IQWiG Reports – Commission No. A20-19

Asfotase alfa (hypophosphatasia) –

Addendum to Commission A19-89[1]

Addendum

Commission: A20-19
Version: 1.0
Status: 20 March 2020

[1] Translation of addendum A20-19 *Asfotase alfa (Hypophosphatasie) – Addendum zum Auftrag A19-89* (Version 1.0; Status: 20 March 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Asfotase alfa (hypophosphatasia) – Addendum to Commission A19-89

Commissioning agency

Federal Joint Committee

Commission awarded on

24 February 2020

Internal Commission No.

A20-19

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Susanne Haag
- Katharina Biester
- Petra Kohlepp
- Matthias Maiworm
- Thomas Kaiser

Keywords: Asfotase alfa, Hypophosphatasia, Benefit Assessment, NCT00744042, NCT01205152, NCT01176266, NCT01419028, NCT01163149, NCT00952484, NCT01203826, NCT02104219, NCT02235493, NCT03418389, NCT02306720

Table of contents

Page

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BMI	body mass index
BOT-2	Bruininks-Oseretsky Test
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HPP	hypophosphatasia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RGI-C	Radiographic Global Impression of Change
SD	standard deviation
SPC	Summary of Product Characteristics

1 Background

On 24 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-89 (Asfotase alfa – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented, among other information, the results of the study ENB-006-09 (including the extension study ENB-008-10 [hereinafter referred to as "ENB-006-09/ENB-008-10]") for the benefit assessment for children (aged 5 years and older), adolescents and adults with paediatric-onset hypophosphatasia (HPP). These data were unsuitable for the benefit assessment, as they did not contain any comparative results versus the appropriate comparator therapy (ACT) (best supportive care [BSC]) for patient-relevant outcomes.

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure. The G-BA therefore commissioned IQWiG with the following assessment of the analyses submitted by the company in the dossier:

- A subsequent assessment of the patient-relevant outcomes (e.g. Bruininks-Oseretsky Test [BOT-2], 6-minute walk distance) and anthropometric data (e.g. body mass index [BMI], body height and weight) of the ENB-006-09/ENB-008-10 study was to be conducted. This assessment had to include a check of whether normal values can be identified for the healthy population of the corresponding age group that allow conducting a comparison with the healthy population. If possible, the values at baseline and at the end of the observation period – each in comparison with the healthy population – were to be presented.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in the dossier assessment on Commission A19-89, the ENB-006-09/ENB-008-10 study presented by the company for children and adolescents was not included in the benefit assessment because there were no comparative results versus the ACT (BSC) for patient-relevant outcomes.

The reporting of results according to the G-BA's commission is conducted on the basis of the data presented by the company in the dossier. No further data with additional relevance for the present addendum were subsequently submitted in the commenting procedure.

2.1 Study description

The tables describing the characteristics of the study and of the interventions of the ENB-006-09/ENB-008-10 study can be found in the dossier assessment on Commission A19-89 (see Table 30 and Table 31 there).

The ENB-006-09 study was a randomized controlled trial (comparison of different dosages of asfotase) of 24 weeks, which included patients with HPP aged 5 to 12 years. The study compared the following dosages of asfotase alfa: 2 mg/kg body weight (3 times/week) und 3 mg/kg body weight (3 times/week). 6 and 7 patients respectively were randomized to the 2 study arms (total N = 13). The use of asfotase alfa in the study arm with 6 mg/kg body weight per week corresponds to the dosage recommended in the Summary of Product Characteristics (SPC) [3].

The ENB-006-09 study was followed by the extension study ENB-008-10, which included patients who had completed the ENB-006-09 study (n = 12). The administration of asfotase alfa was to be continued for at least 72 months. After entering the extension study, all patients initially received asfotase alfa only at the dosage of 3 mg/kg body weight per week. Based on an interim analysis (with a corresponding protocol change), the dosage was then increased to 6 mg/kg body weight per week.

Overall, the patients were not continuously treated with the approved dosage of asfotase alfa.

Primary outcome of the study was the Radiographic Global Impression of Change (RGI-C). Outcomes on morbidity and adverse events were additionally recorded.

2.2 Patient characteristics

Table 1 shows the characteristics and the mean/median treatment duration of the patients in the ENB-006-09/ENB-008-10 study.

Table 1: Characteristics of the study population – study ENB-006-09/ENB-008-10: asfotase alfa (multipage table)

Study **Characteristics** **Category**	**Asfotase alfa** **N[a] = 13**
ENB-006-09/ENB-008-10 (extension)	
Age at baseline [years], mean (SD)	8.8 (2.2)
Age group at baseline, n (%)	
6 to 11 years	11 (85)
12 to 17 years	2 (15)
Sex [F/M], %	15/85
Family origin, n (%)	
Caucasian	12 (92)
Other	1 (8)
HPP phenotype, n (%)	
Infantile (onset of disease < 6 months)	5 (38)
Juvenile (onset of disease ≥ 6 months to < 18 years)	8 (62)
Age at occurrence of first HPP symptoms [months], mean (SD)	10.5 (7.0)
RSS value at baseline[b], mean (SD)	2.8 (1.3)
PPi [µm] at baseline[c], mean (SD)	5.0 (1.0)
PLP [ng/mL] at baseline[b], mean (SD)	214.4 (126.6)
Alkaline phosphatase [U/L] at baseline[e], mean (SD)	46.2 (13.4)
Achieved walk distance at baseline [metres], mean (SD)	345.0 (90.5)
Achieved walk distance at baseline [percent of the distance predicted for the healthy population][f], n (%)	
≥ 25% to ≤ 75%	11 (84.6)
> 75%	2 (15.4)
Treatment duration [days]	
Median [min; max]	2334 [31; 2406]
Mean (SD)	2172 (644)
Treatment duration, n (%)	
< 3 months	1[g] (8)
3 to < 72 months	0 (0)
72 to < 84 months	7 (54)
≥ 84 months	5 (38)
Study discontinuation, n (%)	1 (8)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The RSS scale is used to assess the severity of rickets in the patients' wrists and knees. The scale ranges from 0 to 10 [4]. A total score of 10 corresponds to severe rickets, a score of 0 corresponds to no rickets.
c. Reference range: < 0.75−5.71 µm.
d. Reference range: 5.74−61.15 ng/mL.
e. Reference range: 51−385 U/L.
f. Walk distance predicted depending on sex, age and height, according to Geiger 2007 [5].
g. One patient discontinued treatment after 1 month due to preplanned scoliosis surgery.

Table 1: Characteristics of the study population – study ENB-006-09/ENB-008-10: asfotase alfa (multipage table)

Study Characteristics Category	Asfotase alfa N[a] = 13
F: female; HPP: hypophosphatasia; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of patients included; PLP: pyridoxal-5'-phosphate; PPi: inorganic pyrophosphate; RSS: Rickets Severity Score; SD: standard deviation; U/L: units per litre	

The patients included in the study were mostly male and of Caucasian family origin. The mean age of the patients was almost 9 years. 5 children and adolescents had infantile onset of disease, and 8 had juvenile onset of disease. At study entry, 2 of the 13 children and adolescents (about 15%) were able to walk > 75% of the walk distance predicted for the corresponding healthy population. The median treatment duration was 2334 days (about 334 weeks).

2.3 Results

2.3.1 Outcomes presented in the present assessment

For the following instruments used in the ENB-006-09/ENB-008-10 study to record patient-relevant constructs, the dossier contained analyses with reference values for the healthy population: 6-minute walk distance and BOT-2. Z values for body height, body weight and BMI are available for anthropometric data.

According to the company, the 6-minute walk distance was conducted according to the guidelines of the American Thoracic Society [6]. The calculation of the percentage of the predicted walk distance related to healthy children and adolescents was based on sex, age (in years) and body height (in cm). The predicted walk distance was calculated according to Geiger 2007 [5] and had been preplanned.

The BOT-2 is an instrument that measures the motor skills of children and adolescents aged 4 to 21 years [7]. The BOT-2 considers 4 motor areas (fine motor control, manual coordination, body coordination and strength/dexterity), each comprising 2 subscales. Regarding the sole use of the subscales, the authors refer to a weak reliability. Scaled values for the subscales as well as standardized values for the higher-level motor areas of the BOT-2 provide a comparison with the performance of a healthy person of the same age. In the healthy population, the scaled values have a mean value of 15 points with a standard deviation (SD) of 5. Correspondingly, the standardized values for the motor areas have a mean value of 50 points with an SD of 10. For the ENB-006-09/ENB-008-10 study, the recording of the total value for gross motor skills (strength/dexterity) with the 2 subscales of running speed/dexterity and strength was preplanned.

2.3.2 Results

Table 2 summarizes the results for the 6-minute walk distance and for the BOT-2 from the ENB-006-09/ENB-008-10 study on treatment with asfotase alfa in comparison with the healthy population in children and adolescents with HPP. Table 3 contains the corresponding results for the z values on body height, body weight and BMI.

Table 2: Results on the outcomes with normed analysis (6-minute walk distance, BOT-2) – study ENB-006-09/ENB-008-10: asfotase alfa

Study	**Asfotase alfa**				**Healthy population**
Outcome category **Outcome**	**N[a]**	**Values at baseline mean (SD)**	**N[b]**	**Values at the end of the observation period[c] mean (SD)**	**Reference value Mean (SD)**
ENB-006-09/ENB-008-10 (extension study)					
6-minute walk distance (% of the walk distance predicted for the healthy population)[d]	13	59.06 (14.96)	11	87.95 (9.74)	100 (about 10[e])
BOT-2					
Total value for gross motor skills (strength/dexterity)	13	27.38 (5.50)	11	49.18 (8.62)	50 (10)[f]
Subscale running speed/dexterity	13	3.69 (2.21)	11	14.18 (3.87)	15 (5)[f]
Subscale strength	13	5.23 (3.68)	11	15.09 (4.23)	15 (5)[f]

a. Number of patients at start of study.
b. Number of patients at the time point of the last measurement after start of the ENB-006-09 study.
c. Last documentation time; about 336 weeks (84 months) after the start of the ENB-006-09 study.
d. Walk distance predicted depending on sex, age and height, according to Geiger 2007 [5].
e. Deduced from Geiger 2007 [5] presented by the company.
f. According to Deitz 2007 [7] presented by the company.

BOT-2: Bruininks-Oseretsky Test; N: number of patients; SD: standard deviation

Table 3: Results on anthropometric data (age-dependent z values[a]) – study ENB-006-09/ENB-008-10: asfotase alfa

Study	Asfotase alfa				Healthy population
Outcome category Outcome	N[b]	Values at baseline mean (SD)	N[c]	Values at the end of the observation period[d] mean (SD)	Reference value Mean (SD)
ENB-006-09/ENB-008-10 (extension study)					
Body height	13	−1.94 (1.82)	12	−0.98 (1.57)	0 (1)
Body weight	13	−1.64 (2.37)	12	−0.29 (1.96)	0 (1)
BMI	13	−0.27 (1.12)	12	0.30 (1.21)	0 (1)

a. The z scores for body height, body weight and BMI are based on the CDC 2000 growth charts [8].
b. Number of patients at start of study.
c. Number of patients at the time point of the last measurement after start of the ENB-006-09 study.
d. Last documentation time; ca. 336 weeks (84 months) after the start of the ENB-006--09 study.

BMI: body mass index; CDC: Centers for Disease Control and Prevention; N: number of patients; SD: standard deviation

6-minute walk distance

At the beginning of the ENB-006-09/ENB-008-10 study, the proportion of the patients' mean 6-minute walk distance was found to be notably below the predicted walk distance for corresponding healthy persons (a value close to 100 means that a patient has reached the predicted walk distance for corresponding healthy persons). At the end of the observation period (about 84 months), the mean proportion of the predicted walk distance from the healthy population in the patients of study ENB-006-09/ENB-008-10 was close to normal.

BOT-2

At the beginning of the ENB-006-09/ENB-008-10 study, mean values of the patients for the BOT-2 (in each case for the total value for gross motor skills and for the 2 subscales) were found to be notably below the mean reference value of the corresponding healthy population (values below this reference value mean a restriction compared with a corresponding healthy population). At the end of the observation period (about 84 months), the patients' mean values for both the total value for gross motor skills and the subscales running speed/dexterity and strength were within the range of a corresponding healthy population.

Body height (z value)

The mean body height at the beginning of the ENB-006-09/ENB-008-10 study was almost 2 SDs below the mean value of the healthy population. At the end of the observation period (about 84 months), the mean body height of the patients had approached the mean body height of a corresponding healthy population, but was still almost 1 SD lower.

Body weight (z value)

The mean body weight at the beginning of the ENB-006-09/ENB-008-10 study was about 1.5 SDs below the mean body weight of corresponding healthy persons. At the end of the observation period (about 84 months), the patients' body weight was approximately within the normal range (on average 0.29 SDs below the mean body weight of corresponding healthy persons).

BMI (z value)

The patients' mean BMI at the beginning of the ENB00609/ENB-008-10 study was within the normal range (about 0.27 SDs below the mean BMI of corresponding healthy persons). At the end of the observation period (about 84 months), the patients' mean BMI was 0.30 SDs above the mean BMI of corresponding healthy persons.

2.4 Summary

For all outcomes and anthropometric data considered, there was a clear average improvement in the course of the study. At the end of the study, the mean values for most of the outcomes and anthropometric data considered were almost in the range of those of a healthy population. Overall, the consideration of the results at the end of the observation period (analysis date 336 weeks) did not provide any new insights compared with the data that were already available for the first benefit assessment procedure in 2015 (analysis date 240 weeks) [9,10].

Patients who survive the first years of the disease often experience spontaneous improvement with regard to symptoms and the course of the disease when they enter adolescence [10]. A before-after comparison is therefore not informative in the present situation. Without an adequate comparator group, data recorded in this age group do not allow to distinguish the potential therapeutic effects from a natural course (or a course under treatment with BSC). The company did not provide such data in the dossier.

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Asfotase alfa (Hypophosphatasie): Nutzenbewertung gemäß § 35a SGB V: Dossierbewertung; Auftrag A19-89 [online]. 13.01.2020 [Accessed: 15.01.2020]. (IQWiG-Berichte; Volume 865). URL: https://www.iqwig.de/download/A19-89_Asfotase-alfa_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Alexion Pharma Germany. Asfotase alfa (Strensiq): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 14.10.2019 [Accessed: 17.02.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/505/.

3. Alexion. Strensiq 40 mg/ml Injektionslösung; 100 mg/ml Injektionslösung: Fachinformation [online]. 07.2019 [Accessed: 17.10.2019]. URL: https://www.fachinfo.de.

4. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 2000; 46(3): 132-139.

5. Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V et al. Six-minute walk test in children and adolescents. J Pediatr 2007; 150(4). 395-9, 399 e1-2.

6. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.

7. Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky Test of Motor Proficiency, second edition (BOT-2). Phys Occup Ther Pediatr 2007; 27(4): 87-102.

8. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R et al. CDC growth charts: United States. 2000.

9. Gemeinsamer Bundesausschuss. Asfotase alfa: Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Bewertung von Arzneimitteln für seltene Leiden nach § 35a Absatz 1 Satz 10 i.V.m. 5. Kapitel § 12 Nr. 1 Satz 2 VerfO [online]. 04.01.2016 [Accessed: 22.06.2017]. URL: https://www.g-ba.de/downloads/92-975-1192/2015-12-23_Nutzenbewertung-G-BA_Asfotase%20alfa.pdf.

10. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Asfotase alfa [online]. [Accessed: 22.10.2019]. URL: https://www.g-ba.de/downloads/40-268-3662/2016-03-17_AM-RL-XII_Asfotase-alfa_D-188_TrG.pdf.