

# Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

Highly specialised technologies guidance

Published: 20 July 2016

[www.nice.org.uk/guidance/hst3](http://www.nice.org.uk/guidance/hst3)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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## 1 Guidance

- 1.1 Ataluren, within its marketing authorisation, is recommended for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only when:
- the company provides ataluren with the discount agreed in the patient access scheme
  - the conditions under which ataluren is made available are set out in the [managed access agreement](#) between the company and NHS England, which should include the conditions set out in [sections 5.12–5.15](#) and [5.23](#) of this guidance.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with ataluren was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 2 The condition

- 2.1 Duchenne muscular dystrophy (DMD) is a severe, progressive X-linked recessive disorder that mainly affects males. DMD with a nonsense mutation is caused by a single base variation in a person's DNA, which leads to incomplete dystrophin production in the skeletal, smooth and cardiac muscle fibres. Dystrophin production is usually affected from birth and symptoms of DMD appear by age 3 years. The main symptom of DMD is motor dysfunction but, as the disease progresses, the gastrointestinal tract and vital organs such as the heart are affected. People with DMD have a decline in physical functioning, with subsequent respiratory and cardiac failure that leads to death, usually before age 30 years.
- 2.2 Current management of DMD includes treatment with corticosteroids, which is associated with delay in loss of walking but significant adverse effects. Other interventions include cardiac and respiratory monitoring and support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation. In addition, dietetic advice (and, in some cases, gastric feeding), prevention and treatment of bone fragility, management of the complications of long-term corticosteroid therapy and psychosocial support may be needed. Clinical care is provided by a range of healthcare professionals depending on local services, including neurologists or paediatric neurologists/neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians and primary care physicians.

### 3 The technology

- 3.1 Ataluren (Translarna, PTC Therapeutics) restores the synthesis of dystrophin by allowing ribosomes to read through premature stop codons that cause incomplete dystrophin synthesis in nonsense mutation Duchenne muscular dystrophy (DMD). Ataluren has a conditional marketing authorisation in the UK for treating DMD resulting from a nonsense mutation in the dystrophin gene in patients aged 5 years and older who can walk. The continuation of marketing authorisation is linked to analysis by the European Medicines Agency of results provided from a phase III trial (Study 020).
- 3.2 The summary of product characteristics lists the most frequent adverse reactions as nausea, vomiting and headache (occurring in 1 in 10 people or more). For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.3 The recommended dosage of ataluren is 40 mg/kg body weight per day. The company submission states that the list price of ataluren is £2,532 per box of 30 sachets containing ataluren 125 mg. Assuming a median weight range of 24 kg to 26 kg, the total cost per person per year of treatment with ataluren is £220,256. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ataluren with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The proposed managed access agreement includes further confidential financial components that would apply while it is in force.

## 4 Evidence submissions

The evaluation committee ([section 7](#)) considered evidence submitted by the manufacturer of ataluren, a review of this submission by the evidence review group (ERG) and evidence submitted by clinical experts, patient experts and NHS England. It also considered a proposed [managed access agreement](#) that was developed by several stakeholders.

### *Nature of the condition*

4.1 Evidence from patient experts and patient groups highlighted the substantial impact of Duchenne muscular dystrophy (DMD) on the quality of life of people with the condition and their families:

- People with DMD have a loss of motor function until eventually they become wheelchair dependent, making it difficult to participate in normal activities at home or at school with siblings, family and friends. Parents and carers describe the frustrations experienced by their child when they cannot take part in games with their peers. Often, younger children do not understand the implications of the disease and why it makes them different.
- As the disease progresses, people with DMD lose the ability to breathe unaided and need assisted ventilation. Scoliosis develops as the back muscles weaken, for which surgery is needed. Parents and carers of people with DMD describe the importance of maintaining their child's ability to walk for as long as possible because loss of walking is an indication of disease progression.
- Parents and carers of people with DMD describe the emotional impact of the short life expectancy of people with DMD. They describe the sadness, anxiety and depression of knowing their child will probably die at a young age. The devastating impact of the disease and its prognosis often leads to isolation from friends and family members.
- Parents and carers described the financial impact of looking after a person with DMD. They described giving up work to look after their child full time. In addition, out-of-pocket expenses can be very high (for example, moving house to ensure the home is wheelchair accessible).

## Clinical evidence

### Study 007

- 4.2 The clinical evidence in the company's original submission focused on the safety and efficacy of ataluren, which was investigated in a phase IIb double-blind randomised placebo-controlled trial (Study 007). Study 007 included 174 male patients with nonsense mutation DMD aged 5 years and older. Patients were recruited from 37 study sites in 11 countries and included 7 patients from the UK. They were randomised to ataluren at a total daily dosage of 40 mg/kg (n=57) or 80 mg/kg (n=60), or to placebo (n=57), all for 48 weeks. The primary outcome was change in the patient's ability to walk on a hard, flat surface measured using the 6-minute walk distance (6MWD). The study compared the mean change in 6MWD from baseline to week 48 measured in the placebo group with that in the ataluren group. The secondary outcomes included change in proximal muscle function measured by timed function tests, and change in force exerted during knee flexion and extension. Quality of life was assessed using the Pediatric Quality of Life (PedsQL) inventory, which contains 4 scales: physical, emotional, social and school functioning.
- 4.3 The pre-specified subgroups in Study 007 were: age (less than 9 years and 9 years and older), corticosteroid use (yes or no) and baseline 6MWD (350 m or less and greater than 350 m). The company conducted a post-hoc subgroup analysis in patients who were classified as being in the decline phase (n=31 in the placebo group and n=32 in the ataluren group). The decline phase was defined as patients aged 7–16 years with a baseline 6MWD test of 80% or less of that predicted and, to minimise heterogeneity, a baseline 6MWD of 150 m or more on a stable dose of corticosteroids. The decline phase was considered clinically important because patients younger than 7 years tend to increase their 6MWD over 48 weeks because of normal developmental improvements in walking.
- 4.4 The intention-to-treat analysis showed no statistically significant difference between ataluren and placebo in the change in 6MWD from baseline to 48 weeks. In the corrected intention-to-treat analysis, baseline values for 2 patients (1 taking placebo and 1 taking ataluren 80 mg/kg) were replaced by their values at screening because the patients had lower-limb injuries before the baseline test. In this analysis, there was a mean observed difference at



48 weeks of 31.3 m between ataluren 40 mg/kg and placebo (-12.9 m and -44.1 m respectively). In a mixed model for repeated measures analysis, the estimated mean difference between ataluren 40 mg/kg and placebo was 31.7 m (95% confidence interval [CI] 5.1 to 58.3, p=0.0197). No effect was seen in the ataluren 80 mg group.

- 4.5 In the post-hoc subgroup analysis for patients in the decline phase, patients having ataluren experienced a statistically significantly smaller reduction in 6MWD compared with patients having placebo (difference in mean change in 6MWD of 45.6 m, p=0.0096). In the pre-specified group of patients with a baseline 6MWD of less than 350 m, there was a statistically significantly smaller reduction in 6MWD in the ataluren group compared with the placebo group (difference in mean change in 6MWD of 59.8 m, p=0.0053).
- 4.6 There were no statistically significant differences in quality of life between the ataluren and placebo groups. The company stated there was a positive trend towards improved quality of life with ataluren 40 mg/kg daily in the physical functioning subscale. The company submission also described a positive effect on school functioning and a negative trend in emotional and social subscales.
- 4.7 The company reported that the number of adverse events was similar in the ataluren and placebo treatment groups in Study 007. None of the patients stopped treatment with ataluren or withdrew from the study because of a treatment-related adverse event, and there were no deaths reported. The most common treatment emergent adverse events reported were: gastrointestinal disorders (73.7% of patients in the ataluren 40 mg/kg group and 37% in the placebo group), vomiting (56.1% in the ataluren 40 mg/kg group and 45% in the placebo group) and diarrhoea (19.3% in the ataluren 40 mg/kg group and 28.3% in the placebo group).

## Study 020

- 4.8 In its response to consultation, the company responded to all the committee's requests described in the [evaluation consultation document](#), including the results of the multicentre randomised double-blind placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020).
- 4.9 Study 020's intention-to-treat population included 228 male patients with

nonsense mutation DMD aged between 7 years and 16 years. At baseline, patients had to have a 6MWD of more than 150 m but 80% or less of that predicted for weight and height. Patients were randomised to ataluren or to placebo for 48 weeks. After this, patients eligible for treatment could have ataluren through an open-label extension study. Patients were stratified based on age, duration of corticosteroid use and baseline 6MWD. The primary outcome was mean change in 6MWD from baseline to week 48 in the placebo group compared with the ataluren group. The secondary outcomes included timed function tests and the North Star Ambulatory Assessment, a clinician-reported outcome instrument consisting of 17 items designed to measure ambulatory function in people with DMD. Quality of life was assessed using the Paediatric Outcomes Data Collection Instrument (PODCI) and Activities of Daily Living Questionnaire. The company stated that pre-specified analyses included a meta-analysis of Study 020 (n=228) and the ambulatory decline phase subgroup of the corrected intention-to-treat population from Study 007 (n=63), and a subgroup analysis of patients from Study 020 with baseline 6MWD of 300–400 m (n=99). The company also presented a meta-analysis of results from a subgroup of patients with a baseline 6MWD of 300–400 m in Study 007 (n=44) and Study 020 (n=99).

- 4.10 The primary outcome results from Study 020 showed a 15 m difference in change in 6MWD at 48 weeks favouring ataluren over placebo in the intention-to-treat population, which was not statistically significant ( $p=0.213$ ). In the subgroup of patients with a baseline 6MWD of 300–400 m, there was a statistically significant benefit of 47 m for ataluren compared with placebo ( $p=0.007$ ). The company noted that Study 020 has contributed to improving the clinical knowledge of DMD and clinical trial design for treatments for this condition. Based on this, it considered that, for a 48-week trial such as Study 020 using 6MWD as a primary outcome, the optimum range in the 6MWD at baseline to detect a significant difference is 300–400 m. The company added that patients with a baseline 6MWD of more than 400 m appear to be too stable and those with a baseline 6MWD of less than 300 m appear to have such severe muscle loss it is not possible to detect a statistically significant treatment effect. Results for the 6MWD from the meta-analysis of the intention-to-treat population from Study 020 and the ambulatory decline phase subgroup of the corrected intention-to-treat population from Study 007 showed a benefit of ataluren compared with placebo (difference in 6MWD of 22 m,  $p=0.015$ ). The meta-analysis for the subgroup of people with a baseline

6MWD of 300–400 m from Studies 007 and 020 also showed a benefit of ataluren compared with placebo, with a difference of 45 m in the 6MWD ( $p < 0.001$ ). The company reported that, in the subgroup analysis of patients with a baseline 6MWD of 300–400 m, none of the 47 patients (0%) lost their ability to walk in the ataluren group compared with 4 out of 52 patients (8%) in the placebo group at 48 weeks. The number of people who lost their ability to walk in the intention-to-treat population was provided by the company as commercial in confidence and cannot be reported here.

- 4.11 Results for timed function tests in the intention-to-treat population of Study 020 were provided by the company as commercial in confidence and cannot be presented here. Results for the North Star Ambulatory Assessment in the intention-to-treat population did not show a statistically significant difference for ataluren compared with placebo ( $p = 0.27$ ). In the subgroup of patients with a baseline 6MWD of 300–400 m, ataluren showed benefits compared with placebo in the timed function tests (10 m run/walk,  $-2.1$  seconds,  $p = 0.066$ ; 4 stair climb,  $-3.6$  seconds,  $p = 0.003$ ; and 4 stair descend,  $-4.3$  seconds,  $p < 0.001$ ) and the North Star Ambulatory Assessment ( $p = 0.04$ ).
- 4.12 The company provided graphical results from Study 020 suggesting improvements in quality of life based on changes in 2 dimensions of the PODCI in patients with a baseline 6MWD 300–400 m having ataluren compared with placebo. It also noted that results with the Activities of Daily Living Questionnaire showed that people having ataluren had greater improvement or less deterioration in walking, stair-climbing and upper extremity activities of self-care than people having placebo (results were presented as commercial in confidence and cannot be reported here). The company also provided the results of a survey on the quality of life of caregivers ( $n = 6$ ). The results showed that DMD had a serious impact on multiple aspects of their life including emotional wellbeing and mental health, personal care and the ability to maintain relationships. The results showed that caregivers felt tired, depressed and anxious and that, in many cases, at least another family member in addition to both parents were involved in giving care (for example, siblings and grandparents).

## Economic evidence

### Overview of company's cost–consequence models

- 4.13 Over the course of the evaluation, the company presented several cost–consequence analyses comparing the licensed dose of ataluren (40 mg/kg daily) with best supportive care in people aged 5 years or older who could walk:
- The first model, which used data from Study 007, was part of the original submission (see [sections 4.15–4.19](#)).
  - The second model was submitted in response to consultation and used data from Study 020 as well as Study 007 (see [sections 4.20 and 4.21](#)).
  - A third model was later submitted to show how the financial components of the proposed managed access agreement would affect the value of ataluren (see [sections 4.35 and 4.36](#)).
- 4.14 Each of the company's Markov models had 6 states, representing the progression of DMD from the ambulatory phase to the non-ambulatory phases and death. The cycle length was 3 months. In the first model, the time horizon of the model was limited to the last point when 1 or more patients were in the ambulatory state (because only patients who could walk had treatment). In the second and third models, a lifetime time horizon was adopted. The analysis was carried out from the perspective of the NHS and personal social services, and costs and benefits were discounted at a rate of 3.5% per year (except in the second model, which used a rate of 1.5%).

### Company's first cost–consequence model

- 4.15 To inform the best supportive care transition probabilities for loss of walking, the company used Kaplan–Meier estimates from the literature to derive time-dependent transition probabilities based on patient age. Ricotti et al. (2013) reported long-term outcomes of boys with DMD in the UK, comparing daily and intermittent use of corticosteroids. In this study, loss of walking with daily corticosteroid use occurred at a median age of 14 years. The company considered it reasonable to assume that these data were representative of the placebo arm in Study 007. In its original base case, the company used a Weibull function to fit the data.

- 4.16 To inform the transition probabilities for ataluren compared with placebo in its first model, a linear regression of the values of 6MWD from week 24 to week 48 of Study 007 against time was done. The regression analysis was performed on the data from week 24 to week 48 because the company deemed it to be more representative of the long-term treatment effect of ataluren. The company suggested that this was a conservative assumption because ataluren had a greater benefit compared with best supportive care in improving 6MWD in the first 24 weeks of the study. The linear extrapolation suggested that loss of walking would occur in the best supportive care group at week 313 (6.0 years) and at week 733 (14.1 years) in the ataluren group, which equated to a difference of 420 weeks (8.1 years). The company fitted a Weibull curve and shifted the best supportive care curve to the right so that the difference in median time to loss of walking between ataluren and best supportive care was 8.1 years (that is, the same as that predicted by linearly extrapolating Study 007 data). In its response to clarification, the company explored fitting alternative parametric models.
- 4.17 The company model included health-related quality-of-life data from the literature to inform the utility values in the cost–consequence analysis (Landfeldt et al. 2014) for patients and carers. It explained that it did not use the PedsQL inventory data from Study 007 because the algorithm used to map the data to EQ-5D was adapted from a study by Khan et al. (2014), which was conducted in a healthy population. The company said that no loss of utility for adverse events had been included in the company model because there were no significant differences in the incidence of adverse events between the ataluren and placebo arms in Study 007.
- 4.18 The company estimated that the total cost per year of treatment with ataluren (list price) for an average 8-year-old child weighing 26 kg is £246,448. To calculate the cost per patient in the cost–consequence analysis, an age–weight curve from the Royal College of Paediatrics and Child Health was used to estimate the annual increase in weight for the cohort, with a starting age of 8.5 years. The company assumed no additional costs for monitoring. Health-state costs were taken from a published study (Landfeldt et al. 2014) and were converted using the UK 2012 purchasing power parity (OECD, 2015) and then inflated to 2014 costs using the consumer price index for health (ONS, 2015). For patients in the ambulatory health state, the total costs were £9,605. For patients in a non-ambulatory health state, the total costs were £23,600. In the

non-ambulatory and ventilation-assisted health state, the total costs were also £23,600. In the non-ambulatory with scoliosis (with or without assisted ventilation) health states, the total costs ranged from £25,058 to £46,043.

4.19 In the company's original base case, best supportive care was associated with £235,207 in costs and 2.39 quality-adjusted life years (QALYs) over the lifetime of the model. Ataluren, at list price, was associated with £5,092,540 in costs and 6.15 QALYs, amounting to an incremental cost of £4,857,333 and an additional 3.77 QALYs compared with best supportive care. The incremental costs when applying the initial patient access scheme price for ataluren are confidential and no longer valid because the company subsequently increased the discount and included further financial components in the proposed managed access agreement.

## Company's second cost–consequence model

4.20 After consultation the company provided a response to all the committee's requests described in the [evaluation consultation document](#). The company's second cost–consequence model included the following changes compared with its first model:

- updated parametric curves used to extrapolate time to loss of walking, time to scoliosis, time to ventilation assistance and time to death
- an assumption that patients do not develop scoliosis after puberty
- continued treatment costs with ataluren for 6 months following loss of walking
- a lifetime time horizon
- a change in the discount rate for costs and outcomes to 1.5%, which the company considered appropriate because it believed that ataluren significantly delays loss of walking by 7–12 years up to age 30 years
- an increased disutility associated with scoliosis from 0.1 to 0.3
- full caregiver disutilities ascribed to 3 caregivers rather than 1
- different utility values for people in the ataluren and best supportive care groups after loss of walking (the company assumed that, because ataluren prolongs the time that patients are able to walk, loss of walking would occur after puberty at a stage of

- greater physical development in the ataluren group leading to a better quality of life even after walking is lost compared with patients who stop being able to walk at a younger age)
- costs for ventilation assistance
- an assumption that people who are able to walk cannot die from DMD-related causes
- data from Study 020 and 2 different extrapolation methods:
  - linear extrapolation of 6MWD
  - stepped decline in 6MWD.

The linear extrapolation method used the 6MWD results for the ataluren and placebo groups from a meta-analysis that included patients from Study 007 and Study 020. The company noted that, based on this approach, there was a difference of 12.2 years in time to loss of walking for ataluren compared with placebo. The stepped decline extrapolation method used a weighted average of the 6MWD results in Study 007 and Study 020 for the subgroups with a baseline 6MWD of 400 m or more, 300–400 m, and 300 m or less. However, the company suggested that, because the 6MWD was not sensitive enough to show differences in the treatment effect of ataluren in the subgroups of patients with a baseline 6MWD 300 m or less and of 400 m or more, it was more appropriate to use the following assumptions for its extrapolation rather than data from the trials:

- In the subgroup of patients with a baseline 6MWD of 300 m or less the company assumed that the treatment effect with ataluren would be 20% to account for the improved function with ataluren compared with placebo seen in the timed function tests and the North Star Ambulatory Assessment.
- In the subgroup of patients with a baseline 6MWD of 400 m or more, the company assumed a rate of decline in the best supportive care group taken from the average of the 48-week decline in the 300–400 m and 400 m or more subgroups after 2 years. This was because it considered the results seen in the trials do not appropriately represent the natural history of the condition. Based on this approach, there was a difference of 7.1 years in time to loss of walking for ataluren compared with placebo.

The company argued that all these amendments were based on clinical data from Study 007 and Study 020, the committee's considerations about the original model and

- additional amendments based on further understanding of the natural history of the condition and the clinical effectiveness of ataluren.

4.21 The base-case results from the company's updated model suggested that ataluren provided 8.19 and 11.75 additional QALYs compared with best supportive care (using the stepped decline and linear extrapolation methods respectively), with associated incremental costs using the list price of £5,532,819 and £8,400,164 (using the stepped decline and linear extrapolation methods respectively). The incremental costs when applying the patient access scheme for ataluren are confidential and are no longer valid because the company subsequently increased the discount and included further financial components in the proposed managed access agreement.

### *Company's budget impact model*

4.22 The company presented budget impact analyses to predict the cost of ataluren to the NHS and personal social services. In its original submission, the company estimated that, in year 1, a total of 35 people would have treatment, rising to 65 in year 5. The budget impact in year 1 (using ataluren's list price) was estimated to be about £8,625,680, rising to £16,019,120 in year 5. The results of the original budget impact analysis that incorporated the patient access scheme are confidential and are no longer valid because the company subsequently increased the discount and included further financial components in the proposed managed access agreement. The company submitted a further budget impact model in tandem with the proposed managed access agreement (see [section 4.37](#)).

## *Evidence review group review*

### **Clinical effectiveness**

4.23 The ERG noted that the evidence in the company's original submission reflected the decision problem and considered most of the analyses to be appropriate. The ERG noted several limitations in the clinical-effectiveness evidence presented by the company, including:

- The follow-up time in Study 007 (48 weeks) was potentially too short to measure important outcomes (for example, mortality).



- A summary of serious adverse events from 4 ongoing and 5 completed company-sponsored clinical trials suggested that several of these, including femur fractures, were more common with ataluren than with placebo. However, the ERG was unclear if this was because of longer exposure in the ataluren group.

4.24 The ERG reviewed the evidence from Study 020 submitted by the company in response to the committee's consultation request. It considered that there seemed to be selective reporting bias. It also noted that the company had not provided information on the minimal clinically important differences for the North Star Ambulatory Assessment, the PODCI and the Activities of Daily Living Questionnaire and that, in general, there was a lack of statistical test reporting in the company's analyses.

## Cost effectiveness

4.25 The ERG noted the lack of evidence available on the long-term follow-up of people with DMD and considered that the company's use of external studies to inform model transition probabilities was valid. However, the ERG considered that there were issues with the methods used to extrapolate the data for the models, and investigated these in its exploratory analyses. In addition, the ERG noted that it may not be clinically plausible to assume that the treatment benefit of ataluren over best supportive care remained the same over time.

## ERG exploratory analyses using the company's first model

4.26 The ERG's preferred scenario used a lifetime horizon and included the costs for continuing treatment with ataluren 6 months after loss of walking. It did so because the additional treatment costs had not been included in the company's base-case analysis, even though the company submission said that people would continue to have treatment for up to 6 months following loss of walking. The ERG's preferred scenario also included the best-fitting parametric curves to inform the clinical parameter transition probabilities. Flexible parametric models were selected for all transitions other than for the ambulatory to non-ambulatory state. For transitions to the non-ambulatory state, a log-normal model was used: although a flexible parametric model gave the best statistical fit, the ERG stated that its predictions may not be clinically plausible.

4.27 In the ERG's preferred scenario analysis, best supportive care was associated with £199,194 in costs and 3.80 QALYs over the lifetime of the model. Ataluren,

at list price, was associated with £5,744,175 in costs and 6.86 QALYs, amounting to an incremental cost of £5,544,981 and an additional 3.05 QALYs compared with best supportive care.

## ERG exploratory analyses using the company's second model

4.28 The ERG reviewed the company's cost-consequence analyses using the second model and expressed concerns with some of the company's assumptions. The ERG considered that it was appropriate to explore the following assumptions and amendments:

- alternative parametric curves to extrapolate time to scoliosis and time to ventilation assistance
- that patients could develop scoliosis after puberty (because, although the rate of scoliosis would be expected to be lower after puberty, the ERG was uncertain whether the risk would be completely eliminated)
- a discount rate for costs and outcomes of 3.5% (because the ERG was unclear whether ataluren provided benefits that would restore the patient to full health and whether these benefits are likely to be maintained in the long term)
- disutility because of scoliosis of 0.1 as per the company's original model (because there was no evidence on which to base applying the specific value assumed by the company, which was based on expert opinion)
- caregiver disutilities applied for 2 caregivers rather than 3 (because the ERG was unclear why the same disutility for 1 primary caregiver should be applied to all caregivers)
- the same utility values for people in the ataluren and best supportive care groups after loss of walking (because the ERG was unclear from the source the company had based this assumption on whether quality-of-life data from people who have just lost their ability to walk can be assumed to apply for their whole life time and to be different for patients having ataluren and best supportive care).

4.29 The ERG also expressed concerns about the 2 methods used by the company to extrapolate 6MWD. It considered that the linear extrapolation method was not appropriate because it used rates of decline in 6MWD from the subgroup of people with a baseline 6MWD of 300–400 m and applied them to the whole

population. The ERG preferred the stepped decline approach but had concerns that the company's method of replacing some 6MWD trial data with assumed values favoured ataluren. To correct for this, the ERG presented 2 alternative approaches:

- stepped decline approach 1:
  - using trial data in the subgroup of patients with a baseline 6MWD of 300 m or less
  - taking the average of the 6MWD data from the subgroup of patients with baseline 6MWD of 400 m or more and 300–400 m and applying it to the subgroup of patients with baseline 6MWD of 400 m or more after 2 years in both treatment groups
- stepped decline approach 2:
  - using trial data in the subgroup of patients with a baseline 6MWD of 300 m or less
  - applying the numerical increase in decline rate after 2 years seen in the placebo group to the ataluren group for the subgroup of patients with a baseline 6MWD of 400 m or more after 2 years.

4.30 The results from the ERG's exploratory analyses, when applying its preferred assumptions (see sections 4.28 and 4.29), showed that ataluren provided between 2.03 and 6.41 additional QALYs compared with best supportive care (using the stepped decline approach 2 and the linear extrapolation methods respectively). The incremental costs for ataluren compared with best supportive care that incorporated the patient access scheme for ataluren are confidential and are no longer valid because the company subsequently increased the discount and included further financial components in the proposed managed access agreement.

## ERG's exploratory analyses using the company budget impact model

4.31 Using the company's original budget impact model, the ERG explored changing the average weight of people having treatment to the average weight of people occupying the ambulatory health state in the cost-consequence model (39 kg in the best supportive care group and 53 kg in the ataluren group). Using the list

price and an average weight of 39 kg, the budget impact in year 1 was estimated to be about £13,456,065, rising to £24,989,835 in year 5. The corresponding results using an average weight of 53 kg were £18,286,450 and £33,960,550 respectively. The ERG's exploratory results incorporating the patient access scheme are confidential and are no longer valid because the company subsequently improved the discount and included further financial components in the proposed managed access agreement.

### *Proposed managed access agreement*

- 4.32 The company asked for and received permission from NICE to submit an improved patient access scheme and to begin discussions about a managed access agreement. Facilitated by NICE, a proposed managed access agreement was developed and submitted by a group of stakeholders comprising the company, NHS England, patient community experts and clinical experts. The proposed managed access agreement takes effect once stakeholders have confirmed they are in agreement with the proposed method of supporting delivery of this guidance. If agreed, the proposed managed access agreement would remain in force for up to 5 years after publication of this guidance. The proposed managed access agreement states that, if NICE does not recommend ataluren for NHS funding when the guidance is reviewed, NHS England funding for ataluren will no longer be available for any patient and treatment will stop. Those involved in the proposed managed access agreement will ensure that any patient receiving ataluren whose treatment is funded by NHS England under this proposed managed access agreement is made aware of these funding limitations and, on signing the patient agreement, accepts them on the agreed terms.
- 4.33 The proposed managed access agreement states that ataluren will be considered as a treatment option for all patients aged 5 years and older with DMD resulting from a nonsense mutation and who are able to walk 10 steps unaided:
- Patients should only start treatment once a full set of standard baseline criteria has been obtained and they have signed the proposed managed access patient agreement.
  - Patients should stop treatment no later than 6 months after becoming fully non-ambulant (defined as no longer able to stand even with support and entirely dependent on wheelchair use for all indoor and outdoor mobility, unless this is because of an

- accident or an intercurrent illness).

4.34 Data will be collected from all patients when starting ataluren treatment and at all subsequent clinic visits and will be entered into the NorthStar database. Patients will be monitored according to the standard NorthStar criteria and Child Health Utility 9D quality-of-life data will be collected annually in those aged 7 years and older. Patients receiving ataluren (n=50) will be compared with an historical natural history population and a matched control group of the same age and North Star Ambulatory Assessment (n=100) to assess response to treatment. The historical data and matched control group will be identified from patients included in the NorthStar registry. Over the first 2 years of the proposed managed access agreement, the cohort of patients receiving ataluren is expected to have a decline on the North Star Ambulatory Assessment scale of around 4 points less than the matched control cohort (the anticipated values for each cohort are academic in confidence and cannot be presented here). The company said it calculated the expected decline using similar extrapolations to those seen in Study O20, as well as natural history data (Ricotti et al, 2015). At this time, the ataluren and matched control group declines will be evaluated and the extrapolation over the full 5-year period will be confirmed or recalibrated.

### Company's third cost–consequence model

4.35 In tandem with the proposed managed access agreement, the company submitted a third cost–consequence model. The third model was broadly similar to the second but included:

- an improved confidential patient access scheme
- other confidential financial components to enhance the value proposition to the NHS
- some alternative modelling assumptions:
  - the same parametric survival models for scoliosis and ventilation assistance as in the ERG's exploratory analyses using the company's second model
  - discount rates of 3.5%
  - a decline after 2 years in the ataluren group with a baseline 6MWD of more than 400 m that was assumed to be the midpoint of the declines in the groups with a baseline 6MWD of more than 400 m and 300–400 m

- – disutility for scoliosis of 0.2.

4.36 In its base case, the company assumed that patients would receive ataluren or best supportive care for 5 years (the projected duration of the proposed managed access agreement) then all patients would receive best supportive care. The company also did scenario analyses in which patients receiving ataluren continued treatment until loss of walking and others that adopted the ERG's preferred assumptions (these were subsequently ratified by the ERG). All results were provided using linear extrapolation and stepped-decline extrapolation methods (see [table 1](#)). Incremental QALYs for ataluren compared with best supportive care ranged from 1.913 to 8.562. Total and incremental costs incorporating the patient access scheme and other financial components in the proposed managed access agreement are confidential and cannot be presented here.

**Table 1 Results using the company's third cost-consequence model**

	Linear			Stepped		
	Ataluren	BSC	Incremental	Ataluren	BSC	Incremental
<i>Base case: Company assumptions; 5-year ataluren treatment; PMAA treatment costs</i>						
QALYs	4.087	-0.914	5.001	2.977	-0.914	3.891
<i>Scenario: Company assumptions; ataluren until loss of walking; PMAA treatment costs</i>						
QALYs	7.647	-0.914	8.562	3.647	-0.914	4.561
<i>Scenario: ERG assumptions; 5-year ataluren treatment; PMAA treatment costs</i>						
QALYs	3.694	0.803	2.890	2.716	0.803	1.913
<i>Scenario: ERG assumptions; ataluren until loss of walking; PMAA treatment costs</i>						
QALYs	7.212	0.803	6.409	3.192	0.803	2.389
Abbreviations: BSC, best supportive care; ERG, evidence review group; PMAA, proposed managed access agreement; QALY, quality-adjusted life year.						

4.37 The company also submitted a budget impact model that included the patient access scheme and other confidential financial components in the proposed managed access agreement. The results are confidential and cannot be presented here.

4.38 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the [committee papers](#).

## 5 Consideration of the evidence

The evaluation committee reviewed the data available on the benefits and costs of ataluren, having considered evidence on the nature of Duchenne muscular dystrophy (DMD) and the value placed on the benefits of ataluren by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that ataluren represents and the effective use of resources for specialised commissioning.

### *Nature of the condition*

- 5.1 The committee discussed the nature of nonsense mutation DMD and its impact on people with the condition. It understood that DMD is a serious, progressive condition that reduces life expectancy and causes debilitating symptoms associated with loss of muscle strength that severely affect the quality of life of people with the condition. The committee heard from the patient experts that one of the most important aspects of managing DMD is maintaining their child's ability to walk. It heard that this means their child can continue to lead a more rounded life, for example, going to school on the bus independently, participating more fully with their friends and siblings in social and sporting activities, and spending more time with family and friends. It also heard that a loss in walking is followed by a greater deterioration in functioning that usually means people need constant care to perform routine daily activities such as getting out of bed, eating and going to the toilet. The patient experts explained that the impact of the condition is even more crucial at the point when the disease progresses and the ability to walk is lost (that is, around adolescence). The clinical and patient experts noted that, in general, this is a difficult time for every child and that the impact of the condition at this time makes it even harder. The committee also heard from the patient experts that if the time to loss of walking could be delayed, patients would have the opportunity to have a normal adolescence and to enter adulthood with a better understanding of their condition. The committee concluded that DMD is a serious life-threatening condition that progressively affects quality of life, with the greatest impact after loss of walking.
- 5.2 The committee further discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. It considered the findings of the company's survey on the quality of life of a small number of caregivers, and noted that this showed that DMD had a



serious impact on multiple aspects of caregivers' lives (see [section 4.12](#)). It noted that, in many cases, at least another family member in addition to both parents was involved in giving care (for example, siblings and grandparents). The committee heard from the clinical and patient experts about the severe impact that the condition has on the person with the condition, family and carers' quality of life. The committee understood that, while people are able to walk, they are able to do normal activities of daily living on their own with the support of 1 or more caregivers. It heard, however, that the need for support increases substantially after the person loses their ability to walk. Patient experts highlighted the importance to parents of seeing their children grow and develop in line with their peers for as long as possible. The committee heard from the clinical experts that other more common disorders could produce equally devastating disability. The committee concluded that, although not unique, DMD has a distinctive nature, particularly given the time in the patient's life at which the ability to walk is usually lost. It concluded that delaying loss of walking is important to patients and carers.

- 5.3 The committee considered the current treatment options for nonsense mutation DMD. It heard from the clinical experts that the mainstay of treatment is corticosteroid therapy, which can slow the decline in muscle strength and function. This, in turn, may help to prolong the ability to walk. It also heard, however, that corticosteroids can cause unwanted effects such as growth retardation, bone thinning, mood swings and weight gain. It further heard from the clinical experts that new treatments are desired that prolong the time a person is able to walk by addressing the underlying cause of disease and with a more favourable adverse-event profile. The committee concluded that there is a high unmet medical need and that further treatment options are needed to extend the time to loss of walking and thus maintain quality of life.

### *Impact of the new technology*

- 5.4 The committee heard from the clinical experts that, because ataluren potentially addresses the nonsense mutation that causes DMD to develop, they considered it to be a step change in the management of DMD. The committee agreed that ataluren was an innovative treatment and would be likely to stimulate further research in this therapy area.
- 5.5 The committee discussed how treatment benefit was assessed in the clinical

trials. It was aware that the primary end point in Study 007 and Study 020 was the 6-minute walk distance (6MWD). It heard from the clinical experts that the 6MWD is a well-validated tool used in clinical trials to assess functioning in DMD. The committee considered the secondary outcomes in the trials and heard from the clinical experts that some of these measures, such as time to get up and stand or time to run 10 m, are used more often in clinical practice but are not as clinically informative as the 6MWD. The committee heard the company's suggestion that shorter tests can be less of a burden for patients with a 6MWD of less than 300 m. It appreciated that the North Star Ambulatory Assessment provided information relevant to clinicians, and that it was routinely used in clinical practice, but was unclear on what is thought to be a clinically meaningful difference with this outcome. The committee was unconvinced that it offered more valuable information than 6MWD in this population. The committee concluded that the 6MWD was an appropriate primary outcome to assess the benefits of treatment with ataluren in the clinical trials.

- 5.6 The committee considered the clinical effectiveness of ataluren in the intention-to-treat populations of Study 007 and Study 020. It noted that, in the intention-to-treat analysis in Study 007, there was no statistically significant difference in change in 6MWD at 48 weeks between the ataluren and best supportive care groups but that, in the corrected intention-to-treat analysis, there was a statistically significant difference favouring ataluren. The committee accepted that the company's post-hoc adjustment could be justified (see [section 4.4](#)) but considered that the results of Study 007 were uncertain. Likewise, it noted that there was no statistically significant difference in 6MWD at 48 weeks between ataluren and best supportive care in the intention-to-treat population in Study 020, even though the enrolment criteria for this confirmatory study had been intended to enrich the population in the decline phase of DMD (that is, when a treatment effect had been detected in a post-hoc analysis in a similar subgroup in Study 007; see [section 4.5](#)). The committee concluded that there was not a meaningful improvement in the rate of decline in 6MWD with ataluren compared with best supportive care in the intention-to-treat populations of Study 007 and Study 020. The committee noted the company's opinion that neither of the intention-to-treat populations in Study 007 and Study 020 was the optimal patient group for detecting a treatment effect within 48 weeks. It then discussed the results for the company's subgroup analyses separately.

- 5.7 The committee discussed which was the most appropriate patient population in the clinical trials to inform its decision-making. The committee heard from the clinical experts that the decline phase is a clinically observed effect in people with DMD, and that a treatment effect on slowing the rate of decline in muscle strength would be more likely to be detected during a period of rapid decline than of stability. The committee heard from the company that the patient populations in Study 007 and Study 020 have contributed to clinical knowledge about DMD and clinical trial design for treatments for the disease. It noted the company's assertion that, in 48-week trials such as Study 007 and Study 020 that have change in 6MWD as a primary outcome, the optimum range in the 6MWD at baseline to detect a difference is 300–400 m. The company suggested that patients with a baseline 6MWD of more than 400 m appear to be too stable for a treatment effect to be detected within 48 weeks. It further suggested that patients with a baseline 6MWD of less than 300 m have such severe muscle loss it is not possible to detect a statistically significant treatment effect. The committee heard from the clinical experts that the company's rationale was plausible because a similar effect had been seen in patients who had treatment with corticosteroids. However, it still had concerns that a small and non-statistically significant difference had been found in the intention-to-treat population. The committee agreed to consider the 48-week clinical trial data from a subgroup of patients with a baseline 6MWD of 300–400 m but expressed concerns about the uncertainty and generalisability of the results to the broader ambulant population.
- 5.8 The committee considered the company's results of a pre-specified subgroup analysis of patients in Study 020 with a baseline 6MWD of 300–400 m and a meta-analysis of the results from Study 007 and Study 020 for this subgroup. The committee noted that both sets of results for this subgroup showed statistically significant differences in the 6MWD at 48 weeks between ataluren and best supportive care (see [section 4.10](#)). The committee noted that the results from the timed function tests and the North Star Ambulatory Assessment were consistent with the 6MWD results but recalled its previous concerns about what difference could be regarded as clinically meaningful (see [section 4.11](#)). The committee noted that the company presented the results of the other subgroups (including the subgroups with a baseline 6MWD of more than 400 m and less than 300 m from Study 020) as commercial in confidence, so these could not be reported here. The committee concluded that the results of the clinical primary and secondary outcomes in Study 020 showed a benefit

at 48 weeks of ataluren compared with best supportive care in patients with a baseline 6MWD of 300–400 m.

- 5.9 The committee asked the clinical experts when they would consider starting treatment with ataluren in clinical practice. It heard that they would ideally start treatment early, with the expectation of delaying loss of walking before the decline phase starts. The committee understood that a statistically significant benefit with ataluren compared with best supportive care had not been shown in the population in which it was intended to be used in clinical practice (that is, in line with its marketing authorisation for patients aged 5 years and older who can walk). Therefore, the committee concluded that, although ataluren seemed to provide a benefit compared with best supportive care in the 6MWD and other functional tests for some patients, the size of this benefit in the overall ambulant population (in which the drug is intended to be used in clinical practice) remains highly uncertain.
- 5.10 The committee considered whether all the possible treatment benefits associated with ataluren had been captured in Study 007 together with further evidence from Study 020. It noted that, in Study 007, there was no statistically significant difference in quality of life reported in the ataluren group compared with the best supportive care group (see [section 4.6](#)). Results of the Paediatric Outcomes Data Collection Instrument and Activities of Daily Living questionnaire from Study 020 were provided by the company as commercial in confidence and so cannot be presented here. The committee considered that the results of the Pediatric Quality of Life inventory in Study 007 did not reflect the statements received by the patient experts. The committee heard from the patient experts that they had seen meaningful stabilisation or improvements in their child's walking ability after having ataluren, which meant their child could continue daily activities unaided, such as getting out of bed, getting in the car and going to school. This was restated in the comments received from the patient organisations during consultation, which noted that the impact of ataluren on quality of life in people with DMD had not been appropriately captured. The committee further noted that the duration of Study 007 and Study 020 was 48 weeks, and considered that this was too short to determine any long-term benefits of treatment with ataluren (including loss of walking and mortality). This was important because the company had assumed in its submission that the decline in the ability to walk based on the 6MWD and so, loss of the ability to walk was correlated to mortality. Therefore, by slowing the

rate of decline and delaying the loss of walking, ataluren has the potential to improve survival. The committee concluded that it was likely that the quality-of-life data collected during Study 007 and Study 020 had not fully captured the short-term benefits experienced by patients having ataluren, and that there was uncertainty about the longer-term benefits of ataluren treatment because of the limitations in the evidence base.

- 5.11 The committee considered the evidence on adverse events reported in Study 007 and Study 020. It noted that there was no significant difference in adverse events reported in Study 007. It heard from the clinical experts that, in their experience, ataluren is well tolerated and treatment has not been stopped because of adverse events. The committee understood that regulatory requirements around the risks associated with ataluren treatment are outlined in the summary of products characteristics and the European public assessment report for ataluren. The committee noted that the company stated that, in Study 020, there were similar adverse events in the ataluren and best supportive care groups. The committee concluded that there were no specific safety concerns associated with ataluren.
- 5.12 The committee considered the general structure of the proposed managed access agreement:
- It was satisfied with the definition of patient eligibility for treatment with ataluren, and by the starting and stopping criteria.
  - It heard from the clinical experts that the rate of decline in physical functioning was largely uniform across different types of DMD and therefore found it reasonable to have a control group that did not have nonsense mutation DMD.
  - It noted the proposed exit strategy. The committee agreed that ongoing funding should not be provided by NHS England when the proposed managed access agreement ends if the clinical outcome data gathered while it is in force do not support continued treatment when the guidance is reviewed. The committee concluded that, when starting treatment, those involved in the proposed managed access agreement must ensure that any patient receiving ataluren whose treatment is funded by NHS England under such an agreement is made aware of these funding limitations and that the patient accepts the terms of such an agreement on signing the patient agreement. The committee was advised by NICE that this made it sufficiently clear to people starting treatment with ataluren in the context of the proposed managed access agreement

- that the treatment period could be finite.

5.13 The committee then focused on whether the data collection from patients in the proposed managed access agreement would generate meaningful data to inform a review of this guidance. The committee was largely satisfied with the proposed patient outcomes and noted that the clinical experts considered the North Star Ambulatory Assessment offered a comprehensive assessment of physical functioning. However, it was concerned that the 6MWD was not included because this was the primary outcome in Study 007 and Study 020 and it was this clinical evidence that underpinned the company's cost-consequence models. It heard from the clinical experts that, although 6MWD was often a primary outcome in clinical trials, it was not routinely used in clinical practice. Reasons for this included a lack of trained personnel, insufficient space and that it was unsuitable for children with behavioural problems. The committee further heard that the North Star Ambulatory Assessment offered a more comprehensive assessment and was routinely used in all centres. The committee had reservations about being able to combine data generated via a managed access agreement with existing data from Study 007 and Study 020 to inform the review of guidance. However, it heard from the company that North Star Ambulatory Assessment data were available for all patients in Study 020 and was eventually persuaded that omitting 6MWD was acceptable because the phase III Study 020 data could be combined with data collected during the proposed managed access agreement. The committee concluded that it accepted the list of patient outcomes that would be recorded as part of the proposed managed access agreement because they would meaningfully inform a review of this guidance.

5.14 The committee considered the quality-of-life data that would be captured as part of the proposed managed access agreement:

- It noted the proposal to capture carer utility using EQ-5D. The committee recalled that DMD had a serious impact on multiple aspects of caregivers' lives (see [section 4.12](#)) and that a significant caregiver disutility had been applied to multiple carers in the company's cost-consequence model to reflect this. It concluded that it is imperative that its future review of guidance includes carer utility data.
- The committee noted that the proposed managed access agreement included collection of Child Health Utility 9D quality-of-life data for boys aged 7 years and older. It considered it essential that quality-of-life data are captured for all boys

- receiving ataluren, including proxy data for younger children (that is, those aged less than 7 years).

5.15 The committee discussed the proposed monitoring in the proposed managed access agreement. It had some concerns about the governance of the data generated during the proposed managed access agreement and encouraged independent oversight. It had significant reservations about the potential that the extrapolation of the declines in the ataluren and matched control group would be recalibrated at 2 years and required that a formal analysis plan be agreed at the outset.

### *Cost to the NHS and Personal Social Services*

5.16 The committee considered the results of the company's budget impact model. It noted that, at list price, the total cost per person per year of treatment with ataluren is £246,448 (assuming a weight of 26 kg). It further noted that the company had estimated that, in year 1, the total cost of treating nonsense mutation DMD with ataluren (at list price) is £8.6 million, rising to £16 million in year 5 (see [section 4.22](#)). The committee noted that the patient numbers in the budget impact model that accompanied the proposed managed access agreement were slightly different to the original version, and that these had been deemed confidential. It acknowledged that the costs would be lower than those using the list price when using the price incorporating the patient access scheme and confidential financial components that formed part of the proposed managed access agreement, but considered that, even when including this discount, the budget impact of ataluren was still high.

5.17 The committee considered the cost of ataluren in the context of the costs incurred by the company for research, development and manufacturing. It heard from the company that the cost of ataluren is driven by the need to recoup the high costs of research and development (and to fund future investment in other therapy areas), as well as manufacturing and marketing a treatment that can only be used by a small number of patients. It noted that, in response to the committee's request, the company provided figures associated with the investment on the discovery, development and commercialisation of ataluren in England and worldwide. The committee also heard from the company that it will incur further costs in continuing to gather data on the natural history of the disease and the clinical effectiveness of ataluren in DMD through a registry. The committee acknowledged that developing orphan and ultra-orphan treatments

was associated with challenges that were different from treatments with bigger patient populations. But, it noted that there were no exceptional features in the development or production of ataluren that would justify the cost of ataluren being materially greater than for other treatments for small populations. The committee compared the cost of ataluren per patient with other highly specialised technologies available to NHS patients (using the list price of each technology). After taking other cost implications such as patient access schemes and managed access agreements into consideration where possible, the committee considered that it had been presented with sufficient evidence to show that the cost of ataluren was not materially greater than that for other treatments for small populations in relation to the benefits it offered. Furthermore, after considering the size of the investment by the company on ataluren and the number of patients likely to have ataluren in England and worldwide, the committee concluded that, when including the patient access scheme and confidential financial components in the proposed managed access agreement, the cost of ataluren per patient could be considered reasonable in the context of recouping manufacturing, research and development costs from sales to a small population in comparison with other highly specialised treatments for small populations.

## *Value for money*

- 5.18 The committee considered the company's third cost-consequence model, which used clinical data from Study 007 and Study 020 for the subgroup of patients with a baseline 6MWD of 300–400 m and incorporated the patient access scheme and the other financial components included in the proposed managed access agreement. It noted that the company had addressed some of the concerns about the original model that had been expressed by the committee in the [evaluation consultation document](#) and by the evidence review group (ERG) in its critique of the second model (see [sections 4.28 and 4.29](#)). The committee also noted that, by including costs associated with ventilation assistance and increasing the disutility faced by caregivers, the company's third model partially addressed consultation comments from patient organisations. These stated that the company's original model did not appropriately reflect the impact of the condition and ataluren on the patient and caregivers' quality of life, or fully capture the costs associated with each health state. The committee concluded that several of the company's changes were appropriate, such as including the cost of ataluren for 6 months after loss of walking, extending the time horizon to



be lifetime and using a discount rate of 3.5% for costs and benefits. The committee determined that ataluren did not meet the criteria in NICE's [guide to methods of technology appraisal](#) for considering a non-reference case discount rate of 1.5% for costs and benefits because ataluren did not restore people to full health and it was unclear if its benefits were sustained over a very long period (normally 30 years). The committee was concerned about the values the company used for the disutility associated with scoliosis and the disutility faced by caregivers, and was unconvinced that scoliosis never occurred after puberty or that different utility values for ataluren and best supportive care should be applied after loss of walking. The committee acknowledged the arguments put forward by the company and ERG about the methods used to extrapolate the clinical trial results to the lifetime horizon, and considered that both had merits and flaws. The committee concluded that it would use the company's and the ERG's analyses in its decision-making.

- 5.19 The committee discussed whether it was reasonable to assume that scoliosis will never occur after puberty. It heard from the clinical experts that, although the risk of developing scoliosis is substantially reduced after puberty and close to zero, it is not possible to conclude it would be completely eliminated. The committee agreed with the clinical experts' view, and concluded that it was not appropriate to assume that the risk of developing scoliosis will be completely eliminated after puberty.
- 5.20 The committee discussed whether it was appropriate to apply different utility values to the ataluren and best supportive care groups after loss of walking. The committee noted the company's assumption that the quality of life of patients when they lose their ability to walk would be greater with ataluren because loss of walking would occur later. The committee heard from the company and the clinical experts that this would be plausible if patients who have ataluren have greater upper limb muscle strength when they lose their ability to walk. The committee understood that there was no available evidence showing superior muscle strength after loss of walking with ataluren compared with best supportive care. The committee concluded that it was unreasonable to assume different utility values for each treatment group once the ability to walk is lost because there was no evidence available to support this assumption.
- 5.21 The committee noted that the company used 2 methods to extrapolate the clinical trial results to the lifetime horizon: a linear extrapolation and a stepped

decline method. The committee noted the ERG's concerns about the linear extrapolation method because the company applied the data from the subgroup of people with a baseline 6MWD of 300–400 m to the overall population in the model (see [section 4.29](#)). The committee considered that it was unclear whether the results for this subgroup could be considered applicable to the overall ambulant population, given the small and non-statistically significant benefit of ataluren in the intention-to-treat population (see [section 5.6](#)). The committee also noted the ERG's critique on the stepped decline extrapolation method, which stated that the company had not directly used the data from the trials for the subgroups of people with a baseline 6MWD of less than 300 m and of more than 400 m, but had replaced these with other values that favoured ataluren. The committee considered that both extrapolation methods favoured ataluren in the long term. The committee noted the ERG's exploratory analyses using both the linear and stepped decline extrapolation methods, which applied assumptions less likely to favour ataluren than those in the updated company's model (see [section 4.29](#)). The committee concluded that, given the lack of long-term evidence on the benefit of ataluren, it was uncertain which extrapolation method would lead to more clinically plausible results. It therefore considered both approaches in its decision-making based on the company and ERG's analyses.

- 5.22 The committee discussed the results of the company's third cost–consequence model. It considered that the company's analyses, in which patients switched from ataluren to best supportive care after 5 years (that is, when the proposed managed access agreement ended), were not relevant to its decision-making and set them aside. This was because it had heard from the clinical experts that, if recommended, ataluren would be used in clinical practice until loss of walking. It noted that the results of analyses using the company's model showed that ataluren was associated with between 2.389 and 8.562 additional quality-adjusted life years (QALYs) compared with best supportive care, depending on the method used to extrapolate the treatment effect and whether the company's or ERG's preferred assumptions were used. The incremental costs for ataluren compared with best supportive care that incorporated the patient access scheme and financial components in the proposed managed access agreement were considered commercial in confidence and cannot be reported. The committee noted that the cost–consequence results showed a greater increase in the incremental QALYs gained when adopting the company's preferred assumptions rather than the ERG's, and recalled that it did not find all

of these to be reasonable (see [section 5.18](#)). The committee concluded that, based on the uncertainty around the evidence available, the incremental QALY gain for ataluren compared with best supportive care was associated with a high degree of uncertainty and was therefore likely to fall between the ERG's exploratory estimates and the company's estimates.

5.23 The committee considered the overall value for money provided by ataluren. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. The committee noted that the company had estimated the total budget impact (list price) for 35 patients in year 1 to be £8.6 million rising to £16.0 million in year 5, and that the total cost per year of treatment with ataluren (list price) assuming an average weight of 26 kg is £246,448 per patient. The committee acknowledged that the cost per patient per year and total budget impact would be lower when using the price incorporating the patient access scheme and incorporating the confidential financial components in the proposed managed access agreement. The committee considered the overall value of ataluren, taking into account both its health benefits measured in QALYs gained and associated incremental costs in the context of other highly specialised technologies that it had evaluated (described in the [evaluation consultation document](#)) and others. It recalled that NICE guidance on [eculizumab for treating atypical haemolytic uraemic syndrome](#) stated that incremental QALYs for eculizumab compared with standard care were estimated to be 25.22 by the company and 10.14 by the ERG. Similarly, incremental QALYs for [elosulfase alfa for treating mucopolysaccharidosis type IVa](#) were estimated to be 18.18 by the company and 10.03 by the ERG. The committee noted that, compared with these other highly specialised technologies, ataluren was associated with substantially lower incremental QALYs (see [section 4.36](#)). However, the committee considered that the nature of DMD meant that it might be appropriate to view the QALYs gained differently because of the time in a child's life when the QALYs are predominantly gained compared with best supportive care (that is, delaying loss of walking in childhood and adolescence). The committee was aware that total costs to the NHS of some of the other technologies that it had previously evaluated would be lower than the list price and acknowledged that the total costs of ataluren would also be lower than the list price when the patient access scheme and confidential financial components in the proposed managed access agreement were applied. In reaching its conclusion on value for money, the committee considered the evidence of

improved outcomes from clinical trials and the patient testimonies, as well as the results of the company's cost-consequence models and ERG's exploratory analyses. The committee considered that the condition was distinct, there was unmet need and some of the potential quality-of-life benefits of ataluren still might not have been not fully captured in the model. Although it remained concerned that the overall health benefits of ataluren had not been shown in the population for which it would be used in clinical practice, the committee considered that, based on current evidence, the potential benefits associated with ataluren treatment were great enough to justify its cost to the NHS when the patient access scheme and confidential financial components in the proposed managed access agreement were applied. The committee therefore concluded that, because of the uncertainty about the clinical benefits in the relevant population in clinical practice, ataluren would represent acceptable value for money to the NHS only when it was given in the context of a proposed managed access agreement at a price that incorporated the patient access scheme and included other financial components that reduced the total costs to the NHS.

- 5.24 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating ataluren. The committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of ataluren. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by ataluren.

### *Impact of the technology beyond direct health benefits and on the delivery of the specialised service*

- 5.25 The committee acknowledged the potential wider societal benefits of ataluren treatment proposed by the company and patient experts, including the ability to contribute to society, continue education and spend more time with friends and family. It heard from the patient experts that, because ataluren is expected to delay the loss of walking, it will enable people with DMD to maintain their

independence for longer and this will lead to cost savings. The committee heard that potential cost savings include parents and carers staying in work for longer, a reduction in out-of-pocket expenses for travel to appointments and delaying moving house or making home modifications. The committee acknowledged the expected cost savings but considered that, because ataluren was not a curative treatment, some costs may only be delayed until the disease progressed. However, on balance, the committee was persuaded that the non-health effects of ataluren were likely to be of value in the short term.

- 5.26 The committee considered the impact of ataluren on the delivery of the highly specialised service, and acknowledged statements from NHS England showing that treatment with ataluren is unlikely to involve additional services or monitoring costs. It heard from the clinical experts that services are already in place to monitor and treat people with DMD and, if ataluren were to be recommended for use, additional funding would not be needed. However, it noted that, in response to the [evaluation consultation document](#), a professional group highlighted that additional diagnostic laboratory tests may be needed and that currently only 1 laboratory in the UK offers this analysis for DMD. The committee considered that, apart from these possible additional diagnostic needs, no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment.

## Conclusion

- 5.27 The committee discussed the appropriate recommendations for ataluren for nonsense mutation DMD. It appreciated that DMD is a serious condition that has severe effects on the lives of people with the condition, as well as their families and carers and that it is associated with a high unmet need. The committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that ataluren represents an important development in the treatment of nonsense mutation DMD. Based on the results from Study 007 and Study 020, it accepted that ataluren was associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care in the subgroup of patients with a baseline 6MWD of 300–400 m over a

48-week period. The committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still considerable uncertainty about long-term benefits. It considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD. The committee was satisfied that the proposed managed access agreement offered an opportunity to address some of this uncertainty when this guidance is reviewed. It accepted the definition of patient eligibility for treatment with ataluren, and the starting and stopping criteria. It considered that the patient outcomes in the proposed managed access agreement would meaningfully inform a review of this guidance. The committee noted that the proposed managed access agreement would capture caregiver quality-of-life data and considered it imperative that its future review of guidance includes these data, given the large associated effect in the company's cost–consequence model. It also considered it essential that Child Health Utility 9D quality-of-life data are captured for all boys receiving ataluren, not just those aged 7 years and older, and that proxy data for younger children should also be collected. The committee was aware of its need to consider the extent to which the cost to the NHS of providing ataluren was reasonable. The committee concluded that, because of the uncertainty of the clinical benefits in the relevant population in clinical practice, ataluren would represent acceptable value for money to the NHS only when it was given in the context of a managed access agreement at a price that incorporated the patient access scheme and included other financial components that reduced the total costs to the NHS. The committee considered that the proposed managed access agreement offered an opportunity to allow patients access to ataluren in the NHS while collecting both longer-term data and data from the full population with nonsense mutation DMD covered in the marketing authorisation, and to limit the financial risk associated with introducing ataluren in the NHS given the uncertainty around its benefits. Therefore, the committee recommended ataluren for treating nonsense mutation DMD.

## Summary of evaluation committee's key conclusions

HST3	Evaluation title: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	Section
<b>Key conclusion</b>		
<p>Ataluren, within its marketing authorisation, is recommended for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only when:</p> <ul style="list-style-type: none"> <li>the company provides ataluren with the discount agreed in the patient access scheme</li> <li>the conditions under which ataluren is made available are set out in the <a href="#">managed access agreement</a> between the company and NHS England, which should include the considerations set out in <a href="#">sections 5.12–5.15</a> and <a href="#">5.23</a> of this guidance.</li> </ul> <p>The committee concluded that, because of the uncertainty about the clinical benefits in the relevant population in clinical practice, ataluren would represent acceptable value for money to the NHS only when it was given in the context of a managed access agreement at a price that incorporated the patient access scheme and included other financial components that reduced the total costs to the NHS.</p>		1.1, 5.23
<b>Current practice</b>		
<p>Nature of the condition, including availability of other treatment options</p>	<p>The committee heard from the patient experts that DMD is a serious, progressive condition that reduces life expectancy and causes debilitating symptoms associated with loss of muscle strength that severely affect the quality of life of people with the condition, and their parents and siblings.</p> <p>The committee heard from the clinical experts that the mainstay of treatment is corticosteroid therapy, which can slow the decline in muscle strength and function. This, in turn, may help to prolong walking. It also heard, however, that corticosteroids can cause unwanted effects such as growth retardation, bone thinning, mood swings and weight gain.</p>	5.1, 5.2, 5.3
<b>The technology</b>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee heard from the clinical experts that, because ataluren potentially addresses the nonsense mutation that causes DMD to develop, they considered it to be a step change in the management of DMD.</p>	<p>5.4</p>
<p>Adverse reactions</p>	<p>The committee concluded that there were no specific safety concerns associated with ataluren.</p>	<p>5.11</p>
<p><b>Clinical evidence</b></p>		
<p>Availability, nature and quality of evidence</p>	<p>The committee concluded that the 6-minute walk distance (6MWD) was an appropriate primary outcome to assess the benefits of treatment with ataluren in the clinical trials.</p> <p>The committee concluded that there was not a meaningful improvement in the rate of decline in 6MWD with ataluren compared with best supportive care in the intention-to-treat populations of Study 007 and Study 020.</p>	<p>5.5, 5.6</p>



<p>Uncertainties generated by the evidence</p>	<p>The committee noted that, in Study 007 and Study 020, there was no statistically significant difference in change in 6MWD between the ataluren and best supportive care groups in the intention-to-treat analyses.</p> <p>The committee noted the company's assertion that, in 48-week trials such as Study 007 and Study 020 that have change in 6MWD as a primary outcome, the optimum range in the 6MWD at baseline to detect a difference is 300–400 m. It agreed to consider the 48-week clinical trial data from a subgroup of patients with a baseline 6MWD of 300–400 m in Study 020. However, the committee expressed concerns about the uncertainty and generalisability of the results to the broader ambulant population.</p>	<p>5.6, 5.7</p>
<p>Impact of the technology</p>	<p>The committee concluded that the results of the clinical primary and secondary outcomes in Study 020 showed a benefit at 48 weeks of ataluren compared with best supportive care in patients with a baseline 6MWD of 300–400 m. However, it also concluded that the size of this benefit in the overall ambulant population (in which the drug is intended to be used in clinical practice) remains highly uncertain.</p>	<p>5.8, 5.9</p>
<p><b>Cost evidence</b></p>		
<p>Availability and nature of evidence</p>	<p>The committee considered the company's updated cost–consequence model, which incorporated results from Study 020, and addressed some of the concerns about the company's original model that had been expressed by the committee in the <a href="#">evaluation consultation document</a> and further amendments considered appropriate by the company.</p> <p>The company presented a budget impact analysis to predict the costs of ataluren in the NHS and Personal Social Services.</p>	<p>5.16, 5.18</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p>	<p><b>Cost-consequence analysis</b></p> <p>The committee considered the company's third cost-consequence model, which used clinical data from Study 007 and Study 020 for the subgroup of patients with a baseline 6MWD of 300–400 m and incorporated the patient access scheme and the other financial components included in the proposed managed access agreement. The committee was concerned about the values the company used for the disutility associated with scoliosis and the disutility faced by caregivers, and was unconvinced that scoliosis never occurred after puberty, or that different utility values for ataluren and best supportive care should be applied after loss of walking. The committee acknowledged the arguments put forward by the company and evidence review group (ERG) about the methods used to extrapolate the clinical trial results to the lifetime horizon, and considered that both had merits and flaws. The committee concluded that it would use the company's and the ERG's analyses in its decision-making.</p>	<p>5.18, 5.21</p>
<p>Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee noted that, by increasing the disutility faced by caregivers, the company's third model partially addressed consultation comments from patient organisations, which had stated that the company's original model did not appropriately reflect the impact of the condition and ataluren on the patient and caregivers' quality of life, or fully capture the costs associated with each health state.</p> <p>The committee considered that the nature of DMD meant that it might be appropriate to view the quality-adjusted life years (QALYs) gained differently because of the time in a child's life when the QALYs are predominantly gained compared with best supportive care (that is delaying loss of walking in childhood and adolescence).</p>	<p>5.18, 5.23</p>

<p>Cost to the NHS and Personal Social Services</p>	<p>The committee noted that the company had estimated that, in year 1, the total cost of treating nonsense mutation DMD with ataluren (at list price) is £8.6 million, rising to £16 million in year 5. It acknowledged that the costs would be lower than using the list price when using the price incorporating the patient access scheme and confidential financial components that formed part of the proposed managed access agreement but considered that, even when including this discount, the budget impact of ataluren was still high.</p>	<p>5.16</p>
<p>Value for money</p>	<p>In reaching its conclusion on value for money, the committee considered the evidence of improved outcomes from clinical trials and the patient testimonies, as well as the results of the company's cost-consequence models and the ERG's exploratory analyses. The committee considered that the condition was distinct, there was unmet need and some of the potential quality-of-life benefits of ataluren still might not be not fully captured in the model. Although it remained concerned that the overall health benefits of ataluren had not been shown in the population for which it would be used in clinical practice, the committee considered that, based on current evidence, the potential benefits associated with ataluren treatment were great enough to justify its high cost when the patient access scheme and confidential financial components in the proposed managed access agreement were applied.</p>	<p>5.23</p>
<p>Impact beyond direct health benefits and on the delivery of the specialised service</p>	<p>The committee acknowledged the potential wider societal benefits of ataluren treatment proposed by the company and patient experts, including the ability to contribute to society, continue education and spend more time with friends and family. It heard that potential cost savings include parents and carers staying in work for longer, a reduction in out-of-pocket expenses for travel to appointments and delaying moving house or making home modifications.</p> <p>The committee noted that additional diagnostic laboratory tests may be needed and that currently only 1 laboratory in the UK offers this analysis for DMD. The committee considered that, apart from these possible additional diagnostic needs, no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment.</p>	<p>5.25, 5.26</p>
<p><b>Additional factors taken into account</b></p>		

Patient access schemes (PPRS)	The company has proposed a patient access scheme in which ataluren would be provided at a discounted cost; the discount is commercial in confidence and so cannot be reported here. The proposed managed access agreement includes further financial components to reduce the cost to the NHS for the proposed duration of the agreement.	3.3
	The Committee concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the value for money offered by ataluren.	5.24
Equalities considerations and social value judgements	No equality issues that needed to be taken into consideration by the committee were identified.	-

## 6 Implementation

- 6.1 Section 8(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 6.2 When NICE recommends a treatment, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene and the doctor responsible for their care thinks that ataluren is the right treatment, it should be available for use, in line with NICE's recommendations.
- 6.3 The Department of Health and the company have agreed that ataluren will be available to the NHS with a patient access scheme that makes ataluren available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Ian Davidson, Marketing Director, UK and Ireland, PTC Therapeutics (01483 246865; [idaavidson@ptcbio.com](mailto:idaavidson@ptcbio.com)).

## 7 Evaluation committee members and NICE project team

### *Evaluation committee members*

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### *NICE project team*

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the associate director for the highly specialised technologies programme.

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ISBN: 978-1-4731-1965-9