of percentage change in spleen volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo, the extent of which is not quantifiable.

In the quality of life category, no statistically significant difference was found between the treatment groups for the endpoint SF-36.

In the overall assessment, there are no advantages or disadvantages of olipudase alfa in the side effects category.

However, the significance of the results of the ASCEND RCT is limited by the small number of patients enrolled in the study.

The overall assessment results in a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

b) Children and adolescents with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

For the assessment of the additional benefit of olipudase alfa for children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, the pivotal, multicentre, single-arm phase I/II ASCEND-Peds study was submitted by the pharmaceutical company.

The ASCEND-Peds study produced results on mortality, morbidity, quality of life and side effects.

For the present assessment, no control group is available for comparative assessment.

There were no deaths in the ASCEND-Peds study.

In the single-arm ASCEND-Peds study, an increase in age-related body height (z score) at week 52 was observed in the intraindividual comparison to baseline.

The administration of olipudase alfa shows a relevant reduction in spleen volume at week 52 compared to baseline.

Overall, the presented data on body height and spleen volume can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in direct comparison to the natural course of the disease.

In the ASCEND-Peds study, endpoints were also collected to examine symptomatology using the PedsQL Multidimensional Fatigue Scale and PedsQL Paediatric Pain Questionnaire. Health-related quality of life was assessed with the PedsQL measurement instrument suitable for the paediatric patient population. In the present assessment, however, no valid statements can be derived on these endpoints due to the lack of a control group and the open-label study design.

With regard to the results on side effects, severe and serious adverse events occurred in part during treatment with olipudase alfa. No subject discontinued treatment due to AEs. No valid statements can be derived since there is no comparison with a control group.

The significance of the evidence from the single-arm ASCEND-Peds study is limited due to the lack of comparative assessment.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for olipudase alfa for the treatment of children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, because the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

Patients with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

The number of patients is the target population in statutory health insurance (SHI). The information is based on patient numbers based on the information provided by the pharmaceutical company in the dossier.

However, the number of patients in the statutory health insurance target population stated by the pharmaceutical company is subject to uncertainties overall due to the methodological procedure, and is an underestimate.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Xenpozyme (active ingredient: olipudase alfa) at the following publicly accessible link (last access: 23 November 2022):

https://www.ema.europa.eu/en/documents/product-information/xenpozyme-epar-product-information_en.pdf

Treatment with olipudase alfa should only be initiated and monitored by doctors experienced in ASMD therapy.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). In particular, the training material contains information and warnings on the risk of severe hypersensitivity or anaphylaxis.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2023).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. The average body weight of adults is 77.0 kg and of children under 1 year 7.6 kg[4].

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Olipudase alfa	Continuously, 1 x every 14 days	26.1	1	26.1

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Olipudase alfa	Children under 1 year				
	3 mg/kg = 22.8 mg	22.8 mg	2 x 20 mg	26.1	52.2 x 20 mg
	Adults				
	3 mg/kg = 231 mg	231 mg	12 x 20 mg	26.1	313.2 x 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olipudase alfa 20 mg	25 PCI	€ 103,428.86	€ 2.00	€ 10,125.00	€ 93,301.86
Abbreviations: PCI = powder for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 March 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Olipudase alfa

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 29 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of olipudase alfa to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 02 January 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 January 2023.

The oral hearing was held on 6 February 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 24 February 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023	Conduct of the oral hearing
Working group Section 35a	15 February 2023 1 March 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure

Subcommittee Medicinal products	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken