IQWiG Reports – Commission No. A19-89

Asfotase alfa (hypophosphatasia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Asfotase alfa (Hypophosphatasie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January 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) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
15 October 2020

Internal Commission No.
A19-89

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

Medical and scientific advice

- Anibh Das, Hannover Medical School, Germany

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.

IQWiG employees involved in the dossier assessment

- Kirsten Janke
- Katharina Biester
- Susanne Haag
- Petra Kohlepp
- Matthias Maiworm
- Daniela Preukschat
- Min Ripoll
- Dominik Schierbaum
- Dorothea Sow

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

Table of contents

Page

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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)
RCT	randomized controlled trial
RGC-I	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 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 asfotase alfa. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 October 2019.

Research question

The aim of the present report is the assessment of the added benefit of asfotase alfa in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with paediatric-onset hypophosphatasia (HPP) to treat the bone manifestations of the disease.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of asfotase alfa

Therapeutic indication	**ACT**[a]
Long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease	Best supportive care[b]

a. Presentation of the ACT specified by the G-BA.
b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HPP: hypophosphatasia

The company named BSC as comparator therapy and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. A minimum study duration of 24 weeks was required. This concurred with the company's inclusion criteria.

Results

The company did not conduct an information retrieval for the ACT, but presented data from a study conducted by the company in infants with perinatal or infantile HPP based on medical records. The approach of not conducting a systematic search for the ACT was inadequate and was not justified by the company. As a result, the study pool may be incomplete. For the present benefit assessment, due to the special data constellation (sufficiently large group difference in overall survival that is not solely attributable to potential bias), it was examined for the population of infants up to 5 years of age whether there were relevant data on the ACT beyond the comparative data presented by the company. Since it is not assumed that the data from the additionally identified studies would change the overall conclusion on the added benefit, the

inadequate information retrieval and study selection remain without consequence for the present assessment.

Study pool and study populations

In the present benefit assessment, the added benefit was based on a comparison of data from 2-single-arm studies with asfotase alfa treatment (ENB-002-08 [including the extension study ENB-003-08] and ENB-010-10) versus a study based on medical records on the ACT (ENB-011-10) presented by the company. Due to the special data constellation (see below), conclusions on the added benefit of asfotase alfa in comparison with the ACT for the patients included in the studies (infants [0 to 5 years] with perinatal or infantile HPP) were derived on the basis of the data presented by the company.

Studies with asfotase alfa treatment

The studies ENB-002-08 (including the extension study ENB-003-08) and ENB-010-10 were single-arm studies to investigate asfotase alfa in infants with perinatal or infantile HPP (documented onset of disease before the age of 6 months). At enrolment, the patients had to be ≤ 36 months (ENB-002-08/ENB-003-08) or ≤ 5 years (ENB-010-10) of age. The ENB-002-08/ ENB-003-08 study included 11 patients, and the ENB-010-10 study included 69 patients who were treated in compliance with the approval. The median treatment durations were 6.6 years (ENB-002-08/ENB-003-08) and 2.3 years (ENB-010-10). Both studies were conducted between 2008 and 2016.

Study based on medical records on supportive measures

ENB-011-10 was a study based on medical records, for which 48 patients worldwide were recruited into the study and data were extracted from medical records. Apart from the primary outcome “overall survival” and various operationalizations to record respiratory function, no other outcomes were investigated. The patients included in the recording received both drug and non-drug supportive measures.

At the time of data collection (data extraction period: 2012 to 2013), 35 patients had already died and 13 were still alive. The year of birth of the patients included was between 1970 and 2011. The diagnostic phase for the included patients lasted 3 decades.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for asfotase alfa in the approved therapeutic indication. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Patients in both study arms were to receive adequate treatment as part of an overall therapeutic concept.

Overall, the measures of the ENB-011-10 study documented in the medical records do not represent a complete implementation of the ACT. Due to the special data constellation, this did not lead to an exclusion of the study, however, but it was assumed that the results allow drawing

conclusions on the added benefit of asfotase alfa in comparison with the ACT for infants up to 5 years of age with perinatal and infantile onset of disease.

Similarity of the study populations

Concurring with the company, a population that was similar in terms of the inclusion criteria was considered for the benefit assessment. From the 2 studies on asfotase alfa (based on the inclusion criteria for the ENB-011-10 study), these were those patients who met at least 1 of the 3 following inclusion criteria of the ENB-011-10 study: respiratory compromise, vitamin B6-dependent seizures, rachitic chest. These were 78 of the total of 80 patients (97.5%) from the 2 asfotase alfa studies.

In principle, however, the comparability of the data from the single-arm studies on asfotase alfa treatment compared with the analyses on supportive measures based on medical records is limited by the differences in data collection. In the studies on asfotase alfa, data were recorded exclusively within the observation period of the study, i.e. only from the time point of the start of the study (median age at baseline: 66 weeks), whereas data on patients in the comparator group documented from the medical records were recorded from birth. This means that the observation period for the analyses from the single-arm studies with asfotase alfa also deviated from the observation period of the analyses based on medical records. In addition, there were differences or uncertainties for all 3 studies for the comparison of asfotase alfa with supportive measures, particularly with regard to age at disease onset and the phenotype of HPP (perinatal versus infantile).

The year of diagnosis also played a role, as the data collected from medical records cover several decades (birth years 1970 to 2011). It can be assumed that both the diagnosis and the supportive measures for symptomatic treatment changed during this time.

Overall, there were therefore differences between the patient collectives that received asfotase alfa and exclusively supportive measures. The company addressed the age at baseline and the [calendar] year of diagnosis using sensitivity analyses. There were no sensitivity analyses on the phenotype.

Despite the deficiencies in the available data, it was assumed due to the present data constellation that conclusions can be drawn on the added benefit of asfotase alfa in comparison with the ACT for infants up to 5 years of age with perinatal and infantile onset of disease.

Results

Since single-arm studies were used for the present assessment, the aspects of risk of bias for the studies or for the outcomes included were not assessed. Based on the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

In principle, only those outcomes for which comparative analyses versus the comparator therapy were available were considered for the assessment of the added benefit in order to

derive a conclusion on the added benefit of asfotase alfa in comparison with the ACT. These are the outcomes “overall survival” and “respiratory function”.

Overall survival

The comparative analysis showed that notably fewer infants with perinatal or infantile HPP died in the asfotase alfa studies presented by the company than in the study based on medical records (11.5% versus 72.9%). However, the analysis on overall survival was biased in favour of asfotase alfa due to several factors. The 2 factors “year of diagnosis” and “age at study entry” were of particular importance and were addressed by the company as potentially biasing factors by means of sensitivity analyses. There were no sensitivity analyses on the phenotype.

The sensitivity analyses showed that, in the comparison presented by the company, the 2 known confounding factors “calendar year of diagnosis” and “age at enrolment” distorted the result in favour of asfotase alfa, since in all sensitivity analyses the difference in mortality rates was smaller than in the original analysis (asfotase alfa: 11.5% versus supportive measures: 72.9%). Regarding the limitation of the population for the investigation of confounding factors for comparing asfotase alfa versus supportive measures, the smallest difference in mortality rates was 19.5% versus 48.0%. The sensitivity analyses investigating the influences of the year of diagnosis and the age at enrolment overall showed a difference in favour of asfotase alfa versus the comparator therapy in each case and hence did not raise doubts about the result of the primary analysis. The observed difference for the outcome “overall survival” was estimated to be large enough that it cannot be explained by the influence of confounding variables alone. The size of the difference between the treatment groups remained unclear.

Taking into account these analyses, there was therefore overall a hint of an added benefit of asfotase alfa in comparison with the comparator therapy for the outcome “overall survival”.

Further outcomes

No usable analyses in comparison with the ACT were available for the outcome “respiratory function”. The reason for this was that, due to the patients considered, the studies on asfotase alfa and the data based on medical records had different objects of investigation. None of the 3 studies investigated the outcome category of health-related quality of life. No comparative analyses versus the comparator therapy were available for the outcome category of side effects.

Data not relevant for the benefit assessment

The company presented different studies on children (aged 5 years and older), adolescents and adults with paediatric-onset HPP. These included one randomized controlled trial (RCT), several single-arm studies, data based on medical records and one registry. These studies presented were not relevant for various reasons:

- The RCT ENB-009-10 presented by the company was not considered suitable for the assessment of the added benefit of asfotase alfa versus the ACT due to the dosing

(underdosing) of asfotase alfa in the randomized phase, which deviated notably from the approval, and was therefore not included in the present benefit assessment.

- The data from single-arm studies and data based on medical records were unsuitable for the present benefit assessment. This was due to the fact that either no data were available for the ACT or only results for radiological outcomes.
- The analysis from the ALX-HPP-501 registry were unsuitable for the present benefit assessment. Both the data collection and the data analysis are unsuitable for comparative benefit assessments and thus also for the present assessment, and to a large extent they also do not comply with national and international standards for such collections and analyses.

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 asfotase alfa in comparison with the ACT is assessed as follows:

Infants with perinatal or infantile hypophosphatasia

Due to the special data constellation, a comparison of data from 2 single-arm studies with asfotase alfa treatment versus one study based on medical records was used for the assessment of the added benefit of asfotase alfa in comparison with the ACT for infants with perinatal or infantile HPP.

Suitable data for conclusions on the added benefit of asfotase alfa versus the ACT were only available for the outcome “overall survival”. There were either no data or no suitable data for further outcomes from the categories of morbidity, health-related quality of life and side effects. Nevertheless, under consideration of all data presented by the company, it was assumed that treatment with asfotase alfa is associated with a survival advantage for the patients in comparison with the ACT BSC. Due to the special data constellation (large group difference in overall survival, which was not caused by potential bias alone), the survival advantage was not called into question by the lack of comparative data, particularly regarding risk of harm. Due to the limited evidence for infants with perinatal or infantile HPP, no more than hints of an added benefit could be derived. In this data constellation, no conclusions could be drawn on the size of the difference between asfotase alfa and the ACT, so that a quantification of the extent of the added benefit was not possible.

[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].

In summary, there is therefore a hint of a non-quantifiable added benefit of asfotase alfa versus the ACT BSC for infants (up to 5 years of age) with perinatal or infantile HPP.

Further patient groups in the approved therapeutic indication

Since the company either submitted no data (infants with juvenile HPP) or submitted no data suitable for a benefit assessment (children [aged 5 years and older], adolescents and adults with perinatal, infantile or juvenile onset of disease) for the other patient groups in the approved therapeutic indication, an added benefit is not proven for these patients.

Table 3 shows a summary of probability and extent of the added benefit of asfotase alfa.

Table 3: Asfotase alfa – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease	Best supportive care[b]	Infants with perinatal or infantile HPP (onset of disease before the age of 6 months) ▪ hint of a non-quantifiable added benefit
		Infants with juvenile HPP (onset of disease between the age of 6 months and 18 years) ▪ added benefit not proven
		Children, adolescents and adults with perinatal, infantile or juvenile HPP (onset of disease before the age of 6 months, between the age of 6 months and 18 years) ▪ added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HPP: hypophosphatasia		

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2015. In that assessment, the G-BA had determined a non-quantifiable added benefit of asfotase alfa for all patients (≤ 5 years and > 5 years of age) with paediatric-onset HPP. However, in that assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.2 Research question

The aim of the present report was the assessment of the added benefit of asfotase alfa for long-term enzyme replacement therapy in comparison with BSC as ACT in patients with paediatric-onset HPP to treat the bone manifestations of the disease.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of asfotase alfa

Therapeutic indication	**ACT[a]**
Long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease	Best supportive care[b]
a. Presentation of the ACT specified by the G-BA. b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HPP: hypophosphatasia	

The company named BSC as comparator therapy and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. A minimum study duration of 24 weeks was required. This concurred with the company's inclusion criteria.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

Randomized controlled trials

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

Sources of the company in the dossier:

- study list on asfotase alfa (status: 21 August 2019)
- bibliographical literature search on asfotase alfa (last search on 22 July 2019)
- search in trial registries for studies on asfotase alfa (last search on 21 August 2019)

To check the completeness of the study pool:

- search in trial registries for studies on asfotase alfa (last search on 24 October 2019)

The check of the completeness of the study pool produced no suitable RCTs for the assessment of the added benefit of asfotase alfa.

This deviates from the approach of the company, which included the RCT ENB-009-10 in its benefit assessment. The exclusion of the study from the present benefit assessment is justified in Section 2.3.2.

Further investigations

The study pool for further investigations was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on asfotase alfa (status: 21 August 2019)
- bibliographical literature search on asfotase alfa (last search on 22 July 2019)
- search in trial registries for studies on asfotase alfa (last search on 21 August 2019)

To check the completeness of the study pool:

- bibliographical literature search on asfotase alfa (last search on 29 October 2019)
- search in trial registries for studies on asfotase alfa (last search on 24 October 2019)
- bibliographical literature search on the historical course of disease in HPP (last search on 29 October 2019)
- search in trial registries on the historical course of disease in HPP (last search on 28 October 2019)

The check of the literature search on further investigations identified further non-randomized studies that were potentially relevant for the present benefit assessment. On the one hand, these were the 2 single-arm studies with asfotase alfa treatment AA-HPP-405 [3-5] and HPPJEAP-01 [6-8], which the company had identified, but excluded. The company conducted no information retrieval for the ACT, but presented data from studies it had conducted based on medical records. This approach was inadequate and was not justified by the company. As a result, the study pool may be incomplete. For the present benefit assessment, due to the special data constellation (see Section 2.4), it was examined for the population of infants up to 5 years of age whether there were relevant data on the comparator therapy beyond the comparative data presented by the company. Further studies were identified from this [9-11]. However, the fact that the company did not consider these potentially relevant studies remains without consequence for the present assessment, as the overall conclusion on the added benefit would not change if the data available in these studies were taken into account (see Section 2.7.3.2.2 of the full dossier assessment).

2.3.2 Evidence provided by the company

Table 5 shows the evidence presented by the company and the information for which populations the company used the data and whether they were included in the present benefit assessment.

Table 5: Evidence presented by the company

Study	Study category			Population for which the company presented the data in the dossier[b]	Data on treatment with/without asfotase alfa
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)		
Relevant studies for the benefit assessment					
Single-arm studies					
ENB-002-08/ ENB-003-08 (extension study)	Yes	Yes	No	Infants	Yes/no
ENB-010-10	Yes	Yes	No	Infants	Yes/no
Study based on medical records					
ENB-011-10	Yes	Yes	No	Infants	No/yes
Non-relevant studies for the benefit assessment					
RCT					
ENB-009-10	Yes	Yes	No	Children and adolescents, adults	Yes/yes
RCTs on the dose comparison with control group based on medical records					
ENB-006-09[c]; ENB-008-10 (extension study)	Yes	Yes	No	Children and adolescents	Yes/yes; yes/no
Studies based on medical records					
ALX-HPP-502	No	Yes	No	Children and adolescents	No/yes
ALX-HPP-502s	No	Yes	No	Children and adolescents	No/yes
Observational study (with prospective and retrospective data collection)					
EmPATHY	No	No	Yes	Adults	Yes/no
Registry study					
ALX-HPP-501	No	Yes	No	Children and adolescents; adults	Yes/yes

a. Study for which the company was sponsor.
b. The company includes patients up to the age of 5 years as infants, patients up to the age of 17 years as children and adolescents, and patients aged 18 years and older as adults (in each case with paediatric onset of disease).
c. Patients were randomized to 2 different asfotase alfa dosages (6 or 9 mg/kg/BW/week, distributed over 3 injections per week); analyses on patients based on medical records were used as control group. The patients in this control group received supportive measures.

BW: body weight; RCT: randomized controlled trial

Non-relevant data for the benefit assessment

The data presented by the company on children (aged 5 years and older), adolescents and adults with paediatric-onset HPP were unsuitable for the present benefit assessment. This is justified below.

RCT

In its dossier, the company used the RCT ENB-009-10 [12-18] for the assessment of the added benefit. This study included 19 patients with HPP from 13 to 65 years of age; these were patients with infantile (n = 4), juvenile (n = 14) and adult (n = 1) onset of disease. The patients were randomly allocated to 2 treatment groups with different dosages of asfotase alfa (0.3 mg/kg body weight per day: N = 7; 0.5 mg/kg body weight per day: N = 6), and a control group without asfotase alfa treatment (N = 6). The open-label randomized study phase was 24 weeks. This was followed by an open-label extension phase where all patients received a uniform dosage of asfotase alfa for up to 72 months.

In both study arms, the dosage of asfotase alfa during the randomized treatment phase was not in compliance with the approval. The approval recommends a weekly dosage of 6 mg/kg body weight, for which 2 different dosing regimens are possible [19]. In the ENB-009-10 study, the dosage in both treatment groups (2.1 mg/kg body weight per week and 3.5 mg/kg body weight per week) was notably below the dosage recommended in the approval. Only in the course of the single-arm extension phase was the dosage increased to the amount recommended in the approval by amendment to the study protocol.

Deviating from the company, the RCT ENB-009-10 was not included for the assessment of the added benefit of asfotase alfa in comparison with the ACT due to the clear underdosing in the randomized phase. Information on the characteristics of the study and of the intervention used can be found in Table 28 and Table 29 in Appendix B of the full dossier assessment.

Further investigations

Besides the RCT ENB-009-10, the company presented data from further investigations for the assessment of the added benefit of asfotase alfa in comparison with the ACT in children, adolescents and adults. These data were unsuitable for the present benefit assessment. This was mainly due to the fact that either no data were available for the ACT or only results for radiological outcomes.

Detailed information on the characteristics of the studies and investigations and of the interventions used can be found in Table 30 and Table 31 in Appendix B of the full dossier assessment. The reasons for exclusion of the studies are mentioned below.

For children (aged 5 years and older) and adolescents, the company presented the ENB-006-09 study [16,17,20-26], an RCT in which patients were randomized to 2 different dosages of asfotase alfa (6 or 9 mg/kg body weight per week, distributed to 3 injections per week). Analyses on patients based on medical records where the patients received supportive measures were used as control group. The company presented a non-randomized comparison on treatment with asfotase alfa with supportive measures for this study. Besides, the data presented only referred to radiological outcomes. The company did not present any data that show that these outcomes are a valid surrogate for a patient-relevant outcome. It also did not comment on the question for which patient-relevant outcome the radiological outcomes are a valid surrogate.

For further outcomes, the company only presented data on the comparison of the 2 investigated dosages of asfotase alfa, and no data on the comparison with the ACT. The analyses were therefore unsuitable for the benefit assessment, and the ENB-006-09 study was not relevant for the benefit assessment. Due to the missing data on the ACT, the single-arm extension study ENB-008-10 [16,17,20-26] was also not relevant for the present benefit assessment.

Study ALX-HPP-502 [16,27] was an investigation based on medical records, which the company cited in its study pool, but it only used individual patients from the corresponding substudy ALX-HPP-502s [28,29] as part of the control group on supportive measures for the ENB-006-09 study.

For adults, the company – using the EmPATHY study [30,31], an observational longitudinal study – presented only analyses of changes under asfotase alfa treatment recorded retrospectively. Due to missing data on the ACT, the data were unsuitable for the derivation of the added benefit of asfotase alfa versus the ACT.

Analyses from the ALX-HPP-501 registry

The ALX-HPP-501 registry [32-35] is an international registry sponsored by the company, which includes patients with HPP both with and without asfotase alfa treatment. In its dossier, the company presented various analyses from this registry, comparing "patients treated with asfotase alfa at any time" with "patients never treated with asfotase alfa".

Both the data collection and the data analysis are unsuitable for comparative benefit assessments and thus also for the present assessment, and to a large extent they also do not comply with national and international standards for such collections and analyses [36,37]. This is particularly due to the following reasons:

Data collection

- No measures are apparent that would ensure that selection bias is minimized and that the sample is representative. On the contrary, measures are recognizable that make selection and lack of representativeness likely. On the one hand, special efforts were made to recruit patients who were treated with asfotase alfa in studies. On the other hand, the documentation effort made for patients treated with asfotase alfa differed notably from the effort made for those not treated with asfotase alfa (see also the following point).
- There is a lack of adequate measures to standardize the recording for a wide range of data. On the contrary, the examinations and treatments as well as therapy management in the individual centres had to be carried out according to the standards applicable there. The same applies to the type and scope of documentation; the information had to be transferred from medical records to the registry. It can be assumed that the implementation and documentation of the points mentioned above are not consistent in other countries and, moreover, do not meet the standards in Germany. For Germany, it is therefore largely not guaranteed, that there is a collection of data that is standardized and

related to clinical practice in the registry. Neither the registry protocol nor the dossier contained any discussion of the influence this has on the usability of the data, especially for the German health care context.

- The prospective documentation was largely limited (investigations, morbidity, adverse events [AEs]) to patients treated with asfotase alfa. The documentation was therefore per se incomplete for patients not treated with asfotase alfa.
- Only for Germany, there is an explicit restriction of treatment with asfotase alfa (and thus of the patients recorded) to the approval according to the Summary of Product Characteristics (SPC). Neither the registry protocol nor the dossier addressed possible deviations in other countries.
- The registry protocol did not show any discussion of potential confounders before the start of the registry. In particular, there was no systematic compilation of known relevant confounders in the therapeutic indication, e.g. on the basis of scientific literature in consultation with experts. It remains unclear whether all known relevant confounders were recorded in the data set. Irrespective of this, due to the lack of standardization of the data collection (see above), it cannot be assumed that even the potentially recorded confounders could be adequately considered in analyses.

Data analysis

- There were no plans at all for conducting a registry study for the purpose of the benefit assessment. The protocol submitted by the company described the planning for the registry, but there was no study protocol for a registry study based on it. The registry protocol also did not contain any planning for a comparative study. However, the appropriate planning and execution of a comparative study are a necessary prerequisite for the usability of registry data for the purpose of a comparative benefit assessment.
- Accordingly, there were no plans for the type, duration and scope of data collection for the purpose of the benefit assessment. The data collection was largely incomplete in terms of a comparison (see above). The registry protocol only mentioned an overall recruitment target for sample size planning; there was no sample size planning for a comparative analysis. The observation period was also not based on the goal of a comparative study, but the “life cycle of asfotase alfa” was mentioned instead.
- The analysis in the dossier was performed without any adjustment for confounders, although the company itself described major differences in patient baseline characteristics in the dossier.
- The analysis submitted by the company contained no content-related discussion of missing values, although the registry protocol provided for such a discussion in all analyses, among other things in order to derive appropriate imputation methods from it.

- The statistical analysis plan (SAP) was not created prospectively, but in knowledge of registry results (date of the SAP: 22 May 2019; date of the second progress report with analyses from the registry: 23 August 2018).
- Overall, no independent analyses are guaranteed for the registry, as the sponsor has reserved itself a fundamental right to review and comment on the resulting publications.

2.3.3 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 6: Study pool - non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with asfotase alfa			
ENB-002-08/ ENB-003-08 (extension study)	Yes	Yes	No
ENB-010-10	Yes	Yes	No
Study on supportive measures			
ENB-011-10	Yes	Yes	No
a. Study for which the company was sponsor.			
HPP: hypophosphatasia; RCT: randomized controlled trial; vs.: versus			

For the assessment of the added benefit for infants with perinatal or infantile onset HPP, the company presented the results of 2 single-arm studies with asfotase alfa treatment (ENB-002-08 [including extension study ENB-003-08] and ENB-010-10). For the comparator therapy (referred to as "supportive measures" in the present report), it presented data from one study based on medical records (ENB-011-10). Due to the special data constellation, these data were used for the derivation of the added benefit of asfotase alfa in comparison with the ACT in infants with perinatal or infantile onset HPP. Section 2.4 explains the reasons for this.

Section 2.6 contains a reference list for the studies included.

2.3.4 Study characteristics

Table 7 and Table 8 describe the studies used for the benefit assessment.

Table 7: Characteristics of the studies included – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Studies with asfotase alfa						
ENB-002-08/ ENB-003-08[b]	Single-arm	Patients (≤ 36 months) with ▪ documented diagnosis of severe HPP[c] ▪ onset of symptoms prior to 6 months of age	▪ Asfotase alfa ▫ ENB-002-08 (N = 11[d]) ▫ ENB-003-08 (extension [N = 10])	▪ Screening: 2 weeks ▪ Treatment: ▫ ENB-002-08: 6 months ▫ ENB-003-08: extension up to at most 84 months[e] ▪ Observation: outcome-specific until end of study	10 study centres in Canada, United Arab Emirates, United Kingdom, USA ▪ ENB-002-08: ▪ 10/2008–5/2010 ▪ ENB-003-08: ▪ 4/2009–8/2016	Primary: ▪ change in RGI-C at week 24 Secondary: ▪ mortality ▪ morbidity (e.g. respiratory status) ▪ AEs
ENB-010-10[f]	Single-arm	Patients (≤ 5 years)[g] with ▪ documented diagnosis of HPP[h] and ▪ onset of symptoms prior to 6 months of age	▪ Asfotase alfa (N = 69)	▪ Screening: 4 weeks ▪ Treatment: up to 72 months[i] ▪ Observation: outcome-specific until end of study	22 study centres in Australia, Canada, France, Germany, Italy, Japan, Russia, Saudi Arabia, Spain, Turkey, United Kingdom, USA 7/2010–9/2016	Primary: ▪ change in RGI-C at week 24 Secondary: ▪ mortality ▪ morbidity (e.g. respiratory status) ▪ AEs

Table 7: Characteristics of the studies included – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study on supportive measures						
ENB-011-10	Epidemiologic study on supportive measures for the treatment of severe perinatal and infantile HPP based on medical records	Patients ▪ with documented diagnosis of severe HPP[j] ▪ onset of symptoms prior to 6 months of age ▪ no treatment with asfotase alfa at any time point before data extraction ▪ consideration of living and deceased patients at enrolment	▪ Supportive measures (N = 48)	Not applicable, as study was based on medical records ▪ period of diagnosis of the patients included covered 3 decades ▪ birth years of the patients included: 1970 to 2011	12 study centres in Australia, Canada, Germany, Spain, Switzerland, Taiwan, USA Period of data extraction: 9/2012–4/2013[k]	Primary: ▪ overall survival Secondary: ▪ respiratory function (e.g. ventilator-free survival [invasive and non-invasive])

Table 7: Characteristics of the studies included – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain data on chosen outcomes from the information provided by the company in Module 4 of the dossier.
b. 10 amendments to the original protocol were prepared, including extensive changes during the study period with regard to inclusion and exclusion criteria, dosage, study duration and study outcomes.
c. Besides the criterion "total serum ALP of at least 3 standard deviations below the mean for this age group and PLP at least 4 times the upper limit of normal and HPP-related findings", diagnosis of HPP also had to be documented by at least one of the following conditions: history or presence of non-traumatic post-natal fracture or delayed fracture healing, history of elevated serum calcium, functional craniosynostosis with decreased head circumference growth, nephrocalcinosis, respiratory compromise, rachitic chest deformity and/or vitamin B6-dependent seizures or failure to thrive.
d. One patient left the study on day 1 due to infusion-related reaction not associated with the investigational preparation.
e. Following Amendment 7 (5 December 2013), the duration of the study was extended until approval (and commercial availability) of the drug or to a maximum of 84 months.
f. 7 amendments to the original protocol were prepared, including extensive changes during the study period with regard to inclusion and exclusion criteria, dosage, study duration and study outcomes.
g. Chronological age (or adjusted age for premature infants born in or after 37 weeks gestation) of 5 years or younger.
h. Besides the total serum ALP below the lower limit of normal for this age group and plasma PLP above the upper limit of normal (unless patient was receiving pyridoxine, e.g. for seizures) and HPP-related findings, diagnosis of HPP also had to be documented by at least 2 of the following HPP-related findings: history or presence of non-traumatic post-natal fracture or delayed fracture healing, nephrocalcinosis or history of elevated serum calcium, functional craniosynostosis, respiratory compromise or rachitic chest deformity, vitamin B6-dependent seizures or failure to thrive.
i. Following Amendment 9 (15 September 2014) and Amendment 10 (10 April 2015), the duration of the study was extended until approval and/or commercial availability of the drug or to a maximum of 72 months. The maximum duration of continued patient participation in the United Kingdom was 48 months.
j. Diagnosis of HPP, proven by one or more of the following: documented gene mutation(s) of tissue-nonspecific ALP, serum ALP below the age-adjusted normal range and either plasma PLP or urinary PEA above the upper limit of normal, or serum ALP below the age-adjusted normal range and HPP-related radiographic abnormalities. Enrolment into the study also required meeting at least one of the 3 following characteristics of HPP: respiratory compromise, rachitic chest and/or vitamin B6-dependent seizures.
k. The data collection covers the first 5 years of life of the patients included (exception: continuous observation of the outcome "overall survival").

AE: adverse event; ALP: alkaline phosphatase; HPP: hypophosphatasia; N: number of randomized or included patients; PEA: phosphoetanolamine; PLP: pyridoxal-5'-phosphate; RCT: randomized controlled trial; RGI-C: Radiographic Global Impression of Change; vs.: versus

Table 8: Characteristics of the intervention – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study	Intervention
Studies with asfotase alfa	
ENB-002-08/ ENB-003-08	Asfotase alfa ▪ ENB-002-08: ▫ 2 mg/kg BW, IV (single infusion); then 1 week washout ▫ followed by 1 mg/kg BW, SC (3 times per week) ▪ ENB-003-08: ▫ SC (3 times per week), continuation of final dose from primary treatment phase (corresponding to last visit at week 24) Dose adjustments were allowed[a]
	Non-permitted pretreatment ▪ prior treatment with bisphosphonate ▪ treatment with an investigational preparation within 1 month before first dose of study medication ▪ current participation in other study that includes investigational preparations, devices or treatments for HPP (e.g. bone marrow transplantation) **Prior and concomitant treatment** ▪ There were no restrictions regarding prior and concomitant medication. Any prior and concomitant medication and therapy (including dietary supplements, prophylactic treatments and medical interventions) had to be documented continuously (from the screening phase) until the end of the study.
ENB-010-10	▪ Asfotase alfa, SC (until at most 72 months): ▫ total dose of 6 mg/kg BW per week distributed to: - 1 mg/kg BW 6 times per week or - 2 mg/kg BW 3 times per week Dose adjustments were allowed[b]
	Non-permitted pretreatment ▪ prior treatment with bisphosphonate ▪ treatment with an investigational preparation within 1 month before first dose of asfotase alfa treatment ▪ current enrolment in other studies associated with an investigational preparation, device or treatment for HPP (e.g. bone marrow transplantation) **Prior and concomitant treatment** ▪ There were no restrictions regarding prior and concomitant medication. Any prior and concomitant medication and therapy (including dietary supplements, prophylactic treatments and medical interventions) had to be documented continuously (from the screening phase) until the end of the study.
Study on supportive measures	
ENB-011-10	Supportive measures for symptoms, such as inhalants, corticosteroids, or antiepileptics, as well as respiratory support measures, such as invasive ventilation[c]

Table 8: Characteristics of the intervention – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study	Intervention
a. The dose could be adjusted according to body weight or when toxicities occurred. After the first month of treatment, the dose could be increased to 1.5 mg/kg or 2 mg/kg (3 times per week) if lack of efficacy was found in 2 of the 3 following parameters: 1) no noticeable improvement of rickets in radiological findings, 2) deterioration of lung function, 3) deterioration of failure to thrive. After 3 months of treatment, the dose could also be increased to 2 mg/kg (3 times per week) if no improvement was shown in only one of the parameters mentioned. After 3 months of treatment, the dose could be increased to 3 mg/kg (3 times per week) if still no improvement was shown in 2 of the parameters mentioned. In the extension phase, the dose was adjusted according to body weight at each study visit, additional adjustments could be made due to lack of efficacy or due to toxicity. Following Amendment 6 (21 February 2012), the maximum daily dose was limited to 40 mg SC.	
b. The dose was adjusted according to body weight. Further adjustments were possible due to lack of efficacy or due to toxicity in the following cases: no improvement identifiable from X-rays and laboratory values after 3 months of treatment with consistent dosage; at any time when an acute deterioration of the clinical condition was observed, i.e. when intubation was necessary and there were difficulties in suspending mechanical ventilation; at any time when there were problems with tolerability. In case of dose increases due to lack of efficacy, regional standards regarding maximum dose had to be considered. In Australia, Germany, France, Italy, Saudi Arabia, Spain and the United Kingdom, a maximum permitted dose of 9 mg/kg per week could not be exceeded.	
c. For study ENB-011-10, a list of documented drugs and therapies is available, as well as a list of the type of respiratory support for patients up to 5 years of age (see Table 18 and Table 19 of the full dossier assessment).	
BW: body weight; HPP: hypophosphatasia; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus	

Studies with asfotase alfa

ENB-002-08/ENB-003-08

The ENB-002-08 study was a multinational, completed, single-arm study investigating asfotase alfa in children (≤ 36 months at enrolment) diagnosed with severe HPP. Onset of HPP symptoms had to be under the age of 6 months. The patients had perinatal or infantile onset HPP.

11 patients were enrolled in the study. The treatment duration of the ENB-002-08 study was 24 weeks. After a single administration of 2 mg/kg body weight IV per week, the patients were subsequently treated with a dosage of 1 mg/kg body weight (3 times per week). After 1 month of treatment, the dose could be increased (to 2 mg/kg body weight 3 times per week) if there was a lack of efficacy[4]. After 3 months, the dose could be increased to 3 mg/kg body weight (3 times per week) if there was a lack of efficacy[4]. The dosage at the beginning of the study did not correspond to the dosage of 6 mg/kg body weight (per week, divided into 3 or 6 single doses) recommended in the SPC [19]). However, the dose was increased in 10 of the 11 patients during the course of the study, and 8 of them were treated with the dosage recommended in the

[4] 2 of the 3 following parameters had to be fulfilled: no noticeable improvement of rickets in radiological findings/deterioration of lung function/deterioration of failure to thrive

SPC. There were no restrictions regarding prior and concomitant medication. However, prior and concomitant medication and other therapies (including dietary supplements, prophylactic treatments and medical interventions) were recorded and documented continuously until the end of the study.

All 10 patients who had completed the ENB-002-08 study continued treatment with asfotase alfa in the ENB-003-08 extension study. Treatment in the extension study was possible for a maximum of 84 months (7 years) or until commercial availability. Treatment duration ranged from 1 to 2743 days (0 to 7.5 years) with a median treatment duration of 2416 days (6.6 years). The corresponding 25% and 75% quartiles were 2231 and 2701 days (6.1 and 7.4 years), respectively. The patients continued treatment with the asfotase alfa dosage they had received at the last study visit (week 24) in the ENB-002-08 study.

The primary outcome of the ENB-002-08 study was change in rickets based on skeletal radiographs at week 24. The assessment was performed using the Radiographic Global Impression of Change (RGC-I), a scale that measures changes in the most common skeletal manifestations of HPP [23]. Patient-relevant secondary outcomes were mortality, morbidity, (e.g. respiratory function) and AEs.

ENB-010-10

The ENB-010-10 study was a multinational, completed, single-arm study investigating patients with documented diagnosis of HPP. The patients had to be under 5 years of age at study entry, and onset of HPP symptoms had to be under the age of 6 months; hence, the patients included were patients with perinatal or infantile onset HPP.

69 patients were enrolled in the study and treated with asfotase alfa. The dosage was 6 mg/kg body weight per week (either 1 mg/kg body weight, 6 times per week, or 2 mg/kg body weight, 3 times per week), and was therefore in compliance with the dosage recommended in the SPC [19]. Dose adjustments were admitted due to tolerability or lack of efficacy. There were no restrictions regarding prior and concomitant medication. However, prior and concomitant medication and other therapies (including dietary supplements, prophylactic treatments and medical interventions) were recorded and documented continuously until the end of the study.

Following Amendment 7, the duration of the study was extended until approval or commercial availability of the drug or to a maximum of 72 months (6 years). Treatment duration ranged from 6 to 2116 days (0 to 6.1 years) with a median treatment duration of 829 days (2.3 years). The corresponding 25% and 75% quartiles were 511 and 997 days (1.4 and 2.7 years), respectively.

The primary outcome of the study was the change in RGI-C at week 24. Patient-relevant secondary outcomes were mortality, morbidity (e.g. respiratory function) and AEs.

Study based on medical records (supportive measures)

ENB-011-10

The ENB-011-10 study was a global study conducted by the company on the basis of data from medical records. It included a total of 48 patients with severe perinatal or infantile HPP, which was defined as onset of disease before the age of 6 months and at least one of the following symptoms:

1) respiratory compromise (up to and including respiratory failure) requiring institution of respiratory support measures and/or medications for management of symptoms, and/or associated with other respiratory complications
2) vitamin B6-dependent seizures
3) rachitic chest

The data extraction included, for example, demographic characteristics, clinical laboratory parameters, information on medical history and supportive medication as well as on non-drug interventions for the treatment of HPP. Any information on survival status (e.g. time point, cause [if available]) and respiratory support measures was extracted. The data collection primarily covered the first 5 years of life of the included patients (exception: the outcome "overall survival" was continued to be monitored).

The year of birth of the patients included was between 1970 and 2011. At the time of data collection, 35 patients had already died and 13 were still alive. The diagnostic phase for the included patients lasted 3 decades. The data were from a total of 12 study centres from 7 countries. The data collection based on medical records was between September 2012 and April 2013.

The patients included in the recording received both drug and non-drug supportive measures (see below).

Apart from the primary outcome "overall survival" and various operationalizations to record respiratory function, no other outcomes were investigated. AEs were also not recorded in the study.

Implementation of the appropriate comparator therapy in study ENB-011-010

The G-BA specified BSC as ACT for asfotase alfa in the approved therapeutic indication (see Section 2.7.1 of the full dossier assessment). BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Patients in both study arms were to receive adequate treatment as part of an overall therapeutic concept.

The company concurred with the G-BA's specification on the ACT (see Section 2.7.1 of the full dossier assessment). However, the company did not address the question to which extent BSC was implemented for the patients included in the ENB-011-010 study.

For study ENB-011-10, a list of documented drugs and therapies was available (see Table 18 of the full dossier assessment), as well as a list of non-drug respiratory support measures (see Table 19 of the full dossier assessment). The data were available for the first 5 years of life of the included patients.

The list of documented drugs shows that 64.6% of all patients included in the ENB-011-10 study received concomitant medication or therapy. When considering individual drug groups, the proportion of patients with such concomitant therapy appears to be low: For example, only 6 patients (12.5%) received a drug from the group of non-steroidal anti-inflammatory and anti-rheumatic drugs. Only 3 patients (6.3%) received beta-lactam antibiotics or penicillins, for example.

The list of types of non-drug respiratory support shows that of the 45 patients for whom this information was available, 29 (64.4%) received such respiratory support. 19 patients (42.2%) thereof received invasive ventilation.

HPP causes a very variable clinical picture [38] and requires a multidisciplinary team for optimal treatment [39,40] in order to provide patients with the best possible care. In addition to concomitant drug treatment (e.g. with analgesics, antibiotics), remedies (especially physiotherapy and occupational therapy), aids (orthopaedic aids, walking aids, respiratory aids) and, if necessary, surgical measures may be indicated.

It is not clear from the data presented whether the same measures were available to all patients. It also remains open whether the patients who received drug interventions were the same patients who also received non-drug interventions. It remains unclear whether the documented measures were embedded in an overall concept. Since the data collected retrospectively from medical records cover a broad period of time, it is also possible that both the diagnosis and the treatment of HPP with supportive measures were heterogeneous during this period and, in addition, may no longer correspond to the current state of supportive measures.

Overall, the measures of the ENB-011-10 study documented in the medical records do not represent a complete implementation of the ACT. Due to the special data constellation (see Section 2.4), this did not lead to an exclusion of the study, however, but it was assumed that the results allow drawing conclusions on the added benefit of asfotase alfa in comparison with the ACT for infants up to 5 years of age with perinatal and infantile onset of disease.

Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study Characteristics	**Studies with asfotase alfa**		**Study on supportive measures**
Category	**ENB-002-08/ ENB-003-08**	**ENB-010-10**	**ENB-011-10**
	N[a] = 11	**N[a] = 69**	**N[a] = 48**
Age [weeks] at baseline			
Mean (SD)	58 (59)	113 (109)	–[b]
Median [min; max]	29 [2; 156]	69 [0; 312]	–[b]
Median [min; max]	Pooled data: N = 78[c] 66 [0; 312][d]		
Age at diagnosis of HPP [weeks]			N = 47
Mean (SD)	ND	ND	23 (41)
Median [min; max]	ND	ND	8.6 [0; 178]
Age at disease onset [weeks]	N = 9		N = 47
Mean (SD)	6.2 (8.4)[d]	6.5 (7.1)[d]	4.9 (7.2)[d]
Median [min; max]	4.4 [0; 25.2][d]	4.4 [0; 23.9][d]	0.1[e] [0; 25.6][d]
HPP phenotype, n (%)			
Perinatal or infantile	11 (100)	69 (100)	48 (100)
Thereof perinatal	4 (36.4)[f]	7 (10.1)[f]	14 (29.2)[f]
Sex [F/M], %	64/36	52/48	46/54
Family origin, n (%)			
Caucasian	10 (90.9)	54 (78.3)	40 (83.3)
Asian	0 (0)	7 (10.1)	2 (4.2)
Other	1 (9.1)	3 (4.3)	6 (12.5)[d, g]
Unknown	0 (0)	5 (7.2)	0 (0)
Geographical region	Pooled data: N = 78[c]		
USA/Canada	39 (50.0)		37 (77.1)
Europe	27 (34.6)		8 (16.7)
Asia	5 (6.4)		1 (2.1)
Rest of the world	7 (9.0)		2 (4.2)
TNSALP gene mutation			
Yes	11 (100.0)	62 (89.9)	–[h]
No	0 (0)	7 (10.1)	–[h]
PPI [µM][i]	N = 8	N = 65	
Mean (SD)	5.6 (2.3)	6.9 (2.4)	ND
Median [min; max]	5.2 [2.9; 10.5]	6.3 [2.7; 13.3]	ND
PLP [ng/mL][j]	N = 9	N = 60	N = 6
Mean (SD)	380.0 (256.7)	3143.5 (5964.4)	623.3 (1153.6)[k]
Median [min; max]	421.0 [100; 880]	520.5 [48; 24 600]	150.0 [43; 2972][k]

Table 9: Characteristics of the study populations – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study Characteristics / **Category**	**Studies with asfotase alfa**		**Study on supportive measures**
	ENB-002-08/ ENB-003-08	**ENB-010-10**	**ENB-011-10**
	N[a] = 11	**N[a] = 69**	**N[a] = 48**
ALP [U/L]	N = 9	N = 65	N = 41
Mean (SD)	26.8 (12.47)	29.3 (19.3)	18.1 (15.4)[k]
Median [min; max]	21 [9; 46]	20.0 [18; 122]	15.0 [0.0; 55.0][k]
Z score (weight)[l]		N = 68	
Mean (SD)	−3.4 (1.5)	−3.2 (3.3)	ND
Median [min; max]	−3.8 [−5.4; −0.5]	−2.5 [−24; 0]	ND
Z score (length)[l]		N = 67	
Mean (SD)	−4.1 (2.2)	−3.2 (2.1)	ND
Median [min; max]	−3.7 [−9.2; −0.7]	−2.7 [−10; 1]	ND
Respiration/respiratory support at baseline, n (%)			
No support	4 (36.4)[d]	45 (65.2)	ND
Supplemental oxygen (without mechanical ventilation)	0 (0)	6 (8.7)	ND
CPAP ventilation	1 (9.1)	4 (5.8)	ND
Mechanical ventilation (invasive)	3 (27.3)	13 (18.8)	ND
BiPAP	0 (0)	0 (0)	ND
Other	1 (9.1)	1 (1.4)	ND
Unknown	2 (18.2)[d]	0 (0)	ND
RSS score			
Mean (SD)	8.25 (1.736)	4.72 (3.217)	ND
Median [min; max]	8.25 [5.5; 10.0]	4.00 [0.0; 10.0]	ND
Fractures, n (%)	6 (54.5)	21 (30.4)[m]	ND
Treatment duration [weeks]			
Mean (SD)	295.1 (141.0)	121.6 (72.1)	ND
Median [min; max]	345.1 [0.1; 391.9]	118.4 [0.86; 302.3]	ND
Treatment discontinuation, n (%)	ND	ND	–
Study discontinuation, n (%)	2 (18.2)	9 (13.0)	–

Table 9: Characteristics of the study populations – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Study Characteristics	Studies with asfotase alfa		Study on supportive measures
Category	ENB-002-08/ ENB-003-08	ENB-010-10	ENB-011-10
	Na = 11	Na = 69	Na = 48

a. Number of included patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. 35 of the 48 patients had already deceased at the time of data extraction. The mean age of the patients still alive was 507 weeks (9.7 years).
c. Information refers to the pooled data of the studies ENB-002-08/ENB-003-08 and ENB-010-10 (N = 78), which were used for the derivation of the added benefit.
d. Institute's calculation.
e. Hence, in 50% of the patients in ENB-011-10, onset of disease was on day 1.
f. Institute's calculation (see Section 2.7.7.1 of the full dossier assessment): For both studies on asfotase alfa (N = 80), this results in a total of at least 11 patients with perinatal phenotype (13.8%), based on the definition of perinatal = in utero (as in study ENB-011-10).
g. Native American or Alaskan, African American or other.
h. Mutation analyses were only available for 21 of the 48 patients (43.8%). 19 patients (90.5%) thereof had TNSALP mutation.
i. Normal PPI reference range = 1.33 to 5.71 µM.
j. Normal PLP reference range = 11.76 to 68.37 ng/mL (ND for reference range of the ENB-011-10 study).
k. For the ENB-011-10 study based on medical records, it is unclear whether these are "baseline values" or from which point in time the data originate. It can only be inferred from the study documents that the values are those values that were as close as possible to the time of diagnosis of HPP.
l. Z scores for length and weight are based on CDC 2000 growth charts.
m. Fractures (including vertebral fractures) and/or delayed fracture healing.

ALP: alkaline phosphatase; BiPAP: biphasic positive airway pressure; CDC: Centers for Disease Control and Prevention CPAP: continuous positive airway pressure; F: female; HPP: hypophosphatasia; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of patients included; ND: no data; PLP: pyridoxal-5'-phosphate; PPI: inorganic pyrophosphate; RCT: randomized controlled trial; RSS: Rickets Severity Score; SD: standard deviation; TNSALP: tissue nonspecific alkaline phosphatase; vs.: versus

The mean age of the patients at enrolment in the single-arm studies was 58 weeks (ENB-002-08) and 113 weeks (ENB-010-10) respectively. The median age at enrolment was 66 weeks (15.3 months) for the pooled analysis of both studies with asfotase alfa (N = 78). The minimum age of the patients (at the time of enrolment) was 2 weeks in the ENB-002-08 study, and 0 weeks in the ENB-010-10 study. Due to the study design (data collection based on medical records), this information was not available for the ENB-11-10 study. Of the 48 patients included in the ENB-11-10 study, 13 patients were still alive at the time of data extraction.

The mean age at disease onset in the single-arm studies was about 6 weeks and thus comparable to the one in the study based on medical records (about 5 weeks). However, the corresponding data for the median differ largely (study on asfotase alfa: 4.4 weeks, versus study based on medical records: 0.1 weeks). Hence, in the study based on medical records, 50% of the patients were not older than 1 day at disease onset. The patients in the single-arm asfotase alfa studies thus had a later onset of HPP (in relation to age) than those in the study based on medical records.

All 3 studies included only patients with perinatal or infantile HPP. However, the proportion of patients with perinatal HPP (the most severe form of HPP with the highest risk of mortality [38]) was not clear from the available documents (for the 2 studies on asfotase alfa). The proportion of patients with perinatal onset of disease (here recorded by means of symptoms already in utero) was 29.1% in the study based on medical records. No exact figures were available for the single-arm studies. However, on the basis of the study documents it can be estimated that for both studies (N = 80) at least 11 patients (13.8%) had a perinatal phenotype (Institute's calculation, see Section 2.7.7.1 of the full dossier assessment).

In all 3 studies, most patients were of Caucasian family origin and most patients were from North America and Europe. The patients in the 2 single-arm studies were below the normal length (mean z scores −3.4 and −3.2) and were underweight (mean z scores −4.1 and −3.2). Corresponding data for the ENB-011-10 study were not available.

With regard to respiratory support at baseline, there were clear differences between the single-arm studies: while 36.4% of patients in the ENB-002-08 study managed without respiratory support, this was the case for 65.2% in the ENB-010-10 study. Corresponding data for the study based on medical records were not explicitly available. Only data on the type of respiratory support for patients up to the age of 5 years were available (see Table 19 of the full dossier assessment and Section 2.3.4 [Implementation of the appropriate comparator therapy in study ENB-011-010]). The patients in the ENB-002-08/ENB-003-08 study had a mean Rickets Severity Score (RSS) of 8.25, indicating severe rickets [41], and a fracture rate of 54.5%. The mean RSS score in the ENB-010-10 study was 4.7 points, which is interpreted to be moderate rickets. The fracture rate was 30.4%. Information on the RSS score or on the fracture rate for the ENB-011-10 study was not available.

Similarity of the study populations

In principle, the comparability of the data from the single-arm studies on asfotase alfa treatment compared with the analyses on supportive measures based on medical records is limited by the different data collection. In the studies on asfotase alfa, data were recorded exclusively within the observation period of the study, i.e. only from the time point of the start of the study (median age at baseline: 66 weeks), whereas data on patients in the comparator group documented from the medical records were recorded from birth. This means that the observation period (in relation to age) for the analyses from the single-arm studies with asfotase alfa also deviated from the observation period of the analyses based on medical records. In addition, as, described above, there were differences or uncertainties for the 3 studies for the comparison of asfotase alfa with supportive measures, particularly with regard to age at disease onset and the phenotype of HPP (perinatal vs. infantile).

In order to achieve sufficiently similar populations both for treatment with asfotase alfa and for supportive measures, the company considered those patients from the 2 studies on asfotase alfa who met at least 1 of the 3 following inclusion criteria on prognostic factors from study ENB-011-10: respiratory compromise, vitamin B6-dependent seizures, rachitic chest

deformity. The recording of the factors for the studies with asfotase alfa referred to the medical history at the beginning of the study and, in the ENB-011-10 study, on data within the first 5 years of life of the included patients. 78 of the 80 patients (97.5%) from the 2 studies with asfotase alfa fulfilled at least 1 of the 3 inclusion criteria of the ENB-011-10 study regarding prognostic factors and were therefore eligible for a comparative analysis according to the company (see Table 10).

Table 10: Inclusion criteria (study ENB-011-10) on prognostic factors – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP)

Inclusion criterion	Asfotase alfa[a, b] (ENB-002-08/ENB-003-08 + ENB-010-10)	Supportive measures (ENB-011-10)[c]
	Patients with event n (%)	Patients with event n (%)
	N = 78[d]	N = 48
Prognostic factors		
Rachitic chest deformity	74 (94.9)	40 (83.3)
Respiratory impairment (including respiratory arrest)	53 (67.9)	40 (83.3)
Vitamin B6-dependent seizures	20 (25.6)	10 (20.8)
Information summary		
At least one of 3 prognostic factors	78 (100.0)	47 (97.9)
All 3 prognostic factors	16 (20.5)	8 (16.7)

a. For the comparative analyses, the company pooled the results of the 2 asfotase alfa studies ENB-002-08/ENB-003-08 and ENB-010-10, and considered only those patients who met the inclusion criteria of the ENB-011-10 study.
b. Information on the medical history at baseline.
c. Information from the medical records on the patients' first 5 years of life.
d. 2 of the total of 80 patients from the studies ENB-002-08/ENB-003-08 and ENB-010-10 did not exhibit any of the prognostic factors mentioned above and were therefore not eligible for comparative analysis.

HPP: hypophosphatasia; n: patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

With over 80%, the majority of patients in both treatment groups had rachitic chest deformity and at least 2 thirds had respiratory impairment. A smaller proportion of patients had vitamin B6-dependent seizures.

HPP is a progressive disease, the course of which depends on the severity of the disease. The criteria considered by the company to achieve comparable populations only partly addressed the disease severity of the patients included. The severity of the disease is also influenced to a major extent by the time of disease onset, the so-called perinatal or infantile phenotype (disease onset intrauterine or between birth and 6 months of age). As described above, the information on phenotype was processed insufficiently in the available documents. However, the data on

the proportion of patients with perinatal disease onset were relevant for the assessment of the present comparison, since patients with perinatal HPP have a notably higher risk of death [38].

The year of diagnosis also played a role, as the data collected cover several decades (birth years 1970 to 2011). It can be assumed that both the diagnosis and the supportive measures for symptomatic treatment changed during this time.

Overall, there were therefore important differences between the patient collectives that received asfotase alfa and exclusively supportive measures. The company addressed the age at baseline and the [calendar] year of diagnosis using sensitivity analyses (see Section 2.4.3). There were no sensitivity analyses on the phenotype.

Despite the deficiencies in the available data, it was assumed due to the present data constellation (see Section 2.4) that conclusions can be drawn on the added benefit of asfotase alfa in comparison with the ACT for infants up to 5 years of age with perinatal and infantile onset of disease.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.7.3.2 of the full dossier assessment).

- Mortality
  - overall survival
- Morbidity
  - respiratory function
- Health-related quality of life
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.7.3.2 of the full dossier assessment).

Table 11 shows for which outcomes in the included studies data were available both for treatment with asfotase alfa and for the comparator therapy.

Table 11: Matrix of outcomes – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP)

Study	Outcomes			
	Overall survival	Respiratory function	Health-related quality of life	Side effects
Studies with asfotase alfa				
ENB-002-08/ENB-003-08	Yes	–[a]	No[b]	Yes
ENB-010-10	Yes	–[a]	No[b]	Yes
Study on supportive measures (based on medical records)				
ENB-011-10	Yes	–[a]	No[b]	No[c]

a. The comparative analyses presented by the company for the outcome "respiratory function" (survival without invasive ventilation) are not usable (see Section 2.7.7.3.2 of the full dossier assessment).
b. This outcome category was not recorded in any of the 3 studies.
c. Outcome not recorded.

HPP: hypophosphatasia; RCT: randomized controlled trial; vs.: versus

Data for the outcomes "overall survival" and "respiratory function" were available both for asfotase alfa and for the comparator therapy. The analyses presented by the company for the outcome "respiratory function" were not usable, however (see Section 2.7.7.3.2 of the full dossier assessment). Hence, only results for the outcome "overall survival" were available for the assessment of the added benefit of asfotase alfa in comparison with the ACT. Despite the missing data on morbidity, health-related quality of life and side effects, it was assumed due to the special data constellation that, based on the results, conclusions can be drawn on the added benefit of asfotase alfa in comparison with the ACT for infants up to 5 years of age with perinatal and infantile onset of disease.

2.4.2 Results

Results of a comparison of data from 2 single-arm studies with asfotase alfa treatment versus data on the comparator therapy from a study based on medical records were available for the assessment of the added benefit of asfotase alfa in patients with paediatric-onset HPP. Due to the present special data constellation, it is nonetheless possible to draw conclusions on the added benefit of asfotase alfa in comparison with the ACT.

An assessment of individual aspects of the risk of bias for the included studies and outcomes was not conducted (see Section 2.7.7.2 of the full dossier assessment). Based on the available data, no more than a hint, e.g. of an added benefit, can be determined.

Kaplan-Meier curves relevant for the benefit assessment are presented in Appendices A.2 and A.3 of the full dossier assessment.

Table 12 summarizes the results on the comparison of asfotase alfa versus the comparator therapy in infants up to 5 years of age with perinatal or infantile onset HPP.

Table 12: Results (mortality, morbidity, side effects) – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP)

Outcome category Outcome	Asfotase alfa (ENB-002-08/ENB-003-08 + ENB-0110-10)		Supportive measures (ENB-011-10)		Asfotase alfa vs. supportive measures
	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][a]	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][a]	HR [95% CI]; p-value[b]
Mortality					
Overall survival (primary analysis of the company)[c]					
	78	9 (11.5) NA; [73; 3955]	48	35 (72.9) 271 [155; 428]; [1; 7211]	–[d]; < 0.001
Morbidity					
Respiratory function		–[e]		–[e]	–[e]
Side effects					
AEs, SAEs, discontinuation due to AEs		–[f]		Not recorded	–

a. Measured from birth until event or until censoring. Patients treated with asfotase alfa who had not died were censored on their last study visit. ENB-011-10: Patients who had not died (at the time of the last data extraction: April 2013) or whose survival status was unknown (at the time of the last contact) were censored.
b. p-value: log-rank test.
c. For the comparative analyses (data of analysis: August 2018), the company pooled the results of the 2 asfotase alfa studies ENB-002-08/ENB-003-08 (data cut-off: May 2017) and ENB-010-10 (data cut-off: April 2017) and considered only those patients who met the inclusion criteria of the ENB-011-10 study (N = 78, see Section 2.3.4). One patient died in the ENB-002-08/ENB-003-08 study (9.1%); 9 patients died in the ENB-010-10 study (13.0%). Thus, one deceased patient was not included by the company in the pooled analysis.
d. No presentation of effect estimation and CI, as the corresponding HR from the Cox proportional hazards model is not meaningfully interpretable (see Section 2.7.7.3.1 of the full dossier assessment).
e. The comparative data presented by the company are not usable for the benefit assessment (see Section 2.7.7.3.2 of the full dossier assessment).
f. No analyses available on the comparison of asfotase alfa with the comparator therapy.

CI: confidence interval; HPP: hypophosphatasia; HR: hazard ratio; n: patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

In terms of the time to death from birth, the comparison of the (pooled) 2 single-arm studies on asfotase alfa versus the comparator therapy showed a clear difference in favour of asfotase alfa (see also Figure 5 of the full dossier assessment; for the Kaplan-Meier curves separated by

studies, see Figures 1 to 4 of the full dossier assessment). Due to important confounding factors, the size of the group difference is unclear.

The observed group difference in overall survival was investigated with sensitivity analyses to address potentially biasing factors (see Section 2.4.3). For this purpose, sensitivity analyses of the 2 factors (calendar) year of diagnosis and age at the time of enrolment were considered by means of different cut-off values (see Section 2.7.7.3.1 of the full dossier assessment). There were no sensitivity analyses on the phenotype of the disease. Sensitivity analyses chosen for the benefit assessment are presented in Section 2.4.3. It was derived from these analyses that the observed difference for the outcome "overall survival" was large enough that it cannot be explained by the influence of confounders alone. The size of the difference between the treatment groups remained unclear.

Taking into account the sensitivity analyses, there was overall a hint of an added benefit of asfotase alfa in comparison with supportive measures for the outcome "overall survival".

This concurs with the assessment of the company, which also derived a hint of an added benefit for the outcome "overall survival".

Morbidity

- Respiratory function

No usable analyses in comparison with the ACT were available for the outcome "respiratory function", which was due to the different subjects investigated (see Section 2.7.7.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of asfotase alfa in comparison with the comparator therapy for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which, based on the comparative analyses it considered relevant (including sensitivity analyses), derived a hint of an added benefit of asfotase alfa for the outcome "respiratory function".

Health-related quality of life

No outcomes of the outcome category "health-related quality of life" were investigated in the single-arm studies ENB-002-08/ENB-003-08, ENB-010-10 and ENB-011-10. This resulted in no hint of an added benefit of asfotase alfa in comparison with the comparator therapy in this outcome category; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

For the outcome category "side effects", there were no comparative analyses versus the ACT (see Section 2.7.7.3.2 of the full dossier assessment), as a systematic recording of AEs only took place in the studies ENB-002-08/ENB-003-08 and ENB-010-10. This resulted in no hint

of greater or lesser harm of asfotase alfa versus the comparator therapy; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.3 Sensitivity analyses on the outcome "overall survival"

As described in Section 2.4.2, sensitivity analyses on the outcome "overall survival" were used to check whether the result of the primary analysis on this outcome was robust or can be questioned depending on the age of the patients at enrolment or the year of diagnosis.

The following 3 potentially biasing factors were to be addressed by sensitivity analyses:

(Calendar) time point of diagnosis (year of diagnosis)

The studies on asfotase alfa (ENB-002-08/ENB-003-08 and ENB-010-10) were conducted in the period between 2008 and 2016. In contrast, the data on the historical course of the disease from the study based on medical records originated from the period from 1970 to 2011. Influences by a changed indication over time or a changed medical treatment of symptoms (optimized concomitant treatment) are conceivable and probable.

Age at the time of enrolment

In the 2 studies with asfotase alfa, survival from enrolment (start of treatment with asfotase alfa) was recorded for all patients, whereas in the study based on medical records, the survival of the deceased patients was considered from birth. The median age at enrolment in the pooled asfotase alfa studies was 66 weeks or 15 months (see Table 9). At this age (15 months), however, about 65% of the patients in the study based on medical records had already died (see Figure 4 of the full dossier assessment). Thus, while on the basis of the medical records children were considered from birth, the 2 studies on asfotase alfa investigated the survival of children who had already survived to the age reached at enrolment and had not died in the first months of life. Hence, there was a risk of bias in favour of asfotase alfa for the results on the basis of the comparison presented.

Phenotype (perinatal/infantile onset of disease)

Patients with perinatal disease onset have the highest mortality risk of all HPP patients [38,42,43]. The proportion of patients with perinatal phenotype in the study based on medical records was 29%. The proportion of patients with perinatal phenotype in the studies on asfotase alfa was unclear (Institute's calculation: at least 13.8%; see Table 9) and an uneven distribution was therefore possible. The dossier did not contain any sensitivity analyses on the influence of the phenotype (perinatal/infantile onset of disease) (see also Section 2.7.7.3.1 of the full dossier assessment).

Table 13 shows the sensitivity analyses considered for the benefit assessment. The respective Kaplan-Meier curves (Figures 6 to 12) are presented in Appendix A.3 of the full dossier assessment.

Table 13: Sensitivity analyses (outcome: overall survival) – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Outcome category **Outcome** **Year of diagnosis**	**Asfotase alfa[a] (ENB-002-08/ENB-003-08 + ENB-010-10)**		**Supportive measures (ENB-011-10)**		**Asfotase alfa vs. supportive measures**
	N	**Patients with event n (%)** **Median time to event in days [95% CI]; [min; max][b]**	**N**	**Patients with event n (%)** **Median time to event in days [95% CI]; [min; max][b]**	**HR [95% CI]; p-value[c]**
Mortality					
Sensitivity analyses: calendar year of diagnosis					
Overall survival – sensitivity analysis 1: study ENB-011-10 considered patients by year of diagnosis					
	78	9 (11.5) NA; [73; 3955]			
Before 1990			13	13 (100) 32 [1; 210]; ND	ND
1990-1999			14	10 (71.4) 268 [11; NC]; ND	ND
After 2000			21	12 (57.1) 494 [170; NC]; [1; 4397]	–[d]; < 0.001
Overall survival – sensitivity analysis 2: study ENB-011-10 considered patients diagnosed after the year 2005					
	78	9 (11.5) NA; [73; 3955]	16	9 (56.3) 767 [159; NC]; [1; 2805]	–[d]; < 0.001
Sensitivity analyses: age at enrolment					
Overall survival – sensitivity analysis 3: study ENB-011-10 considered only patients who survived at least 38 weeks[e]					
	78	9 (11.5) NA; [73; 3955]	25	12 (48.0) NA; [268; 7211]	–[d]; < 0.001
Overall survival – sensitivity analysis 4: the single-arm studies on asfotase alfa considered only patients who were at least 72 weeks of age at study entry, in comparison with patients in the ENB-011-10 study who survived at least 14 days[g]					
	41	8 (19.5) NA; [73; 2955]	36	23 (63.9) 400 [268; NC]; [28; 7211]	–[d]; < 0.001
Overall survival – sensitivity analysis 5: the single-arm studies on asfotase alfa considered only patients who were at least 72 weeks of age at study entry, in comparison with patients in the ENB-011-10 study who survived at least 38 weeks[e]					
	41	8 (19.5) NA; [73; 2955]	25	12 (48.0) NA; [268; 7211]	–[d]; 0.039

Table 13: Sensitivity analyses (outcome: overall survival) – non-RCTs: comparison of single-arm studies with data from medical records: asfotase alfa vs. supportive measures (infants with perinatal or infantile HPP) (multipage table)

Outcome category Outcome Year of diagnosis	Asfotase alfa[a] (ENB-002-08/ENB-003-08 + ENB-010-10)		Supportive measures (ENB-011-10)		Asfotase alfa vs. supportive measures
	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][b]	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][b]	HR [95% CI]; p-value[c]
Sensitivity analyses: age at enrolment and calendar year of diagnosis					
Overall survival – sensitivity analysis 6: the study based on medical records considered only patients who survived at least 38 weeks[e], separated by year of diagnosis					
	78	9 (11.5) NA; [73; 3955]			
Before 1990			3	3 (100) 474 [295; 1123]; [295; 1123]	–[d]; < 0.001
1990-1999			7	3 (42.9) NA [273; NC]; [273; 7211]	–[d]; 0.019
After 2000			15	6 (40.0) NA [371; NC]; [268; 4397]	–[d]; 0.007
Overall survival – sensitivity analysis 7: the study based on medical records considered only patients diagnosed after the year 2005 and who survived at least 38 weeks[e]					
	78	9 (11.5) NA; [73; 3955]	11	4 (36.4) NA; [268; 2805]	–[d]; 0.032

a. The company pooled the results of the 2 asfotase alfa studies ENB-002-08/ENB-003-08 (data cut-off: May 2017) and ENB-010-10 (data cut-off: April 2017) for the comparative analyses (date of analysis: August 2018).
b. Measured from birth until event or until censoring. Patients treated with asfotase alfa who had not died were censored on their last study visit. ENB-011-10: Patients who had not died (at the time of the last data extraction: April 2013) or whose survival status was unknown (at the time of the last contact) were censored.
c. p-value: log-rank test.
d. No presentation of effect estimation and CI, as the corresponding HR from the Cox proportional hazards model is not meaningfully interpretable (see Section 2.7.7.3.1 of the full dossier assessment).
e. Justification of the company for the selected time point in Module 4 A: 38 weeks correspond to the median survival time in the study based on medical records, but there is a different justification, which is factually incorrect, at other points in Module 4 A (see Section 2.7.7.3.1 of the full dossier assessment). The study documents also contain analyses on the time point of 27 weeks. These show comparable results (N = 27, of which 14 patients died; p < 0.001).
f. Justification of the company for the selected time point: In the study based on medical records, the risk of dying seemed to be notably reduced in patients who lived 72 weeks and longer.
g. Justification of the company for the selected time point: In the study based on medical records, the risk of dying seemed to be highest in the first 2 weeks after birth.

CI: confidence interval; HPP: hypophosphatasia; HR: hazard ratio; n: patients with event; max: maximum; min: minimum; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; vs.: versus

Sensitivity analyses with consideration of the calendar year of diagnosis

For the ENB-011-10 study, sensitivity analysis 1 depicts 3 groups, stratified according to the calendar year of diagnosis. The highest mortality rate was shown in patients diagnosed with HPP before 1990. There were no survivors in this subpopulation. Patients who were diagnosed with HPP after the year 2000 showed the lowest mortality rate (57.1%). Sensitivity analysis 2 refers to the (calendar) year of diagnosis on the cut-off value "diagnosis after 2005". From the ENB-011-10 study, 16 patients were included in the analysis. 56.3% of these patients died.

The sensitivity analyses to examine the influence of the year of diagnosis each showed a difference in favour of asfotase alfa in comparison with the comparator therapy (see also Figures 6 and 7 of the full dossier assessment) and therefore did not question the result of the primary analysis.

The approach differed from that of the company, which did not include the sensitivity analysis for the year of diagnosis from 2005 in its benefit assessment, and did not consider the periods of diagnosis (< 1990, 1990 to 1999 and ≥ 2000) separately, but only together with the sensitivity analysis for age at enrolment (cut-off value 38 weeks; sensitivity analysis 6).

Sensitivity analyses with consideration of the age at enrolment

Sensitivity analysis 3 comprised patients of the ENB-011-10 study who had survived at least 38 weeks. Sensitivity analysis 4 included patients treated with asfotase alfa who were 72 weeks or younger at the time of enrolment. Only those patients from the ENB-011-10 study were additionally considered who had survived at least 14 days. In sensitivity analysis 5 (analogous to sensitivity analysis 3), patients of study ENB-011-10 who had survived at least 38 weeks were included in the analysis and compared with the population under asfotase alfa treatment (as in sensitivity analysis 4), who were no more than 72 weeks of age at the time of enrolment.

The sensitivity analyses to examine the influence of the year of diagnosis each showed a difference in favour of asfotase alfa in comparison with the comparator therapy (see also Figures 8 to 10 of the full dossier assessment) and therefore did not question the result of the primary analysis.

The approach concurs with that of the company.

Sensitivity analyses (consideration: age at enrolment and calendar year of diagnosis)

Sensitivity analysis 6 considered those patients of the ENB-011-10 study who had survived at least 38 weeks, additionally separated according to calendar period of diagnosis (before 1990, 1990 to 1999, after 2000). Although, as expected, mortality decreased notably over time (over the calendar years) in the ENB-011-10 study, it was still notably higher in all 3 groups of the study than the mortality rate in the pooled single-arm asfotase alfa studies. Sensitivity analysis 7 also considered those patients of the ENB-011-10 study who had survived at least 38 weeks, and the period of diagnosis used in sensitivity analysis 6 was restricted further (after 2005). The mortality rate for these patients was 36.4% (4 of the 11 patients died), which was still above the

mortality rate in the single-arm asfotase alfa studies (11.5%) (see also Figure 12 of the full dossier assessment).

These analyses (see also Figures 11 and 12 of the full dossier assessment) therefore did not question the result of the primary analysis.

The approach deviates from that of the company insofar, as the company did not include sensitivity analysis 7 in its benefit assessment.

Summary assessment of the sensitivity analyses (outcome "overall survival")

The sensitivity analyses for estimating the effects of the year of diagnosis and the age of the patients at enrolment showed that the result of the primary analysis is robust in relation to the factors investigated. In the overall conclusion, the sensitivity analyses confirmed the sufficiently large difference in favour of asfotase alfa versus the comparator therapy. Although in each case the size of the group difference was smaller than in the primary analysis, it persisted throughout. Regarding the limitation of the population for the investigation of confounding factors for comparing asfotase alfa versus supportive measures, the smallest difference in mortality rates was 19.5% versus 48.0%. Taking into account these sensitivity analyses, the results for the outcome "overall survival" on the basis of the evidence presented were used for the assessment of the added benefit of asfotase alfa. The observed difference for the outcome "overall survival" was estimated to be large enough that it cannot be explained by the influence of confounding variables alone.

2.5 Probability and extent of added benefit

On the basis of the results presented in Sections 2.3 and 2.4, the probability and the extent of the added benefit is assessed as follows.

For the assessment of the added benefit of asfotase alfa in comparison with the ACT, the company presented usable data exclusively for infants (up to 5 years) with perinatal or infantile HPP (disease onset before the age of 6 months). The company did not present any data for infants with juvenile HPP (disease onset between 6 months and 18 years of age). The company did not present any suitable data for the assessment of the added benefit of asfotase alfa for children (aged 5 years and older), adolescents and adults with perinatal, infantile or juvenile onset of disease. For this reason, the added benefit of asfotase alfa is derived separately for these patient groups.

Infants with perinatal or infantile hypophosphatasia (onset of disease before the age of 6 months)

Due to the special data constellation, a comparison of data from 2 single-arm studies with asfotase alfa treatment versus one study based on medical records was used for the assessment of the added benefit of asfotase alfa in comparison with the ACT for infants with perinatal or infantile HPP.

Suitable data for conclusions on the added benefit of asfotase alfa in comparison with the ACT were available only for the outcome "overall survival". There were either no data or no suitable data for further outcomes from the categories of morbidity, health-related quality of life and side effects. Nonetheless, under consideration of all data presented by the company, it was assumed that treatment with asfotase alfa in comparison with the ACT BSC has a survival advantage for the patients. Due to the special data constellation (large group difference in overall survival, which cannot be due to potential bias alone), the survival advantage was not questioned by the lack of comparative data, particularly on the risk of harm. Due to the limited evidence for infants with perinatal or infantile HPP, no more than hints of an added benefit can be derived. In this data constellation, no conclusions can be drawn on the size of the difference between asfotase alfa and the ACT so that the extent of added benefit cannot be quantified.

In summary, there is therefore a hint of a non-quantifiable added benefit of asfotase alfa versus the ACT BSC for infants (up to 5 years of age) with perinatal or infantile HPP.

Infants with juvenile HPP and children (aged 5 years and older), adolescents and adults with perinatal, infantile or juvenile onset of disease

Since the company either did not present any data (infants with juvenile HPP) or did not present any data suitable for the benefit assessment (children [aged 5 years and older], adolescents and adults with perinatal, infantile or juvenile onset of disease) for further patient groups in the approved therapeutic indication, an added benefit is not proven for these patients.

The result of the assessment of the added benefit of asfotase alfa in comparison with the ACT is summarized in Table 14.

Table 14: Asfotase alfa – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Long-term enzyme replacement therapy in patients with paediatric-onset HPP to treat the bone manifestations of the disease	Best supportive care[b]	Infants with perinatal or infantile HPP (onset of disease before the age of 6 months) ▪ hint of non-quantifiable added benefit
		Infants with juvenile HPP (onset of disease between the age of 6 months and 18 years) ▪ added benefit not proven
		Children, adolescents and adults with perinatal, infantile or juvenile HPP (onset of disease before the age of 6 months, between the age of 6 months and 18 years) ▪ added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HPP: hypophosphatasia		

The assessment described above deviates from that of the company, which, under consideration of the evidence presented by the company (see Section 2.3.2), derived an added benefit both

for infants (“major”) and for children, adolescents and adults (“considerable”). It did not determine probability.

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

Supplementary note

The result of the assessment deviates from the result of the G-BA’s assessment in the framework of the market access in 2015. In that assessment, the G-BA had determined a non-quantifiable added benefit of asfotase alfa for all patients (≤ 5 years and > 5 years of age) with paediatric-onset HPP. However, in that assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.6 List of included studies

ENB-002-08 (including the extension study ENB-003-08)

Alexion Europe. CTD section 2.7.3: summary of clinical efficacy; asfotase alfa in hypophosphatasia; study results [unpublished]. 2018.

Alexion Pharma. Extension study of enb-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in severely affected infants and young children with hypophosphatasia (HPP) [online]. In: EU Clinical Trials Register. [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-009369-32.

Alexion Pharma. A multicenter, open-label study of the safety, tolerability and pharmacology of asfotase alfa in up to 10 severely affected patients with for the treatment of severely affected patients with infantile hypophosphatasia (HPP) [online]. In: EU Clinical Trials Register. 07.08.2016 [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007406-11/results.

Alexion Pharma. A multicenter, open-label study of the safety, tolerability and pharmacology of asfotase alfa in up to 10 severely affected patients with for the treatment of severely affected patients with infantile hypophosphatasia (HPP): clinical trial results [online]. In: EU Clinical Trials Register. 07.08.2016 [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007406-11/results.

Alexion Pharmaceuticals. Safety and efficacy study of asfotasealfa in severely affected infants with hypophosphatasia (HPP): study details [online]. In: ClinicalTrials.gov. 01.04.2019 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00744042.

Alexion Pharmaceuticals. Extension study of protocol ENB-002-08 - study of asfotase alfa in infants and young children with hypophosphatasia (HPP): study details [online]. In: ClinicalTrials.gov. 13.03.2019 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01205152.

Alexion Pharmaceuticals. Safety and efficacy study of asfotasealfa in severely affected infants with hypophosphatasia (HPP): study results [online]. In: ClinicalTrials.gov. 01.04.2019 [Accessed: 11.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00744042.

Alexion Pharmaceuticals. Extension study of protocol ENB-002-08: study of asfotase alfa in infants and young children with hypophosphatasia (HPP); study results [online]. In: ClinicalTrials.gov. 13.03.2019 [Accessed: 11.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01205152.

Alexion Pharmaceuticals. A multicenter, open-label study of the safety, tolerability, and pharmacology of ENB-0040 (enobia`s human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in up to 10 severely affected patients with infantile hypophosphatasia (HPP): study ENB-002-08/ENB-003-08; final clinical study report [unpublished]. 2017.

Enobia Canada Limited Partnership. A multicenter, open-label study of the safety, tolerability and pharmacology of ENB-0040 (enobia's human recombinant tissue non-specific alkaline phosphatase fusion protein) in up to 6 severely affected patients with infantile hypophosphatasia (HPP) [online]. In: EU Clinical Trials Register. [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007406-11.

Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a novel scoring system for changes in skeletal manifestations of hypophosphatasia in newborns, infants, and children: the radiographic global impression of change scale. J Bone Miner Res 2018; 33(5): 868-874.

Whyte MP, Greenberg CR, Salman NJ, Bober MB, McAlister WH, Wenkert D et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med 2012; 366(10): 904-913.

Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. J Clin Endocrinol Metab 2016; 101(1): 334-342.

Whyte MP, Simmons JH, Moseley S, Fujita KP, Bishop N, Salman NJ et al. Asfotase alfa for infants and young children with hypophosphatasia: 7 year outcomes of a single-arm, open-label, phase 2 extension trial. Lancet Diabetes Endocrinol 2019; 7(2): 93-105.

ENB-010-10

Alexion Europe. CTD section 2.7.3: summary of clinical efficacy; asfotase alfa in hypophosphatasia; study results [unpublished]. 2018.

Alexion Pharma. An open-label, multicenter, multinational study of the safety, efficacy and pharmacokinetics of asfotase alfa (human recombinant tissue nonspecific alkaline phosphatase fusion protein) in infants and children ≤5 years of age with hypophosphatasia (HPP) [online]. In: EU Clinical Trials Register. [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-019850-42.

Alexion Pharmaceuticals. Open-label study of asfotase alfa in infants and children ≤ 5 years of age with hypophosphatasia (HPP): study details [online]. In: ClinicalTrials.gov. 13.03.2019 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01176266.

Alexion Pharmaceuticals. An open-label, multicenter, multinational study of the safety, efficacy and pharmacokinetics of asfotase alfa (human recombinant tissue nonspecific alkaline phosphatase fusion protein) in infants and children ≤5 years of age with hypophosphatasia (HPP): clinical trial results [online]. In: EU Clinical Trials Register. 11.11.2017 [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019850-42/results.

Alexion Pharmaceuticals. Open-label study of asfotase alfa in infants and children ≤ 5 years of age with hypophosphatasia (HPP): study results [online]. In: ClinicalTrials.gov. 13.03.2019 [Accessed: 11.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01176266.

Alexion Pharmaceuticals. An open-label, multicenter, multinational study of the safety, efficacy, and pharmacokinetics of asfotase alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in infants and children ≤ 5 years of age with hypophosphatasia (HPP): study ENB-010-10; final clinical study report [unpublished]. 2017.

Hofmann CE, Harmatz P, Vockley J, Högler W, Nakayama H, Bishop N et al. Efficacy and safety of asfotase alfa in infants and young children with hypophosphatasia: a phase 2 open-label study. J Clin Endocrinol Metab 2019; 104(7): 2735-2747.

Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a novel scoring system for changes in skeletal manifestations of hypophosphatasia in newborns, infants, and children: the radiographic global impression of change scale. J Bone Miner Res 2018; 33(5): 868-874.

Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. J Clin Endocrinol Metab 2016; 101(1): 334-342.

ENB-011-10

Alexion Europe. CTD section 2.7.3: summary of clinical efficacy; asfotase alfa in hypophosphatasia; study results [unpublished]. 2018.

Alexion Pharmaceuticals. A retrospective study of the natural history of patients with severe perinatal and infantile hypophosphatasia (HPP): study details [online]. In: ClinicalTrials.gov. 01.04.2019 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01419028.

Alexion Pharmaceuticals. A retrospective study of the natural history of patients with severe perinatal and infantile hypophosphatasia (HPP): study results [online]. In: ClinicalTrials.gov. 01.04.2019 [Accessed: 11.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01419028.

Alexion Pharmaceuticals. A retrospective, non-interventional epidemiologic study of the natural histoty of patients with sever perinatal and infantile hypophosphatasia (HPP): study ENB-011-10; clinical study report [unpublished]. 2014.

Whyte MP, Leung E, Wilcox WR, Liese J, Argente J, Martos-Moreno GA et al. Natural history of perinatal and infantile hypophosphatasia: a retrospective study. J Pediatr 2019; 209: 116-124.e4.

Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. J Clin Endocrinol Metab 2016; 101(1): 334-342.

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. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J 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.

3. Alexion Pharmaceuticals. Expanded access program for asfotase alfa treatment for patients with infantile- or juvenile-onset hypophosphatasia (HPP): study details [online]. In: ClinicalTrials.gov. 29.03.2019 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT02496689.

4. Alexion Pharma International. An open-label, multicenter, expanded access program for asfotase alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) treatment for patients with infantile- or juvenile-onset hypophosphatasia (HPP) [online]. In: EU Clinical Trials Register. [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000809-39.

5. Alexion Pharmaceuticals. An open-label, multicenter, expanded access program for asfotase alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) treatment for patients with infantile - or juvenile-onset hypophosphatasia (HPP): clinical trial results [online]. In: EU Clinical Trials Register. 23.09.2018 [Accessed: 11.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000809-39/results.

6. HPP Study Group. A multicenter study of the safety and efficacy of asfotase alfa (ALXN1215) (human recombinant tissue nonspecific alkaline phosphatase fusion protein) in patients with hypophosphatasia (HPP) [online]. In: UMIN-CTR Clinical Trial. 02.09.2015 [Accessed: 11.11.2019]. URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017019.

7. Translational Research Center for Medical Innovation. Safety and efficacy of asfotase alfa in patients with hypophosphatasia (HPP) [online]. In: ClinicalTrials.gov. 31.03.2016 [Accessed: 11.11.2019]. URL: https://ClinicalTrials.gov/show/NCT02456038.

8. Kitaoka T, Tajima T, Nagasaki K, Kikuchi T, Yamamoto K, Michigami T et al. Safety and efficacy of treatment with asfotase alfa in patients with hypophosphatasia: results from a Japanese clinical trial. Clin Endocrinol (Oxf) 2017; 87(1): 10-19.

9. Leung ECW, Mhanni AA, Reed M, Whyte MP, Landy H, Greenberg CR. Outcome of perinatal hypophosphatasia in manitoba mennonites: a retrospective cohort analysis. JIMD reports 2013; 11: 73-78.

10. Saglam H, Erdöl S, Dorum S. Clinical and genetic findings of Turkish hypophosphatasia cases. J Clin Res Pediatr Endocrinol 2017; 9(3): 229-236.

11. Taketani T, Onigata K, Kobayashi H, Mushimoto Y, Fukuda S, Yamaguchi S. Clinical and genetic aspects of hypophosphatasia in Japanese patients. Arch Dis Child 2014; 99(3): 211-215.

12. Alexion Pharmaceuticals. Final clinical study report ENB-009-10. 2017.

13. ClinicalTrials.gov. Safety and efficacy study of asfotase alfa in adolescents and adults with hypophosphatasia (HPP) [online]. URL: https://clinicaltrials.gov/ct2/show/NCT01163149.

14. Gospe SM 3rd, Santiago-Turla C, DeArmey SM, Cummings TJ, Kishnani PS, Bhatti MT. Ectopic ocular surface calcification in patients with hypophosphatasia treated with asfotase alfa. Cornea 2019; 38(7): 896-900.

15. Kishnani PS, Rockman-Greenberg C, Rauch F, Bhatti MT, Moseley S, Denker AE et al. Five-year efficacy and safety of asfotase alfa therapy for adults and adolescents with hypophosphatasia. Bone 2019; 121: 149-162.

16. Phillips D, Griffin D, Przybylski T, Morrison E, Reeves AL, Vallee M et al. Development and validation of a modified performance-oriented mobility assessment tool for assessing mobility in children with hypophosphatasia. J Pediatr Rehabil Med 2018; 11(3): 187-192.

17. Phillips D, Tomazos IC, Moseley S, L'Italien G, Gomes da Silva H, Lerma Lara S. Reliability and validity of the 6-minute walk test in hypophosphatasia. JBMR Plus 2019; 3(6): e10131.

18. E. U. Clinical Trials Register. A randomized, open-label, multicenter, multinational, dose-ranging, concurrent control study of the safety, efficacy, and pharmacokinetics of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in adolescents and adults with hypophosphatasia (HPP) [online]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001831-38/3rd.

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

20. Alexion Pharmaceuticals. Final clinical study report ENB-006-09/ENB-008-10. 2017.

21. ClinicalTrials.gov. Extension study of protocol ENB-006-09: study of asfotase alfa in children with hypophosphatasia (HPP) [online]. URL: https://clinicaltrials.gov/ct2/show/NCT01203826.

22. ClinicalTrials.gov. Safety and efficacy of asfotase alfa in juvenile patients with hypophosphatasia (HPP) [online]. URL: https://clinicaltrials.gov/ct2/show/NCT00952484.

23. Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a novel scoring system for changes in skeletal manifestations of hypophosphatasia in newborns, infants, and children: the radiographic global impression of change scale. J Bone Miner Res 2018; 33(5): 868-874.

24. Whyte MP, Madson KL, Phillips D, Reeves AL, McAlister WH, Yakimoski A et al. Asfotase alfa therapy for children with hypophosphatasia. JCI Insight 2016; 1(9): e85971.

25. E. U. Clinical Trials Register. Extension study of protocol ENB-006-09 evaluating the long-term safety and efficacy of asfotase alfa (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in children with hypophosphatasia (HPP) [online]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003153-42/3rd.

26. E. U. Clinical Trials Register. A randomized, open-label, multicenter, multinational, dose-ranging, historical control study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of ENB-0040 (human recombinant tissue-nonspecific alkaline phosphatase fusion protein) in children with hypophosphatasia (HPP) [online]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-001128-52/3rd.

27. Alexion Pharmaceuticals. Clinical study report ALX-HPP-502. 2014.

28. Alexion Pharmaceuticals. Clinical study report ALX-HPP-502s. 2014.

29. ClinicalTrials.gov. Non-interventional substudy of ALX-HPP-502 to assess natural history of patients with juvenile-onset HPP who served as historical controls in ENB-006-09 [online]. URL: https://clinicaltrials.gov/ct2/show/NCT02235493.

30. ClinicalTrials.gov. Evaluate and monitor physical performance of adults treated with asfotase alfa for hypophosphatasia (EmPATHY) [online]. URL: https://clinicaltrials.gov/ct2/show/NCT03418389.

31. Niemitz S, von Hehn U, Seefried L. 12-months clinical study report EmPATHY. 2019.

32. Alexion Pharmaceuticals. ALX-HPP-501 first progress report. 2017.

33. Alexion Pharmaceuticals. ALX-HPP-501 second progress report. 2018.

34. Alexion Pharmaceuticals. ALX-HPP-501 data tables, data download date: 03-jun-2019. 2019.

35. ClinicalTrials.gov. An observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia (HPP) [online]. URL: https://clinicaltrials.gov/ct2/show/NCT02306720.

36. Müller D, Augustin M, Banik N, Baumann W, Bestehorn K, Kieschke J et al. Memorandum Register für die Versorgungsforschung. Gesundheitswesen 2010; 72(11): 824-839.

37. Gliklich RE, Dreyer NA, Leavy MB. Registries for evaluating patient outcomes: a user's guide; AHRQ publication no. 13(14)-EHC111; volume 1. Rockville: Agency for Healthcare Research and Quality; 2014. URL: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-guide-3rd-edition_research.pdf.

38. Jakob F, Hofmann C, Gierschick H, Seefried L. Diagnostik und Management der Hypophosphatasie. Bremen: UNI-MED Verlag AG; 2017.

39. Choida V, Bubbear JS. Update on the management of hypophosphatasia. Ther Adv Musculoskelet Dis 2019; 11: 1-8.

40. Kishnani PS, Rush ET, Arundel P, Bishop N, Dahir K, Fraser W et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa. Mol Genet Metab 2017; 122(1-2): 4-17.

41. 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.

42. Beck C, Morbach H, Stenzel M, Collmann H, Schneider P, Girschick HJ. Hypophosphatasia: recent advances in diagnosis and treatment. The open bone journal 2009; 1: 8-15.

43. Hofmann C, Girschick HJ, Mentrup B, Graser S, Seefried L, Liese J et al. Clinical aspects of hypophosphatasia: an update. Clin Rev Bone Miner Metab 2013; 11(2): 60-70.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-89-asfotase-alfa-hypophosphatasia-benefit-assessment-according-to-35a-social-code-book-v.12639.html.