

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Evaluation consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ataluren in the context of national commissioning by NHS England. The Highly Specialised Technologies Evaluation Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this evaluation (see section 8) and the public. This document should be read along with the evidence base (the [evaluation report](#)).

The Evaluation Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of ataluren in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Evaluation Committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE's guidance on using ataluren in the context of national commissioning by NHS England.

For further details, see the [Interim Process and Methods of the Highly Specialised Technologies Programme](#).

The key dates for this evaluation are:

Closing date for comments: 6th November 2015

Second Evaluation Committee meeting: 17th November 2015

Details of membership of the Evaluation Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Evaluation Committee's preliminary recommendations

- 1.1 Ataluren is an important development in treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. However, the Evaluation Committee has not yet been presented with an adequate justification for its considerable cost, in light of the available evidence of its effect on health outcomes relevant for patients, carers and family members.
- 1.2 The Committee is therefore minded to not recommend ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene.
- 1.3 The Committee recommends that NICE requests further clarification from the company on the size of the benefit ataluren provides for patients, carers and family members, taking into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020).
- 1.4 The Committee also recommends that NICE requests the company to provide further justification for the cost of ataluren per patient, taking into account the size of the benefit after further clarification (see 1.3), and compared with the benefit obtained with other highly specialised technologies available to NHS patients.

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. 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 ambulatory patients aged 5 years and older. The marketing authorisation is linked to results being

provided from the phase III trial (Study 020). This is investigating the ability of ataluren to slow disease progression in a subset of patients with nonsense mutation DMD. The European public assessment report states that the final study report is expected by the fourth quarter of 2015.

- 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 £2532 per box of 30 sachets containing ataluren 125 mg. Assuming a median weight range of 24–26 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. If ataluren had been recommended, this scheme would have provided 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 would not constitute an excessive administrative burden on the NHS.

4 Evidence submissions

The Evaluation Committee (section 8) considered evidence submitted by the manufacturer of ataluren, a review of this submission by the Evidence Review Group (ERG; section 9) and evidence submitted by clinical experts, patient experts and NHS England.

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 ambulation 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

4.2 The safety and efficacy of ataluren was investigated in a phase 2b 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 Inventory, which contains 4 scales: physical, emotional, social and school functioning.

- 4.3 The prespecified 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. The decline phase was defined as patients aged 7–16 years with a baseline 6MWD test of 80% or more 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).

Economic evidence

- 4.8 The company presented a cost–consequence analysis comparing the licensed dose of ataluren (40 mg/kg daily) with best supportive care in people aged 5 years or older who were ambulatory. The company's Markov model 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 and 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 were ambulatory had treatment). 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.

- 4.9 To inform the best supportive care transition probabilities for loss of ambulation, 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 ambulation 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 base case, the company used a Weibull function to fit the data.
- 4.10 To inform the transition probabilities for ataluren compared with placebo, 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 ambulation 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 ambulation 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.

- 4.11 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 paediatric quality-of-life 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.
- 4.12 The company estimated that the total cost per year of treatment with ataluren 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 £9605. 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.
- 4.13 In the company’s 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 patient access scheme price for ataluren are confidential.

- 4.14 The deterministic sensitivity analysis indicated that the results were most sensitive to the discount rate for benefits and costs; changing this parameter changed the total QALYs by -21% to 41%. Apart from the discount rate, the results were most sensitive to ambulatory patient utility; changing this parameter changed the total QALYs by -19% to 19%. No probabilistic sensitivity analysis was presented.
- 4.15 The company presented a budget impact analysis to predict the cost of ataluren to the NHS and personal social services. 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 the ataluren list price) was estimated to be about £8,625,680, rising to £16,019,120 in year 5. The results of the budget impact analysis that incorporate the patient access scheme are confidential.

Evidence Review Group review

Clinical effectiveness

- 4.16 The ERG noted that the submitted evidence 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 following:
- The company's methods used in the systematic review were not clearly described, providing the opportunity for error and bias.
 - There were inconsistencies in the reported p values for the change in 6MWD between the company submission and the European Medicines Assessment agency report.
 - 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.

Cost effectiveness

- 4.17 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 model, which it investigated in its exploratory analyses. In addition, the ERG noted that the model assumed that the treatment benefit of ataluren over best supportive care remained the same over time, which may not be clinically plausible.
- 4.18 The ERG noted that the company had not used the Pediatric Quality of Life Inventory data collected during Study 007 in its economic model. It disagreed with the company's view that it was inappropriate to map the data onto the EQ-5D scale using an algorithm adapted from a study conducted in a healthy population. The ERG believed that, in principle, the utility data derived from the clinical trial should be preferred to values from the literature.
- 4.19 The company submission stated that people could continue to have ataluren 6 months after loss of ambulation. The ERG noted that these costs had not been included in the company's model.

ERG exploratory analyses

- 4.20 The ERG noted that the statistically best-fitting parametric models had not always been chosen by the company to inform the clinical parameter transition probabilities in the model. It conducted further exploratory analyses to reconstruct individual patient data and Kaplan–Meier curves using the data from the literature to assess appropriate parametric model

fits. 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.

- 4.21 The ERG produced several additional sets of analyses. The ERG's preferred scenario used a lifetime horizon and included the costs for continuing treatment with ataluren 6 months after loss of ambulation. The ERG included this assumption because, although the company submission said that people would continue to have treatment for up to 6 months following loss of ambulation, these costs were not included in the company's base-case analysis. The ERG's preferred scenario also included the best-fitting parametric curves discussed in section 4.20).
- 4.22 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.
- 4.23 The ERG also presented exploratory analyses to explore the effects of key assumptions on the company's budget impact estimates. 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 results incorporating the patient access scheme are confidential and may not be presented.

- 4.24 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 [Evaluation report](#).

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. 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, and their parents and siblings. 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 ambulation 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 Committee concluded that DMD is a serious life-threatening condition that progressively affects quality of life, with the greatest impact after loss of ambulation.

- 5.2 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 ambulation. 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 further treatment options are needed to extend the time to loss of ambulation and thus maintain quality of life.

Impact of the new technology

- 5.3 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.
- 5.4 The Committee discussed how treatment benefit was assessed in the clinical trial. It was aware that the primary end point in Study 007 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 endpoints in the trial 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 concluded that the 6MWD was an appropriate primary endpoint to assess the benefits of treatment with ataluren in the clinical trial.
- 5.5 The Committee considered the robustness of the results of Study 007. It noted that, in the intention-to-treat analysis, there was no statistically significant difference in change in 6MWD between the ataluren and best supportive care groups but that, in the corrected intention-to-treat analysis, there was a statistically significant difference of 31.7 m favouring

ataluren. The Committee accepted that the company's post-hoc adjustment could be justified (see section 4.4) but was concerned that the results of 2 patients had influenced the overall conclusions of efficacy with ataluren, and questioned whether the study had been sufficiently powered. The Committee considered, therefore, that the results of Study 007 were uncertain. The Committee concluded that the results of Study 007 suggested ataluren is associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care; however, there is considerable uncertainty in the robustness of the results.

5.6 The Committee discussed which was the most appropriate patient population 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. However, it further heard from the clinical experts that they would ideally start a treatment to delay loss of ambulation before the decline phase begins. The Committee noted the conclusions of the European public assessment report, which stated that the company's analysis of the decline phase subgroup was clinically and scientifically justified but should be considered exploratory. The Committee further noted that, although they were associated with uncertainty, the company's post-hoc subgroup analysis of patients in the decline phase of walking ability in Study 007 showed a greater improvement with ataluren treatment compared with best supportive care (see section 4.5). The Committee was aware of the company's obligation to the European Medicines Agency in ataluren's European marketing authorisation to do a trial to confirm the clinical benefit in the decline phase subgroup. It noted that a phase III trial, Study 020, is examining the effect of ataluren compared with best supportive care in patients in the decline phase and that study results are due at the end of 2015. The Committee considered that Study 020 would provide valuable information

that could reduce the uncertainty around the results of Study 007. The Committee concluded that it was reasonable to use the subgroup analysis of patients in the decline phase in its decision-making, even though the results for this subgroup, in which effects should be detected most readily, remained uncertain because of the post-hoc nature of the analyses.

5.7 The Committee considered whether all the possible treatment benefits associated with ataluren had been captured in Study 007. It noted that 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). However, the Committee considered that the results of the Paediatric Quality of Life Inventory questionnaire 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. The Committee further noted that the duration of Study 007 was 48 weeks, and considered that this was too short to determine any long-term benefits of treatment with ataluren (for example, an effect on mortality). This was important because the company had assumed in its submission that the loss of ambulation was correlated to mortality and, by delaying the loss of ambulation, ataluren has the potential to improve survival. The Committee concluded that it was likely that the quality-of-life data collected during Study 007 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.

5.8 The Committee considered the evidence on adverse events reported in Study 007. 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 concluded that there were no specific safety concerns associated with ataluren.

Cost to the NHS and Personal Social Services

- 5.9 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 £220,256 (assuming a median weight range of 24–26 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 4.15). The Committee acknowledged that these costs would be lower when using the price incorporating the patient access scheme.
- 5.10 The Committee considered the assumptions in the company's budget impact analysis. It noted that the ERG had questioned the appropriateness of the weight range (24–26 kg) used in the company's budget impact calculation. This was because the weights of people at baseline in the trial did not necessarily represent the average weight of people across all affected age ranges who would be starting or continuing treatment in clinical practice. The Committee considered it unlikely that the average weight of the expected patient population over the first 5 years would be 24–26 kg and that it was therefore not representative of the anticipated patient population. It further noted that the ERG's preferred exploratory estimates, which used the average weight of people receiving best supportive care in the ambulatory state in the company's model, were higher than the company's. The Committee concluded that the company's calculations, whether using the list price or the price incorporating the patient access scheme, had likely underestimated the total budget impact of ataluren for treating nonsense mutation DMD.

5.11 The Committee considered the cost of ataluren in the context of the costs incurred by the company for research, development and manufacturing, and asked the company for an explanation for the cost of the drug. 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. The Committee acknowledged that developing orphan and ultra-orphan treatments was associated with challenges that were different from treatments with bigger patient populations; however, it was not convinced that the high cost per patient of ataluren was justified compared with other treatments for rare conditions. The Committee was unsure if there were any clinical or safety needs during clinical development that might justify the development cost of ataluren being materially greater than for other treatments for small populations. Furthermore, the Committee was not satisfied that there was an explanation of the relationship between the development costs of ataluren and the price being proposed for the NHS. Based on the information with which it had been presented, the Committee concluded that it was uncertain if the proposed cost of ataluren was justified by the incremental therapeutic improvement over standard therapy.

Value for money

5.12 The Committee considered the company's model structure. It concluded that the model structure likely reflected the disease progression of nonsense mutation DMD. However, the Committee noted that the company had not included a lifetime time horizon in its base-case analysis. It concluded that it was more appropriate to use a lifetime time horizon, as the ERG had done in its exploratory analyses, to adequately capture the total costs and benefits of treatment.

5.13 The Committee discussed how the transition probabilities in the company's economic model had been generated. The Committee noted

that some of the extrapolations used by the company were not the statistically best-fitting curves. It heard from the company who explained that some of the statistically best-fitting curves produced clinically implausible scenarios. The Committee considered the ERG's exploratory analysis that explored the most appropriate curve fits taking into account both statistical fit and clinical plausibility (see section 4.20). It accepted the ERG's preferred approach of using flexible parametric models for most transitions and a log-normal model for the transition from the ambulatory to non-ambulatory state. The Committee concluded that the ERG's preferred approach to extrapolating data to inform the transition probabilities should be used in its decision-making, although it noted that differences between the scenarios considered were not overwhelming.

5.14 The Committee considered the utility values used in the company's model. It noted that the company had used utility values from the literature rather than using quality-of-life data from Study 007 (see section 4.11). The Committee acknowledged that the ERG considered utility values generated from trial data to be preferable, in principle, to data from the literature. However, the Committee recalled that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren (see section 5.7) and concluded that the values taken from the literature should be used in its decision-making.

5.15 The Committee discussed how the company had modelled the costs of treatment. It noted that the company had not included the cost of continuing treatment with ataluren for up to 6 months after the loss of ambulation, despite stating in the company submission that people would be eligible to continue treatment during this time. The Committee heard the clinical experts confirm that people would have ataluren for up to 6 months after a loss in ambulation was suspected. The Committee was aware that the ERG had included these additional costs in its exploratory analysis and concluded that the ERG's approach was appropriate.

5.16 The Committee discussed the results of the company's cost–consequence model. It noted that the results of the company's base-case analysis showed that 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. Total costs and incremental costs for ataluren compared with best supportive care that incorporated the patient access scheme were considered commercial in confidence and cannot be reported. However, after considering its discussions in sections 5.10–5.15, the Committee concluded that the assumptions used in the ERG's exploratory analysis were more plausible. In the ERG's exploratory 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. The total cost of ataluren and incremental costs incorporating the patient access scheme were considered commercial in confidence and cannot be reported here. The Committee concluded that it was likely that treatment with ataluren generated around 3 additional QALYs compared with best supportive care.

5.17 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, meaning that the estimated cost of ataluren per patient for year 1 (list price) would be £245,714. 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. The Committee considered the overall value of ataluren, taking into account both its health

benefits (around 3 additional QALYs) and associated costs in the context of other highly specialised technologies:

- It recalled that NICE guidance on [eculizumab for treating atypical haemolytic uraemic syndrome](#) stated that eculizumab produced greater incremental QALY gains than standard care (estimated to be 25.22 by the company and 10.14 by the ERG). NICE estimated the total budget impact of eculizumab in year 1 to be £57.8 million, whereas a patient organisation supplied an estimate of £36 million. When assuming that 170 patients would have treatment in year 1 (as estimated by NHS England), this equates to an annual cost per patient of £211,000–340,000.
- Similarly, the second evaluation consultation document for [elosulfase alfa for treating mucopolysaccharidosis type IVa](#) states that the technology produced greater incremental QALY gains than standard care (estimated to be 18.18 by the company and 10.03 by the ERG), with an estimated total budget impact of elosulfase alfa (list price) in year 1 of £17.3 million. For elosulfase alfa, NICE estimated the average annual cost (list price) per patient to be £394,680 (the annual cost per patient incorporating the patient access scheme would be lower but is confidential and cannot be reported here).

Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model, the Committee remained concerned that the health benefits associated with ataluren treatment were not great enough to justify its high cost. In the absence of clear evidence explaining the reasons for ataluren's high cost and its lower incremental QALY gains than other highly specialised technologies that have been evaluated by NICE, the Committee was unconvinced that ataluren represented overall good value for money to the NHS.

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

5.18 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 and continue education. It heard from the patient experts that, because ataluren is expected to delay the loss of ambulation, 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 more time spent with friends and family. 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.

5.19 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. The Committee was therefore satisfied that no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment.

Conclusion

5.20 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. 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. It accepted that ataluren is likely to be associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care, particularly in patients in the decline phase, and that this is likely to prolong time to loss of ambulation. However, the Committee believed that there is considerable uncertainty in the robustness of the results from Study 007. The Committee considered that Study 020, an ongoing phase III trial comparing ataluren with best supportive care in patients in the decline phase, would provide valuable information that could reduce the uncertainty in the current evidence base (although uncertainty about long-term benefits would remain). The Committee noted that the use of ataluren would be of significant value to patients with nonsense mutation DMD, but it was aware of its need to consider the extent to which the cost to the NHS of doing so was reasonable. The Committee was particularly concerned about the high cost per person in relation to a QALY gain that was considerably lower than that provided by other highly specialised technologies evaluated by NICE. The Committee regretted that it had not been given enough justification for the high cost per patient of ataluren, or for the overall cost of ataluren with reference to what could be expected to be reasonable in the context of a highly specialised service. Overall, the Committee was uncertain whether the proposed cost of ataluren was justified by the incremental benefits over standard therapy. Based on the current evidence, the Committee was minded not to recommend ataluren for people with nonsense mutation DMD. The Committee recommended that NICE requests further analyses from the company, which should be made available to the Evaluation Committee, and should include further information:

- on the size of the benefit with ataluren for patients, carers and family members, taking into account the results of Study 020.

- further justification for the cost of ataluren per patient, taking into account the size of the benefit of ataluren compared with the benefit obtained with other highly specialised technologies available to NHS patients (see section 4.17).

Summary of Evaluation Committee’s key conclusions

Evaluation title: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene		Section
Key conclusion		
<p>Ataluren is an important development in treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. However, the Evaluation Committee has not yet been presented with an adequate justification for its considerable cost, in light of the available evidence of its effect on health outcomes relevant for patients, carers and family members. The Committee is therefore minded to not recommend ataluren for treating Duchenne muscular dystrophy (DMD) with a nonsense mutation in the dystrophin gene.</p> <p>The Committee recommends that NICE requests further clarification from the company on:</p> <ul style="list-style-type: none"> • the size of the benefit ataluren provides for patients, carers and family members, taking into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020). • further justification for the cost of ataluren per patient, taking into account the size of the benefit after further clarification, and compared with the benefit obtained with other highly specialised technologies available to NHS patients. 		1.1–1.4
Current practice		
Nature of the condition, including availability of other treatment options	<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 ambulation. 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
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	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.	5.3
Adverse reactions	The Committee concluded that there were no specific safety concerns associated with ataluren.	5.8
Clinical evidence		
Availability, nature and quality of evidence	The Committee concluded that the 6-minute walk distance (6MWD) was an appropriate primary endpoint to assess the benefits of treatment with ataluren in the clinical trial. The Committee concluded that it was likely that the quality-of-life data collected during Study 007 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 limitations in the evidence base.	5.4, 5.7
Uncertainties generated by the evidence	The Committee noted that in Study 007 there was no statistically significant difference in change in 6MWD between the ataluren and best supportive care groups in the intention-to-treat analysis but that there was in the corrected intention-to-treat analysis. It accepted that the company's post-hoc adjustment could be justified but questioned whether the study had been sufficiently powered. The Committee was aware that a phase III confirmatory trial, Study 020, is examining the effect of ataluren compared with best supportive care in patients in the decline phase. The Committee considered that the results of Study 020 (due at the end of 2015) would provide valuable information that could reduce the uncertainty around Study 007 results.	5.5, 5.6
Impact of the technology	The Committee concluded that it was reasonable to use the post-hoc subgroup analysis of patients in the decline phase in its decision-making. It further concluded that the results of Study 007 suggested ataluren is associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care; however, there is considerable uncertainty in the robustness of the results.	5.5, 5.6
Cost evidence		

<p>Availability and nature of evidence</p>	<p>The company submitted a cost–consequence analysis comparing ataluren with best supportive care. The analysis was conducted from the perspective of the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.</p> <p>The company presented a budget impact analysis to predict the costs of ataluren in the NHS and Personal Social Services.</p>	<p>4.8, 4.9, 4.15</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p>	<p><u>Cost consequence analysis</u></p> <p>The Committee concluded that it was more appropriate to use a lifetime time horizon, as the Evidence Review Group (ERG) had done in its exploratory analyses, to adequately capture the total costs and benefits of treatment.</p> <p>The Committee concluded that the ERG’s preferred approach to extrapolating data to inform the transition probabilities should be used in its decision-making, although it noted that differences between the company’s and ERG’s scenarios considered were not overwhelming.</p> <p><u>Budget impact model</u></p> <p>The Committee noted the weight range (24–26 kg) used in the company’s budget impact calculation and considered it unlikely that this represented the average weight of the expected patient population over the first 5 years.</p>	<p>5.12</p> <p>5.13</p> <p>5.10</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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 recalled that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren and concluded that the values taken from the literature should be used in its decision-making.</p>	<p>5.14</p>

<p>Cost to the NHS and Personal Social Services</p>	<p>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 £220,256 (assuming a median weight range of 24–26 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.</p> <p>The Committee concluded that the company’s calculations, whether using the list price or the price incorporating the patient access scheme, had likely underestimated the total budget impact of ataluren for treating nonsense mutation DMD.</p>	<p>5.9, 5.10</p>
<p>Value for money</p>	<p>The Committee concluded that the assumptions used in the ERG’s exploratory analysis were more plausible than those in the company’s base case. In the ERG’s exploratory 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. The total cost of ataluren and incremental costs incorporating the patient access scheme were considered commercial in confidence and cannot be reported here.</p> <p>Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model, the Committee remained concerned that the health benefits associated with ataluren treatment were not great enough to justify its high cost. In the absence of clear evidence explaining the reasons for ataluren’s high cost and its lower incremental QALY gains than other highly specialised technologies that that have been evaluated by NICE, the Committee was unconvinced that ataluren represented overall good value for money to the NHS.</p>	<p>5.16, 5.17</p>

Impact beyond direct health benefits and on the delivery of the specialised service	The Committee acknowledged the potential wider societal benefits of ataluren treatment could include the ability to contribute to society and continue education. 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 more time spent with friends and family. The Committee was satisfied that no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment.	5.18, 5.19
Additional factors taken into account		
Access schemes	The company has proposed a patient access agreement in which ataluren would be provided at a discounted cost; the discount is commercial in confidence and so cannot be reported here.	3.3
Equalities considerations and social value judgements	No equality issues that needed to be taken into consideration by the Committee were identified.	-

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

There is no related guidance for this technology.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, Highly Specialised Technologies Evaluation Committee

October 2015

8 Evaluation Committee members, guideline representatives and NICE project team

Evaluation Committee members

The Highly Specialised Technologies Evaluation Committee is a standing advisory committees of NICE. Members are appointed for a 3-year term and a Chair and Vice Chair are also appointed for 3 years. A list of the Committee members who took part in the discussions for this evaluation appears below.

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

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.

Peter Jackson (chair)

Consultant Physician and Honorary Reader in Clinical Pharmacology

Ron Akehurst

Health Service Researcher, Strategic Director

Steve Brennan

Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

Trevor Cole

Clinician - Geneticist/Consultant in Clinical and Cancer Genetics/Honorary Reader in Medical Genetics

Sarah Davis

Senior Lecturer in Health Economics, the University of Sheffield

Jonathan Howell

Public Health Physician – Consultant in Public Health

Vincent Kirkbride

Consultant Paediatrician, Sheffield NHS Foundation Trust

Jeremy Manuel

Lay member

Linn Phipps

Lay member

Mark Sheehan

Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford

Lesley Stewart

Director, Centre for Reviews and Dissemination, York

Sheela Upadhyaya (non-voting member)

Highly Specialised Program of Care Lead (London Region), NHS England

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.

Vicky Kelly

Technical Lead

Linda Landells

Technical Adviser

Leanne Wakefield

Project Manager

Meindert Boysen

Programme Director

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this evaluation was prepared by Warwick Evidence

Auguste P, Colquitt C, Freeman K et al. Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene: A Highly Specialised Technology Evaluation. Warwick Evidence 2015

B. The following organisations accepted the invitation to participate in this evaluation as consultees and commentators. They were invited to comment on the draft scope and the evaluation consultation document. Organisations listed in I, II and III were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final evaluation determination.

I. Company:

- PTC Therapeutics

II. Professional/specialist and patient/carer groups:

- Action Duchenne
- Joining Jack
- Muscular Dystrophy UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

National Institute for Health and Care Excellence

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- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Welsh Government

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the evaluation consultation document.

- Dr Michela Guglieri, nominated by Action Duchenne - Clinical Expert
- Dr Adnan Manzur, nominated by Muscular Dystrophy UK - Clinical Expert
- Gary Hill, nominated by Muscular Dystrophy UK - Patient Expert
- Robert Meadowcroft, nominated by Muscular Dystrophy UK - Patient Expert
- Bernie Mooney, nominated by Action Duchenne - Patient Expert

D. The following individuals were nominated as NHS Commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the evaluation consultation document.

- Edmund Jessop selected by NHS England

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- PTC Therapeutics