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

Highly Specialised Technologies Committee [8th September 2022]

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Company: PTC Therapeutics

NICE National Institute for Health and Care Excellence

Key issues

The EAG identify several key issues in the company submission

Table 1: Key issues

Issue	Resolved?	ICER impact
Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population	No	Medium
Inappropriate approach used to estimate incremental caregiver QALYs	No – for discussion	Very Large
Limitations surrounding the company's survival modelling	Partially	Unknown
Uncertainty surrounding the appropriateness of treatment-dependent patient utility values	No – for discussion	Very Large
Uncertainty surrounding modelled acquisition costs of ataluren by age	Yes	Minor
Uncertainty surrounding the discontinuation rate in patients with FVC>50%	No – for discussion	Large
Uncertainty surrounding the most appropriate treatment discontinuation rule	No – for discussion	Large
Weak characterisation of uncertainty	Yes	Unknown

Abbreviations: BSC; best supportive care, QALYs; quality-adjusted life year, FVC; Forced Vital Capacity, EAG; Evidence Assessment Group

Key questions

- Is it appropriate to use treatment-dependent utility values?
    - Should they be applied in all health states?
    - Should they be applied after treatment discontinuation of ataluren?
- How should caregiver quality of life be modelled?
- How appropriate is the company's modelled treatment discontinuation rate?
- What is the most appropriate treatment stopping rule?
- Is the company's approach to modelling the relative effectiveness of ataluren compared to best supportive care appropriate?
    - How robust is the company's indirect treatment comparison?
    - How appropriate are the company's additional treatment benefit assumptions?
    - How appropriate is the company's survival modelling?
- Are there any other issues in the company's submission?

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

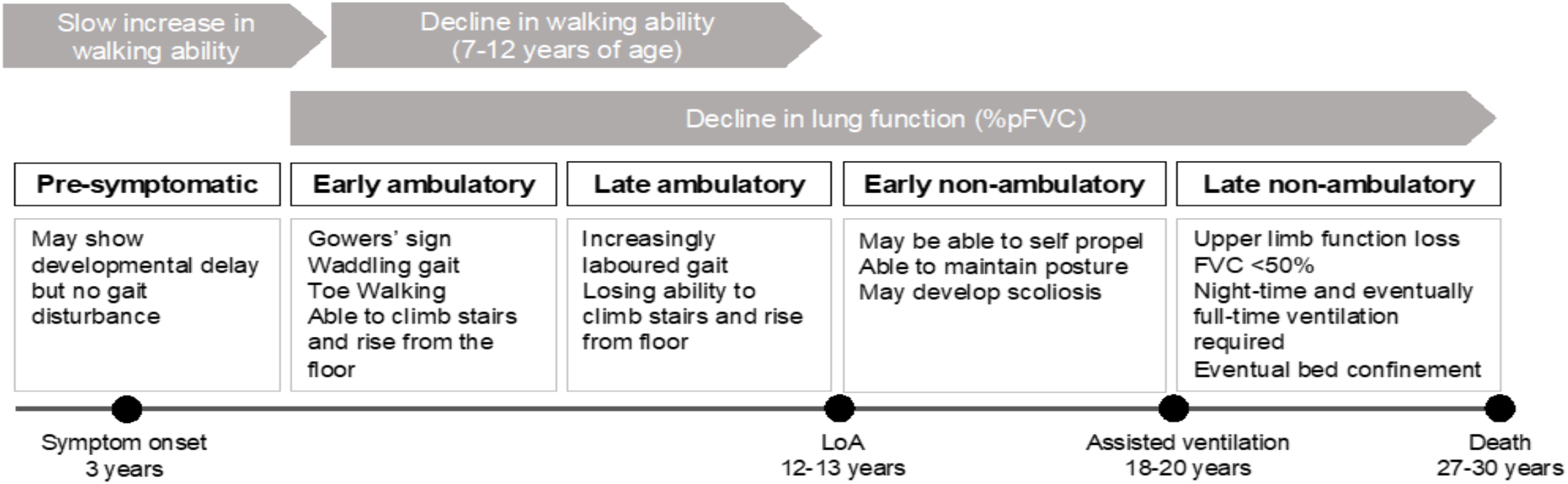
- Prevalence of Duchenne muscular dystrophy is approximately 8.29 in 100,000
- Approximately 10% carry a nonsense mutation in the dystrophin gene, equating to around 225 males aged over 2 years in England using current population size estimates
- The proportion of these people who are able to walk is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

Background on Duchenne muscular dystrophy

Figure 1: Milestones and stages of Duchenne muscular dystrophy



Source: company submission (figure B-1)

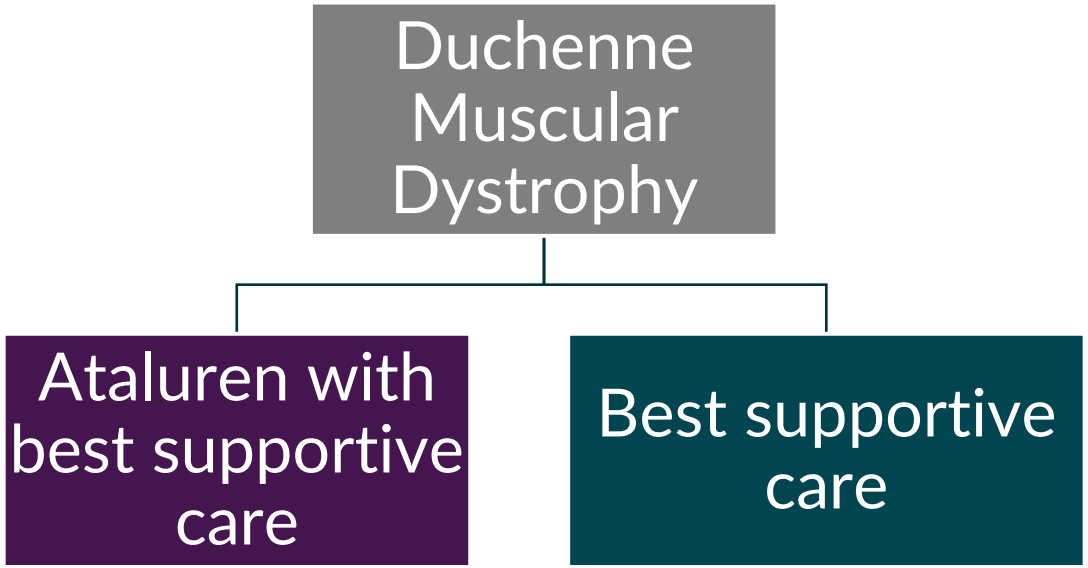
Duchenne muscular dystrophy disease course shows a initial increase in mobility with child development but then a progressive decline in mobility and respiratory ability (requiring the need for ventilation support). Scoliosis may also develop. Upper limb function loss occurs in later stages

LoA: Loss of ambulation, FVC: Forced Vital Capacity

Treatment pathway

Ataluren is the only licensed treatment for Duchenne Muscular Dystrophy

Figure 2: 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)

Table 2: 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 body weight)
Price	• List price per pack: 125mg; £84.40, 250mg; £168.80, 1000mg; £675.20 • List price cost per 3 months of treatment assuming average weight =39.5kg and company assumed compliance rates: Ambulatory: £80,536, non-ambulatory: £78,609 • A Patient Access Scheme (PAS) has been agreed

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

HST3 recommendation

HST3 recommended ataluren use within a Managed Access Agreement

Managed access agreement allowed ataluren use if:

- Patient aged 2 years* and over and able to crawl, stand with support or walk

Stopping rule in managed access agreement:

- Loss of all ambulation (i.e. can no longer stand even with support) and entirely dependent on wheelchair use for all indoor and outdoor mobility
  - In such cases, patients should stop treatment no later than 6 months after becoming fully non-ambulant
- Non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14 month period)

The Managed Access Agreement collected data based on the NorthStar Ambulatory Assessment (NSAA), patient quality of life (CHU9D) and caregiver quality of life (EQ-5D) and aimed to match outcomes to a natural history control

*ataluren licence extended from 5 years and above to 2 years and above after HST3 publication (in 2019)

HST3 conclusions

Table 3: Committee conclusions from HST3 (published July 2016)

Topic	Committee conclusions
Clinical evidence	• 6-minute walk distance (6MWD) is an appropriate primary outcome to assess benefits in RCTs • No meaningful improvement in rate of decline in 6MWD with ataluren v BSC in ITT populations of Study 007 and Study 020
Uncertainties in evidence	• Agreed to consider 48-week clinical trial data from a subgroup of patients with a baseline 6MWD of 300–400m in Study 020 but noted concerns on generalisability to broader population • This subgroup analysis showed a statistically significant benefit – but size of benefit is highly uncertain
Health-related quality of life	• Nature of DMD: might be appropriate to view QALYs gained differently because of time in a child's life when QALYs are predominantly gained (delaying LoA in childhood and adolescence)
Impact beyond health benefits	• Potential wider societal benefits of ataluren treatment – ability to contribute to society, continue education, spend more time with family and friends
QALY weighting and discount rate	• Ataluren did not meet the criteria for QALY weighting or 1.5% discount rate use

Decision problem

Table 4: Population, intervention, comparators and outcomes from the NICE scope

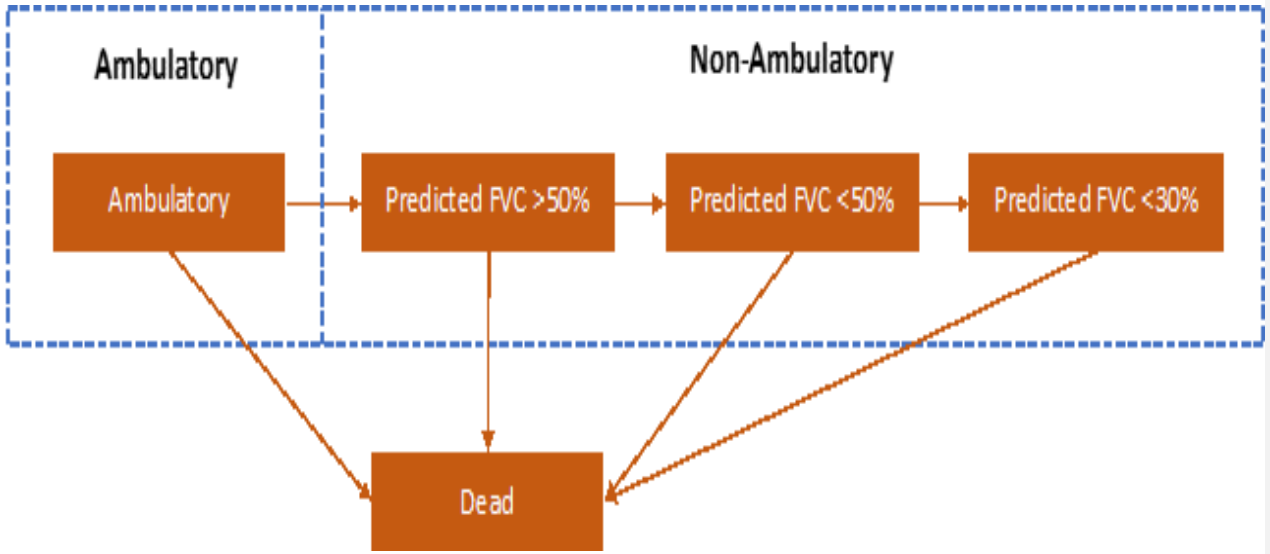
	Final scope	Company comments	EAG comments
Population	People aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk	Treatment beyond loss of ambulation expected to provide benefit by preserving muscle function and vital functions e.g. pulmonary and cardiac	Few patients in STRIDE study started treatment before age 5 [redacted]%)
Intervention	Ataluren	No comments	Unclear how ataluren stopping rule is reflected in STRIDE
Comparators	Best supportive care	No comments	No comments
Outcomes	Walking ability, muscle function, muscle strength, ability to undertake activities of daily living, cardiac function, lung function, time to wheelchair, number of falls, mortality ,adverse effects of treatment, HR-QoL (patients and carers).	Cardiac assessment data are immature and effect on cardiac function is unable to be presented	No empirical evidence presented to demonstrate improved survival. Model assumes substantial survival gain

BSC; Best supportive care, FVC; Forced vital capacity, HR-QoL; Health-related quality of life

Company's model overview

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

Figure 3 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

Patient perspectives

NICE National Institute for Health and Care Excellence

Patient perspectives

Patient organisations outline what it is like to live with DMD for patients and carers

Submissions from Muscular Dystrophy UK, Action Duchenne

Living with DMD

- Impact of DMD on mobility/ambulation requires significantly adapted environment (powerchairs, assistive mobility equipment) – adaptions are major, costly and challenging
- Children with the condition become constrained in activities they can undertake; strains on friendships
- DMD causes serious respiratory, orthopaedic and cardiac complications. Life expectancy between 22 and 28 years on standard care, has increased with improvements in standard care but many patients die before 20

Carer experience

- DMD has acute impact on family/friends. Devastating psychological impact of watching children struggling to walk and becoming non-ambulant. Even more profound impact with respiratory and heart complications
- Parents worried how long their child will live. Carers often suffer depression/anxiety, have prolonged work absences. Depression/anxiety increases with disease progression

Current treatments

- Standard care treatments focus on symptom management and are associated with a high burden of care – corticosteroids can have severe side effects such as impacts on bone health, extreme weight gain, stunted growth and adrenal insufficiency and crisis
- Due to progressive nature of condition and lack of effective treatments, patients can become disengaged
- Ataluren is the first treatment to tackle underlying root cause of DMD

Patient perspectives

Patient organisations outline the experiences of patients and carers of the Managed Access Agreement for ataluren

Submissions from Muscular Dystrophy UK, Action Duchenne

Patient/carer views on managed access agreement

- 100% of survey respondents* stated a very positive experience in accessing and having ataluren
- Respondents stated ataluren was easy to administer as it is a powder sachet – no additional burden on daily life
- 100% noticed improvements in ambulation
- 75% stated heart and respiratory symptoms remained stable
- 88% stated ataluren improved overall quality of life
- 72% stated ataluren had a positive impact on their mental health
- 100% of friends and family respondents stated that ataluren gave them hope

- Ataluren has had clear impact on overall health, not just for patients but for family and friends also
- Ataluren reduces complexity of care – less appointments

"Very positive experience, our son saw an improvement in his ability to walk within a couple of weeks, he's still walking well for a good distance, we also noticed a significant reduction in trips and falls."

"Seeing our child go from non-ambulant to ambulant when we thought he might never walk. It's just amazing and makes us so happy to watch him running around and having so much energy."

*Survey respondents included 4% people with DMD, 81% parents of a child with DMD, and 15% either a carer or a sibling/wider family member

Patient perspectives

Muscular Dystrophy UK and Action Duchenne submission provides a range of quotes from parents of children with DMD

"It has been very positive, as the prognosis at birth for our young person/family member was very bleak; we were told they wouldn't be ambulant by the age of twelve and would need assistance to breathe. We all think it's amazing that Translarna has helped to transform this diagnosis into a more hopeful outcome"

"He used to suffer from recurring chest infections but since being on Translarna this has massively improved, and he hasn't had a chest infection"

"It has given us hope, it allowed us to live a full life, he's still walking really well… in fact asking to go for walks which gives us as family so much joy. It offers us a level of comfort, knowing that a treatment is available to our boy"

Patient perspectives

Patient experts provide insights on living with the condition and the impact on parents/carers

Submissions from patient experts nominated by Action Duchenne

Living with the condition

- It is demoralising and debilitating living with this progressive condition
- Patients need help with every day tasks such as getting out of bed, taking a shower, getting dressed or going to school
- Difficult to keep up with friends and peers leads to social isolation

Impact on parents/carers lives

- Impact on relationships, mental health, career aspirations and ability to maintain a social life. Caring can be physically and emotionally exhausting
- Profound grief, depression, and anxiety in years following diagnosis
- Care also involves dealing with significant cognitive impairments
- Loss of ambulation increases impacts on carers as tasks take longer

" Typically it can take two hours in the morning to get out of bed, take his medication, physio, get washed and dressed and into the wheelchair accessible car, before school."

"Because it's progressive, you always have to keep ahead of it, anticipate what's coming and what can be done to mitigate the effects"

Patient perspectives

Patient expert submissions highlight views on current treatments and benefits of ataluren

Submissions from patient experts nominated by Action Duchenne

Current treatments

- High unmet need. Aside from ataluren there are no treatment options available. Steroids have a wide range of side effects
- Physiotherapy, ventilation, and heart medication have limited effectiveness - don't tackle underlying cause of condition

Patient/carer views on ataluren

- Ataluren has been shown to provide clear benefits
- Maintaining ambulation is extremely important, but so is retaining upper body strength – for example this can allow handwriting, collecting items from cupboards/shelves, feeding, playing games and participation in modified versions of some outdoor sports
- Being able to interact with friends and play sports with use of ataluren bring significant psychosocial benefits
- Ataluren improved energy and stamina. No disadvantages of treatment

"I would say that half of managing DMD is just managing the side effects of steroids, such as vulnerability to fractures, delayed puberty, behavioural challenges, and managing hunger/potential weight gain"

"Delaying lost of ambulation…..means transfers take 2 minutes rather than 15 minutes, massively reducing the impact of care work on the family. It means you can go on holiday/travel without prohibitive cost and barriers to access"

Patient perspectives

Patients and carers would value ataluren treatment beyond loss of ambulation

Submissions from patient experts nominated by Action Duchenne

- Our experience suggests all patients benefit from ataluren, both those who are ambulant and those who have lost ambulation
- DMD causes muscle weakness throughout the body and is not limited to leg muscles. Inappropriate and unfair to withdraw the drug from those who lose ambulation, given importance of maintaining upper body strength
- Ataluren continues slowing disease progression in non-ambulant patients. Psychological benefits to families of continuing an effective treatment can not be overstated - reduces anxiety, empowers people, and gives hope for a longer, more fulfilled life
- Current MAA stopping rules do not reflect critically important role ataluren has in slowing progression regardless of ambulation status – for example slower pulmonary decline and ability to carry out physical tasks
- Current stopping rules not appropriate – drug should be given until it can no longer can be administered. May not be appropriate to have a stopping rule post MAA

"It has significantly preserved his upper body strength and respiratory function. I can't imagine the anguish of parents whose children stop taking ataluren when they lose ambulation."

"There are millions of non-ambulant adults and children who enjoy a very good quality of life and given the progression of Duchenne, it is vital that this is retained for as long as possible where a drug exists."

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Clinical perspectives

A clinical expert outlines current NHS treatment for DMD

Submission from 1 clinical expert

Theme	Comments
Aims of treatment	• To slow down progression in muscle weakness. Expected that LoA occurs between 12-14 years on average on BSC. Delaying LoA preserves independence for longer • Preserving upper body strength supports independent transfers (e.g. from chair to bed). Slowing progression delays onset of respiratory muscle weakness/ventilation
Current treatment options	• No curative treatments – treatment in line with current standards of care recommendations. These guidelines are currently being reviewed • Recommended that all boys are started and maintained on glucocorticoid treatment
Clinically significant treatment response	• Delaying LoA by 1-2 years is a significant benefit • Delaying loss of upper limb function and respiratory symptoms are important to allow patients to fulfil their potential

LoA: Loss of ambulation, BSC: best supportive care

Clinical perspectives

Clinical expert view on ataluren use and considerations around a stopping rule

Submission from 1 clinical expert

Theme	Comments
Ataluren use	• A step change in management of nonsense mutation DMD and addresses unmet need • Preserving muscle strength and delaying onset of respiratory muscle weakness will likely improve life expectancy • Effect of ataluren on cardiac muscle and dilated cardiomyopathy is not yet clear • Likely to be some who respond less well than others to ataluren, but factors predicating response are not clear • Dosing is complex, complying with a 3x daily dose may be daunting for some. Monitoring compliance is important
Stopping rule	• Envisage being able to use ataluren in those who have been shown to benefit from treatment. If treatment is continued after LoA specialist centres need to develop their experience in using the drug and monitoring for benefits/risks of treatment • Treated patients are still expected to decline, but more slowly - difficult to set specific functional test to confirm benefit • If adverse events/difficulty in taking the medication outweigh the expected benefits or if compliance is poor then stopping treatment is appropriate

Key clinical evidence

The company's base case uses real-world evidence for ataluren (STRIDE) and best supportive care (CINRG Duchenne Natural History Study)

Table 5: Clinical trial designs and outcomes

	STRIDE (n= estimated 360*)	CINRG (n= 440)
Design	Ongoing international observational study of the safety and effectiveness of ataluren	Natural history study
Population	Ambulatory and non-ambulatory patients with nmDMD aged ≥2 years	Ambulatory and non-ambulatory patients with DMD aged between 2 and 28
Intervention	Ataluren	Best supportive care
Comparator(s)	None	None
Duration	10 years (5 years target follow-up duration)	10 years (>8 years target follow-up)
Outcome	Safety, efficacy evaluations; 6MWD, TFTs, LoA, NSAA, pulmonary and cardiac assessments	Included median survival, LoA, pulmonary function and TFTs
Locations	Centres: Europe (67), Israel (30) and Brazil (10)	United States, Canada, Puerto Rico, Australia, Argentina, India, Israel, Italy, Sweden
Used in model?	Yes	Yes

*Within company submission n=269 described as "evaluable population"

LoA: loss of ambulation, TFTs: timed function test, 6MWD; 6 minute walk distance, NSAA; North Star Ambulatory Assessment, nmDMD: nonsense mutation DMD

Indirect treatment comparison results used in the model

Company use propensity-score matching to compare ataluren against best-supportive care using STRIDE and CINRG datasets

Table 6: Results of STRIDE/CINRG ITC

Assessment	STRIDE (ataluren + BSC) N=241	CINRG (BSC alone) N=241
Loss of ambulation		
Median age at event, years (95% CI)	17.9 (14.4, NA)	12.5 (11.6, 13.5)
HR (95% CI)	0.374 (0.273, 0.512)	
p-value	<0.0001	
Predicted FVC <50%		
Median age at event, years (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p-value	[redacted]	
Predicted FVC <30%		
Median age at event, years (95% CI)	NA (NA, NA)	25.4 (20.6, 29.4)
HR (95% CI)	0.107 (0.014, 0.813)	
p-value	0.0085	

The STRIDE/CINRG ITC using propensity-score matching (using n=241 from both STRIDE and CINRG database) estimates a median delay of 5.4 years in LoA. Model does not use ITC results for Predicted FVC <30% (clinical assumptions used instead)

EAG comments on company's base case ITC

EAG state methods used in company's ITC are appropriate but are associated with some limitations

EAG comments on methodology

- Overall, EAG considers specific matching methodology applied to be reasonable
- 4 prognostic factors matched (age at 1st symptoms, age at 1st corticosteroid use, deflazacort duration and other steroid duration) – other prognostic factors not included
- Some imbalances exist between groups
- Sensitivity to model structure/methodology not explored, and no discussion of treatment effect identified
- Data quality issues and methodological limitations may have impacted results
- Patients in STRIDE treated mainly in Europe. Whereas CINRG in various locations, mostly North America. Unclear if geographical location impacted type of care available
- Unclear whether tests of statistical significance employed take into account paired nature of data

EAG comments on results of ITC

- ITC results suggests delay in LoA compared to BSC.
  [redacted]
- Limited evidence to support impact on pulmonary outcomes, particularly those experienced further in disease progression – partly due to the limited number of patients reaching these milestones
- Results of ITC should be interpreted with some caution and highlight uncertainty in treatment effectiveness of ataluren compared to BSC.
- STRIDE data source does not reflect the target population (2 years and above)

BSC; Best supportive care, FVC; Forced vital capacity, LoA: loss of ambulation, ITC; Indirect treatment comparison, LoA; loss of ambulation

Additional clinical evidence

The company do not use the managed access agreement data in the economic model

Table 7: Clinical trial designs and outcomes – North Star Registry and Managed access agreement

	North Star Registry (n=145)	Managed access agreement (n=60)
Design	Natural history study	Observational study
Population	Patients with DMD	English managed access agreement population: Ambulatory patients with nmDMD, aged ≥2 years*
Intervention	Best supportive care	Ataluren
Comparator(s)	None	None
Duration	2006 to present	~6 years (ongoing)
Outcomes	NSAA	Included NSAA, patient quality of life (CHU-9D), caregiver quality of life (EQ-5D)
Locations	United Kingdom	England
Used in model?	No	No

*MAA was updated in 2019 to reflect the licence extension to 2 years and older

Additional indirect treatment comparison results

Company also provide ITC for MAA data matched to NorthStar registry

Figure 4: MAA/North Star ITC results (not used in model, matched population = 59)

Company comments on ITC:

- Due to limitations, this ITC struggled to demonstrate meaningful differences
- Several reasons given: imbalance in age between groups (BSC younger), omission of key matching prognostic factor (age at 1st symptom), decline in available data at later timepoints and characteristics of NSAA measurement

Results of MAA/NorthStar ITC:

- **/17 function areas in BSC group lost function compared to ataluren group, In * function areas reverse trend observed

EAG comments:

- Similar concerns to that of company's base case ITC (STRIDE v CINRG)
- ITC provides less compelling evidence compared to STRIDE/CINRG ITC

BSC; Best supportive care, ITC; Indirect treatment comparison, MAA; Managed Access Agreement, NSAA; North Star Ambulatory Assessment

Additional indirect treatment comparison

Company also provide ITC for study 019 (long term ataluren extension study) matched to CINRG

Table 8: Study 019/CINRG ITC results

Assessment	Study 019 (ataluren + BSC) N=60	CINRG (BSC alone) N=60
Loss of ambulation		
Median age at event, years	15.5	13.3
p-value	0.0006	
Predicted FVC<60%		
Median age at event, years	18.1	15.1
p-value	0.0004	
Predicted FVC<50%		
Median age at event, years	19.1	17.8
p-value	0.0548	
FVC <1 litre		
Median age at event, years	NR	21.9
p-value	NR	

Company comments on ITC:

- Clinically and statistically significant delay of 2.2 years in LoA and 3 years delay in reaching FVC<60%
- Results show ataluren can be beneficial throughout different stages of disease, regardless of ambulatory status

EAG comments:

- Similar concerns to that of company's base case ITC (STRIDE v CINRG)
- Imbalance between groups (older patients in CINRG)

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Company model uses ITC and various assumptions for clinical outcomes

Background

- Company model predicts age at loss of ambulation, FVC milestones and death using the STRIDE/CINRG ITC and clinical assumptions. FVC <30% and death milestones are based only on clinical expert opinion. The company also assume additional benefits for early initiation of treatment at age 2
- Each assumption involves shifting survival curves to the right (loss of ambulation = STRIDE curve shifted by [redacted] years; FVC<50% = STRIDE curve shifted by [redacted] years; FVC<30% = CINRG curve shifted by [redacted] years)
- The company's economic model assumes a starting age of 2 years

Table 9: Mean time to milestone in company model (years)

Milestone	Ataluren + BSC	BSC	Modelled mean delay (years)	Delay attributable to STRIDE/ CINRG ITC*	Delay attributable to assumptions about early and/or relative treatment benefit
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC<50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC<30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC; Best supportive care, FVC; Forced vital capacity, N/a; Not applicable, ITC; Indirect treatment comparison

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Company model uses ITC and various assumptions for clinical outcomes

Company

Study 041

- Provide additional unpublished results from study 041 (RCT comparing ataluren v placebo over 72 weeks, n=359)
- Ataluren treated patients showed a statistically significant reduced decline from baseline compared to placebo across a range of outcomes:

Outcome	Ataluren	Placebo	Difference	p-value
6MWD	-53.0m	-67.4m	14.4m	0.0248
Rate of change (weekly)	-0.74m	-0.94m	0.20m	0.0248
NSAA	-3.7	-4.5	0.9	0.0235
10m walk times	3.04s	3.82s	-0.78	0.0422
Stair ascend times	4.98s	6.04s	-1.06s	0.0293

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Company model uses ITC and various assumptions for clinical outcomes

Company

Additional clinical benefit assumptions in the model

- Based on results of a global Delphi panel of nine clinical experts, with experience of using ataluren to treat DMD patients, it is expected that early treatment will results in a delay in LoA and FVC milestones
- Acknowledge uncertainty regarding magnitude of delay in treatment effect but this is a limitation of generating real-world evidence in a rare disease
- Provide a scenario analysis in which early treatment benefit assumption is removed from non-ambulatory health states – consider this a conservative analysis, and not a key model driver

Managed Access Agreement data

- Nature of data from MAA makes it inappropriate to use in economic model
- Primary due to limitations with NSAA; NSAA typically improves in children up to age 7 and matching of MAA population to control in North Star registry not able to include age at 1st symptom (not recorded)
- MAA designed only to show a difference in NSAA decline between ataluren and control group and not to collect data to inform a health economic model
- LoA is a more appropriate endpoint – therefore STRIDE/CINRG ITC is preferrable to use
- Note that most of the MAA population are included in STRIDE

BSC; Best supportive care, FVC; Forced vital capacity, ITC; Indirect treatment comparison, MAA; Managed Access Agreement, LoA; loss of ambulation

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Company model uses ITC and various assumptions for clinical outcomes

EAG comments

- Agree with company view that headline results from Study 041 "*further add to the clinical efficacy and safety-profile of ataluren*" – although EAG unable to critique study in detail as data provided is limited
- However, evidence from Study 041 has not been used in economic model. In addition, it does not provide any evidence on efficacy of ataluren beyond LoA or in patients aged <5 years old
- EAG clinical experts considered that the predicted outcomes from the model was optimistic for ataluren

Clinical expert

- Relative shift of age at which particular milestones of decline in DMD are reasonable
- Significant differences noted in functional outcomes in STRIDE in comparison to matched controls
- In STRIDE and in MAA data, not all patients have reached respiratory milestones – difficult to interpret
- Difficult to show a benefit in younger children; only show a decline after ~7 years. Ataluren has an effect in modifying disease and slowing down decline in muscle powers, so no sense to delay treatment – greatest benefits likely seen in best preserved muscles
- Estimated outcomes from STRIDE/CINRG ITC have been validated by a Delphi panel

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Modelled predicted age at LoA with and without additional early treatment benefit assumptions

Modelled predicted age at FVC<50% with and without early treatment benefit assumptions

Company use results from STRIDE/CINRG ITC and additional early treatment benefits for predicted age at LoA and FVC<50% to shift CINRG curves to the right for all patients

LoA: loss of ambulation, FVC; Forced vital capacity, ITC; indirect treatment comparison

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Modelled predicted age at FVC<30% with relative and early treatment benefit assumptions

Modelled predicted overall survival including treatment benefit assumptions

Assumed relative and early treatment benefit estimated by shifting CINRG curves to the right. Death assumed to occur 3 years from reaching FVC <30% for all patients

NICE ITC; Indirect treatment comparison, FVC; Forced vital capacity

Key issue: Uncertainty surrounding the relative effectiveness of ataluren versus BSC

Company model uses ITC and various assumptions for clinical outcomes

Muscular Dystrophy UK

- Real-world effectiveness of a treatment that delays progression cannot be overstated
- 68% of survey respondents stated that the anticipated age of LoA had been exceeded
- 64% stated there was a difference to what their child and family could do
- 77% felt ataluren had a role in reducing caregiver and patient isolation and benefitted family well-being
- 2 respondents had a child who had taken part in an ataluren trial – they stated that they had noticed a difference in energy and activity levels when their child had switched from placebo to ataluren
- Important to recognise the that NorthStar data collection impacted by COVID-19
- Committee should adopt a positive pragmatic approach to this issue

Is the company's approach to modelling the relative effectiveness of ataluren compared to best supportive care appropriate?

ITC; Indirect treatment comparison, LoA; loss of ambulation

Cost effectiveness

NICE National Institute for Health and Care Excellence

How company incorporated evidence into model

The company use data from STRIDE, CINRG and the literature to inform model

Table 10: Model Inputs and evidence sources

Input	Assumption and evidence source
Baseline characteristics	STRIDE Data – model assumes starting age of 2 years
Efficacy (ataluren vs standard care)	Standard parametric distributions applied to STRIDE (ataluren) and CINRG (standard care) for age at LoA and FVC <50%. Ataluren curves also shifted right by additional number of years to assume early treatment benefits (from age 2)
Utilities (patient)	Landfeldt et al. (2020) - assumes higher utility values for ataluren in each state
Utilities (caregiver)	Landfeldt et al. (2017) - assumes treatment group-independent utility values for caregivers. Assume 2 caregivers in analysis
Bereavement QALY loss	Bereavement-related QALY loss, assumed to be 9% of expected general population QALYs lost at point of patient's death (as in HST7)
Health state costs	Landfeldt et al. (2017)
Treatment adherence	Unpublished global Delphi panel, [redacted]
Treatment discontinuation	Constant rate estimated using data on discontinuations in STRIDE
Treatment stopping rule	Base case stopping rule is when FVC <50%, other stopping rules tested

LoA: loss of ambulation, FVC; Forced vital capacity

Key issue: Caregiver quality of life

The company and EAG model impacts on caregiver quality of life in various ways. This issue has a high impact on the cost-effectiveness estimates

Background

- Company include impact of condition on 2 caregivers in economic model. The EAG believes methods used by the company are inappropriate and provide analysis using a disutility approach

Company

- Initial base case modelled carer QoL with absolute QALYs + assume carer utility is zero when patient dies
- In response to TE, company has updated its base case with an alternative method to include caregiver QoL:
  - Applies carer QALYs for parents of alive patients until joint median OS point of both arms ([redacted] years)
- Also provide analysis using a range of different assumptions regarding carer QoL
- EAG's approach using carer disutility results in a carer QALY loss for ataluren, which is counterintuitive

Table 11: Company caregiver QoL scenarios

Scenario	Description
1	Absolute carer utilities applied until median joint OS in both arms (updated company base case)
2	No carer utilities or disutilities
3	Carer disutilities, which rebound to general population utilities when patient dies (EAG base case)
4	Carer disutility values are capped in ataluren arm to not fall below than of BSC arm in a cycle
5	Absolute carer utilities – with values of worst alive health state (0.77) used when patient dies

QALY: Quality–adjusted life year, BSC; Best supportive care, QoL; Quality of life

Key issue: Caregiver quality of life

The company and EAG model impacts on caregiver quality of life in various ways. This issue has a high impact on the cost-effectiveness estimates

EAG comments

- Company's initial approach inappropriate as it used absolute QALYs which were assumed zero once a patient died. Notes other HSTs used disutility approach when carer QoL included
- Company's updated approach to including caregiver is still inappropriate
  - Same method as in company's original base case (absolute carer QALYs) except that caregiver QALYs of surviving patients are stopped at a certain point [redacted] years; median OS in both arms)
  - QALYs of bereaved caregivers not included. Surviving patients carer QALYs counted until arbitrary point

- Range of alternative scenarios provided by company are subject to limitations
  - Using absolute caregiver QALYs and assuming these to equal the utility of the most severe alive state in the model (FVC <30%: 0.77) when a patient dies appears to introduce double counting as bereavement impacts are already included elsewhere in the model
  - Capping caregiver disutility losses in ataluren to not be higher than BSC arm in each cycle would require a social value judgement that only positive effects on caregivers should be included
  - Using absolute caregiver QALYs and applying background mortality to bereaved caregivers only does not impact results as caregiver QALYs are assumed to be zero for bereaved caregivers

- EAG still prefer use of carer disutility, as in EAG base case

 QALY: Quality–adjusted life year, BSC; Best supportive care, QoL; Quality of life, OS: overall survival

Key issue: Caregiver quality of life

The company and EAG model impacts on caregiver quality of life in various ways. This issue has a high impact on the cost-effectiveness estimates

Muscular Dystrophy UK

- Important to recognise a wide range of formal and informal caregivers provide support and whose quality of life is impacted (68% of survey respondents were non-parent caregivers, such as family members)

- Caregiver responses to survey question on impact of delay in LoA and delayed loss of upper body strength:
  - 73% reported an improvement to their mental wellbeing, ataluren benefits allow respite for family members
  - 73% of respondents cited increasing impact on caregivers as condition progressed

Patient experts

- No doubt that caregiver QoL is impacted as condition progresses, especially at loss of ambulation
- Slower progression can allow parents to hold down jobs and maintain a modest social life
- Overriding anxiety to slow down progression of DMD –slowing down or stabilising disease allows better management of disease and preparation for next stages
- How to maximise quality of life of your child – greater mobility makes this easier. Even use of a wheelchair and upper limb strength makes a big difference

How should caregiver quality of life be modelled?

LoA: loss of ambulation, QoL; Quality of life,

Key issue: Limitations surrounding the company's survival modelling

EAG suggests a broader range of models may produce a better fit to the data

Background

- Company fit parametric models to estimate age at which patients lose ambulation, have FVC of <50% and <30%

Company

- As model is relatively insensitive to survival model used, the company have not undertaken analysis with a broader range of models
- Adopt the Weibull model in updated base case

EAG comments

- Company original model used log-logistic models for age at loss of ambulation and FVC<50% with a log-normal model used for FVC<30%
- EAG considers use of independent models to be reasonable
- Models selected by company do not appear to provide good representation of data for age of LoA or FVC<50% in STRIDE or FVC <50% In CINRG
- EAG clinical advisors state that model predictions in terms of delays in milestones appear optimistic
- Weibull model use was an EAG sensitivity analysis and not part of the EAG's preferred analysis

How appropriate is the company's approach to survival modelling?

FVC; Forced vital capacity LoA: loss of ambulation

Key issue: Treatment-dependent utility values

The company assume that ataluren provides higher utility values than best-supportive care in the same health state in the model (key ICER driver)

Background

- Treatment dependent utilities assume different utility values for each treatment in the same health state

Company

- Use utility values from Landfeldt et al 2020, which involved six Swedish neuromuscular experts who completed the HUI3 questionnaire in Delphi panel study
- Believe it is appropriate to use treatment dependent utility values for each health state as they are strongly supported by clinical experts, the context of ataluren's effect on disease progression and that the economic model does not fully capture additional disease symptoms
- Note that improvements in QoL are reported by patient organisation submissions

Table 12 Utility values used in company base case

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%			

QoL; quality of life, BSC; Best supportive care, FVC; Forced vital capacity, HUI: Health Utility Index

Key issue: Treatment-dependent utility values

The company assume that ataluren provides higher utility values than best-supportive care in the same health state in the model (key ICER driver)

EAG comments

- Treatment dependent utilities are a key model driver. Company has not presented any empirical QoL evidence to support use of treatment dependent utility values
- [redacted]
- Company apply treatment dependent utilities regardless of whether or not person is still receiving treatment
- EAG clinical experts highlight difficulty of commenting on appropriateness of treatment dependent utilities due to lack of evidence
  - 1 expert stated significant QoL differences between treatment arms unlikely, even if endurance slightly increased with ataluren. Non-ambulant patients who have stopped treatment with ataluren may have increased QoL due to reduced risk of scoliosis
  - 1 expert not convinced of a marked difference in QoL in ambulatory patients having ataluren or BSC and there is no evidence supporting a delay in upper limb involvement with ataluren
- EAG base case includes treatment dependent utilities – may be optimistic. Provides range of scenarios
- Appraisal committee judgement required on: (i) whether there is sufficient evidence to assume treatment-dependent patient utility values; (ii) whether assumption should apply to all or some of model health states, and (iii) whether such benefits should apply beyond discontinuation of ataluren

Key issue: Treatment-dependent utility values

The company assume that ataluren provides higher utility values than best-supportive care in the same health state in the model (key ICER driver)

Clinical expert

- Reasonable to assume different utilities by treatment
- A stronger ambulant or non-ambulant patient would have higher utility values
- Slower decline in muscle function leads to a more functioning and less dependence on carers/adaptations
- Maintaining postural control, respiratory function and delaying onset of scoliosis improves quality of life

Muscular Dystrophy UK

- Positive impact knowing your child is on treatment compared to being on BSC at the same disease stage
- Responses from parents of children with condition state significant psychological impact of accessing treatment that slows down progression.
- Limitations of BSC should also be taken into account

Patient experts

- As ataluren slows progression of disease, it is entirely reasonable to use treatment dependent utility values
- Slowing progression allows life events to be enjoyed more and enables participation in a range of activities
- Emotional and psychological benefit of knowing you are on a treatment that slows progression

Should treatment dependent utilities be applied in the model? If so, should they be applied to each health state? Should they be applied when patients are off treatment?

Key issue: Uncertainty surrounding discontinuation rate in patients with FVC>50%

EAG highlight concerns that discontinuation rates are overestimated in company's model, which may underestimate costs of ataluren

Background

- Company base case assumes treatment until FVC <50%. A constant discontinuation rate is applied when FVC >50% based on discontinuation rate in STRIDE

Company

- STRIDE (Jan 2021) most appropriate source: 29/269 discontinued/changed dose. Discontinuation reasons: physician decision, n=[redacted]; loss of ambulation, n=[redacted]; family/participant request, n=[redacted]; AEs, n=[redacted]; non-response, n=[redacted], and other, n=[redacted].
- Base case uses discontinuation rate of [redacted] per 3-month cycle, based on [redacted] patients who discontinued ataluren out of [redacted] over a period of [redacted] years - Rate validated by an independent UK clinical expert

EAG comments

- EAG's clinical advisors stated rate of discontinuation appears implausibly high (given severity of condition and lack of treatment options)
- Discontinuation rate may be double counting events captured in treatment stopping rule
- Unclear if a constant rate is appropriate or if STRIDE data can be applied to treatment starting at age 2
- EAG sensitivity analysis arbitrarily reduces discontinuation rate by 50% - increases ICER significantly
- 1 EAG clinical advisor noted many patients only require nigh time or fulltime ventilation after FVC<50% and FVC<30% thresholds respectively [redacted]

TE; Technical engagement, FVC; Forced vital capacity, AEs; Adverse events

Key issue: Uncertainty surrounding discontinuation rate in patients with FVC>50%

EAG highlight concerns that discontinuation rates are overestimated in company's model, which may underestimate costs of ataluren

Modelled time on ataluren treatment

- 3-monthly discontinuation probability of [redacted]. Applied to each cycle (natural discontinuation) in addition to a stopping rule (FVC<50% in base case)
- Company's approach to estimate treatment discontinuation has no impact on modelled health outcomes

Table 13: % on treatment (company base case)

Timepoint (years)	% on treatment
5	[redacted]
10	[redacted]
15	[redacted]
20	[redacted]

How appropriate is the company's modelled treatment discontinuation rate?

FVC; Forced vital capacity, TTD; Time to treatment discontinuation

Key issue: Uncertainty surrounding the most appropriate treatment discontinuation rule

Company's model applies a treatment discontinuation rule for all patients reaching FVC<50%. EAG highlight several issues with modelling a discontinuation rule

Background

- Current MAA stopping rule is within 6 months of loss of ambulation. The company proposes to extend stopping rule to FVC<50%

Company

- Acknowledge STRIDE imposed no consistent stopping rule
- Experts highlight applying stopping rules to FVC is challenging – difficult obtaining accurate height measurements. Preferred option may be to focus on ventilation status (night-time or full-time)
- Given this uncertainty and impact on cost-effectiveness, company open to considering different stopping rules – current base case of FVC <50% (night-time ventilation) consistent with clinical opinion
- Earlier stopping rule may reduce ataluren costs and improve cost-effectiveness but less consistent with data
- Provides cost-effectiveness results assuming different stopping rules

Treatment stopping rule scenarios
FVC <50% (Base case)
6 months after loss of ambulation (MAA criteria)
FVC <30%

Key issue: Uncertainty surrounding the most appropriate treatment discontinuation rule

Company's model applies a treatment discontinuation rule for all patients reaching FVC<50%. EAG highlight several issues with modelling a discontinuation rule

EAG comments

- Several issues surrounding stopping rules in the model:
  - EAG clinical advisors state wish to use ataluren beyond loss of ambulation
  - Up to [redacted] of patients in STRIDE who lost ambulation continued ataluren – extent to which this is consistent with base case stopping rule of <50% is unclear
  - No long-term data on pulmonary outcomes with continued ataluren treatment after LoA
  - Unclear whether expert elicited estimates considered company's proposed stopping rule (FVC<50%)
  - Model outcomes are not structurally dependent on whether patient is currently receiving treatment (changing time on treatment rates/stopping rules do not impact on model outcomes)

Clinical expert

- Using a stopping rule dependent on FVC% can be challenging to measure in certain patients (esp. non-ambulatory)
- FVC <50% felt to be point at which overnight ventilatory support is required – more practical to use initiation of non-invasive ventilation for more than 21 days (allows for infection/operation) as a stopping rule
- Not treating non-ambulant patients is potentially denying this cohort effective care

What is the most appropriate treatment discontinuation rule to apply?

LoA: loss of ambulation, FVC; Forced vital capacity

Key issue: Weak characterisation of uncertainty

EAG notes that company analyses do not fully reflect uncertainty in cost-effectiveness of ataluren

Background

- EAG noted that the company in their submission included a limited range of sensitivity and scenario analysis. In addition, EAG note PSA mostly uses arbitrarily assumed 20% change

Company

- In response to technical engagement, the company provide further scenario and sensitivity analysis and updated PSA

EAG comments

- Company provide a broader range of analysis
- EAG adapt company's PSA by removing the restriction of rounding down treatment benefit parameters

Key issue: Uncertainty surrounding modelled acquisition costs of ataluren by age

Background

- In company original base case, the company use the average age in STRIDE to model estimates of patient weight (used in dosing costs). EAG believes this method underestimates costs

Company

- Updated their base case to use EAG preferred source of RCPCH to estimate weight by age

EAG comments

- EAG consider issue resolved following company's updated base case

Summary of company and EAG base case assumptions

Company and EAG base case differ primarily in how caregiver quality of life is modelled

Table 14: Key assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Caregiver QoL	Applies caregiver QALYs (absolute) for parents of alive patients until joint median OS of both arms [redacted]	Uses caregiver disutilities
Treatment-dependent utilities	Use treatment dependent utilities from Landfeldt et al 2020	Base case also uses treatment dependent utilities but EAG raise this assumption as a key issue and provide a range of sensitivity analysis
Treatment discontinuation and treatment stopping rules	Discontinuation rate estimated from STRIDE ([redacted] per 3 month cycle). Stopping rule = FVC <50%. Other stopping rule analysis presented	Same as company's analysis but note discontinuation rate may be over estimated (provide sensitivity analysis). Note that its unclear what extent STRIDE data reflects company's proposed stopping rule
Treatment effect	Assumes additional early treatment benefit beyond that estimated from ITC. Uses Weibull distribution for survival curves	Same as company's analysis but use log-logistic models for age at LoA and FVC<50% with a log-normal for FVC<30% (original company base case). Provide sensitivity analysis on assumed additional benefits

OS; Overall survival, FVC; Forced vital capacity, ITC; Indirect treatment comparison, QALY; Quality-adjusted life year, LoA; loss of ambulation

Description of EAG sensitivity analyses

EAG provide a range of sensitivity analysis – the most influential are those relating to assumption of treatment-dependent utilities and rate of discontinuation of ataluren treatment

Table 15: Description of EAG sensitivity analyses

Parameter	EAG analysis
Health state utility values	• Use of treatment independent utility values in ambulatory state • Assuming BSC utility values after ataluren discontinuation • Use of treatment independent utility values
Early treatment benefit assumptions	• Early treatment benefit assumptions halved • Early treatment benefits removed • Survival gain equal to delay in loss of ambulation • Survival gain removed • Use of Weibull model for time-to-event data
Treatment discontinuation and stopping rules	• Discontinuation rate reduced by 50% • Stopping rule: 6 months after loss of ambulation (MAA stopping rule) • Stopping rule: FVC<30%

Company base case results

Results do not include any QALY weighting

Table 16: Deterministic incremental base case results (inclusive of PAS)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (patients) (£/QALY)	ICER (patients and carers)
Standard care	[redacted]	[redacted]				
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic incremental base case ICER = [redacted]

Table 17: Company scenario analyses (deterministic)

No.	Scenario (applied to company base case) v BSC	ICER (£) versus BSC
1	Company base case	[redacted]
2	Early treatment benefit removed for non-ambulatory health states	[redacted]
3	Absolute caregiver utilities accrue beyond patient death (FVC<30% utility)	[redacted]
4	Caregiver background mortality applied after patient death	[redacted]
5	Scenarios 1, 3 and 4 combined	[redacted]
6	Caregiver utilities excluded	[redacted]
7	Stopping rule = FVC <30%	[redacted]
8	Stopping rule = 6 months after LoA	[redacted]

NICE QALY: Quality-adjusted life year ICER: Incremental cost-effectiveness ratio, PAS: Patient access scheme, FVC: Forced vital capacity

EAG Preferred model results

Table 18: Deterministic incremental results (**inclusive of PAS discount**)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (patients) (£/QALY)	ICER (patients and carers)
Standard care	[redacted]	[redacted]				
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: Probabilistic incremental results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (patients) (£/QALY)	ICER (patients and carers)
Standard care	[redacted]	[redacted]				
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results do not include any QALY weighting

EAG deterministic scenario analysis (list price analysis)

Table 22: EAG scenario analyses (deterministic) Results do not include any QALY weighting

No.	Scenario (applied to company base case) v BSC	Incremental costs (£)	Incremental QALYs	ICER (patients)	ICER (£) (patients and carers)
1	EAG base case	[redacted]	[redacted]	£626,317	£639,644
2	Use of treatment independent utility values in ambulatory state	[redacted]	[redacted]	£1,478,870	£1,555,386
3	Assume BSC utility values after ataluren discontinuation	[redacted]	[redacted]	£821,786	£844,882
4	Use of treatment independent utility values in all states	[redacted]	[redacted]	£3,112,151	£3,471,543
5	Early assumed treatment benefits halved	[redacted]	[redacted]	£643,804	£658,923
6	Early treatment benefits removed	[redacted]	[redacted]	£661,574	£678,870
7	Survival gain = loss of ambulation gain	[redacted]	[redacted]	£631,282	£640,920
8	Survival gain removed	[redacted]	[redacted]	£678,887	£648,411
9	Weibull model for time to event data	[redacted]	[redacted]	£588,080	£604,428
10	Discontinuation rate reduced by 50%	[redacted]	[redacted]	£732,699	£748,289
11	Stopping rule = 6 after loss of ambulation	[redacted]	[redacted]	£548,220	£559,885
12	Stopping rule = FVC<30%	[redacted]	[redacted]	£697,608	£712,451

QALY: Quality-adjusted life year ICER: Incremental cost-effectiveness ratio, FVC; Forced vital capacity

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	
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

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QALY: Quality-adjusted life year, ICER: Incremental cost-effectiveness ratio

QALY weighting

Table 21: Undiscounted QALY weighting by scenario – **results inclusive of PAS**

Scenario	Undiscounted QALYs modifier	ICER without QALY modifier	ICER with QALY modifier
Company updated base case	1.6	[redacted]	[redacted]
EAG preferred analysis	1.1	[redacted]	[redacted]
EAG analysis: discontinuation rate halved	1.1	[redacted]	[redacted]
EAG analysis: stopping rule = 6 months after LoA		[redacted]	[redacted]
EAG analysis: stopping rule = FVC <30%		[redacted]	[redacted]
All other EAG scenarios	1.0	[redacted]	[redacted]

Note: QALY weighting is applied to the number of QALYs in the analysis. ICER includes both patient and caregiver QALYs

Should a QALY weighting be applied?

QALY: Quality-adjusted life year, LoA; Loss of ambulation, FVC; Forced Vital Capacity

Impact of technology beyond health benefits

- Company state that a substantial proportion of ataluren benefits will occur outside of the NHS, including;
  - Less intensive care needed to be provided caregivers due to slowing down progression. More caregivers could remain employed
  - Higher likelihood of people with DMD being in employment and education
  - Delay occurrence of higher costs associated with the condition
- Company include a scenario including a societal perspective –limited impact on cost-effectiveness results

Other considerations

Potential equality considerations

- Patient experts: Duchenne Muscular Dystrophy is classed as a disability. Important that no patient has to travel excessive distances for treatment
- Clinical expert: Current MAA stopping rules does not allow use in non-ambulant patients. Important to not discriminate against older weaker DMD patients

Innovation

- Company state that ataluren is an innovative, first-in-class drug and the first specific approved therapy for nmDMD that addresses underlying cause of disease
- Clinical expert: Ataluren is a step-change in the management of nmDMD and addresses an unmet need

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Are there any 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 issues

The EAG identify several key issues in the company submission

Table 1: Key issues

Issue	Resolved?	ICER impact
Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population	No	Medium
Inappropriate approach used to estimate incremental caregiver QALYs	No – for discussion	Very Large
Limitations surrounding the company's survival modelling	Partially	Unknown
Uncertainty surrounding the appropriateness of treatment-dependent patient utility values	No – for discussion	Very Large
Uncertainty surrounding modelled acquisition costs of ataluren by age	Yes	Minor
Uncertainty surrounding the discontinuation rate in patients with FVC>50%	No – for discussion	Large
Uncertainty surrounding the most appropriate treatment discontinuation rule	No – for discussion	Large
Weak characterisation of uncertainty	Yes	Unknown

Abbreviations: BSC; best supportive care, QALYs; quality-adjusted life year, FVC; Forced Vital Capacity, EAG; Evidence assessment

Key questions

- Is it appropriate to use treatment-dependent utility values?
    - Should they be applied in all health states?
    - Should they be applied after treatment discontinuation of ataluren?
- How should caregiver quality of life be modelled?
- How appropriate is the company's modelled treatment discontinuation rate?
- What is the most appropriate treatment stopping rule?
- Is the company's approach to modelling the relative effectiveness of ataluren compared to best supportive care appropriate?
    - How robust is the company's indirect treatment comparison?
    - How appropriate are the company's additional treatment benefit assumptions?
    - How appropriate is the company's survival modelling?
- Are there any other issues in the company's submission?

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Thank you.