Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]

Chair's presentation

Highly Specalised Technology 2nd Committee Meeting [15th December 2022]

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Company: PTC Therapeutics

Key questions

- Is the company's updated analysis appropriate?
    - Does the company's ECD response change the committee's view on the appropriateness of treatment-dependent utilities? [Key Issue]
    - Does the company's response in relation to early treatment benefits change the committee's conclusion on this issue?
    - Is the company's updated treatment discontinuation rate appropriate?
- What are the committee's views on other stakeholder responses to the ECD?
- Does the committee have any further comments on how caregiver quality of life is considered?
- Are there any other issues which the committee need to discuss?

Recap

Background on Duchenne Muscular Dystrophy (DMD)

Muscular dystrophies are a group of genetic disorders which cause muscle weakness and progressive disability

Causes

- Caused by presence of a variety of mutations on the X-chromosome in the gene for dystrophin, a protein important for maintaining normal muscle structure and function

Epidemiology

- Prevalence of Duchenne muscular dystrophy is approximately 8.29 in 100,000
- Approximately 10% carry a nonsense mutation in the dystrophin gene, equating to around 225 males aged over 2 years in England
- The proportion of these people who are able to walk is unknown

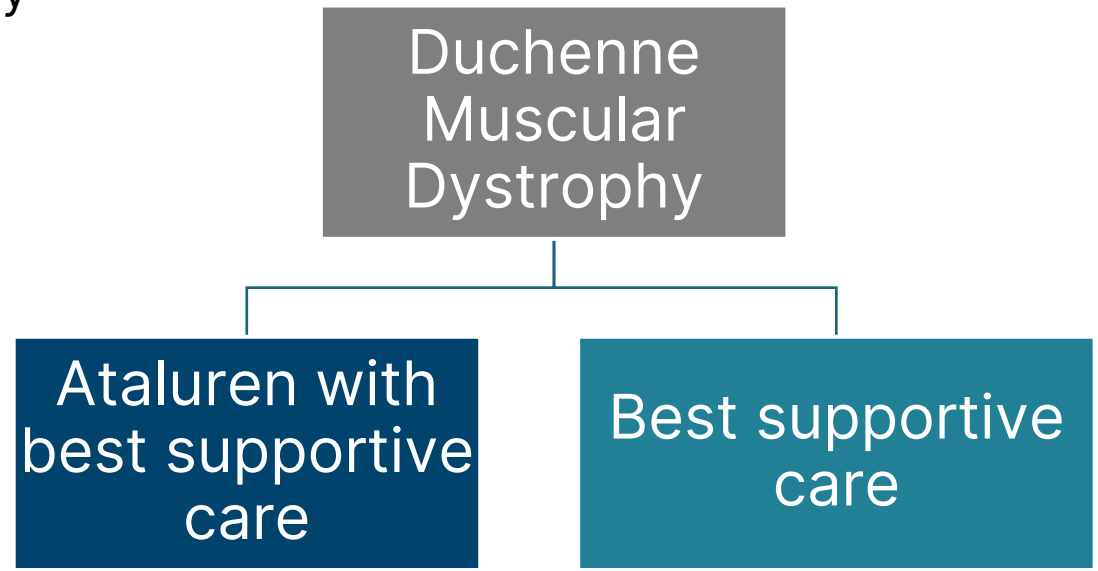
Symptoms and prognosis

- Mean age of diagnosis is around 4.3 years (Van Ruiten et al 2014)
- Severely progressive condition leading to weakness and loss of walking ability during childhood and adolescence. May also include behavioural or learning difficulties. After the age of 12 most children will need to use a wheelchair. During adolescence, breathing muscles can weaken. Cardiomyopathy (weakness of the heart) occurs usually before 18 years of age
- The average lifespan is less than 30 years (with best supportive care)

Treatment pathway

Ataluren is the only licensed treatment for Duchenne Muscular Dystrophy

Figure 1: Treatment pathway



- Best supportive care consists of steroids (associated with side effects), physical aids (wheelchairs, leg braces or crutches), exercise, physiotherapy, and occasionally orthopaedic surgery

- Other supportive treatments such as dietetic advice, prevention and treatment of bone fragility and the management of complications of long-term steroid therapy are required. In later stages, treatments to help improve breathing and increase oxygen levels may be needed if lung function becomes impaired

Ataluren (Translarna, PTC Therapeutics)

Recap

Table 1 Technology details

Marketing authorisation (granted 2014, updated 2019)	• Marketing authorisation granted: For the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years* and older The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing
Mechanism of action	A nonsense mutation in DNA results in a premature stop codon within an mRNA. This premature stop codon in the mRNA causes disease by terminating translation before a full-length protein is generated. Ataluren enables ribosomal readthrough of mRNA containing such a premature stop codon, resulting in production of a full-length protein
Administration	Oral administration: Recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (total daily dose: 40 mg/kg)
Price	• List price per sachet: 125mg; £84.40, 250mg; £168.80, 1000mg; £675.20 • List price cost per 3 months assuming average weight = [redacted] and company assumed compliance rates: Ambulatory: [redacted], non-ambulatory: [redacted] • A confidential commercial arrangement has been agreed in principle

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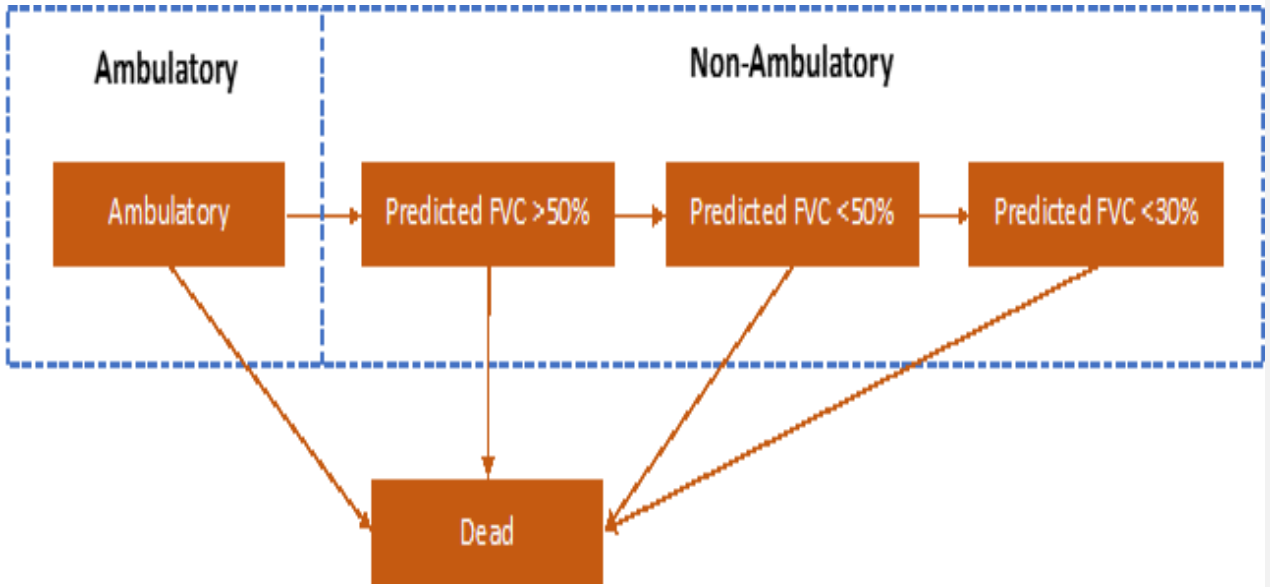
*ataluren licence extended from 5 years and above to 2 years and above

Company's model overview

The company model uses a partitioned survival approach with 5 health states

Figure 2 Model structure



- Technology affects **costs** by:
  - Increasing drug and healthcare resource use costs by the addition of ataluren and longer time spent in various health states
- Technology affects **QALYs** by:
  - Increasing the time spent in better health states and improving survival. Technology also assumed to impact caregiver QALYs
- Assumptions with greatest ICER effect:
  - Treatment-dependent utility values
  - Caregiver quality of life modelling method
  - Discontinuation rate
  - Treatment stopping rule

Model uses a partitioned survival approach. Model structure designed to align with key milestones included in the natural history model in Project HERCULES. 70 year time horizon, 3 month cycles. All patients start in ambulatory state and are assumed to be 2 years of age

Abbreviations: FVC: Forced Vital Capacity, QALY: Quality-adjusted life year ICER: Incremental cost-effectiveness ratio

Summary of committee conclusions from ECM1

Table 2 committee conclusions from ECM1

Topic	Committee conclusion
Treatment-dependent utilities	Evidence to support treatment-dependent utilities in ambulatory state not robust. Lowering risk of scoliosis in non-ambulatory states meant treatment-dependent utilities plausible in these states
Carer quality of life	Exclude from analysis – company approach (absolute carer QALYs) inappropriate and differences between patient expert testimonies v EAG analysis
Treatment discontinuation	The constant discontinuation rate was likely overestimated. Preferred to have no formal stopping rule but assumed stopping at FVC <30% for cost estimation
Assumed early treatment benefits	Company assumption that treatment would begin at 2 years old was not appropriate as diagnosis usually around 4 years in NHS. Therefore it was not appropriate to consider additional assumed treatment benefits
Data sources	Real world evidence (RWE) from STRIDE (ataluren) and CINRG (BSC) appropriate, but also appropriate to consider data from MAA. Company did not include MAA data in model – RWE more mature and more aligned with model structure
Indirect treatment comparison	Propensity score matching (STRIDE v CINRG) comparison appropriate but results were uncertain due to some limitations in analysis
Survival modelling	EAG's preferred parametric models appropriate, but model fit was poor

ECM; Evaluation committee meeting, EAG; External review group, QALY; Quality-adjusted life year, FVC; Forced Vital Capacity, MAA; managed access agreement

Recap

Committee preferred assumptions from ECM1

Ataluren was not recommended at ECM1

Table 3 committee preferred assumptions

Assumption	ECD section
Using original company base case and EAG base case parametric models for survival modelling	3.7
Assuming treatment-independent utility values for ambulatory health state and treatment-dependent utility values for non-ambulatory health states	3.9
Removing carer QALYs from the cost-effectiveness analysis and considering carer impacts qualitatively	3.10
Removing assumed early treatment effect benefits	3.8
A lower treatment discontinuation rate for ataluren based on the EAG's sensitivity analysis	3.11
Not imposing a defined treatment stopping rule; but for the cost-effectiveness analysis, costs in the model would be those if treatment is stopped when predicted FVC is less than 30%	3.12

Committee conclusion on cost-effectiveness:

- ICER substantially above £100,000 per QALY gained
- Ataluren did not meet the criteria for a QALY weighting
- Even when considering other factors such as impact on caregivers' quality of life and the time in a child's life when benefits are gained, ataluren was not considered cost-effective

ECM; Evaluation committee meeting, EAG; External review group, QALY; Quality-adjusted life year, FVC; Forced Vital Capacity, MAA; managed access agreement, ICER; Incremental cost-effectiveness ratio

ECD consultation comments

Several responses to the ECD were received

Consultation comments received from

- Muscular Dystrophy UK and Action Duchenne - joint response
- Two patient experts nominated by Action Duchenne

Company response

- New economic analysis and additional information
- Updated commercial arrangement

Summary of consultation responses

Patient organisations and patient experts

Summary of patient organisation and patient expert responses

Theme	Overview of comments
General comments	• Disappointed by committee's draft recommendations • Welcomed committee's conclusion that ataluren is effective and innovative • Highlight DMD is a rare condition and ataluren is currently the only licensed treatment
Treatment dependent utilities	• Believe that treatment-dependent utility values should be used for the ambulatory state to reflect additional benefits of ataluren
Caregiver quality of life	• Benefits to caregivers should be considered in decision-making • Concerned by removal of caregiver quality of life from the modelling • Carer quality of life underestimated in committee conclusions
Assumed additional treatment benefits	• Not appropriate to disregard benefits of ataluren for children below 5 years of age
Impact beyond direct health benefits	• Important to consider other benefits of ataluren, such as reduction in social care costs

Patient organisation submission

A range of views gathered by Muscular Dystrophy UK and Action Duchenne

"If children are typically diagnosed with Duchenne at age 4 (or sometimes younger), it is wrong to exclude all age years between 2 and 4 when assessing the benefits of Translarna. Excluding the benefit for 4-year-olds, the average age of diagnosis, risks supressing the overall cost-effectiveness calculation for Translarna."

View on assumed early treatment benefits

"Walking is a daily struggle for children with Duchenne, physically and emotionally. If they are receiving the drug, the walking experience is transformed. There are clearly walking-related quality of life improvements for those who are receiving the drug and are still ambulant."

View on impact on treatment-dependent utility values

"As Translarna has given our child a degree of very good health, he is able to attend college three days a week and to go out one afternoon a week without us. As the main caregiver, this means that I have some respite during this time to meet a friend for lunch, go swimming/for walks, or just to rest and relax."

View on impact on caregiver quality of life

Company updated base case

Following ECM1, the company updated its base case analysis

Summary of company approach post ECM1

Issue	Updated company base case	In line with committee preferences?
Treatment-dependent utilities	Maintain the use of treatment-dependent utilities	No
Caregiver quality of life	Omit carer quality of life from their model and consider it qualitatively – however bereavement impacts are still included	Yes (although bereavement impacts are still included)
Assumed early treatment benefits	Maintain additional treatment benefits due to expected earlier use of ataluren	No
Treatment discontinuation rate	Estimate a new lower rate of discontinuation using the STRIDE dataset	For discussion
Treatment stopping rule	No stopping rule proposed but using a modelled stopping rule when FVC is less than 30% for costing purposes	Yes

FVC: Forced Vital Capacity

Key issue: Treatment-dependent utilities

Treatment-dependent utilities are the biggest driver of cost-effectiveness

ECM1 company approach	ECM1 committee preferences
Company apply treatment-dependent utilities from Landfeldt et al 2020 for all model health states	Company did not provide robust evidence to support use of treatment-dependent utilities in non-ambulatory health states. Treatment-dependent utilities plausible in non ambulatory health states due to reduced risk of scoliosis

Company approach post ECM1 – base case maintained

- Retain original company approach of using treatment-dependent utilities from Landfeldt et al 2020 – a Delphi panel study involving 6 neuromuscular experts in Sweden. The company state this source was supported by a second Delphi study and UK expert opinion

Landfeldt et al treatment-dependent utility values

Patient utility values (Landfeldt et al. (2020)			
Model health state	BSC	Ataluren+BSC	Health state valued
Ambulant	0.62	0.93	Ambulatory stage
Non-ambulant, FVC>50%	0.16	0.32	Non-ambulatory stage (levels “b” and “c” on HUI III question on dexterity: “ability to use hands and fingers”)
Non-ambulant, FVC<50%			
Non-ambulant, FVC<30%			

FVC: Forced Vital Capacity, HUI; Health utility index

Key issue: Treatment-dependent utilities

Treatment-dependent utilities are the biggest driver of cost-effectiveness

Company approach post ECM1 – continued

- Both Delphi panels show clinicians consider there are differences in cognition, emotion, pain, ambulation and dexterity of patients receiving ataluren and best supportive care (BSC)
- Study 041 data: shows improved functioning across [redacted] of North Star Ambulatory Assessment (NSAA) and [redacted] in upper limb function in ambulatory patients given ataluren ([redacted]
- Clinical and patient experts supportive of use of treatment dependent utility values
- Study 041 EQ-5D VAS data shows improvement with ataluren (+1.2) compared to BSC (+0.1) after 1 month; shows ataluren has QoL impact after a short period and supports treatment-dependent utilities
- Study 046 measured expression of full length dystrophin in [redacted] patients - results show [redacted] increase in mean dystrophin ([redacted]) Study also reported improved muscle function for ataluren (timed function test) and decrease in serum creatine kinase levels; suggests potential muscle tissue preservation
- Company considers treatment-dependent utilities appropriate for both ambulatory and non-ambulatory states. Treatment benefit anticipated to translate to lasting effect, even after discontinuation

Key issue: Treatment-dependent utilities

Treatment-dependent utilities are the biggest driver of cost-effectiveness

Patient organisations and patient experts

- Muscular Dystrophy UK/Action Duchenne and patient experts disagree with committee conclusions and believe that treatment-dependent utilities should be used in all health states
- Reasons for including treatment-dependent utilities in ambulatory health state include:
  - Stamina – 6 minute walk test results may not have captured improvements in stamina
  - Stability when walking – leads to less falls and lower risk of factures
  - Energy – improvements in energy levels when given ataluren
  - Psycho-social benefits – gained through additional years of ambulation and social inclusion
  - Keeping up with peers and more independent walking
- Cost-savings in reduced healthcare use can be gained through remaining ambulant for longer
- Quality of ambulation is important; ataluren improves ambulation
- 93% of MDUK/Action Duchenne survey respondents disagreed strongly or disagreed with ECD that there was unlikely to be significant QoL differences in ambulatory health state (ataluren v BSC)
- 100% of respondents stated child required less supervision, had more stamina and lead to psychological improvements for carers
- With ataluren; 88% stated greater stamina with reduction in falls/factures, 75% stated greater walking pace, 63% stated child more confident about future and saw improved QoL in other ways

Key issue: Treatment-dependent utilities

Treatment-dependent utilities are the biggest driver of cost-effectiveness

EAG comments

- Landfeldt et al 2020 study design: panel instructed to assess health status assuming a mean patient age of 13 years, with a 6-minute walk test (6MWT) distance of 410 metres for ataluren and 316 metres for BSC, based on observed and extrapolated efficacy data
- Ambulatory utilities (0.93 for ataluren v 0.61 for BSC) applied throughout ambulatory health state, regardless of functioning status or if person is still on treatment or not
- EAG's clinical advisors uncertain if treatment-dependent utility values are reasonable, particularly with respect to impacts on physical functioning, for those still ambulant
- 1 UK clinical expert consulted by the company suggested there would be [redacted]
- EQ-5D VAS data (Study 041) may support treatment-dependent utilities; but, assessment period short (1 month), between-group differences small and instrument used not preference-based
- Study 046 data may support treatment-dependent utilities; but evidence not preference-based
- While additional evidence given - still no empirical evidence using preference-based measure to support treatment-dependent utilities - EAG unsure if treatment-dependent utilities are reasonable – EAG provide alternative scenarios on this issue

Has the committee seen evidence to change its views on the appropriateness of treatment-dependent utilities?

Key issue: Assumed early treatment benefits

Company assume treatment initiation at 2 years of age in model

ECM1 company approach	ECM1 committee preferences
Included additional assumed treatment benefits due to license extension to those aged 2 years and over	Not to include additional assumed treatment benefits due to early treatment as diagnosis of condition in NHS is around 4 years of age

Company approach post ECM1 – base case maintained

- Although only a small number under age of 5 have had ataluren, it is plausible to assume early treatment leads to additional benefits - validated by international Delphi panel of 9 clinical experts
- Licence extended 2018. STRIDE dataset includes older population vs. clinical practice. 20 patients in STRIDE aged 2-4 at treatment initiation not followed up long enough to show benefit- clinical input required. Study 030 (n=14 aged 2-5): over 28 and 52 weeks, showed improvement in ambulatory ability
- Since 2020, of [redacted] patients diagnosed in England with nmDMD and treated with ataluren, [redacted] aged 2-4 years, and [redacted] were 2 years old. 2021-2022: [redacted]% increase in children diagnosed with nmDMD below age of 5. Early genetic testing allows newborn siblings of patients with nmDMD to diagnosed
- Assuming a starting age of 2 most appropriate in model and conservative approach as it assumes patients will be on treatment for the longest duration (increases costs)
- Clinical expert at ECM1 supported additional treatment benefits as earlier treatment has protective effect
- Provide alternative analysis which early treatment benefits halved/removed and a model starting age of 4

Key issue: Assumed early treatment benefits

Company assume treatment at 2 years of age in model

Patient organisations and patient experts

- Limited evidence in children aged 2-5 due to recent licence change. There will be more children over time receiving ataluren under the age of 5
- Not accurate or reasonable to disregard health benefits for those under 5 years of age
- 100% of respondents to MDUK/Action Duchenne survey strongly disagreed or disagreed with committee's preference to not include additional treatment benefits due to earlier treatments
- 18% of respondents were parents of a child currently aged 2-4 and 23% of respondents were parents of children who had begun receiving ataluren before the age of 4

EAG comments

- EAG's clinical advisers agreed its plausible that earlier treatment leads to additional benefits
- Older age of patients at initiation of ataluren in STRIDE (mean age in evaluable population = [redacted] years), any additional benefits associated with earlier treatment will not be reflected
- Not clear what is achievable in terms of reducing age of diagnosis of nmDMD and how earlier treatment might delay disease milestones. But applying estimates from STRIDE without assuming additional benefits may underestimate treatment effects
- Increasing model start age has potential to increase ICER for ataluren more than the inclusion of early treatment benefit assumptions

Key issue: Assumed early treatment benefits

Company assume treatment at 2 years of age in model

Impact of age and early treatment benefit assumptions on the ICER for ataluren versus BSC (generated by the EAG using the company's revised model)

[redacted]

Has the committee seen evidence to change its views on the appropriateness of the company's assumed early treatment benefits?

Key issue: Caregiver quality of life

Company update base case to remove caregiver QoL from model

ECM1 company approach	ECM1 committee preferences
Applied absolute carer QALYs until mean overall survival in both model arms	Exclude caregiver quality of life from modelling, due to issues with both company (absolute caregiver QALYs meant carer QALYs = zero when patient dies) and EAG analysis (disutility approach, as in previous HST topics, resulting in a QALY loss with ataluren, which did not appear to match caregiver testimonies). Committee considered carer QoL qualitatively in decision-making

Company approach post ECM1 – caregiver QALYs removed from model

- While base case amended to align with committee preference, highlight importance of incorporating impact on caregivers in decision-making - significant, progressively increasing caregiver burden
- Impact of ataluren on caregiver QoL; reduced anxiety/stress, and a positive impact on productivity
- Caregivers have stated there is tangible benefit from delaying disease progressing as it allows time to prepare themselves for next stages

EAG comments

- Bereavement-related QALY losses assumed to apply to caregivers are still included in company's revised model – results in small ICER decrease. EAG provide analysis around this assumption

QALY; Quality-adjusted life year, QoL; quality of life, ICER; incremental cost-effectiveness ratio, HST; highly specialised technologies

Key issue: Caregiver quality of life

Company update base case to remove caregiver QoL from model

Patient organisations and patient experts

- Concerned about way caregiver QoL has been included in this evaluation. Committee should give appropriate weighting to qualitative evidence of impact of ataluren on caregivers
- No clarity about how any ‘qualitative way’, as in ECD, has been or could be included in recommendations
- A suitable way of measuring caregiver QALYs needed so benefits can be appropriately included
- Even marginal mobility benefits make significant difference. If a person can feed themselves, this saves a lot of caregiver time. Caregivers able to work, family relations aren’t skewed by care needs
- Ataluren gives families/caregivers hope and provides a reduction in anxiety – very important aspects
- Clear and compelling caregiver testimony on positive impact of ataluren on their QoL has been presented throughout evaluation process – while this cannot be captured quantitively, it should not be overlooked
- 93% of MDUK/Action Duchenne survey respondents either ‘very concerned’ or ‘concerned’ by approach taken in ECD. Respondents also stated:
  - Not including significant positive impact on caregiver QoL in calculations undermines entire process
  - If caregivers state positive impacts, that should be enough

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Does the committee have any further comments on how caregiver quality of life is assessed in this evaluation?

Key issue: Treatment discontinuation

Company update treatment discontinuation rate in model

ECM1 company approach	ECM1 committee preferences
Company estimated treatment discontinuation rate from STRIDE dataset ([redacted] each 3 month cycle)	Company's estimated discontinuation rate likely overestimated discontinuation and underestimated treatment costs. Committee preferred EAG's scenario analysis, which reduced rate by 50%. But noted this reduction was arbitrary

Company approach post ECM1 – Company update estimated treatment discontinuation rate

- Update treatment discontinuation rate. Original [redacted] rate based on [redacted] patients discontinuing ataluren over a median follow-up duration of [redacted]
- Updated rate based on removing 7 patients who discontinued due to loss of ambulation, which results in an updated rate of [redacted]

EAG comments

- The EAG believes that updated treatment discontinuation rate estimate of [redacted] is more appropriate and markedly lower than company's original estimate

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Is the company's updated treatment discontinuation rate appropriate?

Key issue: Treatment stopping

Company adopt stopping rule of FVC <30% for costing purposes

ECM1 company approach	ECM1 committee preferences
Company proposed a stopping rule when FVC <50%	The committee did not prefer to impose a formal treatment stopping rule, but preferred to use a stopping rule of when FVC <30% to model treatment costs

Company approach post ECM1 – adopt committee preferences and provide alternative analysis

- Company adopt the committee preferences in terms of a modelled treatment stopping rule
- Provided alternative analysis with its updated case and a stopping rule of FVC <50%

EAG comments

- Treatment stopping rules in model only impact on costs – potential that applying a treatment stopping rule of FVC <30% underestimates ataluren effectiveness (magnitude of which is uncertain)

Does the committee have any further comments on treatment stopping?

Key issue: Survival modelling

Company adopt committee's preferred modelling choices and provide additional modelling using more flexible methods

ECM1 company approach	ECM1 committee preferences
Standard parametric models fitted to STRIDE and CINRG datasets for time to event data	Preferred EAG's choice of standard parametric models for time to event data but noted that these models provided a poor fit to the data

Company approach post ECM1 – adopt committee preferences and provide alternative analysis

- Company adopt the committee preferences for survival modelling. Also provide additional survival modelling using more flexible models
- Flexible models resulted in better model fit, and reduced the ICER estimate, but also resulted in survival models for age at loss of ambulation and age at FVC<50% crossing. Clinical experts consulted preferred use of Weibull models for time to event data

EAG comments

- Use of standard parametric models appropriate given issues with flexible models. Reiterate model fit is poor and EAG clinical experts stated current modelling potentially overestimates ataluren effectiveness
- Unclear how and when company obtained clinical expert opinion regarding Weibull model preference

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Does the committee have any further comments on the survival modelling?

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include a confidential commercial arrangement

that has been agreed in principle

Committee preferred assumptions from ECM1

Ataluren was not recommended at ECM1

Committee preferred assumptions

Assumption	ECD section
Using original company base case and EAG base case parametric models for survival modelling	3.7
Assuming treatment-independent utility values for ambulatory health state and treatment-dependent utility values for non-ambulatory health states	3.9
Removing carer QALYs from the cost-effectiveness analysis and considering carer impacts qualitatively	3.10
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Not imposing a defined treatment stopping rule; but for the cost-effectiveness analysis, costs in the model would be those if treatment is stopped when predicted FVC is less than 30%	3.12

Committee conclusion on cost-effectiveness:

- ICER substantially above £100,000 per QALY gained
- Ataluren did not meet the criteria for a QALY weighting
- Even when considering other factors such as impact on caregivers' quality of life and the time in a child's life when benefits are gained, ataluren was not considered cost-effective

ECM; Evaluation committee meeting, EAG; External review group, QALY; Quality-adjusted life year, FVC; Forced Vital Capacity, MAA; managed access agreement, ICER; Incremental cost-effectiveness ratio

Cost-effectiveness results: Summary

Company's updated base case:
Treatment-dependent utilities, updated treatment discontinuation rate, no formal stopping rule (FVC<30% used to model costs), caregiver QoL not modelled (but bereavement impacts included)

Scenario analysis:
Weibull models and flexible models for time-to-event data, early treatment benefits halved/removed, model starting age of 4 years, original treatment discontinuation rate, stopping rule of FVC <50%, company's technical engagement base case analysis

EAG analysis:
Committee preferred analysis from ECM1 and scenarios involving treatment dependent utilities (including halving benefit gain), stopping rule of FVC <50%, Weibull models for time-to-event data, changing starting model age and removal of bereavement effects

Cost-effectiveness results: Company

Company provide updated base case results and scenario analysis

Option	LYGs*	QALYs-patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients +carers)	DM
Company's revised base case model following ECD (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base case model following ECD (probabilistic)†								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA1: Weibull survival distributions for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA2: 1-knot restricted cubic spline model for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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DM: Decision modifier (QALY weighting)

Cost-effectiveness results: Company (continued)

Company provide updated base case results and scenario analysis

Option	LYGs*	QALYs-patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients +carers)	DM
SA3: Early treatment benefit removed, ataluren start age = 4 years								
Ataluren+BSC								
BSC								
Incremental								
SA4: Early treatment benefit reduced by half ( )								
Ataluren+BSC								
BSC								
Incremental								
SA5: STRIDE discontinuation rate =								
Ataluren+BSC								
BSC								
Incremental								
SA6: Stopping rule at pFVC <50%								
Ataluren+BSC								
BSC								
Incremental								
SA7: Company's previous base case at technical engagement (including previous PAS)								
Ataluren+BSC								
BSC								
Incremental								

DM: Decision modifier (QALY weighting)

Cost-effectiveness results: EAG

EAG provide further analysis around updated company base case

Option	LYGs*	QALYs-patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients +carers)	DM
Company's revised base case model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1: Appraisal Committee's preferred assumptions (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1: Appraisal Committee's preferred assumptions (probabilistic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2: Appraisal Committee's preferred scenario + treatment-dependent utility values								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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DM: Decision modifier (QALY weighting)

Cost-effectiveness results: EAG (continued)

EAG provide further analysis around updated company base case

Option	LYGs*	QALYs-patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients +carers)	DM
EA3: Appraisal Committee's preferred scenario + treatment-dependent utility gain in ambulatory state halved								
Ataluren+BSC	[redacted]							
BSC								
Incremental								
EA4: Appraisal Committee's preferred scenario + start age = 4 years								
Ataluren+BSC	[redacted]							
BSC								
Incremental								
EA5: Appraisal Committee's preferred scenario + bereavement QALY loss included								
Ataluren+BSC	[redacted]							
BSC								
Incremental								
EA6: Appraisal Committee's preferred scenario + Weibull models								
Ataluren+BSC	[redacted]							
BSC								
Incremental								
EA7: Appraisal Committee's preferred scenario + FVC<50% stopping rule								
Ataluren+BSC	[redacted]							
BSC								
Incremental								

DM: Decision modifier (QALY weighting)

Equalities

The committee addressed potential equality issues in the ECD

Committee discussion on equalities in ECD

- Some stakeholders said it was important that people with DMD did not have to travel excessive distances for treatment. The committee acknowledged that clinical expertise would usually be concentrated at a small number of centres
- One stakeholder also said that the current managed access agreement stopping rules did not allow use in people who could not walk, and that this may discriminate against older DMD patients. The committee noted that it had not included a formal treatment stopping rule in its preferred assumptions
- No other potential equality issues were identified by the committee

Consultation responses from patient organisations and patient expert highlighted concerns that current ECD recommendation could be discriminatory on the grounds of age and disability; both protected characteristics under the Equality Act 2010

Does the committee have any further comments on potential equality issues?

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

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QALY: Quality-adjusted life year QoL; Quality of life

Key questions

- Is the company's updated analysis appropriate?
    - Does the company's ECD response change the committee's view on the appropriateness of treatment dependent utilities? [Key Issue]
    - Does the company's response in relation to early treatment benefits change the committee's conclusion on this issue?
    - Is the company's updated treatment discontinuation rate appropriate?
- What are the committee's views on other stakeholder responses to the ECD?
- Does the committee have any further comments on how caregiver quality of life is considered?
- Are there any other issues which the committee need to discuss?

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Thank you.