NICE National Institute for Health and Care Excellence

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Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) ID3927

Lead team presentation

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Company: Alexion Pharma UK

12th October 2022

Key issues

Issue	Resolved?	Impact
Clinical effectiveness		
1. Discrepancy between the population in decision problem and the main source of efficacy data	No – to discuss	
2. Results not presented using the accepted categories of paediatric – onset HPP (i.e., age of HPP symptoms onset)	No – to discuss	
3. (a) Historical control data may not be representative of current BSC	No – to discuss	
3. (b) Potential for immortal time bias in survival analysis	No – to discuss	
4. Comparative efficacy analysis only conducted for survival outcomes	No – to discuss	
5. No matching of patients or attempt to adjust for confounders	No – to discuss	
Cost-effectiveness		
6. Modelling weight to estimate asfotase alfa (AA) related treatment costs	No – to discuss	
7. Uncertainty in transition probabilities	No – to discuss	
8. Uncertainty in utility values and carer disutilities	No – to discuss	

Key:

Model driver	
Unknown impact	

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Key questions – clinical effectiveness evidence

1. Are the results of comparative analysis from perinatal/infantile-onset HPP patients generalisable to juvenile-onset HPP patients?
2. Is age of onset a determinant of HPP prognosis?
3. Is the historical control data representative of current BSC for paediatric-onset HPP? Should all data including UK MAA and Global HPP registry be used for BSC?
4. Is the risk of immortal time bias adequately addressed in the survival analysis?
5. Is evidence of comparative efficacy of AA for survival outcomes (OS and VFS) only sufficient for decision making?

Key questions – cost effectiveness evidence

1. In the model to predict AA treatment costs is the predicted weight clinically plausible?
2. Are the utilities for patients and carer disutilities (including parental disutility for infant death) appropriate for decision making?
3. Is it appropriate to apply a QALY weight of 3 in the cost-effectiveness analysis?

Background on hypophosphatasia (HPP)

HPP is a rare, chronic, genetic metabolic disease characterised by insufficient bone mineralisation which can lead to premature death and a range of skeletal and systemic complications

Causes

- Mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene reduce its activity. This disrupts mineralisation, a process in which calcium and phosphorous are deposited in developing bones and teeth

Clinical forms

- Perinatal-onset: onset before birth*
- Infantile-onset: present at or soon after birth (0–6 months)*
- Juvenile-onset (also referred as childhood onset): onset between 6 months and 18 years*
- Adult-onset (onset ≥ 18 years of age)#
- Odonto-HPP (only dental clinical symptoms)#

* Paediatric-onset HPP includes everyone with HPP of perinatal, infantile, or juvenile onset

Evaluation does not include adult-onset disease or odonto-hypophosphatasia

Background on hypophosphatasia (HPP)

Epidemiology

- Prevalence and incidence estimates for paediatric-onset HPP in England are limited
- A European study reported an estimated prevalence rate as 1 per 300,000 live births
- A survey estimated an incidence of HPP of 0.8 per 1,000,000 for children under age of 18 and 2.8 per 1,000,000 for children under age of 1
- Highly Specialised Technology (HST) 6: '…Evidence submissions NICE received from company and clinical experts estimated that between 1 and 7 people are diagnosed with perinatal- and infantile-onset hypophosphatasia each year in England'

Symptoms

- Include rickets, weakening of the bones (osteomalacia), bone deformity and fractures
- HPP can also lead to chronic debilitating pain, muscle weakness, generalised seizures (because of vitamin B6 deficiency), and renal and respiratory complications

Prognosis

- High mortality rate in the first 6 months of life (50–100% of babies die within the first year)
- Juvenile-onset HPP is associated with a substantially lower mortality rate, but is often debilitating and leads to bone deformities resulting in delayed walking, limb weaknesses, skeletal pain and non-traumatic fractures

Patient perspectives – Submission from Metabolic Support UK

Patient's experience living with paediatric-onset HPP

- Debilitating condition in all age ranges that impacts patients physically, socially & emotionally
- Poor mobility makes everyday activities and independent living difficult for adults and children
    - May require walking aids or home adaptions as well as help from others
- Working with HPP can be very challenging
    - Physical limitations, mental challenges, sickness, time off to attend appointments, etc.
- Difficult to live a normal and enjoyable social life
    - Need to plan events or activities in advance means little spontaneity
    - Mobility issues affect leisure activities (i.e. walking or activities requiring prolonged sitting)
- Negatively impacts certain aspects of education such as physical education
- Impact on mental health and mood, in particular due to the physical symptoms (i.e low vitamin D)

"I find everyday tasks difficult because of my pain and weakness"

"I have never been able to hold down a full-time job for long therefore I have tended to work from home or be on part time contracts"

"I take anti-depressants to help me cope emotionally. I am tearful sometimes. I have paid for courses to learn 'mindfulness techniques' to try and distract myself"

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Abbreviations: HPP: Hypophosphatasia

Patient perspectives – Submission from Metabolic Support UK

Carer experience

- Parents and carers experience a huge impact on their ability to work
  - A survey found 57% are full-time carers, 29% have part time job and 14% are self-employed
- Manage child care and hospital appointments together. Attending appointments comes with high degree of burden associated with travelling to appointments
- There is often very little information or advice provided due to rarity of the condition
- Parents can suffer long term mental health problems
  - Navigate their own feelings and emotions as well as support the wellbeing of their children
- Families have to adapt their hobbies and social lives around their child's HPP

"I've had to leave my job….. (my child's) dad has to go out and work every hour he can to keep a roof over our family's head"

"We see one particular professor for bones however we have around 10-15 other professionals that look after us"

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Abbreviations: HPP: Hypophosphatasia

Patient perspectives – Submission from Metabolic Support UK

Experience with current treatments (not including AA)

- No disease modifying treatment for HPP routinely available.
- Current management is symptomatic & supportive. It does not address underlying cause of HPP
- AA offers a chance for better, more normal life and brighter future for patients & their families

"nothing was offered, all pain relief did not work but there is nothing out there to actually heal/help the effects of HPP"

Experience of UK MAA

- AA is life saving for babies and life changing for all patients
    - Clear impact on overall health for patients family and friends
- Benefits include need for fewer medical appointments, improved mobility, children able to breathe independently, regain control of symptoms, improved performance in school, improved work and social life and improved quality of life
- Benefits outweigh difficulties with administration to infants and young children
- In a survey 18% of patients reported peripheral neuropathy and fatigue had worsened since starting AA, and one patient decided to stop treatment

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Abbreviations: AA: Asfotase alfa; HPP: Hypophosphatasia; MAA: Managed access agreement

Evaluation history of HST6

Milestone	Date	Recap
1st ECM	October 2015	• Asfotase was not recommended • Company responded to consultation, including draft MAA
2nd ECM	January 2016	• No guidance was published • Company submitted a further updated MAA and accompanying budget impact model and cost–consequence analysis
3rd ECM	July 2016	• Asfotase recommended for perinatal- and infantile- onset population only • Company responded to consultation, including updated confidential commercial terms and accompanying analyses
4th ECM	November 2016	• Asfotase recommended only for perinatal- and infantile-onset disease, within MAA ○ Not recommended for treating HPP in children or adults with juvenile-onset disease
5th ECM	May 2017	• NHS England and Alexion agreed an updated MAA • Asfotase recommended as an option for treating paediatric-onset HPP within the updated MAA

ECM: Evaluation committee meeting; HPP: Hypophosphatasia; HST: Highly specialised technology; MAA: Managed access agreement

AA (Strensiq, Alexion Pharma UK Ltd)

Marketing authorisation	**'Indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease'** • EMA license received on 28 August 2015, which was converted to a national GB license on 1 January 2021
Mechanism of action	Asfotase alfa (AA) is a human recombinant tissue non-specific alkaline phosphatase (TNSALP)-Fc-deca-aspartate fusion protein enzyme replacement therapy (ERT), promotes mineralisation of the skeleton in patients with hypophosphatasia
Administration and dose	Subcutaneous administration: • 2 mg/kg of body weight administered three times per week, or 1 mg/kg of body weight administered six times per week • The maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time
Price	• The list price of AA in the UK is £58.80 per mg • A Patient Access Scheme (PAS) is in place

AA: Asfotase alfa; EMA: European medicines agency; PAS: patient access scheme

HST6 recommended AA use only within a UK MAA

Starting criteria in the MAA

- All people with perinatal- and infantile-onset HPP, regardless of current age
- Children (aged 1–4 years and 5–18 years) with juvenile-onset disease if they do not reach motor milestones, have pain with significant disability or have restricted mobility
- Adults (18 years and over) with juvenile-onset disease if they have 2 of the following:
    1. Current fractures or a history of fractures characteristic of HPP
    2. Persistent or recurrent pain with disability
    3. Restriction of mobility

Monitoring and data collection

- Data will be collected from everyone who has AA within the MAA, and will be recorded in a dedicated database
- The company stated that NHS England will have access to this database for audit and analysis of individual-level data, and will also be provided with relevant data extracts from the global HPP registry database to assist in assessing AA

AA: Asfotase alfa; HPP: Hypophosphatasia; HST: Highly specialised technology; MAA: Managed access agreement

Decision problem

	Final scope	Company comments	ERG comments
Population	Patients with paediatric-onset HPP	None	Comparative efficacy of AA, in relation to BSC was for patients with perinatal-/infantile-onset HPP only
Intervention	AA	None	None
Comparators	BSC	None	Historical control data unlikely to be representative of current BSC
Outcomes	Mortality, radiographic response, severity of rickets, pain, respiratory function, craniosynostosis and intracranial pressure, growth, tooth loss cognitive development and motor skills, adverse effects of treatment and health-related quality of life (for patients and carers)	• Bone mineralisation added: • Craniosynostosis and intracranial pressure removed	Comparative efficacy analysis only conducted for survival outcomes (OS and VFS), but not for any functional outcomes

AA: Asfotase alfa; BSC: Best supportive care; HPP: Hypophosphatasia; OS: Overall survival; VFS: Ventilator-free survival

Clinical effectiveness

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Clinical trial evidence for AA used in the model

	ENB-002-08/ENB-003-08	ENB-010-10
Design	Phase II, open-label study, with open-label extension study	Phase II open-label study
Population	Patients ≤ 36 months of age with infantile-onset HPP (onset of symptoms prior to 6 months of age)	Patients with perinatal-/infantile-onset HPP (onset of HPP signs/symptoms prior to 6 months of age)
Intervention	AA (n = 11)	AA (n = 69)
Comparator(s)	N/A	N/A
Duration	Up to 7 years	Up to 6 years
Outcomes	Mortality, radiographic response, severity of rickets, respiratory function, cranio-synostosis and intracranial pressure, growth, tooth loss, cognitive development and motor skills, adverse effects of treatment	

AA: asfotase alfa; HPP: Hypophosphatasia; N/A: Not applicable

Clinical trial evidence for AA used in the model

	ENB-006-09/ENB-008-10	ENB-009-10
Design	Phase II, randomised, dose-ranging, open-label study, with open-label extension study	Phase II, open-label, dose-ranging, randomised concurrent control study
Population	Patients aged ≥ 5 and ≤ 12 years of age with HPP	Adolescent and adult patients aged 13 to 65 years with HPP
Intervention	AA (n = 13)	AA (n = 19)
Comparator(s)	N/A	N/A
Duration	Up to 7 years	Up to 5 years
Outcomes	• Mortality, pain, cranio-synostosis and intracranial pressure, growth, cognitive development and motor skills, adverse effects of treatment • **ENB-006-09/ENB-008-10 also included radiographic response, severity of rickets and health-related quality of life (for patients and carers)**	

AA: asfotase alfa; HPP: Hypophosphatasia; N/A: Not applicable

Additional real-world evidence for AA used in the model

	UK MAA	Global HPP Registry (ALX-HPP-501)
Design	Observational study	Observational, prospective, long-term registry
Population	Paediatric-onset HPP (regardless of current age)	Patients of all ages with a confirmed diagnosis of HPP
Intervention	AA [redacted]	Ever-treated with AA [redacted]
Comparator(s)	N/A	N/A
Duration	Up to 4 years	Up to 4 years
Outcomes	• Mortality, pain, respiratory function, growth, mobility and gross motor skills, adverse effects of treatment, health-related quality of life (for patients and carers), mobility assessments and fractures • **Global HPP Registry also included craniosynostosis and intracranial pressure, growth, tooth loss, cognitive development**	

AA: asfotase alfa; HPP: Hypophosphatasia; MAA: Managed access agreement; N/A: Not applicable

Clinical evidence for BSC used in the model – Natural history study

	ENB-011-10
Design	Retrospective chart review of the natural history of patients with perinatal-/infantile-onset HPP
Population	Patients of any age at inclusion, but with onset of disease < 6 months of age (n = 48)
Outcomes	Mortality, respiratory function, craniosynostosis and intracranial pressure, tooth loss, cognitive development and motor skills and medication histories and hospitalisations

HPP: Hypophosphatasia

Comparative analysis

Company :

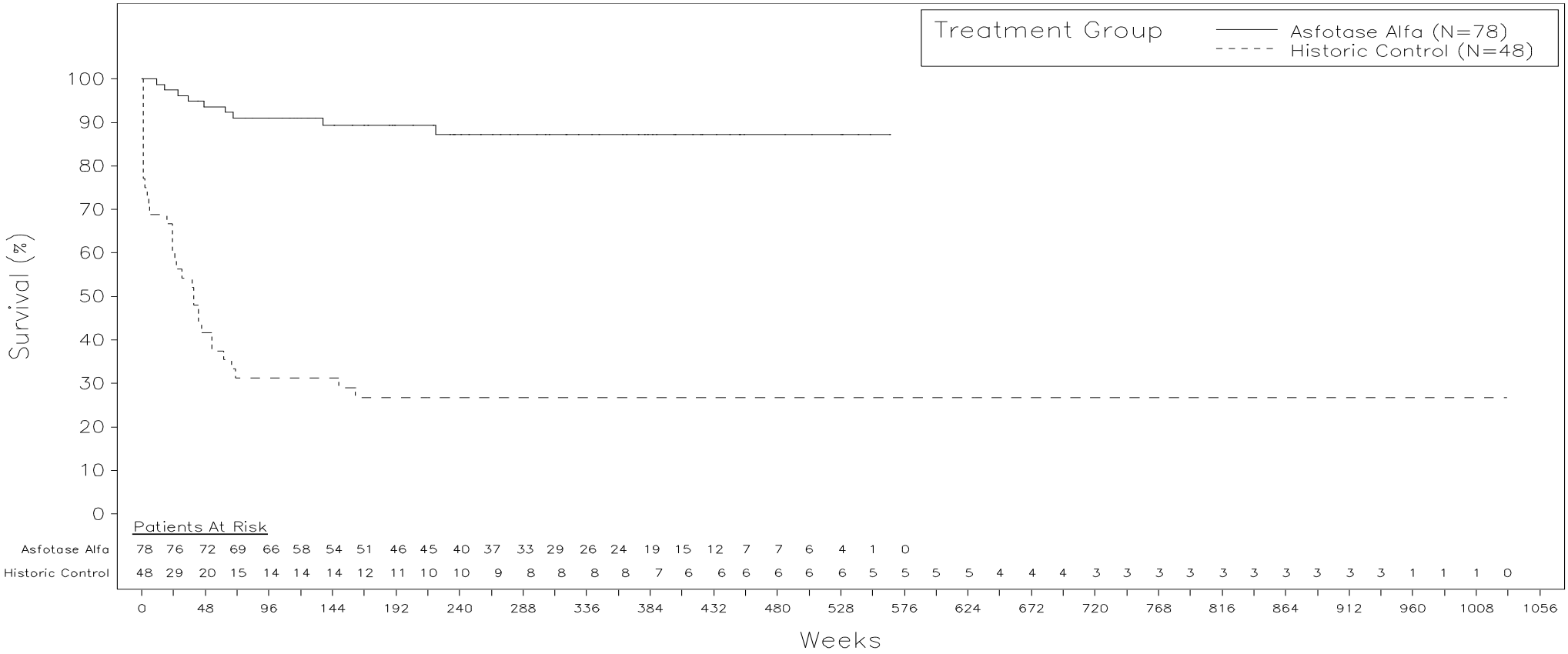
- Stated that indirect treatment comparisons (ITCs) were not considered appropriate
- However, comparative analyses of selected endpoints conducted for patients with perinatal-/infantile-onset HPP for long-term assessment of OS and VFS
    - Data for AA-treated patients was taken from ENB-002-08/ENB-003-08 (n = 11) and ENB-010-10 (n = 69)
    - Data for BSC (untreated patients) was taken from 'untreated historical controls of similar age and with similar HPP characteristics from a retrospective natural history study (ENB-011-10)
- The demographic, baseline and HPP-specific medical histories of the AA-treated patient cohort and the historical control group are considered clinically similar

EAG :

- Considers the comparative analyses to be a form of ITC, but the methods used are substantively flawed
- Insufficient information has been provided to support the statement of clinical similar baseline characteristics. Therefore, the comparability of the study populations used in the comparative analyses is unclear

AA: Asfotase alfa; BSC: Best supportive care; HPP: hypophosphatasia; ITC: indirect treatment comparison; OS: Overall survival; VFS: Ventilator-free survival

OS in perinatal/infantile-onset HPP treated with AA versus BSC



- AA improved OS in patients with perinatal/infantile-onset HPP compared to untreated historical control patients
- Survival at 7 years for AA-treated patients was 87% (95% confidence interval [CI]: 0.77, 0.93) compared to 27% (95% CI: 0.15, 0.40) for untreated historical controls

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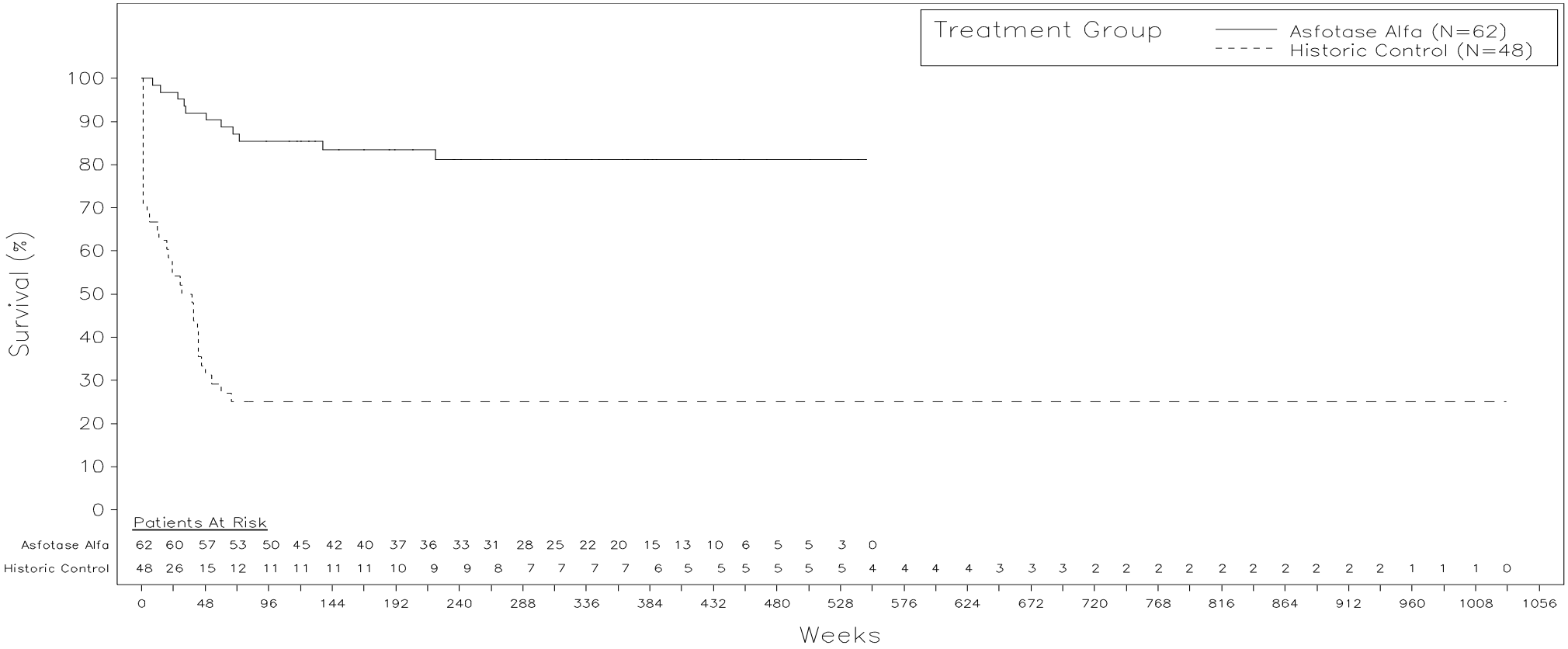
AA: asfotase alfa; BSC: best supportive care; CI: confidence interval; HPP: hypophosphatasia; OS: overall survival

VFS in perinatal/infantile-onset HPP treated with AA versus BSC



- AA improved invasive VFS in patients with perinatal/infantile-onset HPP compared to untreated historical control patients
- VFS at 7 years for AA-treated patients was 81% (95% CI: 0.68, 0.89) versus 25% (95% CI: 0.14, 0.38) for untreated historical controls

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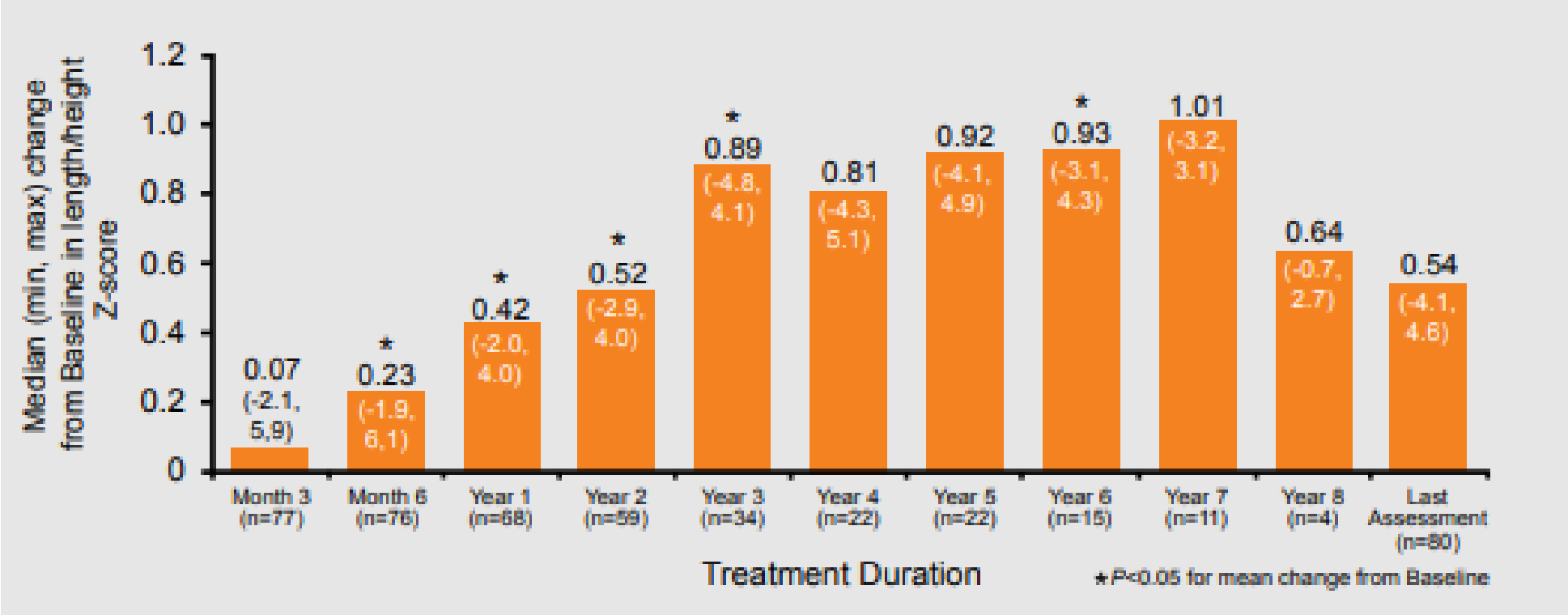
AA: asfotase alfa; BSC: best supportive care; CI: confidence interval; HPP: hypophosphatasia; VFS: ventilator-free survival

Pooled analysis of growth (length/height) in AA-treated patients

Change from baseline in length/height *Z-scores over time in infants and children with paediatric-onset HPP



- The pooled analysis for growth included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10
- The median length/height Z-scores were higher than at baseline from month 3 (0.07 [min, max: -2.0, 5.9]) until year 8 (0.64 [min, max: -0.7, 2.7]) and the median increase from baseline in length or height Z-score was statistically significant at month 6, year 1, year 2, year 3 and year 6 ($p < 0.05$ for all), but not at other timepoints

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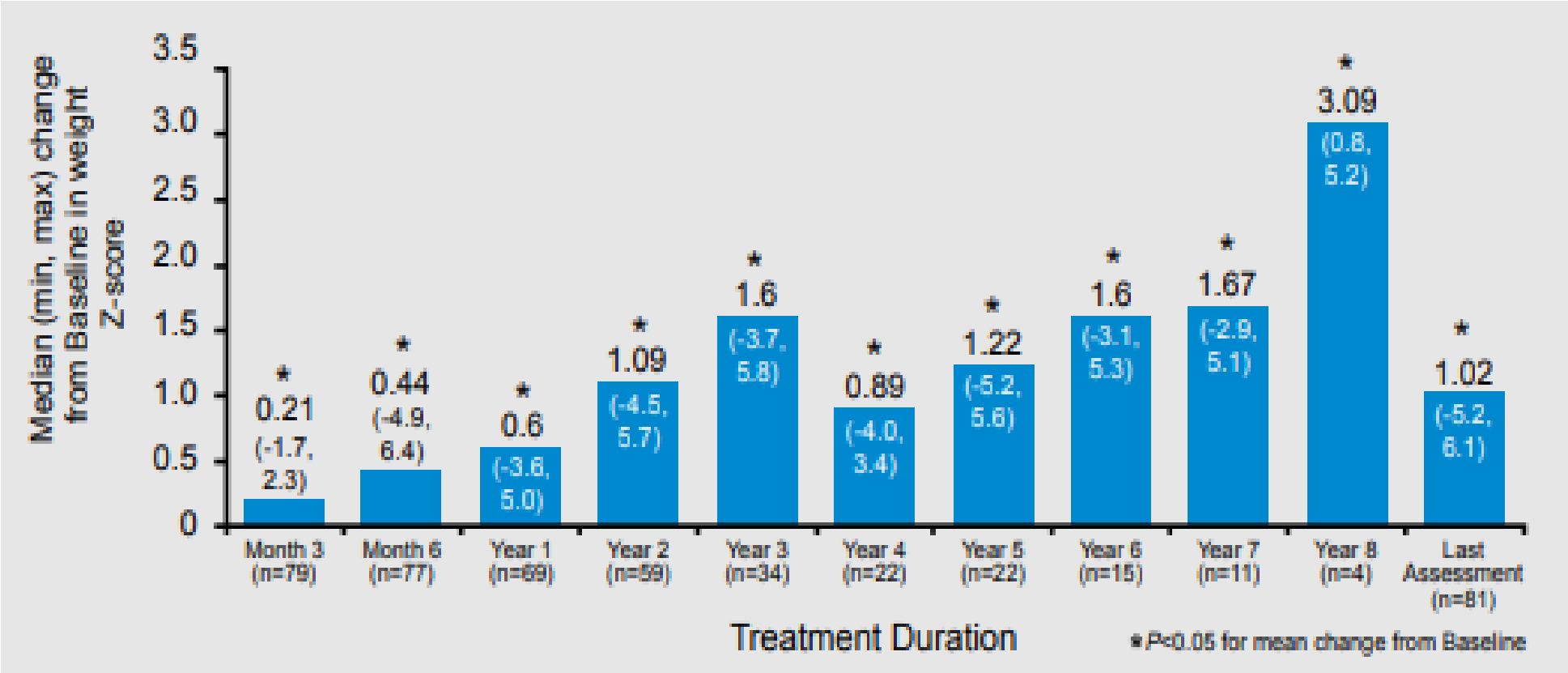
*Z-score: describes the position of a raw score in terms of its distance from the mean, when measured in standard deviation units. The z-score is positive if the value lies above the mean, and negative if it lies below the mean. Z-scores reflect the number of standard deviations each value falls from the age-/sex-matched normal mean

Pooled analysis of growth (weight) in AA-treated patients

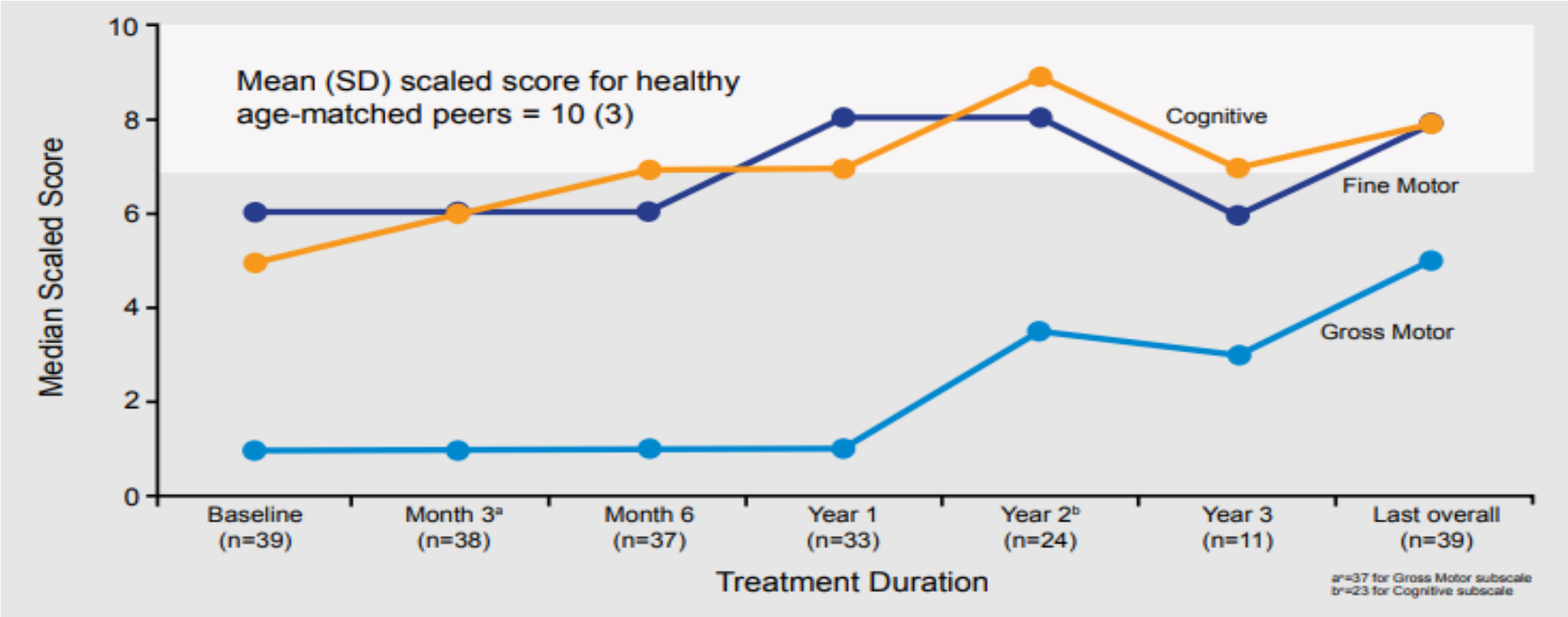
Change from baseline in weight *Z-scores over 8 years of treatment in infants and children with paediatric-onset HPP



- The pooled analysis for growth included AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10
- The pooled median weight Z-scores were higher than at baseline from month 3 (0.21 [min, max: -1.7, 2.3]) until year 8 (3.09 [min, max: 0.8, 5.2]) and the change from baseline was statistically significant ($p < 0.05$) at all points

NICE *Z-score: describes the position of a raw score in terms of its distance from the mean, when measured in standard deviation units. The z-score is positive if the value lies above the mean, and negative if it lies below the mean. Z-scores reflect the number of standard deviations each value falls from the age-/sex-matched normal mean

Median BSID-III Gross Motor, Fine Motor, and Cognitive scaled scores over time in infants and toddlers (< 2 years) with paediatric-onset HPP treated with AA



- Improvements were observed in median BSID-III gross motor, fine motor, and cognitive scaled scores over time in infants and toddlers (< 2 years) with paediatric-onset HPP treated with AA

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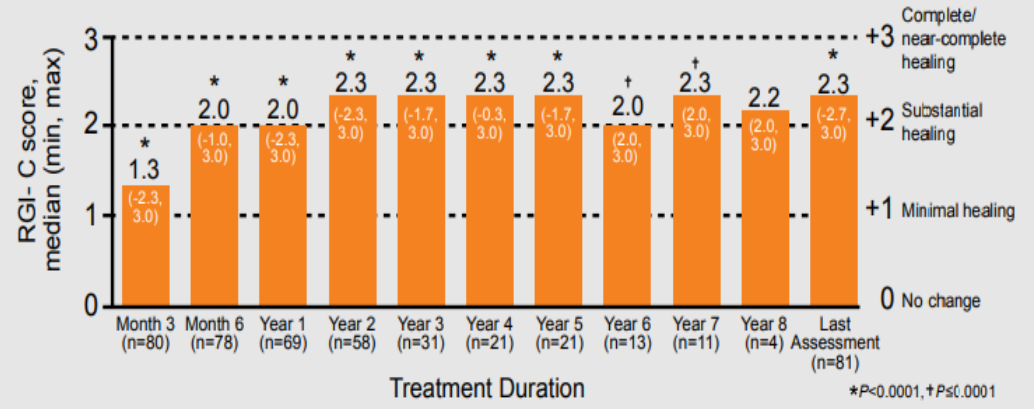
AA: Asfotase alfa; BSID-III: Bayley scales of infant development 3; HPP: hypophosphatasia; SD: standard deviation

Pooled analysis RGI-C scores and RSS, over time, in AA-treated patients

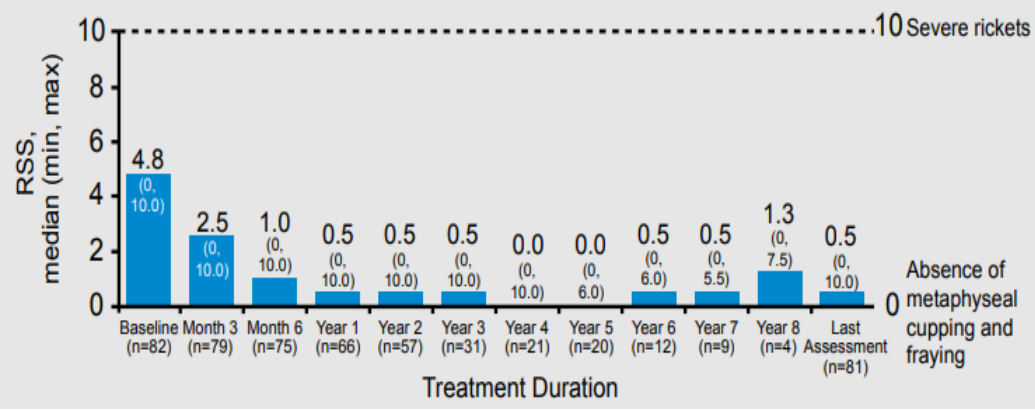
- Pooled analysis RGI-C scores and RSS includes AA-treated patients in ENB-002-08/ENB-003-08, ENB-010-10 and ENB-006-09/ENB-008-10

Median RGI-C scores over 8 years of treatment in infants and children with paediatric-onset HPP:



- Median RGI-C scores indicated that improvements in HPP-related skeletal disease occurred from month 3 (1.3 [min, max: -2.3, 3.0]; p < 0.0001) and sustained over 8 years of treatment (2.2 [min, max: 2.0, 3.0])

Median RSS over 8 years of treatment in infants and children with paediatric-onset HPP:



- Median RSS scores indicated that the improvements occurred from month 3 (2.5 [min, max: 0.0, 10.0]) and sustained over 8 years of treatment (1.3 [min, max: 0.0, 7.5])

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AA: asfotase alfa; HPP: hypophosphatasia; RGI-C; radiographic global impression of change; RSS: rickets severity score

Key issue 1: Discrepancy between the population in decision problem and the main source of efficacy data

Background

- Comparative efficacy analyses does not provide relative efficacy of AA for juvenile-onset HPP
  - Evidence for both AA and BSC included patients with perinatal/infantile-onset HPP only
- At clarification, company did not provide results tables, comparing all AA studies including the UK MAA and natural history studies for each outcome with results grouped by age of onset category (perinatal-, infantile-, and juvenile-onset HPP)
- Pooled efficacy analysis of AA should include all relevant patients from all relevant studies to reduce uncertainty and provide more accurate ICER estimates

Company

- Data for juvenile-onset HPP is included in the paediatric onset population
- Pooled analysis for juvenile-onset HPP inappropriate as:
  - Current clinical status more important than age at onset
  - AA clinical programme designed around age at time of enrolment
  - Age of onset not a key parameter in MAA and subgroup analysis not requested
  - Significant variation in study inclusion criteria make pooling difficult
  - Survival analysis in this subgroup not relevant as disease is not typically life-threating

AA: asfotase alfa; BSC: best supportive care; HPP: hypophosphatasia; ICER: incremental cost-effectiveness ratio; MAA: Managed access agreement

Key issue 1: Discrepancy between the population in decision problem and the main source of efficacy data

Company (cont.)

- Using HPP Global Registry for comparative efficacy analysis inappropriate:
  - Data collection is limited and not mandated. No EQ5D and Bleck score data. Multiple measures of 6MWT (required for model) only collected in 13/559 never-treated patients
  - Baseline characteristics differ between UK MAA treated cohort and HPP Global Registry never-treated. Only 4 patients with multiple 6MWT measures meet MAA start criteria

EAG

- Does not consider that the question of the comparative efficacy of AA vs BSC has been adequately addressed for all populations and all outcomes specified in the NICE scope (for example radiographic response, severity of rickets, pain, respiratory function, growth, tooth loss, cognitive development and motor skills)
- Acknowledges there is some exploration of the potential of the registry data. However, no detail is provided for the 'prognostic factors' explored
- Acknowledges that all of the potential sources of comparator data presented have limitations

Questions for committee

- Are the results of comparative analysis from perinatal/infantile-onset HPP patients generalisable to juvenile-onset HPP patients?
  - Can additional evidence comparing results across all AA studies and natural history studies, for each outcome measure with results grouped by age of onset category address judgements about the efficacy and relative efficacy of AA for juvenile-onset HPP?

6MWT: 6-Minute walk test; EAG: External assessment group; EQ-5D: Euroqol-5 dimensions; HPP: hypophosphatasia; MAA: Managed access agreement

Key issue 2: Results not presented using the accepted categories of paediatric-onset HPP (i.e., age of HPP symptoms onset)

Background

- Results of the UK MAA and ENB-009-10 were not presented using the accepted categories of paediatric-onset HPP as specified in the decision problem and used in AA clinical trials
  - Difficult to assess efficacy data against the decision problem and to compare AA trials
- Accepted categories:
  - Perinatal-onset: onset before birth*
  - Infantile-onset: present at or soon after birth (0–6 months)*
  - Juvenile-onset (also referred as childhood onset): onset between 6 months and 18 years*

Company

- Analysis of MAA data did not require subgroups by age of HPP symptoms onset
- ENB-006-08/ENB-008-10 included subgroup analysis for juvenile-onset. Findings confirm full data set analysis
- ENB-009-10 included 18/19 (94.7%) patients with paediatric-onset HPP

AA: asfotase alfa; EAG: External assessment group; HPP: hypophosphatasia; ICER: Incremental cost-effectiveness ratio; MAA: Managed access agreement

Key issue 2: Results not presented using the accepted categories of paediatric-onset HPP (i.e., age of HPP symptoms onset)

Company

- Reasons for only conducting a pooled analysis of the perinatal/infantile patients from studies:
  - HPP can be life-threatening only in those patients that present with symptoms before the age of 1 year old
  - HPP traditional classification falls short of describing the reality of HPP and the longitudinal course of the disease, and is not directly relevant to the disease prognosis, how the patients are diagnosed, and treatment decisions made in clinical practice.

EAG

- Regardless of historical requirement for categorisation, the NICE scope makes it clear that age of onset was expected. This would require an attempt to categorise all relevant evidence and an attempt of adjustment for confounding when conducting comparative analyses
- It was the method used in both the NICE scope and in the Alexion clinical trials programme for AA
- Acknowledges some data were analysed in the perinatal/infantile subgroup but not all relevant data that might have been available for subgroups covering the whole paediatric population

Question for committee

- Is the traditional HPP categorisation (using age of onset) directly relevant to disease prognosis?

AA: asfotase alfa; EAG: External assessment group; HPP: hypophosphatasia; ICER: Incremental cost-effectiveness ratio; MAA: Managed access agreement

Key issue 3a: Historical controls may not be representative of current BSC

Background

- Historical control data may not be representative of current BSC as most data from patients diagnosed and treated is before 2000, so even without AA treatment outcomes would be better
- ENB-011-10 showed the probability of surviving to 3 months was [redacted]

Company

- Advances in supportive respiratory care unlikely to impact on mortality of BSC patients
- Analysis in HST6 showed no significant difference in survival by period of diagnosis
- ENB-011-10 includes severe patients; ENB-002-08/ENB-003-08 includes those surviving infancy
- Global HPP registry coincided with availability of AA and no posthumous enrolment so very few severe untreated patients

EAG

- Suggested all data (including UK MAA and Global HPP Registry) should be used
- *"it is noted that while patients diagnosed since 2000 onwards tended to survive longer, their ultimate prognosis was unchanged"* - contradictory statement regarding the life expectancy of BSC. If patients survive longer then prognosis has changed, notwithstanding that some events, including death will occur later

Questions for committee

- Is the historical control data representative of current BSC?
- Should all data including UK MAA and Global HPP registry be used for BSC?

Key issue 3b: Potential for immortal time bias in survival analysis

Background

- Potential for immortal time bias in survival analysis as median age at baseline for BSC not reported, but median age in (ENB-002-08/ENB-003-08) [redacted] for AA-treated patients. [redacted]
- Natural history data should be selected to be as comparable as possible to AA data. Exclude patients who die earlier than might be possible to receive AA
- ICER will almost certainly increase if the immortal time bias is addressed appropriately
- The Kaplan-Meier curves based on "survival from birth" can erroneously indicate that AA patients were treated from birth, whereas they were treated only after the study enrolment

Company

- Historical controls were required to have at least 1 of 3 life-threatening complications in HPP
- BSC patients who died on the first day after baseline excluded from analysis as unlikely that these patients would start on AA treatment

EAG

- The company verify the EAG's assertion of likely immortal time bias by stating that the AA study prospectively allowed for enrolment of patients with perinatal/infantile disease who had survived infancy. Therefore, if these data are being used for a comparison with historical controls where death before treatment with AA could have begun, there will be a bias in favour of AA.

Questions for committee

- Is the risk of immortal time bias adequately addressed in the survival analysis?

AA: asfotase alfa; BSC: Best supportive care; EAG: External assessment group; HPP: hypophosphatasia; ICER: incremental cost-effectiveness ratio

Key issue 4: Comparative efficacy analysis only conducted for survival outcomes

Background

- Analyses of the comparative efficacy of AA only conducted for survival outcomes, Overall Survival (OS) and Ventilator Free Survival (VFS)
- Comparative analyses should be conducted for all specified outcomes

Company

- Key outcomes informing value for money were considered
- Global HPP registry data not useful
  - Perinatal/infantile-onset: only n=1 never treated patient
  - Juvenile-onset: lack of 6MWT data and baseline characteristics differ to population in MAA where [redacted] fell into the two most severe health states of the economic model (SL3 and SL4) at baseline, while only 23% did in the sample available from the registry
  - Registry is a prospective observational study that does not mandate any specific data collection (limited data availability for variables relevant to reappraisal, i.e., never-treated)
  - Comparison of the never-treated population in the registry with the UK MMA treated cohort would be inappropriate as the cohorts have very different baseline characteristics, leading to biased results.
  - There would be very few, if any patients with severe perinatal/infantile HPP in the Registry who would have been left untreated (from 2009 onwards) to inform a meaningful comparative analysis with more recently diagnosed patients

6MWT: 6-Minute walk test; AA: Asfotase alfa; EAG: External assessment group; MAA: Managed access agreement; OS: Overall survival; VFS: Ventilator-free survival

Key issue 4: Comparative efficacy analysis only conducted for survival outcomes

EAG

- Inconsistency in the number of never-treated patients with perinatal/infantile onset disease
- Discrepancies in total number juvenile never-treated patients
- Company refer to only one of several outcomes presented in the NICE scope
- Acknowledges the challenges of comparative analysis given the limited observational data which is why the EAG have requested that all relevant data from all sources, both for the AA treated and the non-AA treated be included in analyses for the relevant patient populations
- Generally, scarcity of data does not preclude an orderly comparison of all outcomes using all relevant data in the relevant population and subgroups.

Questions for committee

- Is evidence of comparative efficacy of AA for survival outcomes (OS and VFS) only sufficient for decision making?
- Should Global HPP Registry patients be included in the comparative efficacy analysis?

6MWT: 6-Minute walk test; AA: Asfotase alfa; EAG: External assessment group; MAA: Managed access agreement; OS: Overall survival; VFS: Ventilator-free survival

Key issue 5: No matching of patients or attempt to adjust for confounders

Background

- No attempt to match AA-treated patients and untreated controls by key demographic and clinical characteristics, or to adjust for potential confounders
- Information not sufficient to show demographic, baseline and HPP-specific medical histories of AA patient cohort and historical control indicate that the 2 groups are clinically similar
- All comparative analyses should be conducted by adjusting for potential confounders according to the methods described in NICE TSD 17

Company

- Assessed juvenile-onset patients from Global HPP registry for confounding and only n=4 never-treated patients provided 6MWT data met MAA criteria.
- Data not used due to sample size, balance and overlap of prognostic factors, and longitudinality

EAG

- Stated that all relevant data should be used, “including” the UK MAA and the Global HPP Registry
- Acknowledges challenges given limited observational data

Question for committee

- Should there be matching and adjusting for the potential confounders?

6MWT: 6-Minute walk test; AA: Asfotase alfa; EAG: External assessment group; HPP: hypophosphatasia; ICER: Incremental cost-effectiveness ratio; MAA: Managed access agreement; TSD: technical support document

Cost effectiveness

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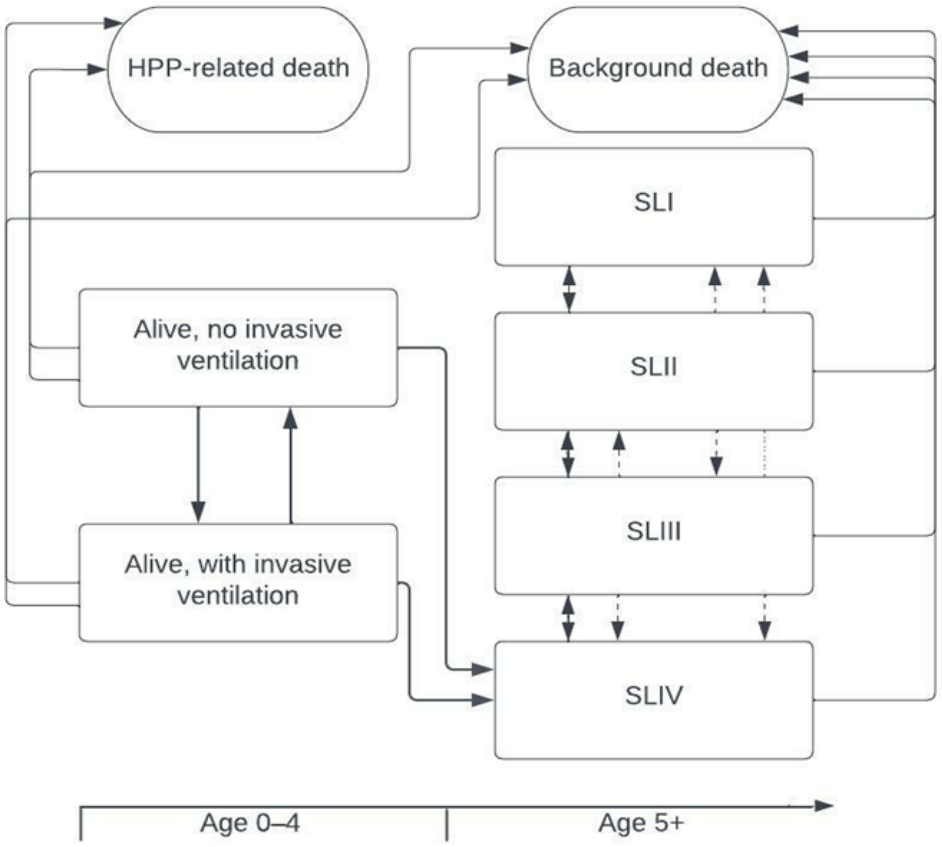
Company's Markov model structure

- Modelling approach is similar to HST 6 evaluation but the model is structured differently for patients aged less than 5 years at HPP onset than those aged more than 5 years at HPP onset (8 health states in total)



Patients aged less than 5 years at HPP onset:

- Invasive ventilation status determines utility decrements and additional medical costs
- HPP-related mortality rates estimated based on trial Kaplan-Meier (K-M) curves and UK MAA
- Base case uses a mean age of HPP onset of 0 months

Patients aged more than 5 years at HPP onset:

- Severity level health states I, II, III and IV (SLI, SLII, SLIII and SLIV) simulate progression using 6-minute walk test (6MWT) as a surrogate for disease severity and does not consider HPP-related mortality
- Base case uses starting age of 5 years

- All paediatric-onset HPP patients enter a death state representing background mortality

EAG

- Broadly happy with the model structure
- Unclear why the company did not use the UK MAA data to inform the baseline cohort characteristics given the UK MAA data is the source for the majority of the new data about AA-treated patients included in submission

Company model features

Input	Type	Source
Baseline characteristics	The model can present results for 2 starting cohorts: • patients aged <5 years • patients aged 5+ years	The HPP trials and the natural history/non-interventional studies .
Efficacy	Transition probabilities for hypophosphatasia (HPP) mortality in the asfotase alfa (AA) arm (aged <5 years)	AA interventional clinical trials, analysis on the ENB-002-08/ENB-003-08 (n=11) and ENB-010-10 (n=69*) trials with two patients excluded and the United Kingdom (UK) Management Access Agreement (MAA) ([redacted])
	Transition probabilities for HPP mortality in the best supportive care arm (aged <5 years)	Historical control study analysis on the ENB-011-10 (n=41) study with seven patients excluded (patients who died on the first day were excluded from the analysis as it was considered likely that these patients would not be started on AA treatment)
	Transition probabilities for invasive ventilation in the AA arm (aged <5 years)	'Assumed to be independent of age and informed from Whyte et al. 2014'
	Transition probabilities for invasive ventilation in the BSC arm	'Assumed to be independent of age and informed from Whyte et al. 2014'
	Transitions between severity states for patients aged 5+ years in the AA arm	6MWT model. AA data from the ENB-006-09/ENB-008-10 and ENB-009-10 interventional clinical trials (n=27) and the UK MAA (n=24)
	Transitions between severity states for patients aged 5+ years in the BSC arm	6MWT model. Baseline and post-baseline visits for patients in ENB-009-10 treated with BSC during the 24-week primary treatment period (n=26)
	Background mortality	Background age-specific death rates for both patient populations, aged <5 years and aged 5+ years, were included using life tales for the UK from the Office for National Statistics (ONS).
	Adverse events were not included in the model and in the CS	- most of the TEAEs were HPP-related but not treatment-related, with the most common TRAEs being Injection-site reaction (ISRs). - AEs from BSC treatment have never been previously evaluated prohibiting their inclusion in the cost effectiveness model

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AA: Asfotase alfa; BSC: Best supportive care; HPP: hypophosphatasia; MAA: Managed access agreement; PAS: Patient access scheme
*the number indicating the 69 patients in the ENB-010-10 is already adjusted to account for the 2 excluded patients. In total these were 71 patients (28+43=71, minus the 2 excluded=69)

Company model features (continued)

Input	Type	Source
Utilities	HRQoL for patients aged <5 years on invasive ventilation	The same source as in the original submission was used to inform the utility values for the health states in the model. Vignette study with UK clinical experts informs utility values for model health states. Note that the utility in the under 5 years on ventilation stage was -0.09 in the study publication and in the original submission, but it has been changed to 0.00 in the current submission without a rationale provided for this change.
	HRQoL for patients aged<5 years without invasive ventilation	
	HRQoL for patients aged +5 years SLI-SLIV'	
	HRQoL for parents due to infant death	TA588 based on the study by Song et al. 2010
	Health-related quality of life in the general population	Ara and Brazier et al
	Carer Disutility	Observational study on the caregiver burden of patients with (DMD) Duchenne's Muscular Dystrophy was used, as this was considered a condition with similar burden on caregivers
Costs	AA drug acquisition costs which depend on the dosing schedule, which varies by patient weight	• age-specific weight used to calculate AA treatment costs was estimated based on the average weight observed in different age ranges of patients from the ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 clinical trials and the MAA UK study • Costs calculated using the list price of £58.80 per mg and a confidential PAS discount applies • Wastage is assumed as partially used vials are not administered to another patient while the excess AA is considered in drug cost calculations
	Administration costs	No administration costs were considered in the model
	• treatment compliance rate of 98.5% • an annual discontinuation rate of 0.54% (translated in a 12-week discontinuation probability of 0.13)	• informed from the UK MAA study, • informed from the ENB-002-08/ENB-003-08, ENB-010-10, ENB-006-09/ENB-008-10 clinical trials, the UK MAA, and the Global HPP Registry
	BSC costs	No treatment costs applied in the model
Resource use	Resource use costs associated with the different HPP health states	primarily based on the previous NICE submission of 2017 updated accordingly and inflated to 2020-21

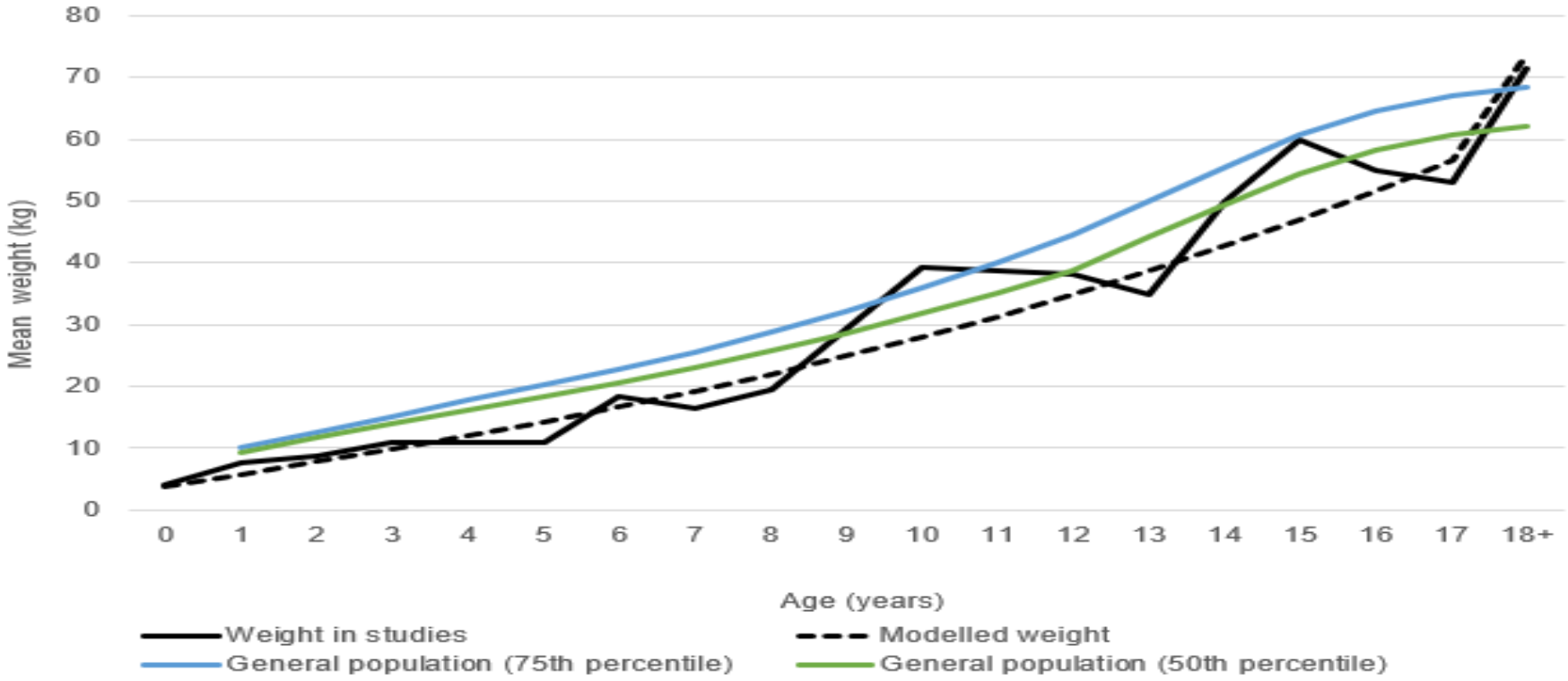
AA: Asfotase alfa; BSC: Best supportive care; HPP: hypophosphatasia; MAA: Managed access agreement; PAS: Patient access scheme

Key issue 6: Modelling weight to estimate AA related treatment costs

Background

- Age-specific weight was estimated based on the average weight observed in different age ranges of patients from ENB-002-08/ENB-003-08, ENB-006-09/ENB-008-10, ENB-009-10, ENB-010-10 clinical trials and the UK MAA study
- Smoothing was applied to the mean weight value curves using a third-degree polynomial model, to address deviations from the weight patterns observed in the general population
- The polynomial model is lower than the weight of the general population

Comparison of weight from studies, modelled prediction and general population:



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AA: Asfotase alfa; MAA: Managed access agreement

Key issue 6: Modelling weight to estimate AA related treatment costs

Background

- Patient's weight based on the polynomial model is much lower than the general population and no information on the goodness-of-fit for polynomial model or other curves explored
- Above the age of 13, the difference between the smoothed curve and the curves from the general population are larger than for the respective differences in the younger ages
- EAG scenario with weight based on median values of the general population. ICER increased for both juvenile onset HPP and perinatal/infantile onset populations

Company

- HPP patients (under 18) have body weight lower than general population
- 3rd degree polynomial had best fit based on AIC and BIC statistics
- Modelled weight-for-age curve tracks the 25th percentile of the UK population, according to the (RCPCH) (diagram on next slide)
- This is consistent with the clinical data reported that children with HPP typically have body weight 1-2 Z scores (standard deviations from the mean) below the general population's
- In adults with HPP, the CEA models a mean weight of 73.6 kg. This is slightly lower than the 50%-50% male-female mean for the UK general population of 78.0 kg according to NHS England. However, AA dosing remains at the same level (2 vials of 80 mg, 3x per week) from body weight of 63 kg to 82 kg; only at 83 kg would dosing increase

Key issue 6: Modelling weight to estimate AA related treatment costs

EAG

- Would like more transparency with interpretation of the data presented and in the information about the goodness of fit for the polynomial model
- Considers that modelling the adult mean weight would not affect CEA results.
- Regarding children, the company indicated that "*the modelled weight-for-age curve tracks the 25th percentile of the UK population*". However, based on the Figure (on the next slide), this only occurs after 8 or 9 years of age. Before that the modelled weight is lower

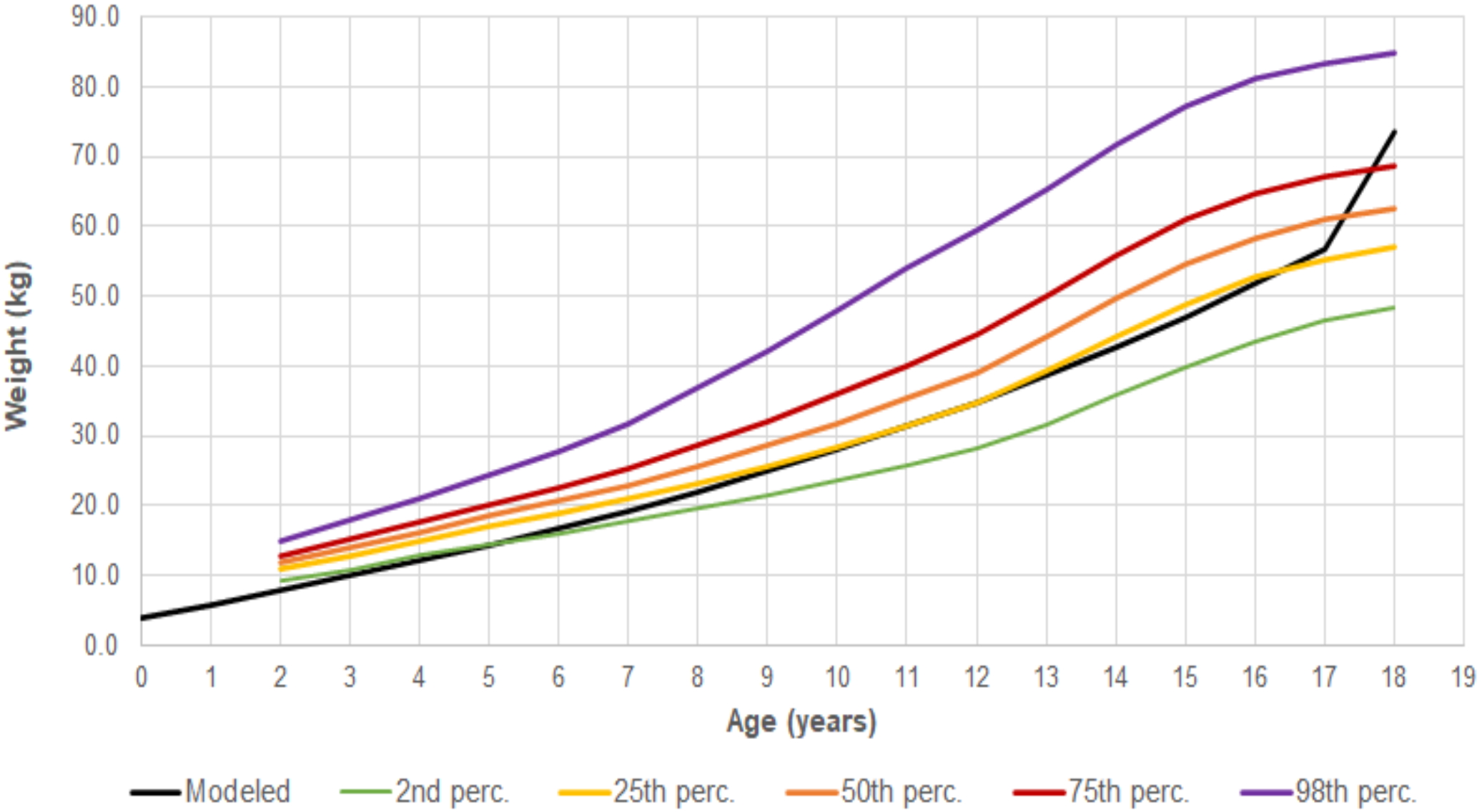
Question for committee

- In the model to predict AA treatment costs is the predicted weight clinically plausible?

AA: Asfotase alfa; EAG: External assessment group; HPP: hypophosphatasia; ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life years

Key issue 6: Modelling weight to estimate AA related treatment costs

Weight-for-age in model and UK Royal College of Paediatrics and Child Health RCPCH growth charts



Question for committee

- In the model to predict AA treatment costs is the predicted weight clinically plausible?

Key issue 7a: Uncertainty in TPs for invasive ventilation (under 5 years)

Background

- Invasive ventilation only considered for perinatal/infantile-onset disease
- Transition probabilities for invasive ventilation estimated using Whyte et al. 2014 study, which reported on the same trials as for HPP-related mortality (ENB-002-08/ENB-003-08, ENB-010-10, and ENB-011-10), but modelled independent of age
- In AA arm, an 84% rate of invasive VFS over 1.8 years is translated to a constant rate of 0.0223 per 12-week period
- For the BSC arm, a 25% rate of invasive VFS over 5.0 years is translated to a constant rate of 0.0638 per 12-week period using data from 48 patients
- Rates are converted to probabilities resulting in a 12-week probability of receiving invasive ventilation of 0.0220 for AA and 0.0618 for BSC
- UK MAA data not used to inform transitions to invasive ventilation for patients aged <5 years in the base-case analysis
- No patients in UK MAA data reported to require invasive ventilation at any of the follow-up time. Because of this, 50% of perinatal-/infantile-onset patients receiving AA and surviving at age 5 entered the model in health state SLIII, with the remaining 50% entered the model in health state SLIV

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AA: Asfotase alfa; BSC: Best supportive care; HPP: hypophosphatasia; MAA: Managed access agreement; VFS: Ventilator-free survival; SLIII: Severity level III; SLIV: Severity level IV

Key issue 7a: Uncertainty in TPs for invasive ventilation (under 5 years)

Background (cont.)

- Risks for invasive ventilation (under 5 years) are constant and age independent
- Time-to-event data may be more appropriate provided few patients require repeated ventilation

Company

- Applying a constant risk of receiving invasive ventilation across the first 5 years of age captures the potential need of patients for repeated invasive ventilation support
- Whyte et al. reported 14/37 AA-treated patients who were on invasive ventilation at baseline were weaned off while on treatment
- Modelling of invasive ventilation has a limited impact on the ICER

EAG

- A time to event analysis would be more informative than a constant risk of invasive ventilation support.
- The EAG acknowledges, however, that if many patients require repeated ventilation support, then a time-to-event analysis would not be the most appropriate approach as argued by the company in response to EAG's clarification question.
- Company referred to the study of Whyte et al. (2016), but in this study there is only 1 patient in the AA arm requiring repeated invasive ventilation support.

Question for committee

- What proportion of patients require repeated ventilation?

AA: Asfotase alfa; EAG: External assessment group; ICER: Incremental cost-effectiveness ratio

Key issue 8a: HRQoL reported by patients not used in the model

Background

- HRQoL used in the model were estimated using a vignette study in which clinical experts scored representations of different severity states (vignettes) on the (EQ-5D)
- No patient reported data were used
- The impact of uncertainty in the patient utility values is unknown since these were obtained from a vignette study done with HPP clinical experts in the UK and not from patients
- HRQoL data collected as part of the MAA and/or Global HPP Registry could be used

Company

- This was not possible due to lack of HRQoL measurements across the range of 6MWT (underpinning severity levels of the CEA model) in the MAA
- Due to start criteria ensuring that only patients with severe disease-initiated treatment, among the N=[redacted] patients aged ≥5 at baseline of the MAA, [redacted] were in SL3 or SL4 (or could not complete the 6MWT). Due to visit restrictions during COVID, limited observations were obtained at improved 6MWT levels
- Utility estimates stratified by 6MWT were therefore concentrated in the more severe states, limiting sample size in SL1-2, preventing use of the MAA data in the CUA

EAG

- This also underlines a shortcoming in the way uncertainty in the utility values was incorporated in the PSA. This aspect has not been further clarified in the company response.

Question for committee

- Are HRQoL from the vignette appropriate for decision making?

HRQoL: Health Related Quality of Life, European Quality of Life-5 Dimensions (EQ-5D). CUA : Cost Utility Analysis

Key issue 8b : Uncertainty in carer disutilities

Background

- Parental disutility associated with infant death included in the company base case
- Data from an observational study on the caregiver burden of patients with DMD was used
- An estimate of the effect of infant death from published literature was used as this same effect was used in a previous NICE HST 7

Company

- NICE scope indicated outcomes should include HRQoL for patients and carers
- Believes that parental disutility associated with infant death should be considered in the base case

EAG

- Size and duration of the disutility for parents/caregivers associated with infant death is a matter of different judgement between the company and the EAG
- CS only presented one source of caregiver burden and no indication that a literature search was conducted
- NICE HST3 (disutility of 0.11) was used for caregivers of DMD patients, EAG considers this value a more appropriate estimate for use in the base- case.
- NICE HST8 which assessed burosumab for treating X-linked hypophosphataemia in children and young people, arguably a condition with similarities to HPP, a disutility of 0.08 was used

EAG: External assessment group; HPP: hypophosphatasia; HRQoL: Health related quality of life; ICER: Incremental cost-effectiveness ratio; MAA: Managed access agreement; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life years

Key issue 8b : Uncertainty in carer disutilities

EAG (continued)

- In the model, caregiver disutility is only applied to patients who at a certain timepoint are alive under both treatment arms. In practice this means that caregiver disutility is only applied in both arms based on the patients alive in the BSC arm at a given timepoint, as mortality is lower in the AA treatment arm. As the source of caregiver disutility is the provision of care to the patient, the disutility should be applied as long as the patient that is cared for is alive

Question for committee

- Do the committee prefer the company or EAG approach?
- Should the disutility be applied for the duration of the patient's life?

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	Weighting
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

- The company's model estimates [redacted] and [redacted] undiscounted QALYs gained for AA compared with BSC for perinatal/infantile-onset HPP and juvenile-onset HPP patients respectively
- As the company base-case estimated undiscounted QALY gains greater than 30 for AA, a QALY weight of 3 was implemented

Question for committee

- Is it appropriate to apply a QALY weight of 3 in the cost-effectiveness analysis results?

AA: Asfotase alfa; BSC: Best supportive care; HPP: hypophosphatasia; ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life years c

Cost effectiveness results

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Company and EAG base case assumptions

Assumption	Company base case	EAG base case
Caregiver disutility	0.17, only applied to patients who at a certain timepoint are alive under both treatment arms	0.11 (caregiver disutilities considered in HST3), applied to those surviving in each of the treatment arms
Parental disutility due to infant death	Included in base case	Not included
AA patent expiry price reduction	Included at 58.5% after 7 years	Excluded
Drug wastage – AA	Rounding down, if the administered dose was 12 mg less than the required weekly dose	Full wastage is assumed to align dosing strategy with the recommended dosage in summary of product characteristics for all patients

Other EAG corrections:

- An error was made in company submission that at t=0, the proportion of patients on invasive ventilation is equal to the risk of invasive ventilation at each cycle, which was 2.2% for AA patients and 6.2% for BSC patients
  - EAG corrected this so the invasive ventilation risk at t=0 is 6.2% in both treatment arms
- Rounding down function for age to calculate AA treatment costs was removed

AA: Asfotase alfa; BSC: Best supportive care; EAG: External assessment group; HST: Highly specialised technology; t: Time

Company's deterministic base-case results with and without QALY weight

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight*
Population: Perinatal-/infantile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	116,470	38,823
AA	[redacted]	[redacted]				
Population: Patients with juvenile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	127,728	42,576
AA	[redacted]	[redacted]				

* As the company base-case estimated undiscounted results for QALY gains greater than 30, a QALY weight of 3 was implemented for health gains.

AA = asfotase alfa; CS = company submission; BSC = best supportive care; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Company's probabilistic base-case results with and without QALY weight

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight*
Population: Perinatal-/infantile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	117,231	39,069
AA	[redacted]	[redacted]				
Population: Patients with juvenile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	139,546	46,519
AA	[redacted]	[redacted]				

* As the estimated undiscounted results for QALY gains greater than 30, a QALY weight of 3 was implemented for health gains.
AA = asfotase alfa; CS = company submission; BSC = best supportive care; HPP = hypophosphatasia; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Isolated impact of the EAG's preferred model assumptions

Preferred assumption	Inc. Costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight*
Population: Perinatal-/infantile-onset HPP				
Company base-case	[redacted]	[redacted]	116,470	38,823
EAG change 1 – Caregiver disutility 0.11	[redacted]	[redacted]	119,695	39,898
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	[redacted]	[redacted]	120,299	40,100
EAG change 3 - Parental disutility due to infant death not included	[redacted]	[redacted]	125,156	41,719
EAG change 4 - Exclude price reduction for asfotase alfa (AA) after 7 years*	[redacted]	[redacted]	253,316	84,439
EAG change 5 - Consider full wastage of AA	[redacted]	[redacted]	118,739	39,580
EAG base-case – all 5 changes combined	[redacted]	[redacted]	**297,527**	**99,176**
Population: Patients with juvenile-onset HPP				
Company base-case	[redacted]	[redacted]	127,728	42,576
EAG change 1 – Caregiver disutility 0.11	[redacted]	[redacted]	138,203	46,086
EAG change 2 – Caregiver disutility applied survivors in each of the treatment arms	[redacted]	[redacted]	127,728	42,576
EAG change 3 - Parental disutility due to infant death not included	[redacted]	[redacted]	127,728	42,576
EAG change 4 - Exclude price reduction for AA after 7 years*	[redacted]	[redacted]	299,634	99,878
EAG change 5 - Consider full wastage of AA	[redacted]	[redacted]	132,267	44,089
EAG base-case – all 5 changes combined	[redacted]	[redacted]	**336,941**	**112,314**

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* Note that the company base case includes a price reduction for AA after 7 years. This has been corrected by the EAG. Further detail is provided in a back up slide.

AA = asfotase alfa; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; PAS = patient access scheme; QALY = quality-adjusted life year

EAG Scenario Analysis on Perinatal-/infantile-onset HPP

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight*
EAG base-case		[redacted]	[redacted]	297,527	99,176
Transition probabilities for SLs	1st model specification	[redacted]	[redacted]	296,901	98,967
	3rd model specification	[redacted]	[redacted]	293,449	97,816
Caregiver disutility	0.08	[redacted]	[redacted]	300,198	100,066
	0.17	[redacted]	[redacted]	292,325	97,442
Number of carers to which disutility is applied	2	[redacted]	[redacted]	288,127	96,042
Disutility bereavement	0.04 for 15 years	[redacted]	[redacted]	286,630	95,543
	0.04 for 30 years	[redacted]	[redacted]	280,663	93,554
	0.04 for lifetime	[redacted]	[redacted]	275,845	91,948
Weight function	Weight of the general population*	[redacted]	[redacted]	320,282	106,761
Drug wastage	'Round down' option	[redacted]	[redacted]	291,949	97,316
	'Closest' option	[redacted]	[redacted]	293,649	97,883
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	356,464	118,821
	100% compliance rate	[redacted]	[redacted]	301,970	100,657
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	361,805	120,602

EAG Scenario Analysis on Patients with juvenile-onset HPP

Scenario	Assumptions	Inc. costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight*
EAG base-case		[redacted]	[redacted]	336,941	112,314
Transition probabilities for SLs	First model specification	[redacted]	[redacted]	434,964	144,988
	Third model specification	[redacted]	[redacted]	339,424	113,141
Caregiver disutility	0.08	[redacted]	[redacted]	351,347	117,116
	0.17	[redacted]	[redacted]	311,404	103,801
Number of carers to which disutility is applied	2	[redacted]	[redacted]	292,904	97,635
Disutility bereavement	0.04 for 15 years	[redacted]	[redacted]	336,941	112,314
	0.04 for 30 years	[redacted]	[redacted]	336,941	112,314
	0.04 for lifetime	[redacted]	[redacted]	336,941	112,314
Weight function	Weight of the general population*	[redacted]	[redacted]	358,772	119,591
Drug wastage	'Round down' option	[redacted]	[redacted]	329,850	109,950
	'Closest' option	[redacted]	[redacted]	331,975	110,658
Discontinuation and Compliance	0% discontinuation rate	[redacted]	[redacted]	400,232	133,411
	100% compliance rate	[redacted]	[redacted]	342,458	114,153
	0% discontinuation and 100% compliance rate	[redacted]	[redacted]	406,714	135,571

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* Based on the new evidence submitted by the company as clarification for the key issues identified by the EAG, the weight of patients <18 years is changed. EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year

EAG's probabilistic base-case results with and without QALY weight

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) without QALY weight	ICER (£) with QALY weight
Population: Perinatal-/infantile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	299,176	99,756
AA	[redacted]	[redacted]				
Population: Patients with juvenile-onset HPP						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	367,923	122,629
AA	[redacted]	[redacted]				

* As the base-case estimated undiscounted results for QALY gains greater than 30, a QALY weight of 3 was implemented for health gains.
AA = asfotase alfa; BSC = best supportive care; EAG = External Assessment Group; HPP = hypophosphatasia; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year

Impact of technology beyond health benefits

- Company include a scenario including productivity losses based on assumptions
- EAG noted:
  - Previous submission included data from European HPP survey on productivity losses and included other societal costs (special schooling, transportation, adaptation of cars and homes, informal care)
  - Omission of this is conservative as AA treatment expected to lead to a reduction of non-healthcare costs

Other considerations (from company)

Potential equality considerations

- Current UK MAA excludes adults, with paediatric-onset HPP accessing AA and may be potential equity considerations if recommendations differentiate by age as age is a protected characteristic

Innovation

- AA has an innovative mode of action and represents a significant change in the management of patients with paediatric-onset HPP. AA offers a life-changing opportunity to patients diagnosed with HPP
- Impact on HPP mortality above age 5 is not captured in model. In severe health states HPP mortality may result from cardiovascular complications and depression, so incremental QALYs underestimated

NICE

Are there any potential equality issues?

AA: Asfotase alfa; HPP: Hypophosphatasia; MAA: Managed access agreement; QALYs: quality-adjusted life year

Key questions – clinical effectiveness evidence

1. Are the results of comparative analysis from perinatal/infantile-onset HPP patients generalisable to juvenile-onset HPP patients?
2. Is age of onset a determinant of HPP prognosis?
3. Is the historical control data representative of current BSC for paediatric-onset HPP? Should all data including UK MAA and Global HPP registry be used for BSC?
4. Is the risk of immortal time bias adequately addressed in the survival analysis?
5. Is evidence of comparative efficacy of AA for survival outcomes (OS and VFS) only sufficient for decision making?

Key questions – cost effectiveness evidence

1. In the model to predict AA treatment costs is the predicted weight clinically plausible?
2. Are the utilities for patients and carer disutilities (including parental disutility for infant death) appropriate for decision making?
3. Is it appropriate to apply a QALY weight of 3 in the cost-effectiveness analysis?