Common Drug Review
Clinical Review Report

April 2017

Drug	asfotase alfa (Strensiq)
Indication	Enzyme replacement therapy in patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP)
Listing request	As per indication
Dosage Form	Solution for subcutaneous injection (40 mg/mL and 100 mg/mL single use vial)
NOC Date	NOCc (with conditions) issued August 2015
Manufacturer	Alexion Pharma Canada Corp.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in pediatrics who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

6MWT	six-minute walk test
AE	adverse event
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CGI-C	Clinical Global Impression of Change
CHAQ	Child Health Assessment Questionnaire
CI	confidence interval
DEXA	dual-energy X-ray absorptiometry scan
HDD	hand-held dynamometry
HPP	Hypophosphatasia
ITT	intention-to-treat (population)
LOCF	last observation carried forward
MCID	minimal clinically important difference
NR	not reported
NA	not applicable
PDMS-2	Peabody Developmental Motor Scales, Second Edition
PLP	pyridoxal-5'-phosphate
PP	per-protocol
PPi	inorganic pyrophosphate
RCT	randomized controlled trial
REF	reference value
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Scale
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
TNSALP	tissue-nonspecific alkaline phosphatase
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Hypophosphatasia (HPP) is a genetic disorder causing loss of function of tissue-nonspecific alkaline phosphatase (TNSALP) enzyme, which is necessary for bone mineralization. Clinically, the manifestation of this disease is variable; the severity of the presentation is largely determined by the age of the onset of symptoms: the earlier the onset, the more severe the condition.[1-3] In its most severe presentation, infants affected by the disease die in utero or shortly after birth, while patients who manifest HPP as infants (i.e., within six months after birth) would have severe presentation, with irreversible bone deformities, rachitic chest changes affecting respiratory functions, and exhibiting an overall one-year survival rate of around 50%.[1-5] In the mildest presentation, patients suffer from teeth loss with little or no other skeletal manifestation.[1-3,5] The incidence of the prenatal and infantile forms of HPP in Canada is estimated to be 1:100,000 live births.[6] The incidence is much higher within the Canadian Mennonite population; it has been reported to be one in every 2,500 births in Manitoba.[7,8]

Currently, except for asfotase alfa (Strensiq), there are no approved treatments for HPP. The main stream of therapy focuses on supportive care, including respiratory support, orthopedic surgery, physiotherapy, a low calcium diet, pain relief, and dental care. Asfotase alfa is a therapeutic protein that acts in place of the defective endogenous TNSALP enzyme.[9]

Results and Interpretation

Included Studies

Three manufacturer-sponsored phase II studies were included in this review: ENB-010-10, ENB-006-09, and its extension, ENB-008-10. All studies were single-arm trials, except one historical control study (ENB-006-09). All of the studies were open label. ENB-010-10 (N = 59) included only patients who manifested symptoms of HPP before the age of six months, thus classifying them as infantile HPP. Study ENB-006-09 (N = 13)/ENB-008-10 (N = 12) included patients between the ages of five and 12 years who had open growth plates. The main outcome in all studies was the Radiographic Global Impression of Change (RGI-C), a seven-point manufacturer-designed scale to measure the change in the severity of rickets using assessment of bone changes on X-rays. A reduction of three points (recorded as "–3") represents severe worsening, and an increase of three points (recorded as "+3") indicates complete healing of the skeletal disease. In addition to the included studies, three studies, and one arm of an included study, with doses of asfotase alfa different from the approved dose are summarized and reviewed in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE, as additional clinical evidence.

The included studies are associated with several limitations. The single-arm trials do not allow for comparison of any treatment effects against those attributable to current management approaches. More importantly, single-arm trials do not allow and cannot control for potential treatment-effect modifiers, and the precise magnitude of any observed treatment effect is highly uncertain. While historical controls ameliorate some of these limitations, historical control trials still suffer from potential biases related to differences in time, practice, and population, and therefore cannot overcome the limitations inherent in the absence of randomization. Other limitations include the fact that because all studies were open label, there is the potential for expectation bias and it is not possible to account for a placebo effect. Finally, clinical validity has not been demonstrated for the outcomes reported, and the minimal clinically important difference in the HPP population is unknown.

Efficacy

RGI-C measured at 24 weeks was the primary outcome in ENB-010-10 and ENB-006-09. In the single-arm trial, ENB-010-10, the median RGI-C score was measured against the value of 0 (indicating "no change" on the RGI-C scale). [redacted]. In the historical control study, ENB-006-09, in patients treated with asfotase alfa, there was a statistically significant ([redacted]) improvement in RGI-C score compared with the historical control group, with the treatment arm that received the approved dose of 2 mg/kg of body weight three times per week [redacted]. The improvement in the primary outcome of ENB-006-09 was observed throughout the extension study, ENB-008-10. The last available assessment of ENB-008-10, conducted after week 240, showed a nominal statistically significant outcome [redacted]. Evidence from the included studies, as well as additional clinical evidence, suggests that patients with infantile HPP treated with asfotase alfa had a much lower mortality rate than what is observed in the natural history of the disease. Although the lack of adjustment for multiple outcomes and testing makes any *P* value in the secondary outcomes nominal, data suggest that improvement is observed in the Rickets Severity Scale (RSS) in the included and the additional clinical evidence studies, in the dual-energy X-ray absorptiometry scan results in ENB-008-10, and in some growth parameters throughout different studies, although the true statistical significance of these outcomes is highly uncertain.

Respiratory support was a secondary outcome in ENB-010-10, [redacted]. The Childhood Health Assessment Questionnaire in ENB-008-10 showed a median change in the disability index at 24 weeks [redacted]. The six-minute walk test was a secondary outcome in ENB-008-10; patients at baseline (of ENB-006-09) were able to walk a median of 60.98% of the predicted distance, at 24 weeks [redacted].

Harms

Adverse events related to asfotase alfa were related primarily to the subcutaneous route of administrating the drug. Across all studies, injection- and infusion-related adverse events (e.g., injection site redness, tenderness, and pain) were the most common. Serious adverse events (SAEs) were noted in ENB-010-10, [redacted]. According to the clinical experts consulted by the CADTH Common Drug Review, these SAEs can be expected as part of the complications of HPP, and not necessarily from the medication. No SAEs related to asfotase alfa were observed in ENB-006-09/ENB-008-10. In addition, six patients died due to HPP complications in ENB-010-10.

Conclusions

The clinical evidence available from three open-label studies of asfotase alfa suggest that 2 mg/kg administered three times per week is associated with an improvement in skeletal development, as reflected by increase in RGI-C scores. Because the included studies were uncontrolled, there is substantial uncertainty as to the magnitude of improvement attributed to asfotase alfa. The main harms associated with asfotase alfa treatment appear to be injection-site and infusion reactions, although safety data are limited.

TABLE 1: SUMMARY OF RESULTS

Outcome	ENB-010-10	ENB-006-09/ENB-008-10	
	2 mg/kg asfotase alfa	Historical control	2 mg/kg asfotase alfa
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
RGI-C at 24 weeks			
N (%)	[redacted]	16 (100%)	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
***P* value**	[redacted]	[redacted]	[redacted]
Harms, n (%)			
Deaths	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 drug-related SAE	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 drug-related AE	[redacted]		[redacted]
WDAE	[redacted]		[redacted]

AE = adverse event; NA = not applicable; NR = not reported; RGI-C = Radiographic Global Impression of Change; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse events.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hypophosphatasia (HPP) is a genetic disorder in which mutations to the genes encoding for tissue-nonspecific alkaline phosphatase (TNSALP) enzyme cause varying degrees of functional loss. There are more than 280 identified mutations that affect the function of the enzyme, and the mode of inheritance can be either autosomal recessive or autosomal dominant.[5,10] The TNSALP enzyme is essential to incorporate phosphate to the bone structure; without such activity, bone mineralization would be severely impaired.

Clinically, the manifestation of this disease is variable; the severity of the presentation is largely determined by the age of the onset of symptoms: the earlier the onset, the more severe the condition.[1-3] In its most severe presentation, infants affected by the disease die in utero or shortly after birth.[1-3,5] In its mildest presentation, patients suffer from teeth loss with little or no other skeletal manifestation.[1-3,5]

Based on the age of the first presentation, HPP can be classified into five categories: prenatal, infantile, childhood, adult, and odonto- (odonto-HPP). Perinatal HPP is usually diagnosed through ultrasound during pregnancy, and is characterized by little or absent bone structure on the ultrasound.[1,2,5,10] This form is usually lethal and leads to a still birth; however, there is a form of this category called "benign prenatal" in which, although a diagnosis is made in utero, spontaneous improvement is observed with an outcome ranging in severity, from infantile to odonto-HPP.[1 4]

Infantile HPP manifests before six months of age; although infants might appear healthy in the beginning, they soon develop poor feeding, failure to thrive, hypotonia, wide fontanelles, and rachitic chest deformities. Infantile HPP can lead to hypercalcemia, hypercalciuria, nephrocalcinosis, functional craniosynostosis, and pulmonary insufficiency. Infantile HPP has a poor survival rate, with a one-year survival rate of approximately 50%.[2,11] Patients who survive can be left with muscle weakness, persistent rickets, loss of primary dentition, susceptibility to non-traumatic fractures, and craniosynostosis,[1-3,5] although spontaneous improvement has been observed in some of these patients.[12]

Childhood HPP manifests after six months of age, with rickets as the main feature.[1-3] Muscle pain and weakness are common findings, along with poorly healing or recurrent fractures, short stature, skeletal deformities, and premature tooth loss.[1-3] Adult HPP can manifest at any point in the adult life, with osteomalacia as a main feature. Adult HPP can cause fractures, pseudofractures, pseudogout, chronic muscle and bone pain, and teeth loss.[1-3,5] The least severe form of HPP, odonto-HPP, has only dental manifestation with a near or total absence of any skeletal-related symptoms and signs; odonto-HPP can occur at any age.[1-3,5]

The incidence of the perinatal and infantile forms of HPP in Canada is thought to be about 1:100,000 live births.[6] The incidence is much higher within the Canadian Mennonites population, which has been reported to be one in every 2,500 births in Manitoba.[7,8]

Prevalence of milder forms of the disease in Canada has not been reported. However, one study reported a molecular-based estimation of moderate and mild forms of HPP in the European population to be one in every 6,370 people, suggesting the presence of some unrecognized cases.[3]

1.2 Standards of Therapy

Currently, asfotase alfa is the only approved treatment for HPP. The main stream of therapy focuses on supportive care, including respiratory support, orthopedic surgery, physiotherapy, a low calcium diet, pain relief, and dental care. There have been some published articles and case studies on using bisphosphonates,[13] bone marrow transplantation,[13] parathyroid hormone,[14] intravenous infusions of plasma enriched in soluble alkaline phosphatase from patients with Paget disease,[15] and alkaline phosphatase purified from human placentas.[13] However, little or no success has been reported.[13,15]

1.3 Drug

Asfotase alfa is a therapeutic protein intended to act in place of the defective endogenous TNSALP enzyme.[9] It received a Notice of Compliance with Conditions (NOCc) from Health Canada on August 14, 2015, indicated as enzyme replacement therapy for patients with confirmed pediatric-onset HPP.[16]

Asfotase alfa is to be given subcutaneously (SC) as either 2 mg/kg three times per week, or 1 mg/kg six times per week.[16]

Indication under review
As enzyme replacement therapy for patients with confirmed diagnosis of pediatric-onset hypophosphatasia
Listing criteria requested by sponsor
Enzyme replacement therapy for patients with confirmed diagnosis of pediatric-onset hypophosphatasia

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of asfotase alfa at a dose of 2 mg/kg three times per week SC, or 1 mg/kg six times per week SC, for the treatment of pediatric-onset HPP in pediatric and adult populations.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult and pediatric patients with a diagnosis of pediatric-onset hypophosphatasia
Intervention	Asfotase alfa at a dose of 2 mg/kg 3 times per week SC, or 1 mg/kg 6 times per week SC
Comparators	Best available care, no treatment, or placebo
Outcomes	**Key efficacy outcomes:** *Skeletal-related outcomes:* a) Bone density b) Osteomalacia severity c) Rickets severity d) Pathologic bone fractures *Survival related outcomes:* a) Overall survival *Respiratory related outcomes:* a) Pulmonary function status b) Use of respiratory assist devices *Growth- and development-related outcomes (pediatric population):* a) Height b) Weight c) Head circumference d) Gross motor development e) Fine motor development *Functionality and QoL-related outcomes:* a) QoL score[a] b) Pain score[a] c) Mobility[a] d) Strength[a] **Other efficacy outcomes:** *Enzyme activity–related outcomes:* a) Level of PLP b) Level of PPi **Harms outcomes:** AEs, SAEs, WDAEs, mortality, levels of anti-asfotase alfa antibodies, hypersensitivity reactions, and injection site–associated AEs.
Study Design	Published and unpublished RCTs

AE = adverse event; DB = double-blind; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneously; WDAE = withdrawal due to adverse events.
[a] These outcomes were identified from the patient input.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Strensiq (asfotase alfa) and hypophosphatasia.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results

The initial search was completed on July 29, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

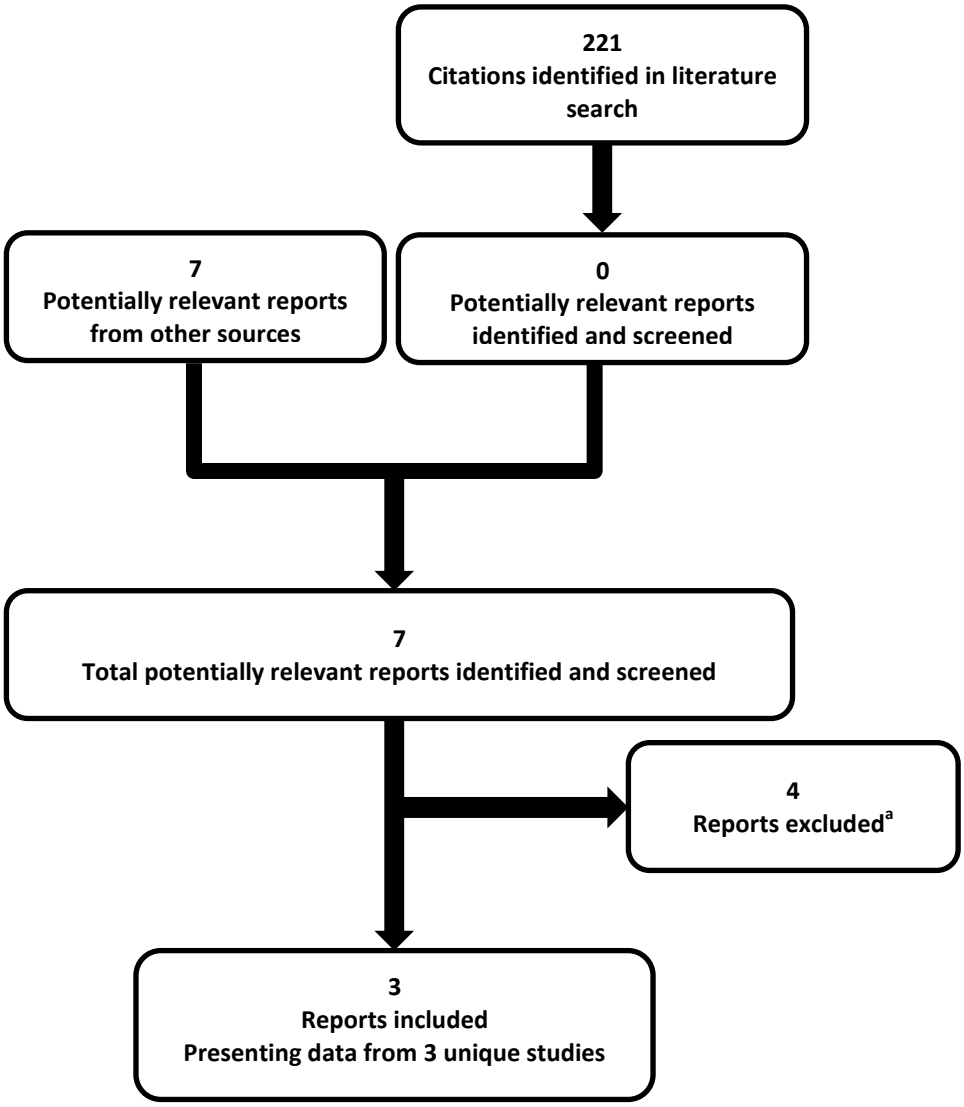
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 221 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



[a] 4 reports presenting data from 3 unique studies are reviewed in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE.

TABLE 3: DETAILS OF INCLUDED STUDIES

		ENB-010-10	ENB-006-09	ENB-008-10
DESIGNS & POPULATIONS	**Study Design**	Phase II, open-label, uncontrolled single-arm trial	Phase II, open-label, randomized, dose ranging, historical control	Extension study of ENB-006-09, single-arm, historical control
	Locations	Canada, US, Taiwan, Germany, Turkey, Japan, UK, France, Italy, Spain	Canada, US	Canada, US
	Enrolled (N)	59	13	12
	Inclusion Criteria	Diagnosis of HPP	History of HPP	The patient completed study ENB-006-09
		Onset of symptoms prior to 6 months of age	Patients aged ≥ 5 and ≤ 12 years with open growth plates	
		Age ≤ 5 years	Tanner stage of 2 or less, indicating prepubescence	
		Medically stable	Serum 25-hydroxy vitamin D level ≥ 20 ng/mL	
	Criteria for Diagnosis of HPP	Total serum ALP below the lower limit of normal for age	Presence of HPP-related rickets on skeletal X-rays	Same as ENB-006-09
		Plasma PLP above the upper limit of normal	Serum ALP activity below the age-adjusted normal range	
		Radiographic evidence of HPP, characterized by flared and frayed metaphyses, severe generalized osteopenia, widened growth plates, and areas of radiolucency or sclerosis	Plasma PLP level at least twice the upper limit of normal	
		Two or more of HPP-related findings of history or presence of non-traumatic postnatal fracture or delayed fracture healing, nephrocalcinosis or history of elevated serum calcium, functional craniosynostosis, respiratory compromise or rachitic chest deformity, vitamin B6–responsive seizures, and/or failure to thrive		
	Exclusion Criteria	Clinically significant condition or major disease	Clinically significant condition or major disease	Same as ENB-006-09
		Low serum calcium, phosphate, [redacted]	Low serum calcium, phosphate, [redacted]	
		Evidence of a treatable form of rickets	Evidence of a treatable form of rickets	
		Prior treatment with bisphosphonate	Prior treatment with bisphosphonate	
DRUGS	**Intervention**	A total of 6 mg/kg/week of asfotase alfa, SC, as either 2 mg/kg 3 times per week, or 1	2 mg/kg 3 times per week, asfotase alfa, SC (6 mg/kg/week)	All patients received asfotase alfa SC at an initial dose of 9

		ENB-010-10	ENB-006-09	ENB-008-10
		mg/ kg 6 times per week	3 mg/kg three times per week, asfotase alfa, SC, (9 mg/kg/week)	mg/kg/week. This was later adjusted through a protocol amendment to a total of 6 mg/kg/week
	Comparator(s)	NA	Historical control	NA
DURATION	**Phase**			
	Run-in	–4 to 0 weeks	–3 to 0 weeks	NA
	Efficacy phase	24 weeks	24 weeks	NA
	Safety phase	42 months (month 6 to month 48)	Extension study ENB-008-10 (42 months [month 6 to month 48])	42 months (ongoing)
OUTCOMES	**Primary End Point**	Change in rickets severity on skeletal radiographs as measured by the RGI-C scale from baseline to week 24 and from baseline to week 48	Change in rickets severity on skeletal radiographs as measured by the RGI-C scale from baseline to week 24 and from baseline to week 48	NA
	Other End Points	RSS	RSS	RGI-C scale
		Respiratory support	SAE	RSS
		Survival analysis	AE	Height and weight z scores
		Height and weight z scores	Injection site–associated AEs	DEXA results
		Head circumference	Death	6MWT
		SAE	Hypersensitivity reactions	BOT-2
		AE	Development of anti-asfotase alfa antibodies	HHD
		Injection site–associated AEs		CHAQ
		Death		SAE
		Development of anti-asfotase alfa antibodies		AE
				Injection site–associated AEs
				Death
				Hypersensitivity reactions
				Development of anti-asfotase alfa antibodies
NOTES	**Publications**	None	None	None

6MWT = six-minute walk test; AE = adverse event; ALP = alkaline phosphatase; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ = Child Health Assessment Questionnaire; DEXA = dual-energy X-ray absorptiometry scan; HHD = hand-held dynamometry; HPP = hypophosphatasia; NA = not applicable; NR = not reported; PLP = pyridoxal-5'-phosphate; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Scale; SC = subcutaneous; SD = standard deviation; WDAE = withdrawal due to adverse events.
Source: Clinical Study Reports.[17,18]

3.2 Included Studies

3.2.1 Description of Studies

No randomized controlled studies were identified in our systematic search. The manufacturer provided CADTH with 29 reports representing 10 unique studies. Of these 10 studies, four were natural history studies and a pooled survival analysis, and six were clinical trials; of the clinical trials, Health Canada considered three to be pivotal, namely ENB-010-10 and ENB-006-09 and its extension, ENB-008-10.[19] The four non-pivotal clinical trials are presented in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE, and the natural history studies are summarized in APPENDIX 7: NATURAL HISTORY OF Hypophosphatasia.

The included studies varied considerably in design: ENB-010-10 (N = 59) was a phase II, open-label, single-arm trial; study ENB-006-09 (N = 13) was a phase II, open-label, randomized, and dose ranging trial, with a historical control; although study ENB-008-10 (N = 12) is the extension study of ENB-006-09, it carried the design of a single-arm trial, with no historical control.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All three studies shared two common inclusion criteria: patients needed to have an established diagnosis of HPP, and be medically stable. They also shared most of the exclusion criteria, including the exclusion of patients with prior bisphosphonates treatment. Beyond that, however, the inclusion and exclusion criteria differ.

The diagnosis of HPP was based on an extensive list of clinical and radiographic criteria. Subsequent to enrolment, a genetic test was conducted to confirm the diagnosis. [redacted]. In ENB-010-10, [redacted].

Study ENB-010-10 included only patients with infantile HPP, and eligible age was five years or younger. Study ENB-006-09, along with its extension ENB-008-10, included patients aged between five and 12 years, with no specific requirement on the time of diagnosis of HPP.

b) Baseline Characteristics

Key baseline characteristics of the study population are displayed in Table 4. It is worth noting that the population of ENB-010-10 had the worst score on the Rickets Severity Scale (RSS).

The historical control used as the trial control in ENB-006-09 either lacked key baseline characteristics values or had a different baseline characteristic from the treatment arm. Notably, the historical control had a younger population, which was diagnosed with HPP earlier, had a different male-to-female ratio, had a better RSS, and higher levels of pyridoxal-5'-phosphate (PLP).

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Study Name	ENB-010-10	ENB-006-09/ ENB-008-10	
Arm	[redacted]	[redacted]	[redacted]
Age, mean (SD)	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]
Caucasian, n (%)	[redacted]	[redacted]	[redacted]
Age (months) at HPP onset, mean (SD)	[redacted]	[redacted]	[redacted]
RSS, mean (SD)	[redacted]	[redacted]	[redacted]
PPi (µM), mean (SD)	[redacted]	[redacted]	[redacted]
PLP (ng/mL), mean (SD)	[redacted]	[redacted]	[redacted]
Respiratory support			
No support, n (%)	[redacted]	[redacted]	[redacted]
Non-invasive support, n (%)	[redacted]	[redacted]	[redacted]
Invasive support, n (%)	[redacted]	[redacted]	[redacted]
Z scores			
Length/height, mean (SD)	[redacted]	[redacted]	[redacted]
Weight, mean (SD)	[redacted]	[redacted]	[redacted]

HPP = hypophosphatasia; µM = micromolar; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; SD = standard deviation.
Source: Clinical Study Reports.[17,18]

3.2.3 Interventions

Patients in study ENB-010-10 had either a dose of 2 mg/kg three times per week, or 1 mg/kg six times per week, both equalling 6 mg/kg/week. In both studies, patients were taking various concurrent medications to address symptoms and complications of HPP, as per the clinical judgment of the treating physician. Study ENB-006-09 randomized patients into one of two doses of asfotase alfa: one arm had a dose of 2 mg/kg three times per week (6 mg/kg/week), and another a dose of 3 mg/kg three times per week (9 mg/kg/week). The results of the 3 mg/kg dose will be discussed in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE, because this dose is higher than the approved dose of 2 mg/kg three times per week. The study compared treatment to a historical control that was not treated with asfotase alfa. Study ENB-008-10 initially administered a total of 3 mg/kg/week to all patients, but this was later changed to a total dose of 6 mg/kg/week for all patients through a protocol amendment. Similarly to ENB-010-10, patients in ENB-006-09/ENB-008-10 were taking various concurrent medications to address the symptoms and complications of HPP, as per the clinical judgment of the treating physician.

3.2.4 Outcomes

a) Radiographic Global Impression of Change

Radiographic Global Impression of Change (RGI-C) was the primary outcome in three of the four trials, excluding the extension studies. The RGI-C scale was designed by the manufacturer to measure the change in the severity of rickets. Rickets refers to the softening and weakening of bones in children.[20] RGI-C is a seven-point change scale that provides an assessment of the change in bone structure associated with the pathophysiology of HPP.[13] A reduction of three points (recorded as "–3") represented severe worsening, and an increase of three points (recorded as "+3) indicated complete healing of the skeletal disease. X-ray radiographs were taken prior to the initiation of treatment, and subsequent radiographs were taken at specific time points. These X-rays were assessed by three independent pediatric radiologists who were aware of which is the baseline X-ray photograph but blinded to the rest of the data, including at which time point the follow-up radiograph was taken. These assessors were trained in using the computer systems and electronic records according to the Good Clinical Practice (GCP) guidelines and in compliance with Title 21 Code of Federal Regulations (CFR) Part 11.[21] The average of the assessment of the three radiologists was then applied as the final RGI-C score.

There are no known studies assessing the validity and/or the minimal clinically important difference (MCID) of RGI-C in HPP patients.

b) Rickets Severity Scale

The Rickets Severity Scale (RSS)[13] was constructed to measure the rickets severity of patients with nutritional rickets. This involves assessment of the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected.[22] RSS is a 10-point scale (four points for the wrists and six points for the knees), in which higher scores indicate more severe rickets.[22] A score of 10 represents severe rickets, while a score of 0 indicates an absence of metaphyseal cupping and fraying.[22] RSS was a secondary outcome in all the studies, except ENB-009-10. An X-ray of knees and wrists was taken prior to treatment and at specific time points. A single assessor scored the radiographs. The assessor was blinded to the patient's identity and the time point at which the radiographs were taken.

There are no known studies assessing the validity and/or the MCID of RSS in HPP patients.

c) Respiratory Support

Early HPP can lead to rachitic chest, which causes deterioration of respiratory function. The need for and the type of respiratory support needed was assessed in ENB-010-10.

d) Z Score for Height, Weight, and Head Circumference

Z score is used to analyze the length and height, weight, and head circumference in clinical research for patients with abnormal growth and development such as HPP.[23] Z scores were based on Centers for Disease Control (CDC) growth charts and methodology.[24] In the CDC growth charts, the z score corresponds exactly to growth percentiles; e.g., z scores of –1.881, –1.645, –1.282, –0.674, 0, 0.674, 1.036, 1.282, 1.645, and 1.881 correspond to the third, fifth, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles, respectively. Z scores were secondary outcomes for ENB-008-10 and ENB-010-10.

e) Dual-Energy X-Ray Absorptiometry

The dual-energy X-ray absorptiometry (DEXA) test measures bone mineral content and density, and was used to compare an established norm or standard.[25] Although no bone density test is 100% accurate,

DEXA can measure the overall mineral content of the bones in grams. DEXA measures were used as a secondary outcome in ENB-008-10.

f) Six-Minute Walk Test

The six-minute walk test (6MWT) is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[26] 6MWT was used as a secondary outcome in ENB-008-10 and ENB-009-10.

CDR reviewers searched for validation studies of 6MWT in HPP. No evidence of validation and MCID was identified.

g) Bruininks-Oseretsky Test of Motor Proficiency, Second Edition

The Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) is an instrument that measures gross motor skills utilizing a composite score from two subtests: running speed and agility, and strength.[18,27] BOT-2 was used as a secondary outcome in ENB-008-10.

CDR reviewers searched for validation studies of BOT-2 in HPP. No evidence of validation and MCID was identified.

h) Hand-Held Dynamometry

Hand-held dynamometry (HHD) assessments were developed to assess muscle strength at various body points. Strength was reported in pounds and bilateral per cent predicted values based upon published normative data were provided (where available).[17,28] HDD was used as a secondary outcome in ENB-008-10.

i) Childhood Health Assessment Questionnaire

The Childhood Health Assessment Questionnaire (CHAQ) is a self-reported functional status (disability) measure.[29,30] CHAQ was used as a secondary measure in ENB-008-10. The CHAQ is a 30-item, self- or parent-administered instrument for measuring functional status in children. It has several new questions relevant to children of all ages, compared with the Health Assessment Questionnaire (HAQ). The eight functional areas measured by CHAQ are dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.[31]

The CADTH reviewers searched for validation studies of CHAQ in HPP. No evidence of validation and MCID was identified.

j) Drug-Related Adverse Events and Serious Adverse Events

For the purpose of this review, adverse events (AEs) and serious adverse events (SAEs) reported by the investigator were included as possibly related to the administration of asfotase alfa.

k) Hypersensitivity Reactions

This refers to AEs related to immune response to the administration of asfotase alfa.

l) Development of Anti-Asfotase Alfa Antibodies

As a complex protein structure, asfotase alfa has the potential to act as an antigen, with antibodies produced against it that could influence its efficacy or cause severe hypersensitivity reactions.

3.2.5 Statistical Analysis

ENB-010-10 was a single-arm trial without a control. The median of the primary outcome, RGI-C, at 24 weeks was calculated against the value of 0 (0 on the RGI-C indicates "no change") using a Wilcoxon signed-rank with statistical significance set for a *P* value less than 0.05. The median of secondary outcomes was calculated against the value at baseline using a Wilcoxon signed-rank test and were presented as the median change from baseline; no method for adjustment for multiple outcomes was planned.

In ENB-006-09/ENB-008-10, the pooled median, from both study arms (2 mg/kg and 3 mg/kg), of the primary outcome, RGI-C, at 24 weeks was compared against the median for the historical control using a Wilcoxon rank sum test with a two-sided alpha of 0.05. If the *P* value was less than 0.05 and the Hodges–Lehman–Sen estimate favoured asfotase alfa, superiority over the historical values was claimed. The same analysis was conducted for each arm separately. However, no adjustment for multiple outcomes was carried out. Similarly, all secondary outcomes do not have a method of adjusting for multiplicity. Power calculation was based on a five-point Clinical Global Impression of Change (CGI-C) instead of the seven-points RGI-C; it was decided that 20 historical control and 12 treated patients would be necessary to provide an 88% power to compare, with statistical significance, the distribution of the five-point CGI-C between the treated and historical control groups.

In all studies, for primary efficacy analysis, imputation of missing data was allowed in the efficacy calculation of the full-analysis (FA) population. The mean of the available scores was used for patients with one or two reader scores . Any patients who were completely missing their week 24 data had the last observation carried forward (LOCF). Patients with no recorded post-baseline values were assigned as having no change (score of 0).

a) Analysis Populations

All included studies had three analysis sets:

a) FA set: An intention-to-treat population that included all randomized patients who received any treatment, or, in the case of single-arm trials, all populations that received any asfotase alfa, regardless of whether they were lost to follow-up or dropped out of the trial; imputations can be applied to efficacy analyses through LOCF
b) Per-protocol (PP) set: Includes all patients in the FA set who did not have any major protocol deviations
c) Safety set: Identical to the FA set, without the ability to apply imputations for safety analyses.

3.3 Patient Disposition

Table 5 summarizes the disposition of enrolled patients. ENB-010-10 had a dropout rate of 10.2%. No dropouts were observed in the 2 mg/kg arm of ENB-006-09. Similarly, no dropouts were observed in the extension phase, ENB-008-10.

TABLE 5: PATIENT DISPOSITION

	ENB-010-10	ENB-006-09/ENB-008-10		
	2 mg/kg asfotase alfa	**2 mg/kg asfotase alfa**	**3 mg/kg asfotase alfa**	**Historical control**
Screened, N	[redacted]	13		16
Randomized, N	NA	6	7	NA
Treated, N (%)	59	6 (100%)	7 (100%)	NA
Discontinued, N (%)	[redacted]	0 (0.0%)	1 (14.3%)	NR
Full-analysis, N	59	6	7	16
Per-protocol, N	[redacted]	[redacted]	[redacted]	NR
Safety, N	59	6	7	NR
Continued to extension	NA	12		NA

NA = not applicable; NR = not reported.
Source: Clinical Study Reports.[17,18]

3.4 Exposure to Study Treatments

Asfotase alfa was the only intervention across studies. [redacted].

Patients were allowed to take the medications for symptomatic relief and supportive therapy that are usually given to HPP patients. No specific medication was prohibited, except those mentioned in the exclusion criteria, and in cases where it was decided by the investigator that the medication interferes directly with asfotase alfa. Patients were exposed to asfotase alfa [redacted] in ENB-010-10, and at the time of writing this report, the study was still ongoing. In ENB-006-09/ENB-008-10, patients had a mean days of exposure [redacted], similarly, ENB-008-10 was still ongoing.

3.5 Critical Appraisal

3.5.1 Internal Validity

The following concepts have been observed as affecting the internal validity of the studies:

a) Changes in Study Protocol and Conduct

Several changes have been applied throughout the conduct of all included studies. Most of these changes were aimed at improving communication, diagnostics, data gathering, or extending the trials. However, ENB-010-10 and ENB-008-10 had changes that were directly related to the studies' outcomes:

- Amendment 4 in ENB-008-10 eliminated some secondary outcomes, changed some exploratory outcomes to secondary outcomes, and changed the dose from 3 mg/kg/week to 6 mg/kg/week for all patients. The dose change was conducted [redacted], in reflection of the results of the interim analysis of ENB-006-09.
- In ENB-010-10, major changes included adding RSS as a secondary outcome, and increasing the number of enrolled patients from 30 to 60.

These changes give the impression that the conduct of these studies was mainly data driven, and attempting to find a significant efficacy outcome rather than testing a pre-established hypothesis.

b) Choice of Control

ENB-010-10 is a single-arm trial with no control group. As such, we cannot determine whether the effect of the intervention is solely caused by the intervention and cannot control for treatment confounders that may influence the outcome. Some of these factors would include natural spontaneous improvement in the course of the disease; placebo effect (mainly in non-physiologic outcomes); effects of symptomatic treatments and supportive therapies; effect of baseline characteristics such as disease severity, gender, race, age, and any other unknown characteristics.

Study ENB-006-09 employed a historical control for the primary outcome analysis. The lack of randomization in the control arm and the fact that the historical control is drawn from a population that is different from the treatment arms minimizes the ability of the historical control to control for biases and confounders. This is reflected when comparing the baseline characteristics between the two populations; the historical control had a younger population, which was diagnosed with HPP earlier, had a different male-to-female ratio, had a better RSS, and higher levels of PLP. It is not clear whether these differences would play in favour of, or against, the intervention. Other inherent problems in utilizing historical control are the uncertainty in the quality of historical data that are collected retrospectively as opposed to the prospective collection in the intervention arms, and the effect of changes in practice between the historical control and the intervention arms.

c) Blinding

None of the studies included were blinded. As such, we cannot account for a placebo effect in non-physiologic measures, and the results of the primary outcome (RGI-C) are prone to expectation bias; both instances will affect the outcome in favour of the intervention.

d) Power Analysis and Sample Size

None of the studies had a methodologically sound power analysis to determine sample size in advance of study initiation. Power analysis in ENB-006-09/ENB-008-10 was based on the five-point CGI-C, which later was changed to the seven-point RGI-C. On the other hand, ENB-010-10 did not include a prior power analysis or a predetermined sample size. This further emphasizes the data-driven approach nature of the studies, as opposed to testing a pre-established efficacy hypothesis.

e) Adjusting for Multiple Comparisons and Interim Analysis

A large number of outcomes were included in these studies; yet, no measure to adjust for multiple testing and comparisons was employed. In addition, at the time of writing of this report, two of the included studies were still ongoing and were provided to us as an interim analysis (ENB-008-10 and ENB-010-10); a measure to adjust for interim analysis is also necessary. These two issues — lack of adjustment for multiple comparisons and interim analysis — allow for a greater probability of finding significance due to chance, since repeating statistical tests inflates the type I error, alpha, where a *P* value of 0.05 might no longer indicate statistical significance. Due to the large number of secondary outcomes, the interim analysis nature in many of them, and the numerous time points in which the same analysis took place repeatedly, all *P* values from secondary outcome are considered nominal and not very informative.

3.5.2 External Validity

The concepts listed below have been observed as affecting the internal validity of the studies.

a) Choice of Primary Outcome Measure

RGI-C is a manufacturer-developed outcome that depends on the assessment of three independent pediatric radiologists to score the healing or worsening of the skeleton through X-ray radiography. These assessors were trained in using the computer systems and electronic records according to the GCP guidelines and in compliance with Title 21 CFR Part 11. The average of the assessment of the three radiologists was then applied as the final RGI-C score. They also received an independent review manual, which described the procedures and outlined the equipment and materials used for the review. X-rays of the chest, bilateral wrists, and bilateral knees were taken pre-baseline and post-baseline on several time points. The assessors were asked to assess the changes in the severity of HPP-associated rickets in these radiographs, and the average score of the three was taken as the final score. However, the assessors were not blinded as to the treatment intervention and the condition being investigated, and they were aware of which X-ray was taken prior to the intervention.

Our clinical experts have expressed that findings of skeletal healing on X-ray radiography is the main measure in following up on patients and assessing their progression in practice. It is thus likely that the measure can be reflective of actual practice. However, a study assessing the validity and/or an MCID of RGI-C could not be found.

However, the fact that no blinding was attempted for the intervention or condition being investigated could bias the assessors, as they would look for signs that confirm their expectation of the intervention and the disease. Because asfotase alfa showed promising initial results, and HPP is a potentially fatal disease with no approved treatment at the time the study was conducted, it is most likely that expectation bias would play in favour of asfotase alfa.

b) Population

Despite HPP being a rare disease, the manufacturer was able to recruit patients who, according to the clinical experts consulted by CDR, would represent the HPP population. However, genetic testing in study ENB-010-10 participants showed that [redacted] had a confirmed mutation consistent with HPP diagnosis. It is not clear if the rest [redacted] of the participants were misdiagnosed, and what effect might this have had on the outcome.

Across studies, the manufacturer has attempted to provide evidence for different phenotypes of HPP. ENB-010-10 included patients aged five years or younger, including patients with severe presentation who are younger than six months, who historically have a one-year survival rate of around 50%. However, the study also includes patients who survived past the first year, who traditionally have a better prognosis. ENB-006-09/ENB-008-10 targeted patients between the ages of five and 12 years who would have fairly stable disease.

c) Diagnosis of Hypophosphatasia

The clinical experts consulted by CDR believe that the clinical criteria in these studies are sufficient to make the correct diagnosis of HPP.

d) Follow-up

Extension phases of up to five years were available in all studies, providing an assessment of the tolerability of asfotase alfa, despite limitations associated with the small sample size.

e) Validity and Minimal Clinically Important Difference

Although the manufacturer has attempted to capture a range of outcomes, many of which are patient-reported outcomes regarding functionality and health-related quality of life, validity and MCID in the HPP population is not available for any of these outcomes. This limits CDR's ability to measure the extent and magnitude of how patients will respond outside the studies.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2). See APPENDIX 5: DETAILED OUTCOME DATA APPENDIX 5: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Skeletal-Related Outcomes

a) Radiographic Global Impression of Change

RGI-C measured at 24 weeks was the primary outcome in ENB-006-09 and ENB-010-10. In ENB-010-10, the median RGI-C score was measured against the value of 0 (indicating "no change" on the RGI-C scale). RGI-C showed a statistically significant outcome [redacted]. In the historical control study ENB-006-09, the 2 mg/kg three times per week dose arm showed a statistically significant comparison to historical control [redacted].

A similar consistency of RGI-C outcome can be noted in ENB-010-10, the last available latest post-baseline assessment of patients in this ongoing trial [redacted]. Although study ENB-008-10 is the extension of ENB-006-09, it no longer contained an RGI-C score for the historical control, and patients were all initially given 3 mg/kg/week and, after [redacted], were changed to 6 mg/kg/week as per the approved dose, and the RGI-C measure was compared with the value of 0 (indicating "no change"). The last available assessment of ENB-008-10, conducted after week 240, showed an outcome with a [redacted] (Table 6).

b) Rickets Severity Scale

RSS was a secondary outcome in all included studies. At week 24, the median change from baseline in RSS was at [redacted] in ENB-010-10; 0 [redacted] in the historical arm of ENB-006-09, and [redacted] in the 2 mg/kg arm of ENB-006-09.

Improvements in the RSS continued to be observed in the last assessment in the extension phase of each of the studies. The median change from the baseline in ENB-010-10 was a median of [redacted], and in ENB-008-10 a median of [redacted].

c) Dual-Energy X-Ray Absorptiometry

DEXA scan was a secondary outcome in ENB-008-10. Patients had a change from the baseline (of ENB-006-09) in ENB-008-10 at 24 weeks, gaining in whole body bone mineral content a median of [redacted] and continuing to show improvement; assessment after week 264 showed gain from baseline of a median of [redacted].

3.6.2 Respiratory Support

Respiratory support was a secondary outcome in ENB-010-10. [redacted]

[redacted].

3.6.3 Growth and Development

a) Z Score for Height and Weight

Growth z scores were secondary outcomes in ENB-008-10 and ENB-010-10. [redacted].

b) Bruininks-Oseretsky Test of Motor Proficiency, Second Edition

BOT-2 was used as a secondary outcome in ENB-008-10. [redacted].

c) Hand-Held Dynamometry

HDD was used as secondary outcome in ENB-008-10. The manufacturer reported observed sustained improvements in torque and median force (both pounds and per cent predicted) bilaterally in the knee flexors and extensors, as well as hip abductors and flexors, after 24 weeks of treatment.

d) Childhood Health Assessment Questionnaire

CHAQ was used as a secondary outcome in ENB-008-10. [redacted].

e) Six-Minute Walk Test

6MWT was used as a secondary outcome in ENB-008-10. Patients at baseline (of ENB-006-09) were able to walk a median of 60.98% of the predicted distance, [redacted].

TABLE 6: KEY EFFICACY OUTCOMES

	ENB-010-10	ENB-006-09		ENB-008-10
	Asfotase alfa	**Historical control**	**Asfotase alfa**	**Asfotase alfa**
RGI-C at 24 weeks				
N (%)	[redacted]	16 (100%)	6 (100%)	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
***P* value**	[redacted]	[redacted]	[redacted]	[redacted]
RGI-C last assessment				
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]

min = minimum value; max = maximum value; NA = not applicable; REF = reference value; RGI-C = Radiographic Global Impression of Change; SD = standard deviation.
Source: Clinical Study Reports.[17,18]

3.7 Harms

Only harms that were suspected to be treatment related were included (see Table 7).

3.7.1 Adverse Events

AEs related to the treatment were largely due to the subcutaneous route of administrating the drug. Across all studies, injection- and infusion-related AEs (e.g., injection site redness, tenderness, and pain) constituted the bulk of all observed AEs.

3.7.2 Serious Adverse Events

SAEs were noted in ENB-010-10; [redacted]. According to the clinical experts consulted by CDR, these SAEs can be expected as part of HPP complications, and not necessarily from the medication. No SAEs related to asfotase alfa were observed in ENB-006-09/ENB-008-10.

3.7.3 Withdrawal Due to Adverse Events

Withdrawal due to adverse events (WDAEs) were noted in ENB-010-10. [redacted]. No WDAEs were noted in ENB-006-09/ENB-008-10.

3.7.4 Mortality

Deaths were registered ENB-010-10. Six patients passed away in ENB-010-10: [redacted]. No deaths were reported in ENB-006-09/ENB-008-10.

3.7.5 Development of Anti-Asfotase Alfa Antibodies

The majority of patients across the studies tested positive for anti-asfotase alfa antibodies: [redacted]. However, this did not translate into a systemic hypersensitivity reaction.

TABLE 7: HARMS

	ENB-010-10	ENB-006-09/ENB-008-10
Treatment duration, mean (SD)	[redacted]	[redacted]
AEs		
Subjects with > 0 drug-related AEs, N (%)	[redacted]	[redacted]
Most common drug-related AEs		
Injection-site reactions	[redacted]	[redacted]
Injection- or infusion-associated reactions	[redacted]	[redacted]
SAEs		
Patients with > 0 drug-related SAEs, N (%)	[redacted]	[redacted]
Most common SAEs		
Severe kyphosis	[redacted]	[redacted]
Severe pneumonia	[redacted]	[redacted]
WDAEs		
WDAEs, N (%)	3 (5.1)	0 (0)
Most common reasons for WDAEs		
Unrelated SAE	[redacted]	[redacted]
Unrelated AE	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	6 (10.2)	0 (0)
Causes of mortality		
Respiratory failure	[redacted]	[redacted]
Cardiopulmonary arrest	[redacted]	[redacted]
Transtentorial and cerebellar tonsillar herniation due to cerebral edema due to severe hypophosphatasia	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[17,18]

4. DISCUSSION

4.1 Summary of Available Evidence

Three manufacturer-sponsored phase II studies were included in this review, and another three manufacturer-sponsored phase II studies have been summarized and appraised in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE as additional clinical evidence. These included studies and the studies described in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE comprise four efficacy studies and two extension studies, namely ENB-002-08, with its extension ENB-003-08; ENB-006-09, with its extension ENB-008-10; ENB-009-10; and ENB-010-10. All studies were single-arm trials except for one historical control (ENB-006-09) and one randomized to a no-intervention control trial (ENB-009-10). All of the studies were open label. Different doses of asfotase alfa were administered, with only ENB-010-10, one arm of ENB-006-09, and the later part of ENB-008-10 having the approved dose of asfotase alfa of 2 mg/kg three times per week. Studies ENB-002-08/ENB-003-08 and ENB-010-10 included only patients who manifested symptoms of HPP before six months, thus classifying them as infantile HPP. This population has a one-year survival rate of around 50%; patients who survive past one year have better prognosis. Study ENB-006-09/ENB-008-10 included patients aged between five and 12 years with open growth plates, and study ENB-009-10 enrolled adolescent and adult patients aged between 13 and 65 years.

4.2 Interpretation of Results

4.2.1 Efficacy

HPP is a rare disease with an estimated incidence in Canada of one in 100,000; as such, it is inherently difficult to conduct well-designed randomized control trials to establish efficacy. However, this doesn't absolve the currently reviewed evidence from the limitations associated with the study conduct and methods.

The primary skeletal outcome result, using the RGI-C, showed statistically significant healing of the severe rickets present in the participants, and this healing was sustained throughout the conduct of the studies. However, there are concerns associated with the methods chosen for these studies. Inherently, single-arm trials are not able to compare the treatment to any other intervention; they are unable to control for many factors, including but not limited to natural history of the disease, possible effect of supportive and symptomatic treatment, placebo effect, and many known and unknown treatment-effect modifiers that can influence the observed outcome. For example, our clinical experts have explained that some patients do improve on their own; such population is in favour of the intervention and remains unaccounted for without appropriate control. Another issue that is left without being accounted for in a proper randomized control is the possibility of misdiagnosed cases affecting the outcome; genetic testing of ENB-010-10 has shown that [redacted] of the population did not have a mutation in the TNSALP gene consistent with the diagnosis of HPP, and it remains unclear how these participants have affected the result of the outcome. Another important issue with regard to the methods is the lack of blinding; this leaves open the possibility that expectation bias from the assessors played a role in inflating the positive result observed in the primary outcome, RGI-C.

Study ENB-006-09/ENB-008-10 attempted to overcome many of the single-arm limitations by employing a historical control arm. Historical control trials also have their limitations, with the control being a non-randomized population taken from a different pool than that of the treatment, which means that potential known and unknown treatment-effect modifiers are not distributed equally among the arms, and thus CDR is still unsure on how these modifiers have affected the outcome. The historical control

arm in ENB-006-09 showed different baseline characteristics than the treatment arms; as such we are not sure of the extent of the usefulness of the historical control arm as a substitute for a randomized control. In addition, study ENB-006-09/ENB-008-10 was also an open-label study, allowing for expectation bias and unaccounted placebo effect.

Study ENB-009-10 would have been a good source of evidence had it not been for the asfotase alfa dose administered to patients being different from the Health Canada–approved dose. While the study randomized to a "no treatment" control arm, the two treatment arms have doses that are 41.7% and 65% less than the approved dose. Therefore, our ability to generalize any of the findings reported in this study is severely limited, notwithstanding other limitations present in this study, and the lack of a statistically significant result in one of the two primary outcomes investigated.

Several important statistical principles were missing in these studies. Major protocol changes during the conduct of the study give the impression that the choice and analysis of outcome were data driven, in an attempt to find a significant finding, as opposed to testing a predefined hypothesis; such changes in the protocol increase the probability that findings can be due to chance alone. Another statistical concept that relates to increasing the probability of findings due to chance alone is the lack of adjusting for multiple outcomes, multiple time-point analysis, and interim analysis. This leads to an inflated alpha; as such, all *P* values for secondary outcomes are nominal, and the *P* value for the primary outcomes in ENB-010-10 and the RGI-C outcome of the individual treatment arms in ENB-006-09 should have been adjusted for interim analysis and multiple outcomes, respectively, in the study protocol phase, prior to statistical analysis of the data being conducted.

Secondary outcomes investigated in these studies provide little evidential value beyond hypothesis generation, since the *P* value is nominal and not very informative, and there is no validation or a MCID value in HPP patients. However, the 6MWT is of relevance to the economic part of this CDR, and has been reported as a secondary outcome in ENB-008-10 and ENB-009-10. The 6MWT as an outcome is prone to learning effect; motivation, encouragement, and cooperation can have a significant positive impact on the results, and the magnitude of these effects could be comparable to the effect of interventions.[32,33] This could be of special concern in situations where blinding is not present as in the studies reviewed here.

Despite the aforementioned critical appraisal points, the magnitude of RGI-C response in patients with severe HPP is large; there is a biological plausibility to supplementing a missing enzyme that is required in bone mineralization; there is a clear temporal relationship; there is similar consistency in the RGI-C outcome between ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10; and there is a drastically lower mortality rate than what is reported in natural history studies. While asfotase alfa appeared to have a beneficial effect on severe HPP beyond chance alone, a number of factors could have potentially biased the results in favour of the intervention, such as expectation bias, unaccounted-for spontaneous improvement, unaccounted-for improvement from supportive and symptomatic therapy, and other unknown unaccounted-for treatment-effect modifiers. Only a properly conducted randomized controlled trial can account for these confounders and assess the true beneficial extent of asfotase alfa.

Input from patients emphasized that fatigue, pain, and poor mobility are three factors that they wish to improve the most. Unfortunately, and despite the manufacturer's efforts to address some of these outcomes, the available evidence informing these aspects is, at best, very limited, and at worst, non-existent.

4.2.2 Harms

HPP is a disease that causes many complications on its own, especially in the early years of life. In the studies provided by the manufacturer, the most common AEs are associated with injection site and infusion. According to the clinical experts consulted for this review, the serious adverse events reported in these studies as related to asfotase alfa are also known to be a part of HPP complications. The extension studies provided almost five years of exposure to asfotase alfa. Despite that, there is a good chance that patients with HPP will take this medication for the rest of their life. Thus, safety related to fertility, conception, possible teratogenic effects, and long-term tolerability should be investigated and closely monitored in patients receiving asfotase alfa.

4.3 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review. To date, therapy for HPP has been symptomatic and includes orthopedic surgery, physiotherapy, pain management, and pulmonary ventilation.[4] Asfotase alfa (Strensiq) is a subcutaneous enzyme replacement therapy that is the first treatment for HPP to address the underlying cause of HPP.[13] As asfotase alfa is the first and only therapy approved for the treatment of asfotase alpha, some believe that all patients with HPP and rickets or bone disease should have access to treatment with asfotase alfa due to the clinical benefits that are possible with this treatment. Subsequent decisions regarding whether asfotase alfa treatment should be continued should be based on assessments of improvement of clinically meaningful outcomes (rickets, pain, mobility, independence from respirator) on an individual patient basis. However, there are insufficient data available that would allow a prediction of the extent of responsiveness to asfotase alfa in the individual case. Post-marketing surveillance will be an important resource for identifying characteristic markers of optimal and poor responders.

Because the skeletal effects of HPP, such as rickets, can be sufficiently severe as to lead to death within the first year of life,[34] it is expected that patients with HPP onset within the first year of life — i.e., a severe form of HPP — will benefit from treatment with asfotase alfa. Early treatment with asfotase alfa (starting in the neonatal or infantile period) has the potential to prevent irreversible bone disease and respiratory insufficiency. Nevertheless, the response to asfotase alfa might be expected to be limited in the most severely affected newborns who have lethal skeletal changes at birth and secondary multisystem involvement.

Due to the broad phenotypic spectrum of HPP, which ranges from mild (adult onset of osteopenia or increased bone fractures and abnormal dentition) to severe (intrauterine lethal, prenatal absence of bone mineralization, infantile onset of rickets), whether to treat patients who have milder forms of the disease presents a challenge, for two reasons. First, it will be a challenge to decide whether the manifestation of disease in a particular individual is sufficiently severe to treat. Second, it will be difficult to assess the value of treatment with asfotase alfa in the face of the more subtle clinical manifestations that would be expected to occur relative to patients with less severe disease. In older patients with a longer history of untreated HPP, and a milder form of the disease, treatment with asfotase alfa would be expected to improve rickets and correct the underlying metabolic abnormality, but restoration of bone health would be expected to be incomplete due to pre-existing irreversible bone deformities.

Based on the available clinical evidence and the existing unmet need, the clinical experts consulted by CDR suggested that the following subgroups of patients with HPP would benefit from asfotase alfa:

1. Newborns and infants with perinatal/infantile-onset HPP
2. Older patients with a definitive diagnosis of HPP *and* a history of perinatal or infantile onset *and* have signs of rickets *or* bone deformities *or* pulmonary function impairment, that are compatible with the natural history of perinatal or infantile onset HPP.

In addition, the clinical experts suggested that asfotase alfa therapy be continued if the following two criteria are met:

1. Radiologic improvement of rickets (e.g., demonstrated by increase in RGI-C score)
   or
2. Improvement of osteopenia shown by bone density measurement
   and at least one of the following:
   a) Improvement of pain
   b) Improvement of motor function
   c) Improvement of pulmonary function.

The clinical experts suggested that treatment with asfotase alfa be discontinued in any of the following circumstances:

1. Failure to meet continuation criteria
2. Non-compliance with treatment
3. Drug intolerance.

The size of the population of HPP patients in Canada is uncertain. The current incidence of HPP in Canada is unknown, but has been estimated to be 1:100,000.[6] In the US and in Europe, the prevalence of HPP is lower, and affects approximately one in 300,000 individuals.[4] In Canada, approximately three or four individuals per year will be born with HPP and potentially be eligible for treatment with asfotase alfa. In British Columbia (BC; population 4.4 million inhabitants), to date six children and adults with infantile onset of HPP, who are potentially eligible for treatment with Strensiq, are known. Based on the prevalence of perinatal and infantile-onset HPP in BC (six people out of 4.4 million) in Canada (population 33.5 million inhabitants), approximately 45 patients might currently be eligible for this therapy. The number of individuals diagnosed with HPP will likely increase in future as previously undiagnosed cases become diagnosed and as HPP becomes seen as a treatable condition.

5. CONCLUSIONS

The clinical evidence available from three open-label studies of asfotase alfa suggest that 2 mg/kg administered three times per week is associated with an improvement in skeletal development, as reflected by increase in RGI-C scores. Because the included studies were uncontrolled, there is substantial uncertainty as to the magnitude of improvement attributed to asfotase alfa. The main harms associated with asfotase alfa treatment appear to be injection-site and infusion reactions, although safety data are limited.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Soft Bones Canada (SBC), provided input for this review. SBC is a source of education, information, encouragement, and support for Canadian individuals and their families affected by hypophosphatasia (HPP), including interested individuals in the medical community. The goals of SBC are to advance education by providing courses, seminars, workshops, and educational materials about HPP to the public, patients, and medical professionals; to promote health by providing HPP patients and their caregivers with access to health counselling, information, and group support programs; and to advance education by supporting and conducting research into the causes and possible treatments of HPP and making the results publicly available.

No conflict of interest is declared.

2. Condition-Related Information

In this section, the information provided by SBC was gathered from patients and caregivers through one-to-one conversations by telephone and email, drawing from personal experiences and by meeting with families. These interactions were with both those on asfotase alfa and those not on the medication.

Patients indicated that HPP has a dramatic impact on patients, often right from birth. The overall important impacts, according to the people who engaged with CADTH, were pain and fatigue. In children, joint pain can be so severe that they cannot even walk. One mother said about her son: "He would scream every night, and cry, saying his legs hurt. We tried pain relief medication, but nothing would work." Adult patients spoke of the inability to function due to joint pain (shoulders, etc.), as well as inflammation and stiffness. Severe muscular and bone pain is also typical, described by one person as "the bones in my wrists and ankles burn like they're on fire." Headaches are frequent, often due to muscle stiffness and spasm. The impact of being in chronic pain and fatigue were mentioned frequently. HPP leaves one physically and emotionally exhausted.

HPP also places a tremendous amount of responsibility on caregivers in virtually all circumstances.

3. Current Therapy-Related Information

Patients with HPP stated that there were no treatments specifically to treat HPP before asfotase alfa was marketed in Canada. Nevertheless, a number of adjunctive therapies were mentioned by the people engaged by CADTH, including physiotherapy, massage therapy, osteopathy (to ensure body alignment), bone healing devices, bone surgery, pain relievers, and anti-inflammatory medications and supplements, and exercise. One person also noted that if she stops taking any of her pain management therapies, "the symptoms come back with a vengeance." Patients indicated that none of the above-mentioned adjunctive therapies really helped with the pain and fatigue of living with HPP.

4. Expectations About the Drug Being Reviewed

The methods of collecting information for this section were the same as those used in Section 3.

The responses from patients who have been on asfotase alfa are positive. It was described as both life-changing and life-saving. Positive effects expressed by parents included much less pain, improvement in physical abilities, that children feel and look "normal,", perform normally for their age group, and have an improved overall quality of life and emotional improvement: they are more confident. The positive effects expressed by adults included improved mobility, emotional improvement, relief of pain, and no more broken bones. Patients and their families noted that asfotase alfa was easy to use. The negative effects expressed by patients were few, and included mild skin reaction (dark or blue spots, pain, etc.) at injection site, fatigue for the first three months on treatment, and low-grade fever for the first month on treatment. In addition, patients indicated that asfotase alfa doesn't retroactively repair bones and teeth to non-HPP levels. One patient noted that despite being on the drug, she will always have some pain because she has osteoarthritis in most of her joints. Overall, all the people CADTH engaged said that the benefits of the treatment far outweighed the negative effects. The following are a few quotes from the patients experienced on asfotase alfa:

"If I had the chance to change anyone's mind on how powerful asfotase alfa has been for us (as a family), I would plead and fight it until the day I die. It's that life-changing for her (their daughter)."

"This medication is a miracle. My child is no longer the same. It has changed his life. He can live and not just survive suffering."

"I expect to live many years able to walk without pain, a cane or a wheelchair and to participate in life as a normal person, to visit galleries and museums, to go hiking with friends on long trails, to travel freely — all the things that other people take for granted, but which I was unable to do outright or without a great deal of pain."

"I am the mother of a child with HPP … I am unbelievably grateful for this drug. It gave me time with my son and I love seeing what it's doing for others with HPP. They are living and thriving thanks to asfotase alfa."

The patients without experience using asfotase alfa also expect that the treatment will help them survive.

In summary, all patients with HPP and the parents of a child with HPP (with or without experience with treatment of asfotase alfa) are expecting to get access to treatment of asfotase alfa.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 24, 2015
Alerts:	Weekly/monthly search updates until January 20, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(asfotase* or alxn1215 or alxn 1215 or strensiq* or enb0040 or "enb 0040").ti,ab,ot,hw,kw,nm,rn.
2	1174277-80-5.rn,nm.
3	1 or 2
4	hypophosphatasia/
5	(hypophosphatasia or hpp or rathbun*).ti,ab.
6	4 or 5
7	enzyme replacement.hw.
8	recombinant fusion proteins/
9	(tnsalp or tnap or tissue non-specific alkaline phosphatase or (human recombin* adj5 (enzyme or fusion or protein*)) or (enzyme adj2 replacem*)).ti,ab.
10	7 or 8 or 9
11	6 and 10
12	3 or 11
13	12 not conference abstract.pt.
14	remove duplicates from 13
15	exp animals/
16	exp animal experimentation/ or exp animal experiment/
17	exp models animal/
18	nonhuman/
19	exp vertebrate/ or exp vertebrates/
20	animal.po.
21	or/15-20
22	exp humans/
23	exp human experimentation/ or exp human experiment/
24	human.po.
25	or/22-24
26	21 not 25
27	14 not 26

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 15, 2015
Keywords:	Strensiq (asfotase alfa) and hypophosphatasia
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Studies not included in the main review have been summarized and reviewed in APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE.

APPENDIX 4: ADDITIONAL CLINICAL EVIDENCE

Studies ENB-002-08/ENB-003-08 and ENB-009-10 were not considered to be pivotal trials by Health Canada.[19] These studies include a different dose of asfotase alfa from the approved dose.[19] Given the paucity of clinical evidence available for this rare condition, the CADTH Common Drug Review (CDR) has provided a review of these studies in this appendix for information purposes. In addition to the previously mentioned trials, study ENB-006-09 also included one arm with a dose different from the approved dose of asfotase alfa. This arm, along with the contrasting historical control, are included in this appendix.

Reviewed Studies

TABLE 8: DETAILS OF REVIEWED STUDIES

		ENB-002-08	ENB-003-08	ENB-006-09	ENB-009-10
DESIGNS & POPULATIONS	**Study Design**	Phase II, open-label, uncontrolled single-arm trial	Extension study of ENB-002-08, single-arm, uncontrolled	Phase II, open-label, randomized, dose ranging, historical control	Phase II, open-label, randomized, dose ranging, no-treatment concurrent control
	Locations	Canada, US, UAE, UK		Canada, US	Canada, US
	Enrolled (N)	11	10	13	19
	Inclusion Criteria	• Diagnosis of severe HPP • Onset of signs prior to age 6 months • Age ≤ 36 months • Medically stable with the exception of ventilator support	• Patient completed study ENB-002-08	• History of HPP • Patients aged ≥ 5 and ≤ 12 years with open growth plates • Tanner stage of ≤ 2 indicating prepubescence • Serum 25-hydroxy vitamin D level ≥ 20 ng/mL	• Pre-established diagnosis of HPP • Patients aged ≥ 13 and ≤ 65 years • Medical contraception for female patients of child-bearing age • Findings of osteomalacia on bone biopsy
	Criteria for Diagnosis of HPP	• Total serum ALP at least 3 SDs below the mean for age • PLP at least 4 times the upper limit of normal • Radiographic evidence of HPP, characterized by flared and frayed metaphyses, severe and generalized osteopenia, and widened growth plates • One or more HPP-related findings of history or presence of non-traumatic postnatal fracture or delayed fracture healing, history of elevated serum calcium, functional craniosynostosis with decreased head circumference growth, nephrocalcinosis, or respiratory compromise		• Presence of HPP-related rickets on skeletal X-rays • Serum ALP activity below the age-adjusted normal range • Plasma PLP level at least twice the upper limit of normal	• Serum ALP below the age-adjusted normal range • Plasma PLP at least twice the upper limit of normal • Evidence of osteopenia or osteomalacia on skeletal radiographs

		ENB-002-08	ENB-003-08	ENB-006-09	ENB-009-10
		• Rachitic chest deformity and/or vitamin B6-dependent seizures • Failure to thrive			
	Exclusion Criteria	• Clinically significant condition or major disease • Low serum calcium, phosphate, [redacted] • Evidence of a treatable form of rickets • Prior treatment with bisphosphonate		• Clinically significant condition or major disease • Low serum calcium, phosphate, or 25-hydroxy vitamin D • Evidence of a treatable form of rickets • Prior treatment with bisphosphonate	• Clinically significant condition or major disease • Orthopedic surgery within 12 months • Prior treatment with bisphosphonates within 2 years of study • Treatment with PTH within 6 months prior to study
DRUGS	**Intervention**	Initial 2 mg/ kg, asfotase alfa, IV. Followed by 1 mg/kg 3 times per week (3 mg/kg/week), asfotase alpha, SC. Dose adjustments were permitted	Asfotase alfa; same dose the patient received on the last week of ENB-008-02, SC	• 2 mg/kg 3 times per week, asfotase alfa, SC (6 mg/ kg/week) • 3 mg/kg 3 times per week, asfotase alfa, SC (9 mg/kg/week)	• 0.3 mg/kg/day, asfotase alfa, SC (2.1 mg/kg/week) • 0.5 mg/kg/day, asfotase alfa, SC (3.5 mg/kg/week)
	Comparator(s)	NA		Historical control	No-intervention control group
DURATION	**Phase**				
	Run-in	[redacted]	[redacted]	[redacted]	[redacted]
	Efficacy phase	24 weeks	NA	24 weeks	24 weeks
	Safety phase	Extension study ENB-003-08 (60 months [month 6 to month 66])	78 months (ongoing)	Extension study ENB-008-10 (42 months [month 6 to month 48])	16 months (month 6 to month 22)
OUTCOMES	**Primary End Point**	Change in rickets severity from baseline to week 24, based on skeletal radiographs measured by the RGI-C scale	NA	Change in rickets severity on skeletal radiographs from baseline to week 24 as measured by the RGI-C scale	Changes in PPi and PLP levels from baseline through week 24
	Other End Points	• RSS • Respiratory support • Overall survival	• RGI-C scale • RSS • Respiratory support	• Rickets severity scale • SAE • AE	• DEXA results • 6MWT • SAE • AE

		ENB-002-08	ENB-003-08	ENB-006-09	ENB-009-10
		• Height and weight z scores • Head circumference • BSID-III • SAE • AE • Injection site–associated AEs • Death • Hypersensitivity reactions • Development of anti-asfotase alfa antibodies	• Overall survival • Height and weight z scores • SAE • AE • Death • Development of anti-asfotase alfa antibodies	• Injection site–associated AEs • Death • Hypersensitivity reactions • Development of anti-asfotase alfa antibodies	• Injection site–associated AEs • Death • Hypersensitivity reactions • Development of anti-asfotase alfa antibodies
NOTES	**Publications**	Whyte et al.[13]	None	None	None

AE = adverse event; ALP = alkaline phosphatase; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DEXA = dual-energy X-ray absorptiometry; HPP = hypophosphatasia; IV = intravenous; NA = not applicable; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; PTH = parathyroid hormone; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Scale; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; UAE = United Arab Emirates; UK = United Kingdom; US = United States.

Description of Studies

The studies varied considerably in design: study ENB-002-08 (N = 11) was a phase II, open-label, single-arm trial; study ENB-006-09 (N = 13) was a phase II, open-label, randomized, dose ranging trial with a historical control; study ENB-009-10 (N = 13) was a phase II, open-label, randomized, dose ranging trial with a concurrent no-intervention control; and study ENB-003-08 (N = 10) was an extension study for ENB-002-08 and ENB-006-09.

Population

All four studies shared two inclusion criteria: an established diagnosis of HPP, and that patients needed to be medically stable (with the exception of the need for respiratory support in ENB-002-08/ENB-003-08). They also shared most of the exclusion criteria, including the exclusion of patients with prior bisphosphonate treatment. Beyond that, however, the inclusion and exclusion criteria differ in terms of age of HPP diagnosis and age of patients upon enrolment.

The diagnosis of HPP was based on an extensive list of clinical and radiographic criteria. Subsequent to enrolment, a genetic test was conducted to confirm the diagnosis. All patients participating in ENB-002-08/ENB-003-08, ENB-006-09, and in ENB-009-10 had gene mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene consistent with the diagnosis of HPP.

Study ENB-002-08, along with its extension study ENB-003-08, included patients who were diagnosed with HPP prior to six months of age (infantile HPP), and only included patients who were younger than 37 months. Study ENB-006-09 included patients aged between five and 12 years, with no specific requirement on the time of diagnosis of HPP. Similarly, study ENB-009-10 did not have a restriction on the time of HPP diagnosis, but recruited older patients, aged between 13 and 65 years.

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS

Title	ENB-002-08/ ENB-003-08	ENB-006-09		ENB-009-10			
Arm	[redacted]	Historical control, N = 16	3 mg/kg asfotase alfa, N = 7	Control group N = 6	0.3 mg/kg asfotase alfa, N = 7	0.5 mg/kg asfotase alfa, N = 6	Asfotase alfa combined, N = 13
Age, mean (SD)	58.79 weeks ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	4 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (months) at HPP onset, mean (SD)	NR (all below 6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPi (µM), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLP (ng/mL), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory support							
No support, n (%)	6 (54.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-invasive support, n (%)	2 (18.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Invasive support, n (%)	3 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Z scores							
Length/ height, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HPP = hypophosphatasia; NR = not reported; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; RSS = Rickets Severity Scale; SD = standard deviation.

Interventions

Study ENB-002-08/ENB-003-08 were single-arm trials in which the intervention was asfotase alfa. In study ENB-002-08, there was an initial intravenous (IV) dose of 2 mg/kg, subsequently followed by a subcutaneous (SC) injection of 1 mg/kg three times per week for the length of ENB-002-08 and its extension study ENB-003-08. This dose was adjustable based on clinical judgment of response and adverse events. Study ENB-006-09 randomized patients into one of two doses of asfotase alfa: one arm had a dose of 2 mg/kg three times per week (6 mg/kg/week), the results of which were reviewed in the main body of this report, and another arm at a dose of 3 mg/kg three times per week (9 mg/kg/week); both arms were compared with a historical control that was not treated with asfotase alfa. Study ENB-009-10 randomized patients into three arms: asfotase alfa at a dose of 0.3 mg/kg/day (2.1 mg/kg/week), 0.5 mg/kg/day (3.5 mg/kg/week), and a concurrent "no treatment" control arm in which asfotase alfa was not given but other supportive treatments and usual care were allowed. In all studies, patients were taking various concurrent medications to address symptoms and complications of HPP, as per the clinical judgment of the treating physician.

Outcomes

APPENDIX 5: DETAILED OUTCOME DATA provides a detailed description of outcomes used in this review.

Radiographic Global Impression of Change

Radiographic Global Impression of Change (RGI-C) was the primary outcome in three of the four trials, excluding the extension studies. The RGI-C scale was designed by the manufacturer to measure the change in the severity of rickets. Rickets refers to the softening and weakening of bones in children.[20] RGI-C is a seven-point change scale that provides an assessment of the change in bone structure associated with the pathophysiology of HPP.[13] A reduction of three points (recorded as "–3") represented severe worsening, and an increase of three points (recorded as "+3") indicates complete healing of the skeletal disease. X-ray radiographs were taken prior to the initiation of treatment, and subsequent radiographs were taken at specific time points. These X-rays were assessed by three independent pediatric radiologists who were aware of which is the baseline X-ray photograph but blinded to the rest of the data, including at which time point the follow-up radiograph was taken. These assessors were trained for in using the computer systems and electronic records according to the Good Clinical Practice guidelines and in compliance with Title 21 Code of Federal Regulations (CFR) Part 11. The average of the assessment of the three radiologists was then applied as the final RGI-C score.

There are no known studies assessing the validity and/or the minimal clinically important difference (MCID) of RGI-C in HPP patients.

Rickets Severity Scale

The Rickets Severity Scale (RSS)[13] was constructed to measure the severity of rickets in the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected.[22] RSS is a 10-point scale (four points for the wrists and six points for the knees), in which higher scores indicate more severe rickets.[22] A score of 10 represents severe rickets, while a score of 0 indicates an absence of metaphyseal cupping and fraying.[22] RSS was a secondary outcome in all studies except ENB-009-10. An X-ray of the knees and wrists was taken prior to treatment and at specific time points. A single assessor would score the radiographs; the assessor was blinded to the patient's identity and the time point at which the radiographs were taken.

Respiratory Support
Early HPP can lead to rachitic chest, which causes deterioration of respiratory function. The need for and the type of respiratory support needed was assessed in two studies: ENB-002-08/ENB-003-08 and ENB-010-10.

Z Score for Height, Weight, and Head Circumference
Z score is used to analyze the length and height, weight, and head circumference in clinical research for patients with abnormal growth and development such as HPP.[23] Z scores were based on Centers for Disease Control (CDC) growth charts and methodology.[24] In the CDC growth charts, the z score corresponds exactly to growth percentiles; e.g., z scores of –1.881, –1.645, –1.282, –0.674, 0, 0.674, 1.036, 1.282, 1.645, and 1.881 correspond to the third, fifth, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles, respectively. Z scores were secondary outcomes for ENB-002-08/ENB-003-08, ENB-008-10, and ENB-010-10.

Dual-Energy X-Ray Absorptiometry
The dual-energy X-ray absorptiometry (DEXA) test measures bone mineral content and density, and was used to compare an established norm or standard.[25] Although no bone density test is 100% accurate, t score and z score are commonly used to present the findings of DEXA in clinical research. DEXA measures were used a secondary outcome in ENB-008-10 and ENB-009-10.

Six-Minute Walk Test
The six-minute walk test (6MWT) is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[26] 6MWT was used as a secondary outcome in ENB-008-10 and ENB-009-10.

CDR reviewers searched for validation studies of 6MWT in HPP. No evidence of validation and MCID was identified.

Plasma Level of Inorganic Pyrophosphate and Pyridoxal-5'-Phosphate
One of the pathognomonic laboratory findings in patients with HPP is subnormal serum activity of alkaline phosphatase (ALP).[35,36] Changes in the levels of inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP) were used as primary outcomes in ENB-009-10.

Drug-Related Adverse Events and Serious Adverse Events
For the purpose of this review, CDR included adverse events and serious adverse events reported by investigators as possibly related to the administration of asfotase alfa.

Hypersensitivity Reactions
Adverse events related to immune response to the administration of asfotase alfa.

Development of Anti-Asfotase Alfa Antibodies
As a complex protein structure, asfotase alfa has the potential to act as an antigen, with antibodies produced against it that could influence its efficacy or cause severe hypersensitivity reactions.

Statistical Analysis
Study ENB-002-08/ENB-003-08 was a single-arm trial without a control. The median of the primary outcome, RGI-C, at 24 weeks was calculated against the value of 0 (0 on the RGI-C indicates "no change") using a Wilcoxon signed-rank with statistical significance set for a *P* value less than 0. ENB-002-

08/ENB-003-08 had a sample size calculated at 10 patients, based on the RSS outcome for nutritional rickets with an 80% power to detect 1.9 points difference with statistical significance at an alpha of 0.05. The median of secondary outcomes was also tested against the value at baseline using Wilcoxon signed-rank. There was no adjustment for multiple secondary outcomes; as such, *P* values are considered nominal.

In ENB-006-09, the pooled median from both study arms of the primary outcome, RGI-C, at 24 weeks was compared against the median for the historical control using a Wilcoxon rank sum test with a two-sided alpha of 0.05. If the *P* value was less than 0.05 and the Hodges–Lehman–Sen estimate favoured asfotase alfa, superiority over the historical values was claimed. Power calculation was based on the five-point Clinical Global Impression of Change scale (CGI-C) instead of the seven-point RGI-C; it was decided that 20 historical control and 12 treated patients would be necessary to provide an 88% power to compare, with statistical significance, the distribution of the five-point CGI-C between the treated and historical control groups. There was no adjustment for multiple secondary outcomes. ENB-006-09 also carried out the same method of statistical analysis to examine each arm against the historical control; no adjustment for multiple testing was planned.

In ENB-009-10, the change in the levels of PPi and PLP from baseline to week 24 was used to compare the asfotase alfa arms to the "no treatment" control arm using a Wilcoxon rank sum test. No statistical power calculation was determined prior to the commencement of the study. However, a post-hoc analysis showed that with 13 randomized patients to asfotase alfa and six to the "no treatment" control, the study has 95% power to detect a difference in PPi and 70% power to detect differences in PLP with an alpha of 0.05. There was no adjustment for multiple primary outcomes or for secondary outcomes.

Analysis Population

All included studies had three analysis sets:

a) Full-analysis (FA) set: An intention-to-treat population that included all randomized patients who received any treatment, who started the trial on the "no treatment control," or, in the case of single-arm trials, all populations that received any asfotase alfa, regardless of whether they were lost to follow-up or dropped out of the trial; imputations can be applied to efficacy analyses through last observation carried forward
b) Per-protocol (PP) set: Includes all patients in the FA set who did not have any major protocol deviations
c) Safety set: Identical to the FA set, without the ability to apply imputations for safety analyses.

Patient Disposition

Table 10 summarizes the disposition of enrolled patients. ENB-002-08/ENB-003-08 had a dropout rate of around 10%. [redacted]. In ENB-006-09, a dropout rate of 14.3% was observed in the 3 mg/kg arm.

TABLE 10: PATIENT DISPOSITION

	ENB-002-08/ ENB-003-08	ENB-006-09		ENB-009-10		
	1 mg/kg asfotase alfa	**3 mg/kg asfotase alfa**	**Historical control**	**0.3 mg/kg asfotase alfa**	**0.5 mg/kg asfotase alfa**	**Control**
Screened, N	11	13	16	[redacted]		
Randomized, N	NA	7	NA	7	6	6
Treated, N (%)	11 (100%)	7 (100%)	NA	[redacted]	[redacted]	[redacted]
Discontinued, N (%)	1 (9.1%)	1 (14.3%)	NR	[redacted]	[redacted]	[redacted]
Full-analysis, N	11	7	16	[redacted]	[redacted]	[redacted]
Per-protocol, N	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
Safety, N	11	7	NR	[redacted]	[redacted]	[redacted]
Continued to extension	10	12	NA	[redacted]		

NA = not applicable; NR = not reported.

Exposure to Study Treatments

While asfotase alfa was the only intervention across studies, the dose at which it was administered varied considerably. It is worth noting that the dose at which asfotase alfa has received approval, and for which it seeks reimbursement, is either 2 mg/kg three times per week, or 1 mg/kg six times per week, both for a total of 6 mg/kg/week. Patients in ENB-002-08/ENB-003-08 had a planned dose of 1 mg/kg three times per week, which was adjustable according to the discretion of the investigator; patients in one arm in ENB-006-09 received 3 mg/kg three times per week; and patients in ENB-009-10 received either 35% in one arm, or 58% in another, of the total approved dose.

Treatment compliance was monitored in all studies through several methods, including patients' and parents' diaries and log entries, tracking supplies dispensed by and returned to the pharmacy, and collecting empty vials at each study visit.

Critical Appraisal

Internal Validity

Changes in Study Protocol and Conduct

There were several changes applied throughout the conduct of all the included studies. Most of these changes were aimed at improving communication, diagnostics, or data gathering. However, in two studies (ENB-003-08, ENB-009-10), some of these changes were directly related to the studies' outcomes, adding, adjusting, or removing primary and secondary outcomes; specifically:

- In ENB-003-08, Amendment 2 changed the measure of rickets severity from a quantitative assessment to a qualitative CGI-C. This was later changed to the RGI-C. In another instance, RSS was added to the study through Amendment 4 as a secondary outcome.
- Amendment 4 in ENB-009-10 moved the primary outcome, in which a bone biopsy was analyzed for signs of osteomalacia, to a secondary outcome. In its place, reductions in PPi and PLP were moved from secondary outcomes to primary outcomes.

These changes give the impression that the conduct of these studies was mainly data driven, and attempting to find a significant efficacy outcome rather than testing a pre-established hypothesis.

Choice of Control

Study ENB-002-08/ENB-003-08 was a single-arm trial with no control group. As such, CDR cannot determine whether the effect of the intervention is caused solely by the intervention and cannot control for treatment confounders that may influence the outcome. Some of these factors would include natural spontaneous improvement in the course of the disease; effects of symptomatic treatments and supportive therapies; effect of baseline characteristics such as disease severity, gender, race, age, and any other unknown characteristics.

Study ENB-006-09 employed a historical control for the primary outcome analysis. The lack of randomization in the control arm and the fact that the historical control is drawn from a population that is different from the treatment arms minimizes the ability of the historical control to control for biases and confounders. This is reflected when comparing the baseline characteristics between the two populations; the historical control had a younger population, which was diagnosed with HPP earlier, had a different male-to-female ratio, had a better RSS, and higher levels of PLP. It is not clear whether these differences would play in favour of or against the intervention. Other inherent problems in utilizing a historical control are the uncertainty in the quality of historical data that are collected retrospectively as opposed to the prospective collection in the intervention arms, and the effect of changes in practice between the historical control and the intervention arms.

ENB-009-10 was the only study that randomized patients to a concurrent “no treatment” control arm.

Randomization

In ENB-009-10, patients were randomized into two treatment arms with different doses of asfotase alfa. Randomization codes were provided to investigational sites in sequentially numbered envelopes; it is not clear, however, how these codes were generated. Despite the randomization, it seems that, perhaps due to the small sample size, it was not completely efficient at distributing patients’ characteristics equally between the control group and the other arms; most strikingly, the control group had younger patients, who had been diagnosed with HPP at a younger age, and had more male patients and fewer Caucasians. These discrepancies cast doubt on the ability of randomization to control for known and unknown potential treatment confounders.

Blinding

None of the studies included were blinded. As such, CDR cannot account for a placebo effect in non-physiologic measures, and the primary outcome, RGI-C, is prone to expectation bias. Both instances will affect the outcome in favour of the intervention.

Power Analysis and Sample Size

None of the studies had a methodologically sound power analysis to determine sample size. In ENB-002-08/ENB-003-08, sample size was calculated based on capturing a difference in the RSS outcomes. However, the study’s primary outcome was the RGI-C and the RSS was a secondary outcome. Similarly, power analysis in ENB-006-09 was based on the five-points CGI-C, which was later changed to the seven-point RGI-C. On the other hand, ENB-009-10 did not include a prior power analysis or a predetermined sample size.

Adjusting for Multiple Comparisons and Interim Analysis
A large number of outcomes were included in these studies; yet, no measure to adjust for multiple testing and comparisons was employed. In addition, at the time of writing this report, two studies were still ongoing and were provided to CDR reviewers as an interim analysis (ENB-003-08 and ENB-009-10); a measure to adjust for interim analysis is also necessary. These two issues — lack of adjustment for multiple comparisons and interim analysis — allow for a greater probability of finding significance due to chance, because repeating statistical tests inflates the type I error, alpha, where a *P* value of 0.05 might no longer indicate statistical significance.

External Validity
The concepts listed below have been observed as affecting the internal validity of the studies.

Choice of the Dose of Asfotase Alfa
Study ENB-002-08/ENB-003-08 initially placed participants on a 1 mg/kg three times per week dose, 50% less than the approved dose. Adjustment of the dose was allowed at the discretion of the clinical investigator based on response and adverse events. In study ENB-009-10, asfotase alfa was administered at 0.3 mg/kg six times per week (65% less than the approved dose), or at 0.5 mg/kg six times per week (41.7% less than the approved dose). While asfotase alfa was administered in the approved dose in one arm of ENB-006-09, in the second treatment arm, asfotase alfa was administered at 3 mg/kg three times per week, a 33.4% increase on the approved dose.

This inconsistency in dose administration across all studies severely limits the available evidence for the external validity of the approved 2 mg/kg three times per week or 1 mg/kg six times per week dose.

Population
Across studies, the manufacturer has attempted to provide evidence for the different phenotypes of HPP. ENB-002-08/ENB-003-08 targeted the most severe form of HPP, which includes patients who are aged six months or younger, who historically have a one-year survival rate of around 50%. ENB-006-09 targeted patients aged between five and 12 years, who would have fairly stable disease. Finally, study ENB-009-10 mainly included adults with stable HPP.

Diagnosis of Hypophosphatasia
The clinical experts consulted by CDR believe that the clinical criteria in these studies are sufficient to make the correct diagnosis of HPP.

Follow-up
Extension phases of up to five years were available in all but one study (ENB-009-10), providing a good overview of the tolerability of asfotase alfa, which is nevertheless limited in terms of the number of participants involved.

Validity and Minimal Clinically Important Difference
Although the manufacturer attempted to capture a range of outcomes, many of which are patient-reported outcomes regarding functionality and health-related quality of life, validity and MCID in the HPP population are not available for any of these outcomes. This limits CDR's ability to measure the extent and magnitude of how patients will respond outside the studies.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See APPENDIX 5: DETAILED OUTCOME DATA for detailed efficacy data.

Skeletal-Related Outcomes

Radiographic Global Impression of Change

RGI-C measured at 24 weeks was the primary outcome in three studies: ENB-002-08, ENB-006-09, and ENB-010-10. In the single-arm trial ENB-002-08, the median RGI-C score was measured against the value of 0 (indicating "no change" on the RGI-C scale). In ENB-002-08, with an adjustable asfotase alfa dose of 1 mg/kg three times per week, RGI-C showed a statistically significant outcome (*P* value 0.0039) with a median of 2.00 (substantial healing) and [redacted].

The findings of RGI-C in ENB-003-08, the extension study of ENB-002-08, showed consistency in the primary outcome finding, with the last assessment of RGI-C at [redacted] showing a statistically significant outcome with [redacted].

Rickets Severity Scale

RSS is a secondary outcome in all studies except ENB-009-10. [redacted]. Improvements in the RSS continue in the last available full analysis in ENB-003-08, [redacted].

Dual-Energy X-Ray Absorptiometry

DEXA scan was a secondary outcome in ENB-009-10. [redacted].

Respiratory Support

Respiratory support was a secondary outcome in ENB-002-08/ENB-003-08. At baseline, of 11 patients, two (18.2%) required non-invasive respiratory support (supplemental O_2, bilevel positive airway pressure [BiPAP], continuous positive airway pressure [CPAP]) and three (27.3%) required invasive respiratory support. At week 24, and out of 10 patients, five (50.0%) required non-invasive support and three (30.0%) required invasive support. [redacted].

Growth and Development

Z Score for Height and Weight

Growth z scores were secondary outcomes for ENB-002-08/ENB-003-08. [redacted].

Bayley Scales of Infant and Toddler Development, Third Edition

Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was used as a secondary outcome in ENB-002-08. [redacted].

Six-Minute Walk Test

6MWT was used as a secondary outcome in ENB-009-10. [redacted].

Other Efficacy Outcomes

Plasma Level of Inorganic Pyrophosphate and Pyridoxal-5'-Phosphate

PPi and PLP at 24 weeks were used as primary outcomes in ENB-009-10. [redacted].

Harms

Only harms that were suspected as being treatment related were included.

Adverse Events

Adverse events related to the treatment were largely due to the subcutaneous route of administrating the drug. Across all studies, injection- and infusion-related adverse events (e.g., injection site redness, tenderness, and pain) constituted the bulk of all observed adverse events.

Serious Adverse Events

Two patients experienced three serious adverse events (SAEs); all were noted in ENB-002-08/ENB-003-08: chronic hepatitis, severe craniosynostosis, and severe conductive hearing loss. According to the clinical experts consulted for this review, these SAEs can be expected as part of the complications of HPP, and not necessarily from the medication. No SAEs related to asfotase alfa were observed in ENB-006-09 or in ENB-009-10.

Withdrawal Due to Adverse Events

Two patients withdrew in ENB-002-08/ENB-003-08; one due to injection- or infusion-associated reactions, and one due to an adverse event unrelated to asfotase alfa. No withdrawals due to adverse events (WDAEs) were noted in ENB-006-09 or in ENB-009-10.

Mortality

One patient passed away in ENB-002-08/ENB-003-8 due to septic shock. No deaths were reported in ENB-006-09 and ENB-009-10.

Development of Asfotase Alfa Antibodies

The majority of patients across the studies tested positive for anti-asfotase alfa antibodies: [redacted]. However, this did not translate into a systemic hypersensitivity reaction.

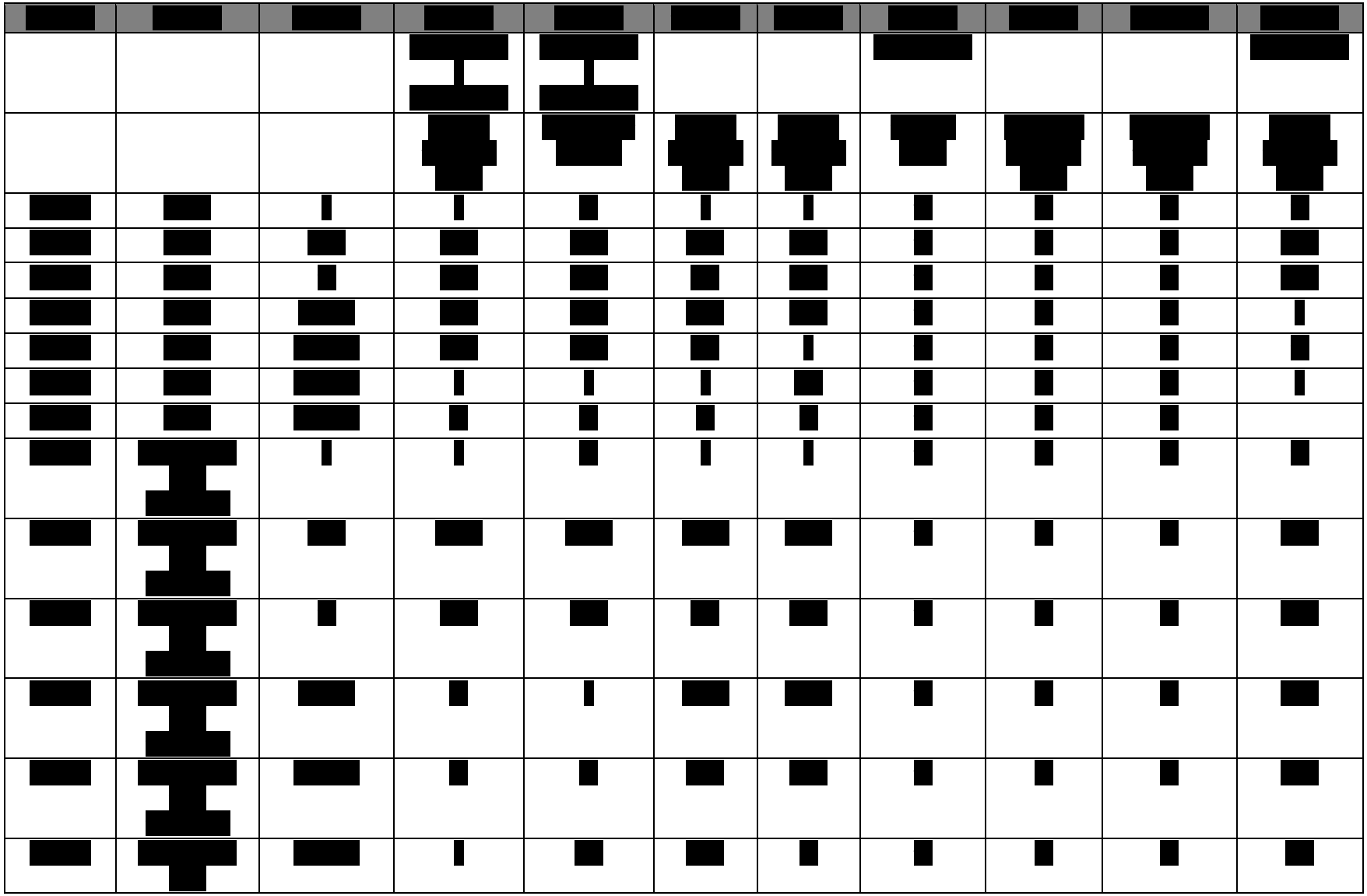
TABLE 11: HARMS

	ENB-002-08/ ENB-003-08	ENB-006-09	ENB-009-10		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs					
Patients with > 0 drug-related AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common drug-related AEs					
Injection-site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection- or infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs					
Patients with > 0 drug-related SAEs, N (%)	[redacted]	[redacted]	[redacted]		
Most common SAEs					
Chronic hepatitis	[redacted]	[redacted]	[redacted]		
Severe craniosynostosis	[redacted]	[redacted]	[redacted]		
Severe conductive hearing loss	[redacted]	[redacted]	[redacted]		
WDAEs					
WDAEs, N (%)	[redacted]	[redacted]	[redacted]		
Most common reasons for WDAEs					
Injection- or infusion-associated reactions	[redacted]	[redacted]	[redacted]		

	ENB-002-08/ ENB-003-08	ENB-006-09	ENB-009-10
Unrelated SAE	[redacted]	[redacted]	[redacted]
Unrelated AE	[redacted]	[redacted]	[redacted]
Deaths			
Number of deaths, N (%)	1 (9)	0 (0)	0 (0)
Causes of mortality			
Septic shock	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

APPENDIX 5: DETAILED OUTCOME DATA



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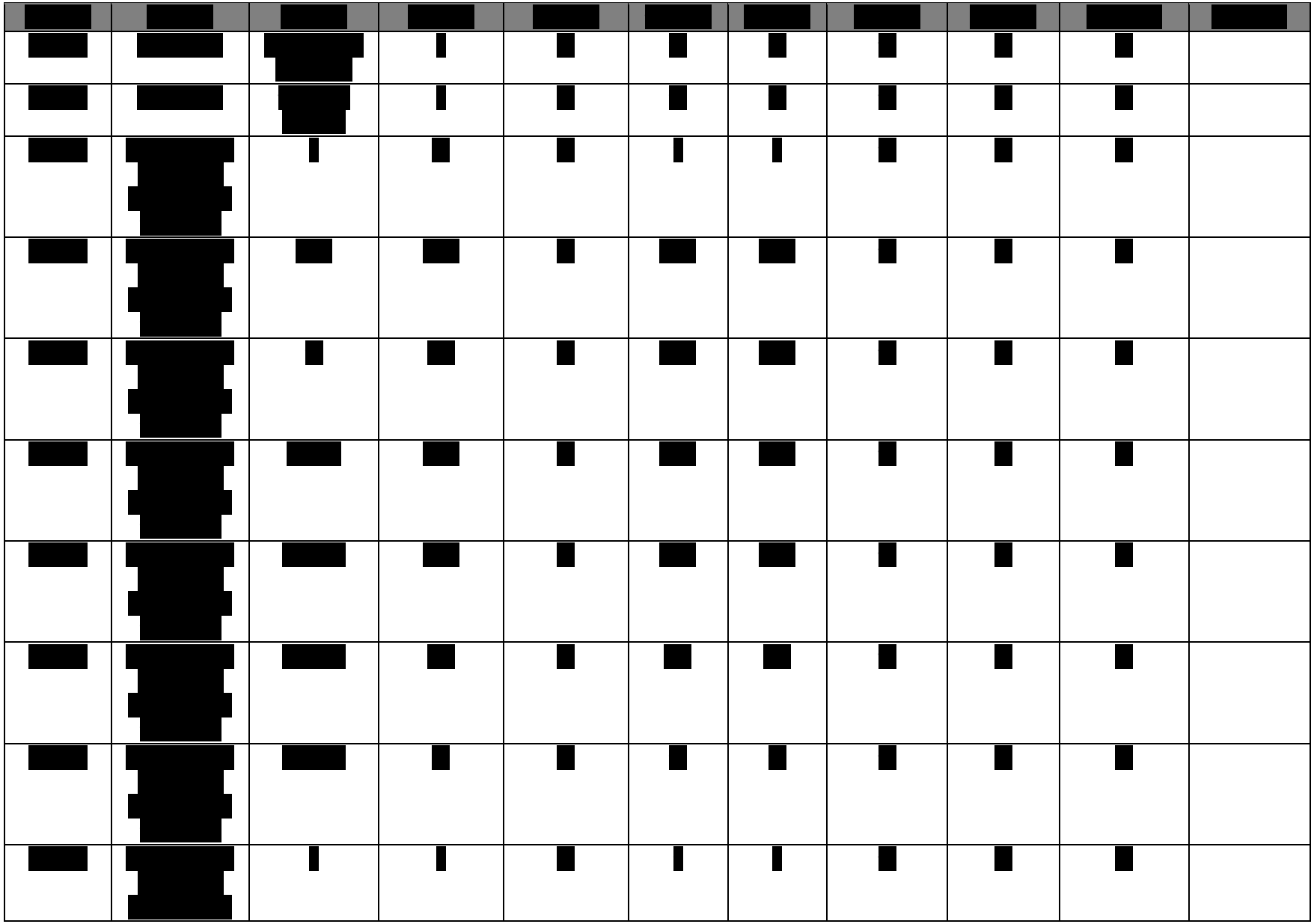

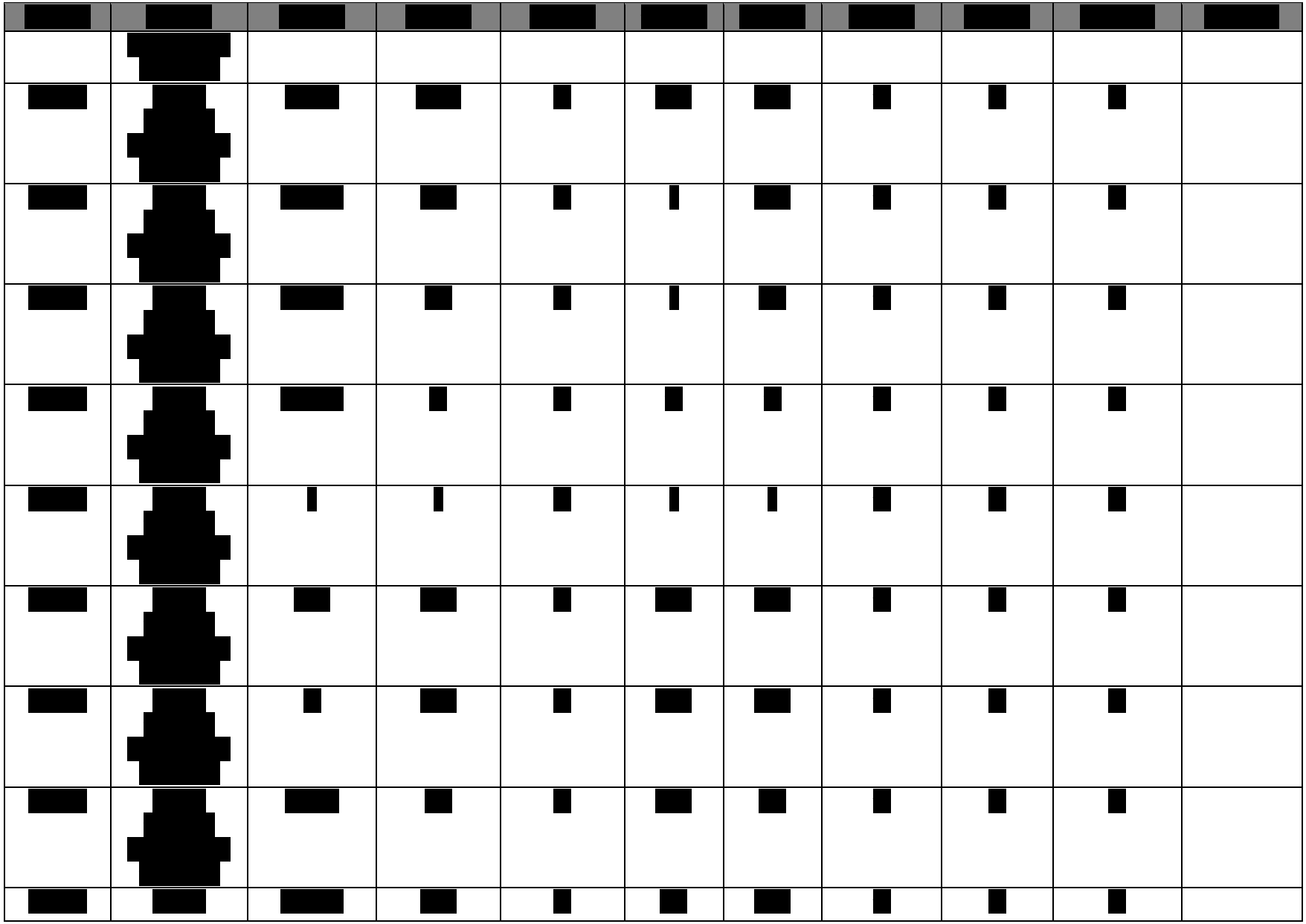

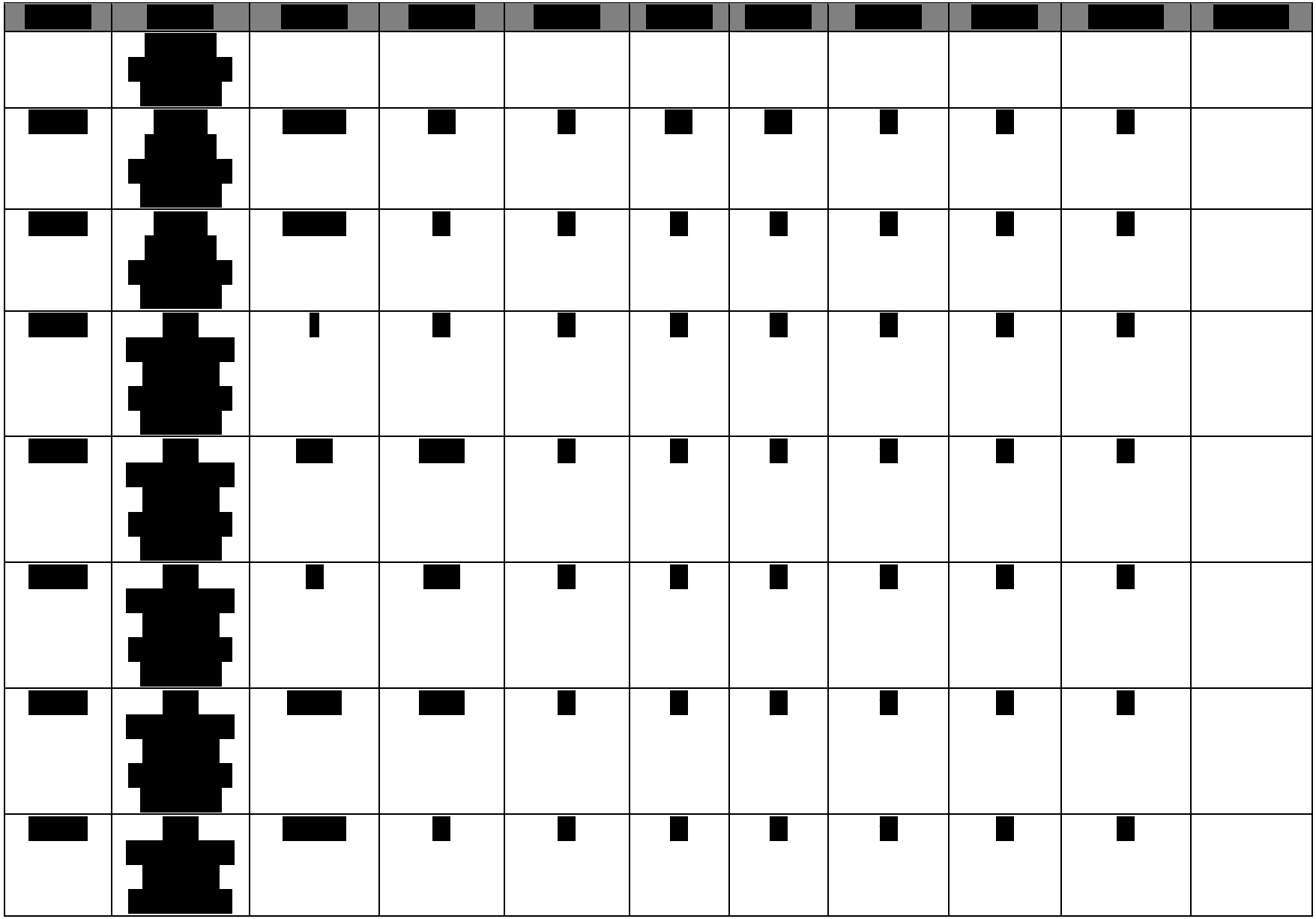

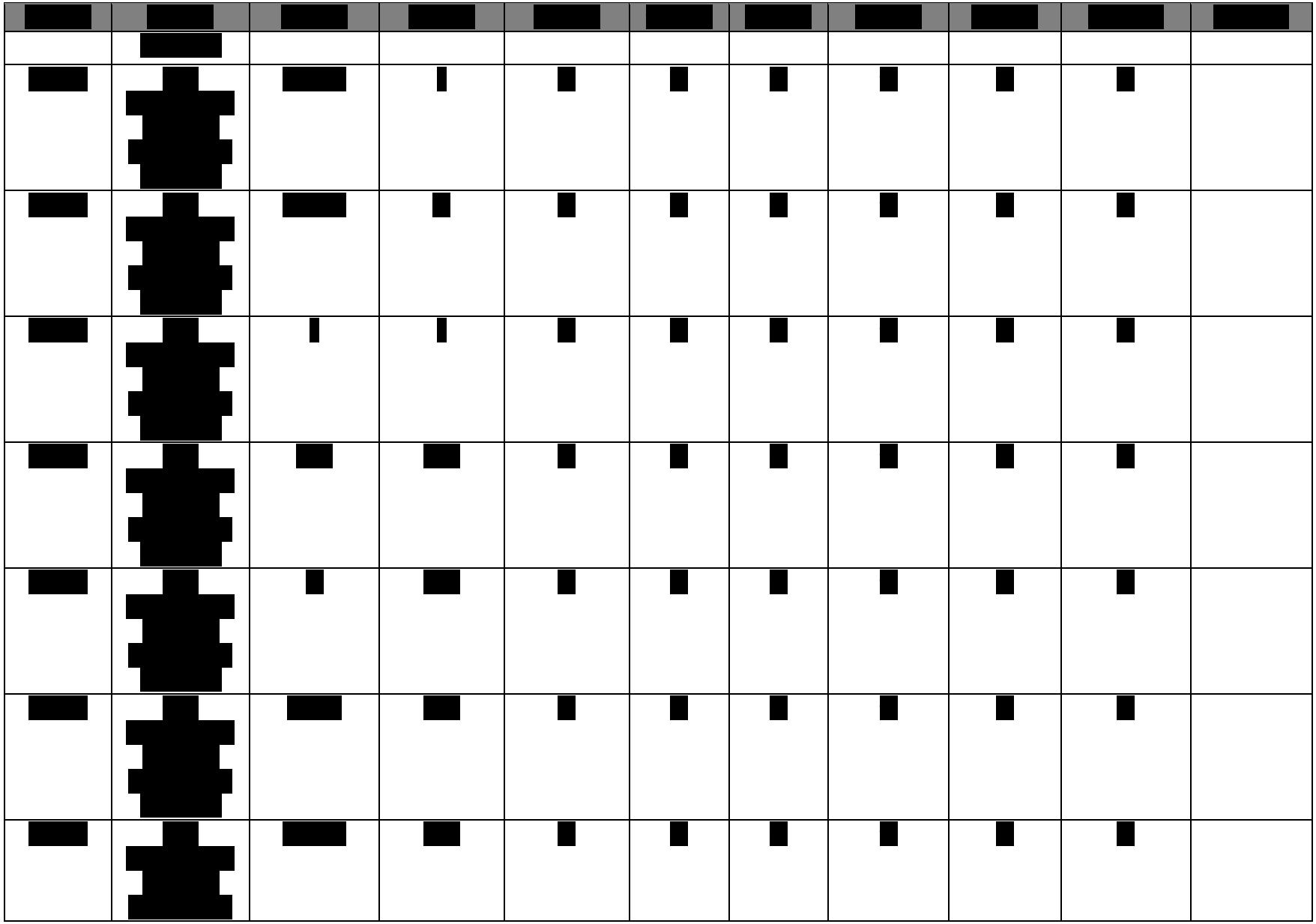

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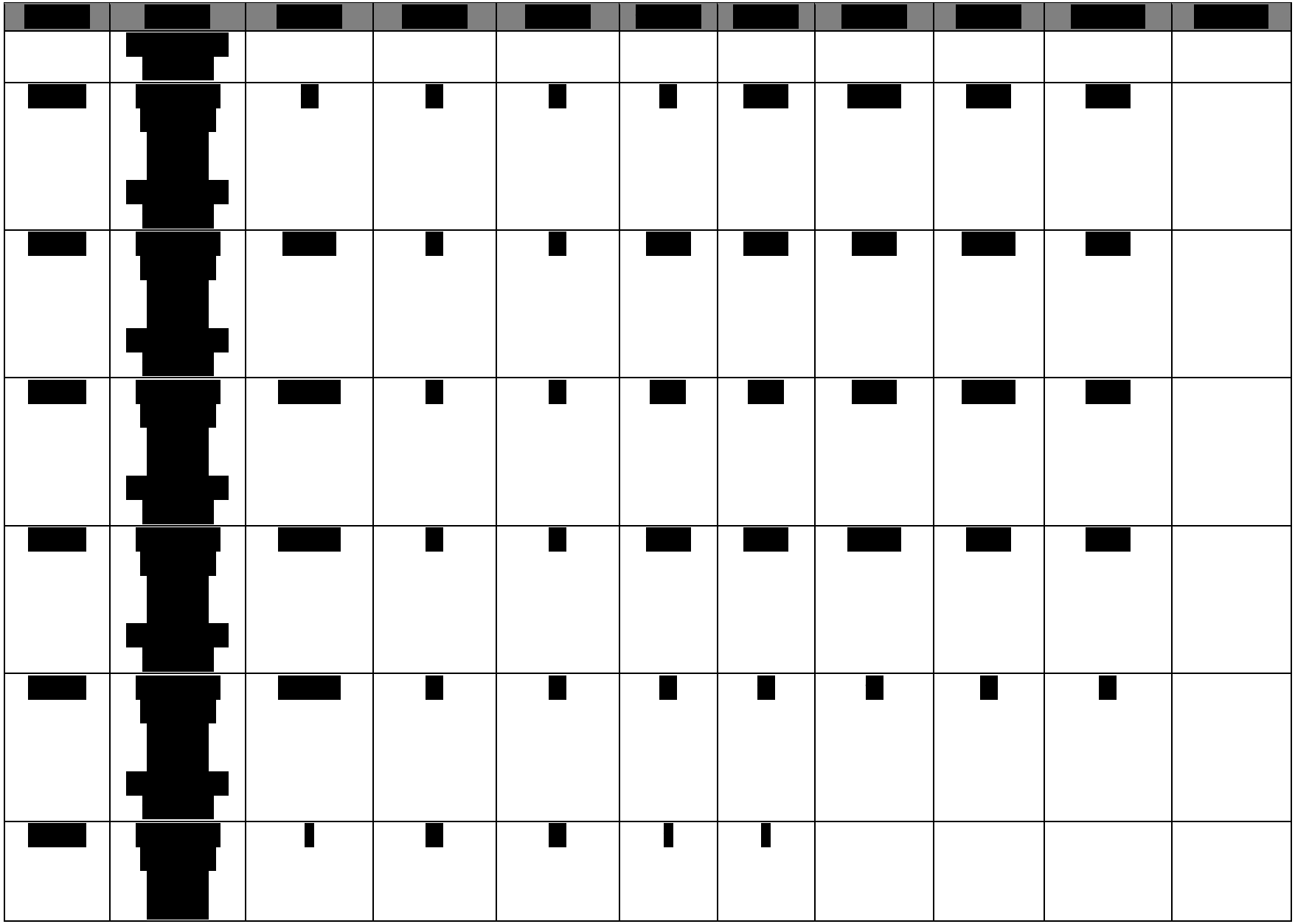

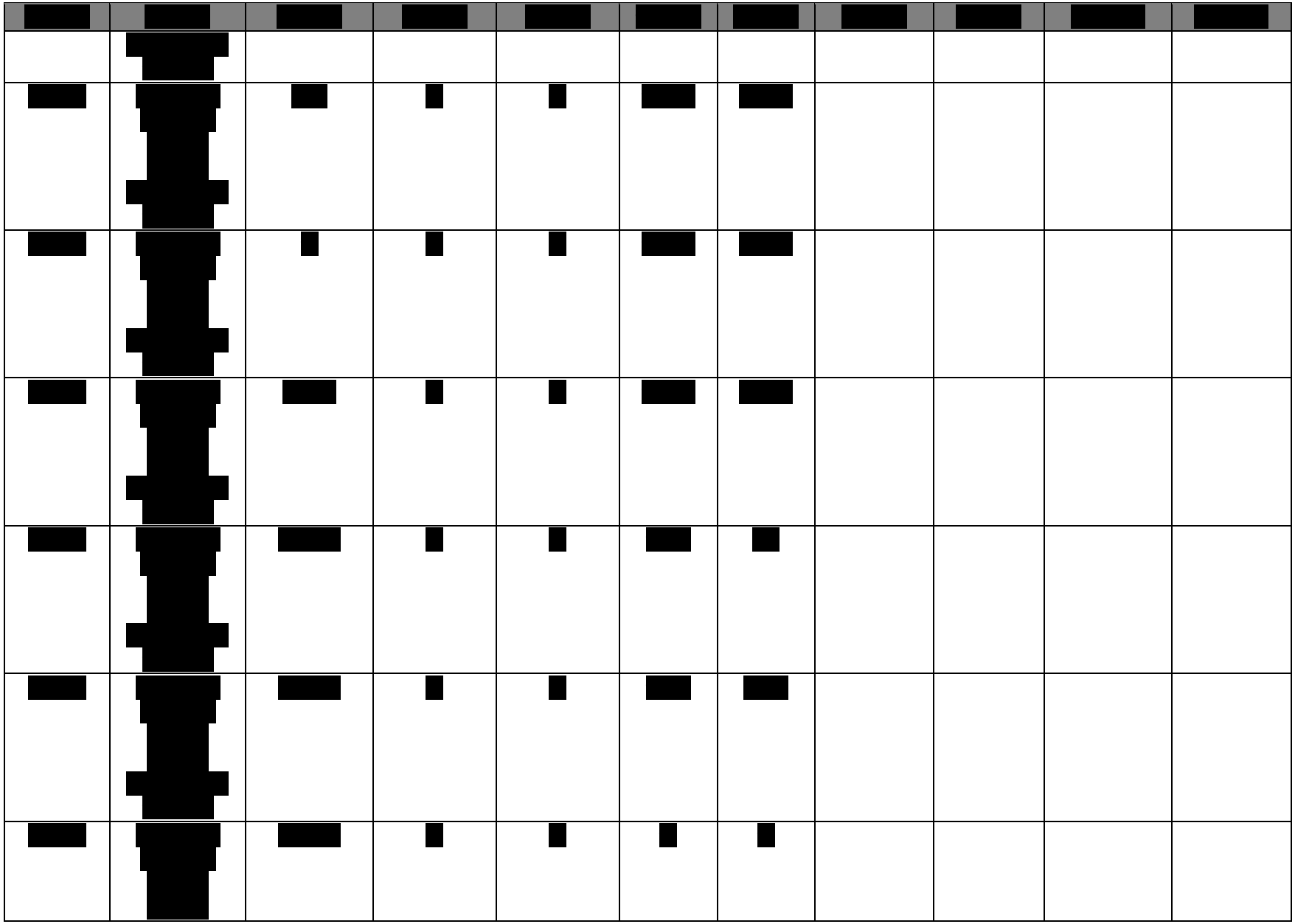

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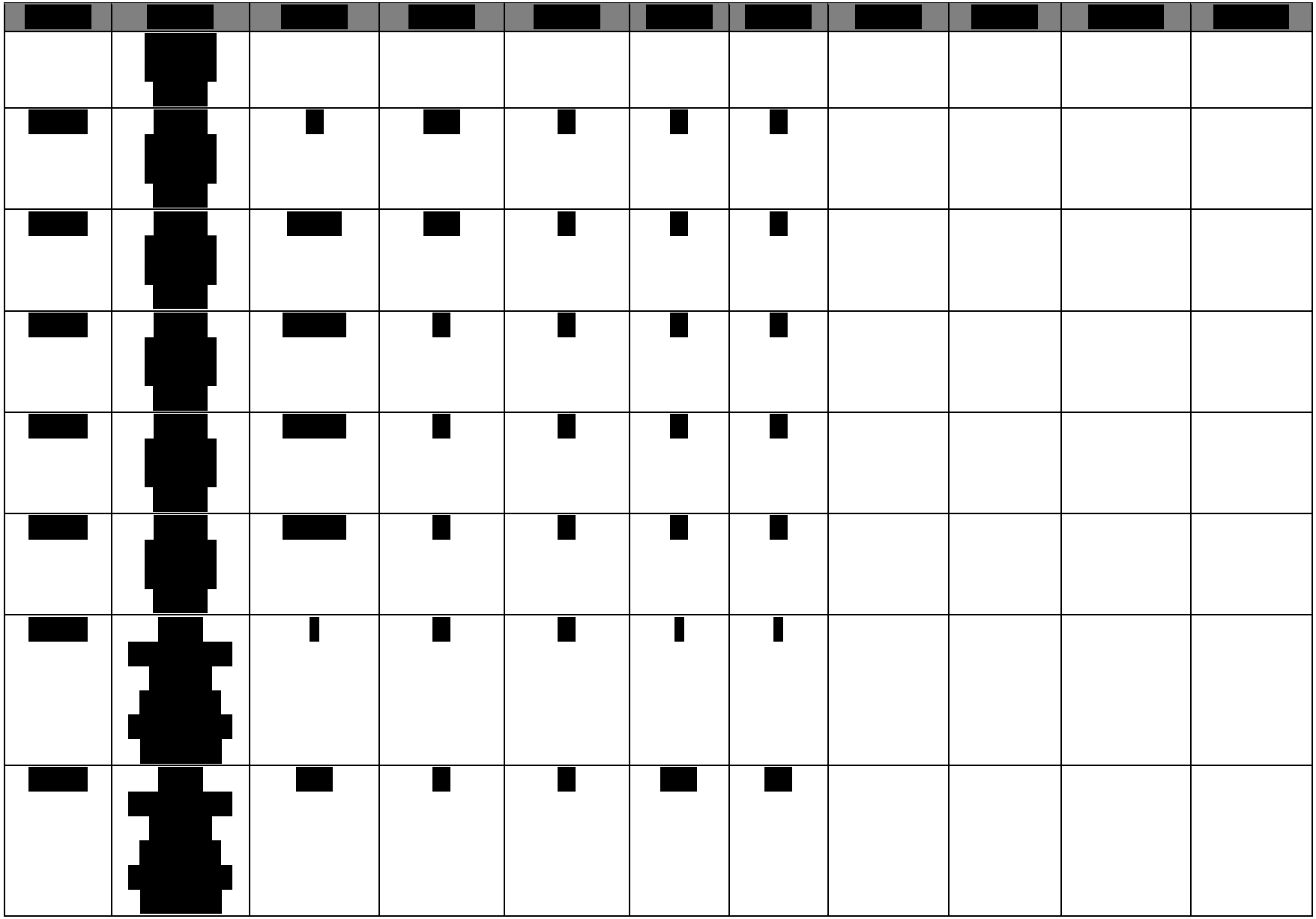

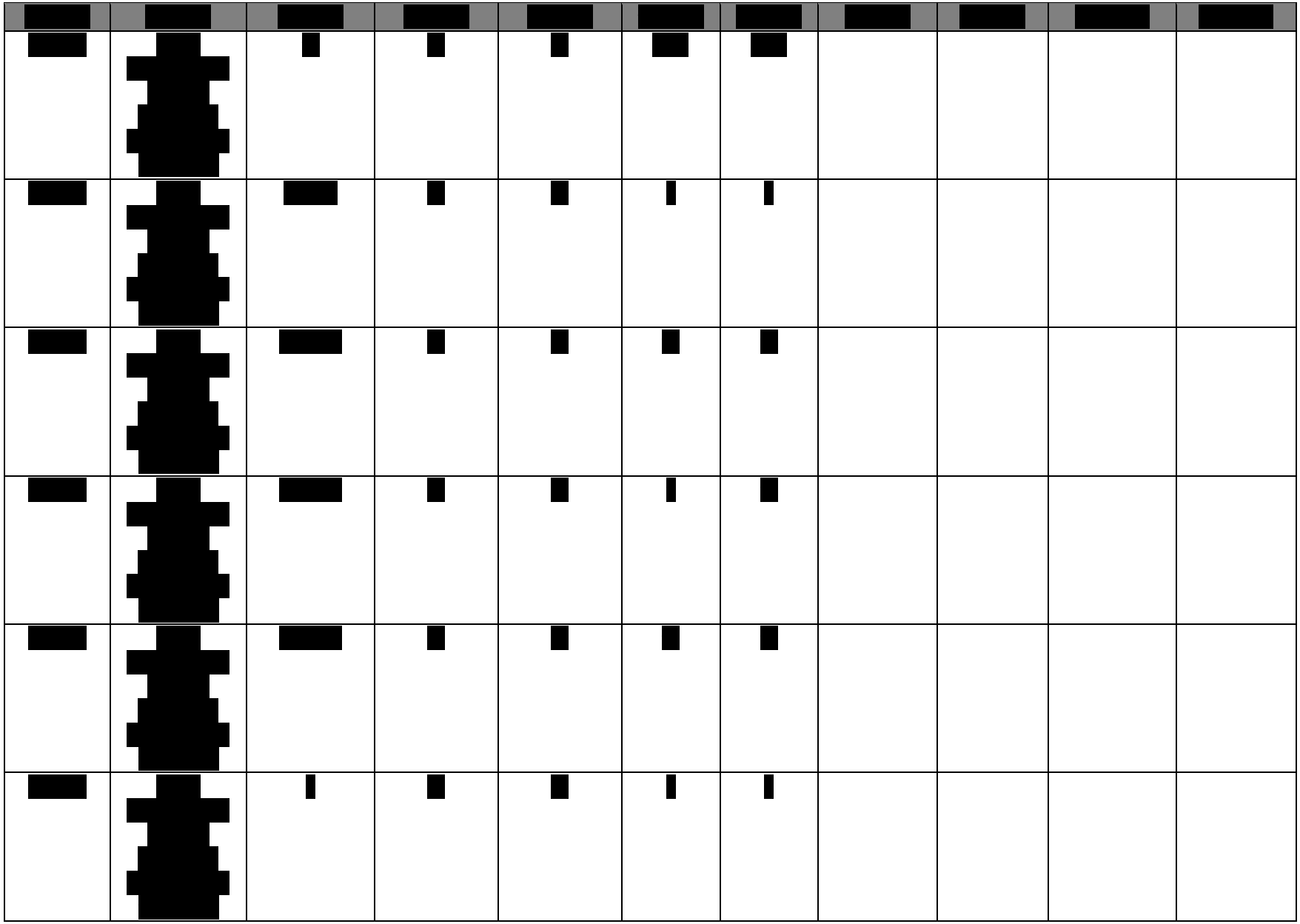

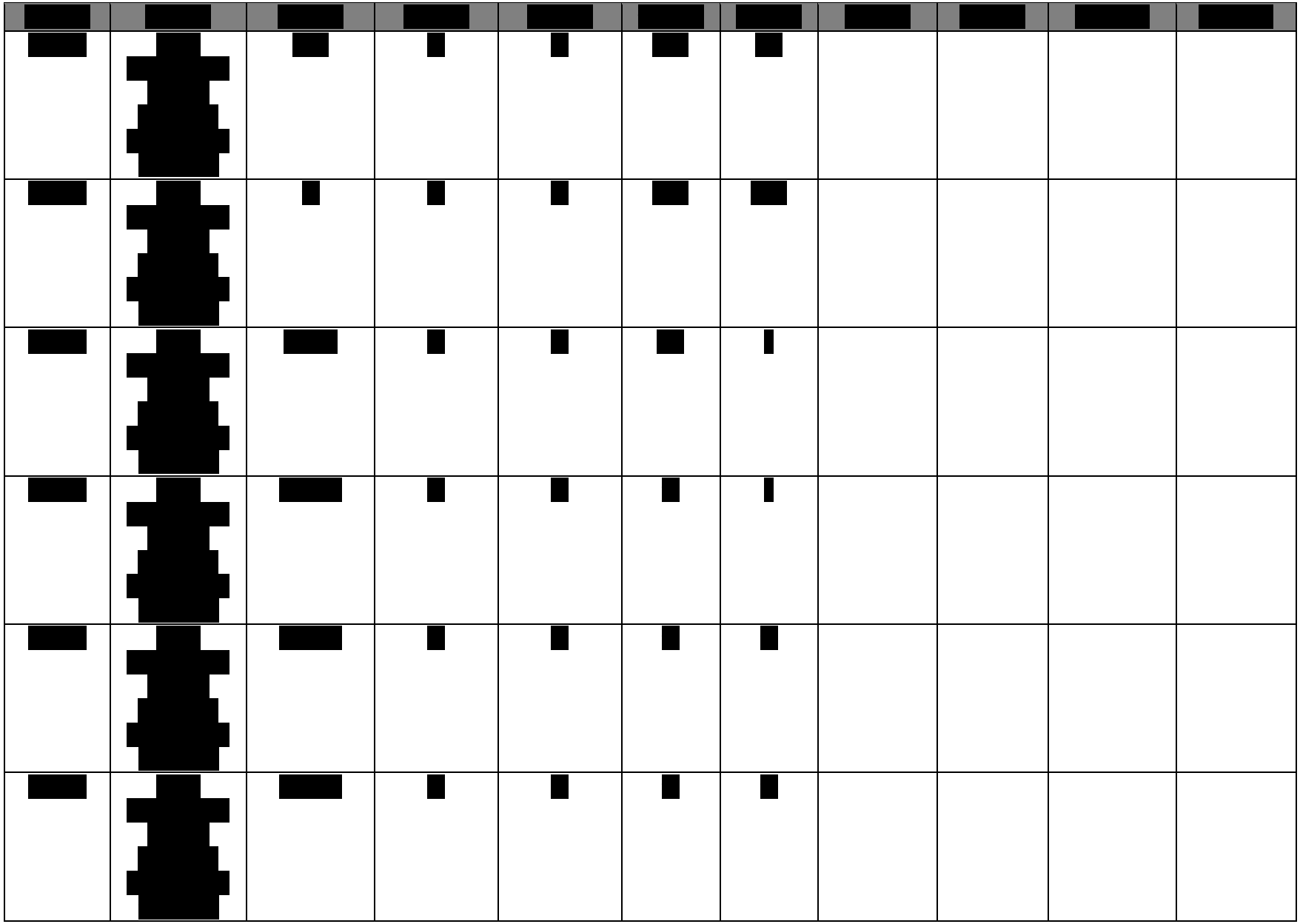

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APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Radiographic Global Impression of Change (RGI-C)
- Rickets Severity Scale (RSS)
- Z score for height, weight, and head circumference
- Dual-energy X-ray absorptiometry (DEXA)
- Six-minute walk test (6MWT)
- Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2)
- Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
- Hand-held dynamometry (HHD)
- Child Health Assessment Questionnaire (CHAQ)
- Changes in the plasma level of inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP).

Findings

Radiographic Global Impression of Change

The RGI-C scale was constructed to measure the change in the severity of rickets. Rickets refers to the softening and weakening of bones in children.[20] RGI-C is a seven-point change scale that provides an assessment of bone structure associated with the pathophysiology of hypophosphatasia (HPP).[13] Usually, bone X-rays (such as chest, wrists, and knees) are obtained for patients younger than 18 years with open growth plates, and are rated for change from baseline by two to three pediatric radiologists. The changes from baseline of RGI-C are based on ratings of the characteristics of severe HPP, including irregularity of the provisional zone of calcification; physeal widening; metaphyseal flaring, fraying, radiolucencies, and patchy osteosclerosis; altered ratio of mid-diaphyseal cortex to bone thickness; gracile bones; absence of some or all bones; and recent fractures. A reduction of three points (recorded as "–3") represents severe worsening, and an increase of three points (recorded as "+3) indicates complete healing of the skeletal disease (Table 12). For each patient, the mean score among the radiologists was used for analysis, with a response to treatment defined as a mean increase of 2 or more points (i.e., substantial healing).

TABLE 12: SCORES ON THE RGI-C AND CLINICAL INTERPRETATION

Rating	Clinical interpretation
–3	Severe worsening (very much worse; i.e., severe worsening of HPP-associated rickets)
–2	Moderate worsening (much worse; i.e., moderate worsening of HPP-associated rickets)
–1	Minimal worsening (minimally worse; i.e., minimal worsening of HPP-associated rickets)
0	No change
+1	Minimal healing (minimally better; i.e., minimal healing of HPP-associated rickets)
+2	Substantial healing (much better; i.e., substantial healing of HPP-associated rickets)
+3	Complete or near complete healing (very much better; i.e., complete or near complete healing of HPP-associated rickets)

HPP = hypophosphatasia; RGI-C = Radiographic Global Impression of Change.
Source: Study ENB-010-10 Clinical Study Report.[18,27]

The CADTH Common Drug Review (CDR) reviewers searched for validation studies of RGI-C in HPP. No evidence of validation and minimal clinically important difference (MCID) in HPP was identified.

Rickets Severity Scale

Rickets is the softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D deficiency. Rickets due to a genetic condition such as HPP may require additional treatment such as enzyme replacement therapy or corrective surgery.[20] The RSS[13] was constructed to measure rickets severity in the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected.[22] RSS is a 10-point scale (four points for the wrists and six points for the knees), in which higher scores indicate more severe rickets.[22] A score of 10 represents severe rickets, while a score of 0 indicates an absence of metaphyseal cupping and fraying (Table 13).[22,23] In clinical research, a single reader (e.g., a radiologist) rated the growth-plate abnormalities at the wrists and knees.

TABLE 13: 10-POINT RADIOGRAPHIC SCORING METHOD FOR RICKETS

Wrist: score both radius and ulna separately (score for worst wrist)		
	Grade	Radiographic features
	0	Normal growth plate without changes of rickets
	0.5	Lucency of metaphyseal margin without fraying or irregularity
	1	Widened growth plate, irregularity of metaphyseal margin, but without concave cupping
	1.5	Partial metaphyseal concavity or incomplete fraying of metaphyseal margin
	2	Metaphyseal concavity with fraying of margins
bones × 2 points = 4 points possible		
Knee: score both femur and tibia separately (score for worst knee)		
Multiply the grade in A by the multiplier in B for each bone, then add femur and tibia scores together		
A	Grade	Degree of lucency and widening of zone of provisional calcification
	0	Normal growth plate without changes of rickets
	1	Partial lucency, smooth margin of metaphysis visible
	2	Partial lucency, smooth margin of metaphysis NOT visible
	3	Complete lucency, epiphysis appears widely separated from distal met
B	Multiplier	Portion of growth plate affected
	0.5	≤ 1 condyle or plateau
	1	2 condyles or plateaus
2 bones × 1 point × 3 points = 6 points possible		
Total: 10 points possible		

Source: Thacher et al. (2000)[22]

We searched for validation studies of RGI-C in HPP. No evidence of validation and MCID was identified.

Z Score for Height, Weight, and Head Circumference

Z score is used to analyze the length and height, weight, and head circumference in clinical research for patients with abnormal growth and development such as HPP.[23] Z scores were based on Centers for Disease Control (CDC) growth charts and methodology.[24] In the CDC growth charts, z score corresponds exactly to growth percentiles; e.g., z scores of –1.881, –1.645, –1.282, –0.674, 0, 0.674, 1.036, 1.282, 1.645, and 1.881 correspond to the third, fifth, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles, respectively. Z scores and corresponding percentiles can be obtained from standard normal

distribution tables found in statistics textbooks. Many computer programs have pre-existing functions that convert z scores to percentiles and vice versa.[24] Descriptive statistics were also presented for each head circumference z score, which was calculated using the World Health Organization (WHO) formulas and methodology.[37]

CDR reviewers searched for validation studies of z score in HPP. No evidence of validation and MCID was identified.

Dual-Energy X-Ray Absorptiometry

The DEXA test measures bone mineral content and density, and was used to compare an established norm or standard.[25] Although no bone density test is 100% accurate, the DEXA test is the single most important predictor of whether a person will have a fracture in the future.[25] T scores and z scores are commonly used to present the findings of DEXA in the clinical research. T scores are calculated by comparing DEXA test results to the ideal or peak bone mineral density of a healthy 30-year-old adult.[25] Based on the WHO definition, a t score of 0 means that bone mineral density (BMD) is equal to the norm for a healthy young adult. Differences between an individual's BMD and that of the healthy young adult norm are measured in standard deviations (SDs). The smaller the SD value (indicated as a negative number), the lower the BMD and the higher the risk of fracture.[25] A t score between +1 and −1 is considered normal or healthy. A t score between −1 and −2.5 indicates low bone mass. A t score of −2.5 or lower indicates osteoporosis. The greater the negative number, the more severe the osteoporosis.[25] However, it was believed that the WHO diagnostic categories for normal, osteopenia, and osteoporosis, based on t scores, are not applicable to children and adolescents who have not yet reached peak bone mass.[38] Few published pediatric reference values for BMD measured with DEXA include factors that are known to affect the results besides age and gender.[38] Z score is calculated by comparing the DEXA results with age- and sex-matched groups.[25,39] Z score can be useful for determining whether an underlying disease or condition is causing bone loss.[25] CDR reviewers searched for validation studies of DEXA in HPP. No evidence of validation and MCID was identified.

Six-Minute Walk Test

The 6MWT is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[26] A specific protocol outlining training, level of support provided to the patient, and standardization of distance available for the patient to walk (30 metres) is provided by the American Thoracic Society.[26]

The 6MWT has been used and validated in multiple adult patient populations with cardiopulmonary conditions (e.g., heart failure, chronic obstructive pulmonary disease [COPD], pulmonary hypertension).[26] There have also been multiple studies that have established a proposed MCID in these populations. Reported distances associated with a noticeable functional improvement range from 54 m in patients with stable COPD and 43 m in patients with heart failure.[26] It should be noted that patients in these populations are significantly older than the majority of patients with HPP who are enrolled in the pivotal studies in this review. Initial improvements in the 6MWT should be interpreted with caution, as there has been a well-documented learning effect in patients previously unfamiliar with the test.[40] Motivation, encouragement, and cooperation can have a significant positive impact on the results, and the magnitude of these effects could be comparable to the effect of interventions.[32,33] This could be of special concern in situations where blinding is not present or is compromised.

A systematic review of the literature on the 6MWT in the pediatric population across nine conditions,

including those with musculoskeletal disorders, identified several issues associated with use of the test in this population.[41] MCID values reported in the systematic review ranged from 36 m in patients with spina bifida to 68 m in obese patients. Other studies have found that the age, height, and weight of a child can have an impact on the distance travelled in six minutes. This may have an impact on 6MWT results obtained from trials of longer duration.[42,43]

CDR reviewers searched for validation studies of 6MWT in HPP. No evidence of validation and MCID was identified in HPP.

Bruininks-Oseretsky Test of Motor Proficiency, Second Edition

The BOT-2 is an instrument that measures gross motor skills, utilizing a composite score from two subtests: running speed and agility, and strength.[18,27] The running speed and agility subtest measures control and coordination of the large proximal musculature involved in locomotion and known to be affected in HPP patients (e.g., running and hopping from one foot to the other), and the strength subtest includes tasks such as sit-ups, push-ups, and long jump. The raw score for each item is converted to a point score. The point scores for all of the items in each subtest are summed to get the total point scores for BOT. The increase of the total point scores represents an improvement. For example, for the standing long jump item, a point of 1 is equal to a jump of 13 to 18 inches, and a point of 2 is equal to a jump of 19 to 24 inches. The BOT-2 is standardized only for patients up to 21 years of age.[18,27]

CDR reviewers searched for validation studies of BOT-2 in HPP. No evidence of validation and MCID in HPP was identified.

Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III is considered to be one of the most widely used and well-validated instruments available for evaluation of developmental functioning in infants and toddlers.[44] It comprises five scales. BSID-III was developed (normed and validated) for use in impaired and healthy children between one and 42 months of age. The BSID-III was to be administered to assess changes in gross motor, fine motor, and cognitive development. For patients aged 43 months or older during the study, the Peabody Developmental Motor Scales, Second Edition (PDMS-2) or BOT-2 should be administered instead. For each subtest, raw, scaled, composite (sum of scaled scores), percentile rank, and age-equivalent scores were recorded. Note that age-equivalent scores indicate the average age at which healthy children typically achieve the raw score obtained by the patient on a given scale (e.g., a raw score of 44 on the gross motor subtest yields an age-equivalent score of 13 months, because this is the average age at which healthy children achieve the same score), while scaled scores, which range from 1 to 19 with a normal mean (±SD) of 10 (±3), reflect the patient's performance relative to healthy same-aged peers.[23]

CDR reviewers searched for validation studies of BSID-III in HPP. No evidence of validation and MCID was identified.

Hand-Held Dynamometry

HHD assessments were developed to assess muscle strength at various body points. In the clinical study, HHD was administered prior to study drug administration and the bone biopsy procedure. The following bilateral muscle groups were tested: grip, knee flexors and extensors, hip flexors and extensors and hip abductors. Strength was reported in pounds and bilateral per cent predicted values based upon published normative data were provided (where available).[17,28]

While the evidence of the reliability and validations of HDD have been reported in community-dwelling older persons,[45] adolescents,[46] and healthy young adults,[47-49] no evidence of validation and MCID was identified for patients with HPP.

Childhood Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ) was originally developed in 1978 at Stanford University for use in adults.[50] It was one of the first self-reported functional status (disability) measures and has become the dominant instrument in many diseases such rheumatoid arthritis (RA).[29,30] The CHAQ is a 30-item, self- or parent-administered, reliable, sensitive instrument for measuring functional status in children. The CHAQ was developed by Singh and colleagues as an adaptation of the Stanford HAQ for use in children aged one to 19 years.[31] It has several new questions relevant to children of all ages compared with HAQ. The eight functional areas measured by CHAQ are dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Responses for the 30 items are recorded using four-point ordinal scales (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to do). Activities that the child is unable to do because he or she is too young are marked as "not applicable for age," while the use of any aids or devices or help from another person (as applicable) is assigned a minimum score of 2 for that domain. Within each of the eight domains, the item with the highest disability score determines the score for that domain. The CHAQ also provides an assessment of discomfort using a 10 cm visual analogue scale (VAS) for the evaluation of pain and a 10 cm VAS for evaluation of overall well-being. The face validity of the instrument has been evaluated in healthy children and parents with RA.[31,51] Also, the CHAQ may suffer from a ceiling effect, whereby scores are clustered at the normal end of the scale (near 0).[52] The ceiling effect makes the scale intrinsically less sensitive to milder levels of disability, in which case false-negative outcomes may ensue.[53] However, no evidence of validation and MCID was identified for the patients with HPP.

Plasma Level of Inorganic Pyrophosphate and Pyridoxal-5'-Phosphate

One of the pathognomonic laboratory findings in patients with HPP is subnormal serum activity of alkaline phosphatase (ALP).[35,36] In general, clinical severity reflects the degree of enzyme deficiency. The most sensitive substrate marker for HPP is an increased PLP plasma level, [35,36] which often correlates with disease severity. In this review, plasma PPi (µM) and PLP (ng/mL) levels from baseline to the end of study were assessed in one study.[35,36] Table 14 presents reference ranges for PPi and PLP levels.

TABLE 14: REFERENCE RANGES FOR PPI AND PLP LEVELS

Biomarker	Age (Years)	Reference Range
PPi (µM)	0 to 12	1.33 to 5.71
	13 to 18	< 0.75 to 4.78
	> 18	1.00 to 5.82
PLP (ng/mL)	0 to 5	11.76 to 68.37
	> 5 to 18	5.74 to 61.15
	> 18	2.81 to 26.70

PLP = pyridoxal 5'-phosphate; PPi = inorganic pyrophosphate.
Source: Study ENB- 09-10 Clinical Study Report.[35,36]

APPENDIX 7: NATURAL HISTORY OF Hypophosphatasia

Hypophosphatasia (HPP) is an ultra-rare, genetic metabolic disease. The clinical experts consulted by the CADTH Common Drug Review (CDR) for this review indicated that 50% of patients die in the first year. HPP is caused by a loss of function of the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP).[5] Clinical symptoms of HPP are heterogeneous, ranging from the rapidly fatal perinatal variant to a milder, progressive osteomalacia later in life. The pathognomonic finding is subnormal serum activity of the TNSALP enzyme. Estimated in 1957, the prevalence of severe HPP in Canada was 1:100,000.[6] In particular, the prevalence was very high (up to 1/2,500) in the Mennonite Canadian population, in which 1:25 individuals may be a carrier.[4] One of the clinical experts involved in this review estimated that three to four newborn patients with HPP will be born in Canada each year who are potentially eligible for treatment with Strensiq. In British Columbia (BC; population 4.4 million inhabitants), to date, six children and adults with infantile onset of HPP are potentially eligible for treatment with Strensiq. Based on the prevalence of perinatal or infantile-onset HPP in BC (six out of 4.4. million) in Canada (population 33.5 million inhabitants), approximately 45 patients might currently be eligible for this therapy. The number will increase as many undiagnosed cases might be diagnosed in the future, given that this is now a treatable condition. In France, the prevalence of severe HPP was estimated at 1:300,000 during the period 2000 to 2009.[3,4] The clinical symptom presentation depends largely on age at initial presentation, ranging from death in utero to relatively simple problems with dentition in adult life. Based on the age of onset, HPP is classified into four types: perinatal, infantile, pediatric, and adult HPP.[6,54] Perinatal HPP is the most pernicious form of HPP. Patients usually present with deformed limbs at birth and rapid death due to respiratory failure. [54] Infantile HPP presents in the first six months of life. Postnatal development often appears normal until the onset of poor feeding and inadequate weight gain, and clinical manifestations of rickets are recognized. A recent study showed 73% mortality at five years in untreated perinatal- and infantile-onset HPP.[2] Juvenile HPP (also known as childhood or pediatric HPP; onset at ≥ six months to < 18 years) has variable clinical expression. Patients usually experience premature loss of deciduous teeth (i.e., before the age of five). Patients may also experience delayed walking. Typically, radiographs show rachitic deformities and characteristic bony defects near the ends of major long bones. Growth retardation, frequent fractures, and osteopenia are common. Adult HPP (onset at ≥ 18 years old) can be associated with rickets, premature loss of deciduous teeth, or early loss of adult dentition and stress fracture followed by relatively good health.[6,54]

Three natural history studies on HPP were identified. Two[11,55-57] were included in the manufacturer's submission for this review, and one study[58] was identified in a CDR literature search. The first study (study ALX-HPP-502)[55,56] was a retrospective non-interventional study. A total of 32 patients with juvenile HPP were observed in this study. Patients were predominately Caucasian males [redacted]. Little or no improvement in either Radiographic Global Impression of Change (RGI-C) or Rickets Severity Scale (RSS) was observed in this group of historical control patients.

The second study (ALX-HPP-502s)[11,57] was an extension evaluation of study ALX-HPP-502[55,56] for characterization of gait performance. Six Caucasian male patients from North America with a mean age of 24 (range: 19 to 28) years were included. All participants were boys. Five patients had bowing of the long bones and all six had gait disturbances. As demonstrated by this gait analysis study, children with

HPP can have clinically significant and persistent gait impairments. The burden of disease in these children affects their participation in the community and their ability to perform activities of daily living.[11,57] The results also showed that clinical management of patients with HPP was mainly supportive (e.g., orthopedic intervention, occupational therapy, pain relief medication). In the absence of any approved disease-modifying therapy, HPP disease activity persisted in all patients despite supportive care, and the majority of patients experienced significant morbidity.

The third study[58] was reported in a conference abstract. The natural history was observed in 177 patients with juvenile HPP for a period of 26 years. It was reported that the main complications were premature tooth exfoliation, joint hypermobility, lower extremity malalignment or bowing, skeletal pain, muscle weakness, craniosynostosis, chest deformity, scoliosis, clubfoot, and fractures. Lower serum alkaline phosphatase (ALP) reflected more severe disease (for ages ≤ 10 years). Elevated plasma pyridoxal-5'-phosphate (PLP) levels correlated with skeletal disease severity. Few radiographic features were observed during follow-up.

In summary, HPP is an ultra-rare genetic disorder, which was classified into four clinical subtypes: prenatal, infantile, juvenile, and adult HPP. The understanding of the natural history of HPP is limited. The prevalence and incidence of HPP in Canada are unknown. Clinical manifestation largely depends on the age of onset. The most common symptoms and signs are bone deformity (59.4%), arthralgia (46.9%), bone pain (43.8%), and fracture (31.3%). It is estimated that half of patients will die in the first year of life. Limited natural history study indicated that little or no improvement in either RGI-C or RSS was observed in HPP patients with no treatment or supportive care alone. In the absence of any approved disease-modifying therapy, HPP disease activity persisted in all patients despite supportive care, and the majority of patients experienced significant morbidity.

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