NICE National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene [ID 428]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Any information supplied to NICE which has been marked as confidential has been

redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the company, the consultees, and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Evaluation Committee meeting and should be read with the full supporting documents for this evaluation.

Key issues for consideration

Clinical effectiveness

- Do the outcomes assessed in Study 007 provide suitable information to adequately assess the benefits associated with ataluren?
  - Is the 6MWD an appropriate measure for assessing ambulation?
  - Are the effects of ataluren fully captured using outcomes that are the most important to patients?
- In Study 007, the intention to treat analysis showed there was a statistically significant benefit for ataluren compared with placebo in the 'corrected intention to treat' analysis but not the intention to treat analysis. What is the Committee's view of the clinical significance of the treatment effects?
- The company's results suggested that the benefit of treatment with ataluren was greater in the subgroup of patients in the decline phase. According to the European public assessment report, analyses in this subgroup were clinically and scientifically justified but should be considered exploratory.

Does the Committee consider the company's post hoc subgroup analyses of patients in the decline phase to be suitable for informing its decision-making?

- Does the evidence provide enough information to anticipate the likely long-term effects of ataluren treatment?
- Does the Committee have enough information to inform its conclusions on the rate of serious adverse events expected with ataluren treatment?

Value

- Is the clinical effectiveness of ataluren and best supportive care appropriately modelled?
  - Does the Committee agree with the company's approach for estimating transition probabilities in the ataluren arm (that is, shifting the best supportive care curve to the right to reflect the difference in loss of ambulation in Study 007)?
  - Is the Committee satisfied by the company's approach of using data from the literature rather than Study 007 to model time to loss of ambulation with best supportive care?
- What are the Committee's preferred assumptions for the economic model?
  - Is it more appropriate to use a lifetime time horizon or one that is limited to the last point when there is at least 1 patient in the ambulatory health state?
  - Is it appropriate to assume 100% adherence to ataluren treatment?
  - The company used a linear extrapolation to predict the difference between ataluren and best supportive care in loss of ambulation. Is it reasonable to assume a constant benefit for the duration of treatment?
  - The company used utility values taken from the literature rather than the Paediatric Quality of Life Inventory data obtained in Study 007. Does the Committee find this reasonable?
- Has the company's model appropriately captured the costs and consequences associated with ataluren?

- Does the Committee find the company's estimates of patient numbers in the budget impact analysis to be reasonable?
- The company's budget impact analysis uses estimates of body weight that correspond to the lower end of the age range of people who would be eligible for treatment. Does the Committee consider this to be appropriate?
- What is the Committee's view on the costs associated with ataluren and the benefits it provides? How does the Committee view the anticipated budget impact?
  - How do these costs compare with other technologies currently provided under Specialised Commissioning (and therefore potentially could be displaced)?
  - Are the costs reasonable in the context of R&D and manufacturing costs for this technology?
- Are there any significant benefits of ataluren, beyond direct health benefits, which have not been taken into account in the economic analysis?

1 Nature of the condition

1.1 Duchenne muscular dystrophy (DMD) is a severe, progressive X-linked recessive disorder which predominantly, though not exclusively, 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 the age of 3 years. People with DMD experience a decline in physical functioning with subsequent respiratory and cardiac failure which leads to death, usually before the age of 30.

1.2 The main symptom of DMD is motor dysfunction, but as the disease progresses, major vital organs such as the gastrointestinal tract and heart are affected. Respiratory muscles can also be

affected, leading to breathing difficulties and the need for ventilation. DMD typically develops as follows:

- Early ambulatory phase: people develop a waddling-type gait, toe-walking and climbing stairs by bringing the second foot to join the first rather than going foot over foot. People usually need to support themselves with hands on thighs when they get up from the floor (Gower's manoeuvre).
- Late ambulatory phase: people have difficulties getting up off the floor and ascending stairs; people often fall while walking.
- Early non-ambulatory phase: people lose the ability to walk independently and become permanently wheelchair dependent. In addition, respiratory symptoms such as chest infections can develop.
- Late non-ambulatory phase: upper-limb function decreases with subsequent complete loss of independence and increased incidence of medical complications.

1.3 The company estimates that 2200 males in England have DMD. The prognosis for people with DMD is poor. The company reports the mean age of death in the UK for people with DMD is 25.3 years. The age at which loss of ambulation occurs is associated with time to respiratory failure. The company reported the results of a study (van Essen 1997) which noted that people who lose the ability to walk before 10 years of age have a median survival of 17.3 years (95% CI 16.7 to 18.0 years) compared with 20.1 years for those who lose the ability to walk at or after 10 years of age (95% CI 19.4 to 20.9 years).

1.4 Patient experts and patient groups highlighted the substantial impact of DMD on the quality of life of people with the condition and their families:

- People with DMD experience a loss of motor function until eventually they become wheelchair dependent making it difficult to partake 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 have to sit out of games with their peers. Often, younger children don't 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 require the use of respiratory ventilation. Scoliosis develops as the back muscles weaken, which requires surgery. 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 experienced by 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 discuss the financial impact of looking after a person with DMD. They describe giving up work to look after their child full time. In addition, out of pocket expenses can be very expensive (for example, moving house to ensure the home is wheelchair accessible).

1.5 A clinical expert explained that the only current pharmacological treatment for DMD is corticosteroids, however the evidence base on which regimen provides optimal benefit is limited. To date, no treatment that modifies the disease process has been available. Patient groups described their experiences of treatment with

ataluren. The main benefit of treatment was maintaining their child's ability to walk. This was deemed the most important outcome because the loss of walking ability signals a decline into more serious respiratory symptoms which lead to death.

1.6 Other interventions include cardiac and respiratory monitoring, occasional inpatient orthopaedic intervention, inpatient spinal surgery and rehabilitation (this is less common for patients taking corticosteroids). In addition, dietetic advice (and, in some cases, gastric feeding), prevention and treatment of bone fragility, and management of complications of long-term corticosteroid therapy may be required, as well as psychosocial support. Clinical care is provided by a range of health-care professionals depending on local services, including neurologists or paediatric neurologists/neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians, and primary-care physicians.

2 The technology

2.1 Ataluren (Translarna, PTC Therapeutics) has a conditional marketing authorisation in the UK for the treatment of 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 3 020 study, which is investigating the ability of ataluren to slow disease progression in patients with nonsense mutation DMD. The European public assessment report states that final study report is expected by the fourth quarter of 2015.

2.2 The nonsense mutation in the dystrophin gene results in a premature stop codon within the messenger RNA. This means a full-length dystrophin protein cannot be generated. Ataluren restores the synthesis of dystrophin by allowing ribosomes to read

through the premature stop codon as far as the normal stop codon. Ataluren is recommended to be taken 3 times per day. The recommended dose of ataluren is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).

2.3 The list price of ataluren is £2532.00 per box of 30 sachets of 125 mg. The total cost per person per year of treatment with ataluren is £220,256. This assumes a median weight range of 24–26 kg. The summary of product characteristics lists the most frequent adverse reactions as nausea, vomiting, and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3 Remit and decision problem

3.1 The remit from the Department of Health for this evaluation was: to evaluate the benefits and costs of ataluren within its marketing authorisation for treating Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene for national commissioning by NHS England.

3.2 Table 1 provides a summary of the company decision problem, which was in line with the final NICE scope. The ERG noted that the population in the company cost-consequence analysis included boys with the ability to walk (that is, more than 0 metres), whereas the pivotal trial included boys aged 5 years or older who could walk at least 75 metres at baseline.

Table 1: Summary of final NICE scope and company decision problem

	Final scope issued by NICE and company decision problem
Population	People aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk
Intervention	Ataluren (Translarna)
Comparator(s)	Established clinical management without ataluren
Outcomes	• Walking ability (ambulation) • Muscle function • Muscle strength • Ability to undertake activities of daily living • Cardiac function • Lung function • Time to wheelchair • Number of falls • Mortality • Adverse effects of treatment • Health-related quality of life.

4 Impact of the new technology

The safety and efficacy of ataluren was investigated in a phase 2b placebo-controlled randomised double-blinded study (Study 007). Study 007 forms the company's main evidence base for ataluren (see Table 2). The company presented further data and analyses from a phase 2a proof-of-concept study, Study 004 (for further details see page 75, table C9.7 of company submission).

Table 2: Summary of relevant clinical studies of ataluren (adapted from tables C9.4-9.7 pages 71, 73-75 of company submission)

Study	Design	Population	Intervention and comparators	Outcomes
Study 004 (Finkel, 2013)	• Phase 2a • Multicentre • Open-label cohort • Sequential dose-ranging proof of concept study.	• n=38 male patients • 5 or more years of age • Diagnosis of nonsense mutation DMD.	Ataluren total daily dose for 28 days: • 16 mg/kg (n=6) • 40 mg/kg (n=20) • 80 mg/kg (n=12)	Primary: • Change in dystrophin expression in muscle biopsy samples at Day 28.
Study 007 (Bushby, 2014)	• Phase 2b • Multicentre • Randomised, double-blind study.	• 174 male patients • 5 or more years of age • nonsense mutation in the dystrophin gene (n=2 had becker DMD) • able to walk ≥75 metres unassisted during a 6MWT at screening • Stable use of concomitant glucocorticoids was allowed	Ataluren total daily dose for 48 weeks: • 40 mg/kg (n=57) • 80 mg/kg (n=60) • Placebo (n=57)	Primary: • Change in 6MWD at week 48[1] Secondary: • Changes in proximal muscle function measured by timed function tests. • Change in activity in the community setting as assessed by step activity monitoring. • Change in force exerted during knee flexion and extension
1 Assessed via the 6MWT following standardised procedures by measuring the 6MWD in metres. Key: 6MWD, 6 minute walk distance; 6MWT, 6 minute walk test.				

4.1 The company explained that the 6 minute walk distance (6MWD) outcome used in Study 007 is a validated tool for the assessment of general functioning in people with DMD. It measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface.

4.2 Patients in Study 007 were recruited from 37 study sites in 11 countries including 7 patients from the UK. They were randomised to receive ataluren at a total daily dosage 40 mg/kg (n=57) or 80 mg/kg (n=60), or placebo (n=57) for 48 weeks. Median age at baseline was 8 years and the median baseline 6MWD was 354 metres in the placebo group, 362.1 metres in the 40 mg/kg group and 368 metres in the 80 mg/kg group. Concomitant treatment with corticosteroids was balanced with regard to type and frequency of administration at baseline (see table C9.10, page 81 of the company submission for further details). The prespecified subgroups in Study 007 were: age (less than 9 years old and 9 years old or older), corticosteroid use (yes or no) and baseline 6MWD (350 metres or less, and greater than 350 metres).

4.3 The company conducted a post-hoc subgroup analysis in patients who were classified as being in the decline phase to compare the mean change in 6MWD from baseline to week 48 measured in the placebo group with the ataluren group. The decline phase was defined as patients aged 7–16 years with a baseline predicted percentage in the 6MWD test of 150 metres 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.

Clinical effectiveness: results

4.4 The company presented the results of Study 007 for the mean change in 6MWD from baseline to week 48 for ataluren 40 mg/kg daily (the licensed dose). The following analyses were presented:

- Intention to treat analysis: all 174 randomised patients (n=1 discontinued at week 6 owing to non-compliance).
- Corrected intention to treat analysis: baseline values for 2 patients (1 taking placebo and 1 taking ataluren 80 mg/kg) were replaced by their screening values because the patients had lower-limb injuries before the baseline test.
- Decline phase subgroup: those aged 7–16 years with a baseline percentage predicted 6MWD 80% or less (see section 4.3).

4.5 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 (Table 3 and Figure 1), at 48 weeks there was a mean observed difference of 31.3 metres between ataluren 40 mg/kg and placebo (-12.9 metres and -44.1 metres respectively). In the mixed model for repeated measures analysis, the estimated mean difference between ataluren 40 mg/kg and placebo was 31.7 metres (95% CI 5.1 to 58.3; p=0.0197). No effect was observed in the ataluren 80 mg group.

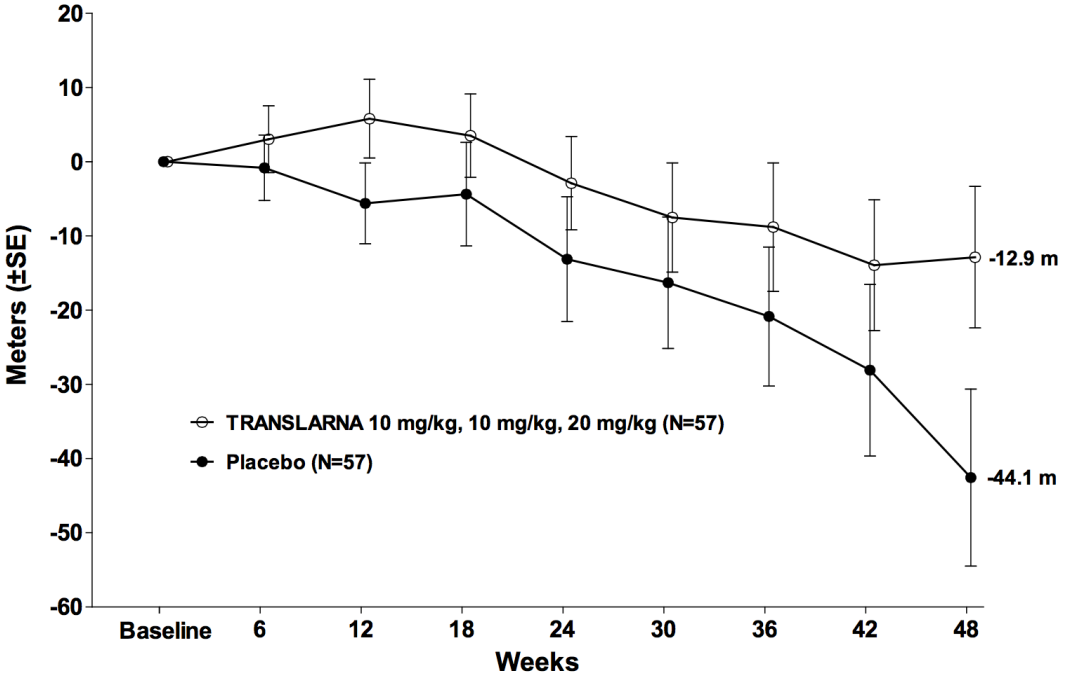
4.6 Subgroup results are presented in Table 3. In the post-hoc subgroup analysis for patients in the decline phase subgroup, patients receiving ataluren experienced a statistically significantly smaller reduction in 6MWD compared with patients receiving placebo (difference in mean change in 6MWD of 45.6 metres, p=0.0096). In the pre-specified group of patients with a baseline 6MWD of less than 350 metres, 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 metres, p=0.0053).

Table 3 Study 007 results: 6MWD from baseline to week 48 (table C9.14, page 90 of company submission)

	Placebo		Ataluren (40mg/kg)		Observed Difference	MMRM Model	
Analysis Sub-group	Baseline, mean (SD)	Difference at week 48 Mean(SD)	Baseline, mean (SD)	Difference at week 48 Mean(SD)	Difference in metres between groups	Difference (95% CI)	p-value
ITT All patients (placebo n=57, ataluren, n=57)	359.6 m (87.7)	-42.6 m (90.1)	350.0 m (97.6)	-12.9 m (72.0)	29.7 m	26.4 m (-4.2, 57.1)	p=0.0905
cITT All patients (placebo n=57, ataluren, n=57)	361.1 m (87.5)	-44.1 m (88.0)	350.0 m (97.6)	-12.9 m (72.0)	31.3 m	31.7 m (5.1, 58.3)	p=0.0197
cITT Decline phase sub-group (placebo n=31, ataluren, n=32)	341.9 m (85.0)	-62.2 m (84.9)	341.0 m (84.8)	-12.3 m (69.4)	49.9 m	45.6 m (11.4,79.9)	p=0.0096
cITT Baseline 6MWD <350 m sub-group (placebo n=22, ataluren, n=25)	272.6 m (54.1)	-107.4 m (104.0),	262.5 m (71.9)	-39.2 m (84.3)	68.2 m	59.8 m (18.0, 101.6)	p=0.0053
Key: ITT, intention to treat; cITT, corrected intention to treat; 6MWD, 6 minute walk distance; CI, confidence interval; MMRM, mixed model for repeated measures.							

Figure 1 Mean change in observed 6MWD from baseline to 48 weeks by visit, corrected intention to treat analysis set (Figure C9.7, page 94 of company submission).



4.7 The company presented the results for the secondary endpoints of Study 007. For further details, see page 60, section 4.2.6 of the ERG report and pages 98–102 of the company submission.

Adverse effects

4.8 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 discontinued 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 and diarrhoea. For further details, see pages 107–110 of the company submission.

Health-related quality of life

4.9 In Study 007, quality of life was measured using the Paediatric Quality of Life Inventory. The inventory contains 4 scales: physical, emotional, social, and school functioning. The inventory was completed at each visit: screening, baseline and every 6 weeks until week 48. The company reported positive trends towards improved quality of life with ataluren treatment. Endpoint scores for physical functioning were numerically higher (indicating higher quality of life) in patients receiving 40 mg/kg ataluren compared with those treated with placebo; however, the differences were not statistically significant.

Strengths and limitations

4.10 The ERG noted that the submitted evidence reflected the decision problem and considered the majority of analyses to be appropriate. The ERG noted the following limitations to the evidence presented by the company:

- The company's methods used in the systematic review were not clearly described, providing the opportunity for error and bias.
- The ERG was unclear why, for the change in 6MWD, the reported p-values for the modelled difference in the mixed model for repeated measures analysis (p=0.0197) was different to the p-value for the same modelled difference in the European Medicines Assessment (EMA) agency report (p=0.0281 for the nominal [unadjusted] p-value). The ERG reviewed the clinical study reports to investigate the discrepancy and found that the company had conducted a permutation test on the difference between the 2 groups in Study 007, which reported a p-value of 0.0561. The ERG questioned the appropriateness of the

reported p=0.0197 in the company submission and the statistically significant difference reported between the 2 groups.

- The ERG noted that post hoc analyses for patients not in the decline and prespecified subgroup analyses of patients with baseline 6MWD great than 350 metres had not been presented, by the company, meaning that an appropriate comparison with the subgroups described in section 4.6 could not be made.
- The ERG considered that 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 serious cardiac disorders, infections and infestations, injury poisoning and procedural complications and total number of serious adverse events were more common with ataluren than with placebo. However, the ERG stated that it is not clear from the information provided whether this is because of longer exposure in the ataluren group.

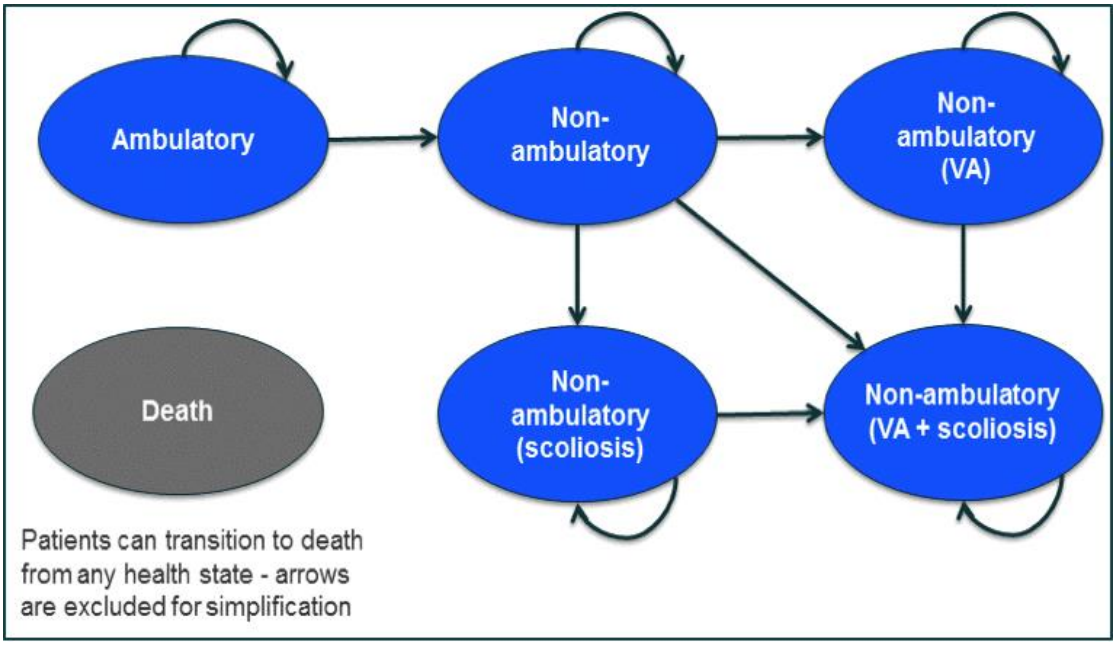
5 Cost to the NHS and personal social services and Value for money

Model structure

5.1 In its original evidence submission, 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 are ambulatory. In a subsequent additional submission, the company submitted an updated model (see section 5.10).

5.2 The company's Markov model had 6 states (Figure 2), representing the progression of DMD from the ambulatory phase to the non-ambulatory phases. 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 received treatment). 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.

Figure 2: Structure of the company's economic model (Figure C12.1, page 155 of company submission)



VA = ventilation assisted

5.3 Patients began in the ambulatory phase when they were 8.5 years old. As disease symptoms progressed, patients transitioned to the non-ambulatory health states. Patients who were non-ambulatory could either transition to ventilation-assisted, scoliosis, or both. Patients could transition to death from any of the 5 DMD health states. Death could occur because of DMD or other causes.

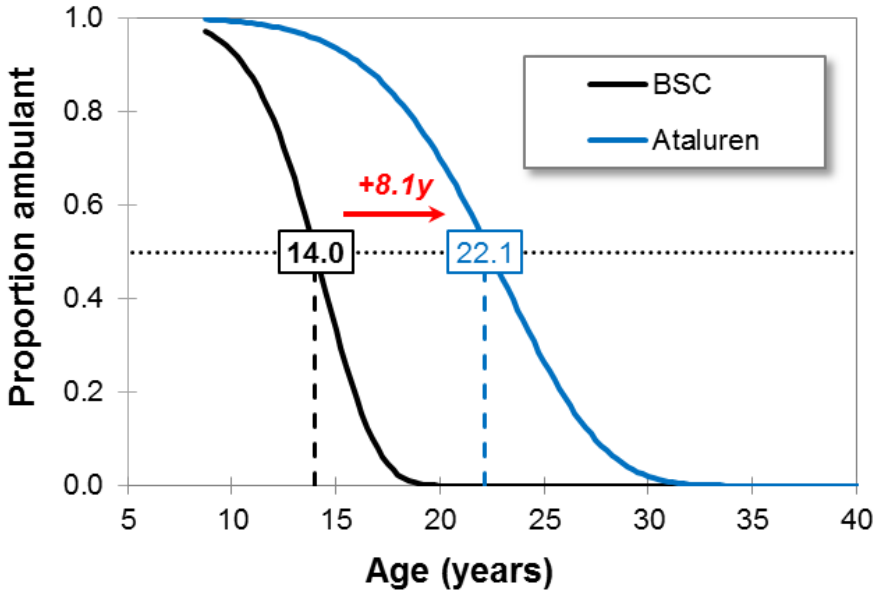
Clinical parameters

5.4 To estimate the time to loss of ambulation for people receiving best supportive care and ataluren the company first performed a regression analysis on Study 007 data for the decline in 6MWD from weeks 24–48 and then linearly extrapolated the data. It calculated that mean time to loss of ambulation was 313 weeks (6 years) with best supportive care and at 733 weeks (14.1 years) with ataluren, which is a difference of 420 weeks (8.1 years).

5.5 To inform the best supportive care transition probabilities for loss of ambulation, the company used Kaplan-Meier estimates from the literature to obtain 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 original model, the company used a Weibull function to fit the data.

5.6 To inform the transition probabilities for ataluren compared with placebo, the best supportive care curve was shifted to the right using a Weibull curve 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) (see Figure 3).

Figure 3 Time to loss of ambulation used in the model (Figure D12.6, page 163 of company submission)



5.7 To inform the transition probabilities for time to ventilation assistance and time to scoliosis, the company conducted a search of the literature. The review found 1 study with Kaplan-Meier estimates. Transition probabilities were estimated based on reconstructed individual patient data and fitted with a Weibull model. See figures D12.8 9 page 167 of company submission for further details.

5.8 The company explained that no clinical or observational studies were available on how non-ambulatory patients could progress to both scoliosis and ventilation assistance simultaneously. Therefore, patient transition probabilities to the 'ventilation assistance and scoliosis' health state were derived from a combination of the ventilation assistance and scoliosis transition probabilities.

5.9 The company estimated time to death for patients receiving best supportive care using data from the literature. The company explained that the age a person with DMD loses the ability to walk is significantly correlated with age of death and therefore a delay in

the time to loss of ambulation has a significant impact on reducing the risk of mortality. The company therefore assumed that ataluren treatment was associated with a reduced risk of death compared with placebo (relative risk=[redacted]). An age-dependent risk of mortality from any cause was applied to every health-state in the model, based on UK general population mortality. See pages 168–170 of company submission for further details.

Updated curve fitting

5.10 In its response to clarification, the company explored using different parametric models to establish the statistically best fitting curves for the clinical effectiveness data. In its updated model, the company updated the cost-consequence analyses by choosing the log-normal distribution for time to loss of ambulation and log-logistic distribution for time to scoliosis and ventilation assistance. A log-normal distribution was chosen for time to death. The results of the updated analyses are given in section 5.14.

Health related quality of life

5.11 Although Study 007 measured health-related quality of life using the Pediatric Quality of Life Inventory, the company did not use these data in its model because it did not find the algorithm for mapping to EQ-5D to be appropriate because it was derived from a healthy population. Instead, 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). The company said that no 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. For further details see page 138 section 10.1.9 of the company submission.

Model costs

5.12 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 ventilation) health states, the total costs ranged from £25,058 to £46,043.

Results of the base-case analysis

5.13 In the base case (discounted) using the company's original model, best supportive care was associated with £235,207 in costs and 2.39 quality-adjusted life years (QALYs). At its list price, ataluren was associated with costs of £5,092,540 and 6.15 QALYs. The incremental cost was £4,857,333 and incremental QALYs were 3.77.

5.14 In the base case (discounted) using the company's updated model, best supportive care was associated with £236,627 in costs and 2.25 QALYs. At its list price, ataluren was associated with costs of £4,784,895 and 6.18 QALYs. The incremental cost was £4,548,269 and incremental QALYs were 3.92.

5.15 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.

5.16 The company presented the budget impact analysis to predict the cost of ataluren to the NHS and personal social services (Table 4). It estimated that there were 2200 people living with DMD in England and that 10% had nonsense mutation DMD. Of these, [redacted] would be aged 5 or older and ambulatory. The median weight of patients used in the budget impact calculation is assumed to be between 24–26 kg. The budget impact in year 1 is estimated to be approximately £8,625,680 rising to £16,019,120 in year 5.

Table 4 Budget impact of ataluren in England over 5 years (table D13.5, page 209 of company submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	7	7	7	7	7	7
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential (theoretical) available patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Level of patient identification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Known patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	35	42	49	57	65	50
Total annual 12 month cost	£8,625,680	£10,350,816	£12,075,952	£14,047,536	£16,019,120	£12,223,821

ERG comments

5.17 The ERG summarised the key sources of uncertainty in the company model in table 38, page 133 of its report.

5.18 The ERG noted the lack of evidence available on the long term follow-up of people with DMD and 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 (see section 5.22). In addition, the ERG noted that the model assumed that the treatment benefit of ataluren over best supportive care remains the same over time, which may not be clinically plausible.

5.19 The ERG noted that the company had not used the health-related the Paediatric Quality of Life Inventory data collected during Study 007 in its economic model (see section 5.11). It was aware that, following a request during clarification, the company had presented aggregate mean utilities from mapping the paediatric quality of life inventory data onto the EQ-5D scale using an algorithm adapted from a study conducted by Khan et al. (2014). Although the company suggested that this approach was not appropriate because the study informing the mapping was conducted in a healthy population, the ERG disagreed and believed that, in principle, the utility data derived from the clinical trial should be preferred to values from the literature.

5.20 The costs and resources used in the model reflected the viewpoint of the analysis (NHS and personal and social services). The ERG noted that the direct costs for the non-ambulatory with or without ventilation assisted health states were the same, and this may have the impact of underestimating the cost of this health state.

5.21 The company submission stated that people could continue to receive ataluren 6 months after loss of ambulation. The ERG noted that these costs had not been included in the company's model.

5.22 The ERG reviewed the company's updated model and noted that the statistically best fitting parametric models had not always been chosen (see table 39, page 136 of ERG report for further details). In addition, an error was found in the updated model structure, which led to overestimated costs and underestimated QALYs in the best supportive care group, and an overestimated treatment benefit of ataluren. The ERG applied a correction factor and the updated results showed best supportive care was associated with £229,396 in costs and 2.269 quality-adjusted life years (QALYs). At its list

price, ataluren was associated with costs of £4,784,859 and 6.178 QALYs.

ERG exploratory analyses

5.23 The ERG conducted further analyses to reconstruct individual patient data and Kaplan-Meier curves using the data from the literature (which the company had identified) to assess appropriate parametric model fits for the economic model. Flexible parametric models were selected for all transitions other than for the ambulatory to non-ambulatory state. For these transitions, a flexible parametric model gave the best statistical fit, but it predicted proportions of people ambulant in the long-term on best supportive care which may not be clinically plausible. Hence, to deal with this problem, a log-normal model was used for transitions to the loss of ambulation state. See section 5.5.4, pages 124–130 of the ERG report for further details.

5.24 The ERG produced 4 additional sets of analyses (based on the company's corrected model):

- Scenario 1: used a lifetime horizon and included costs for continuing treatment with ataluren 6 months after loss of ambulation.
- Scenario 2: used the curves for the model parameters that were presented by the company in its updated model (see sections 5.10 and 5.22) and included the changes made in scenario 1.
- Scenario 3: included scenarios 1 and 2 but changed the distribution for time to loss of ambulation from a log-normal to a generalised gamma. This was because the differences based on mean or median shifts were more substantial than in previous examples where shifting either the median or mean by 8.1 years

(to adjust for delays in loss of ambulation with ataluren) made no difference to the results. The ERG believed that shifting the mean was the more appropriate approach, and therefore used this method to obtain the ataluren curve.

- Scenario 4: included scenario 1 and used the ERG's preferred parametric curves to inform the clinical parameter transition probabilities in the model (see section 5.23). This was the ERG's preferred scenario.

Table 5: Results of the ERG's exploratory scenario analyses in the cost–consequence analysis

	Incremental costs	Incremental QALYs
Base case (using Weibull curve fits)	£4,857,333	3.767
Company's updated analyses	£4,548,269	3.924
Company's corrected analysis	£4,555,499	3.909
ERG scenario 1	£4,753,580	3.908
ERG scenario 2	£4,754,606	3.880
ERG scenario 3	£4,295,464	1.722
ERG scenario 4*	£5,544,981	3.049
*ERG's preferred scenario		

Source: adapted from table 47 on page 141 of the ERG report

5.25 The ERG also presented exploratory analyses to explore the effects of key assumptions on the company's budget impact estimates (Table 6). The ERG explored changing the average weight of people being treated derived from the number of people remaining in the ambulatory health state per cycle (36 kg in the best supportive care group and 53 kg in the ataluren group).

Table 6: Results of the ERG's exploratory scenario analyses in the budget impact analysis (table 48, page 144 of ERG report)

	Net budget impact				
	Year 1	Year 2	Year 3	Year 4	Year 5
Company base case	£8,625,680	£10,350,816	£12,075,952	£14,047,536	£16,019,120
Average weight 39 kg	£13,456,065	£16,147,278	£18,838,491	£21,914,163	£24,989,835
Average weight 53 kg	£18,286,450	£21,943,740	£25,601,030	£29,780,790	£33,960,550

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

6.1 The company listed the costs to the patient and their families for people living with DMD that are not reimbursed by the NHS or personal social services. It noted a study which estimated that the total cost of illness is approximately £53,325 per patient, of which 46% of costs are not incurred by the NHS or personal social services. Patient and carer groups described the costs not reimbursed by the NHS which included moving home and paying for modifications to the house for accessibility purposes, giving up work to care for their child full time, out of pocket expenses for travel to appointments, payments for home help, personal assistants and physiotherapy.

6.2 The company anticipates that treatment with ataluren, which slows disease progression, will enable people with DMD to maintain their independence for longer. The company specified additional cost savings outside the NHS and personal social services, which include the education budget, local government budget and welfare budget.

6.3 The company noted that a registry study is being set up to gather data on ataluren safety, effectiveness, and prescription patterns in routine clinical practice. In addition, data will be generated, post-

authorisation, in the confirmatory phase 3 study (Study 020) which is expected to report initial results during quarter 4 2015.

6.4 The company explained that no additional infrastructure is required to use ataluren in the NHS in England. It is expected that ataluren will be administered only by specialist paediatric neurologists with a specific interest in neuromuscular conditions. NHS England anticipates that there may be some additional costs for genotyping patients whose mutation is currently unknown and extra staff costs for clinic time in monitoring the effect of treatment. Some additional training may also be required to allow for careful monitoring of the effect of treatment, particularly if loss of ambulation is a stopping criterion.

7 Equality issues

7.1 No equality issues that needed to be taken into consideration by the Committee were identified during the scoping process. The company did not note any issues relating to equality in its submission. A potential equality issue was raised in the clinical expert submissions. The clinical expert suggested it could be considered discriminatory to refuse access to treatment on the grounds of cost for such a rare debilitating disease which causes a short life expectancy. In addition, the clinical expert noted that people with DMD in England could be disadvantaged compared with people with DMD in other EU countries because the European Medicines Agency approved ataluren use across the EU based on its current risks and benefits.

8 Innovation

8.1 The company stated that ataluren is the first treatment that addresses the underlying disease process in DMD. It noted that

management of the condition was previously limited to treating the symptoms and addressing its complications.

9 Authors

Victoria Kelly
Technical Lead

Fiona Pearce and Linda Landells
Technical Advisers

with input from the Lead Team: Ron Akehurst, Jonathan Howell and Mark Sheehan.

Appendix A: Supporting evidence

Related NICE guidance or NHS England policy documents

NICE guidance

There is no related NICE guidance for this technology.

National policy documents

Manual for prescribed specialised services. Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48. Specialised Services Commissioning Transition Team.

NHS Outcomes Framework 2014-2015, Department of Health, Nov 2013.

Diagnosis and management of Duchenne muscular dystrophy, Duchenne Muscular Dystrophy Care Considerations Working Group, 2011 (NICE Accredited)

Appendix B: Clinical efficacy section of the draft European public assessment report

The European public assessment report can be found here.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

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

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of ataluren within its marketing authorisation for treating Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene for national commissioning by NHS England.

Background

Muscular dystrophies are a group of genetic disorders which cause muscle weakness and progressive disability. Duchenne muscular dystrophy is the most common and progresses most rapidly. It is caused by the presence of different types of mutations on the X-chromosome in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. The main types of mutation are deletions (where part of the gene is deleted), insertions (where an additional piece of DNA is inserted into the gene), duplications (when part of the gene is repeated) and point mutations (when a single letter in the DNA code is changed and alters the information needed to produce a protein). A point mutation that leads to a stop signal being inserted into the middle of a gene, that stops the protein being produced, is known as nonsense mutation. These changes cause muscle fragility that progressively leads to weakness and loss of walking ability during childhood and adolescence. Boys only have one X chromosome, and thus one single copy of the dystrophin gene, hence they have a much higher probability of developing Duchenne muscular dystrophy than girls. A very small number of girls develop Duchenne muscular dystrophy.

Initial symptoms of Duchenne muscular dystrophy usually present between the ages of 1 and 3 years and children with the disease may appear weaker than other children, and have difficulty walking, standing, or climbing stairs, and may have behavioural or learning difficulties. After the age of 12 most children will need to use a wheelchair. During adolescence, breathing muscles can weaken, causing shallow breathing and a less effective cough mechanism, which can lead to chest infections. Weakness of the heart muscle, called cardiomyopathy, occurs in almost all patients by the age 18. The life expectancy of people with Duchenne muscular dystrophy depends on how quickly and intensely muscle weakness progresses and on how it affects the patient's ability to breathe. The average lifespan is less than 30 years.

The incidence of Duchenne muscular dystrophy is approximately 1 in 3600 – 6000 male live births. Approximately 13% of patients with Duchenne muscular dystrophy carry a nonsense mutation in the dystrophin gene, equating to around 8 – 13 boys born with the condition each year in the UK.

Increasing the time a patient is able to walk is one of the major aims of treatment. Current treatment options do not treat the underlying cause of the disease and focus on alleviating symptoms and maintaining muscle strength. Interventions may include the use of steroids (associated with several side effects) and physical aids (such as wheelchairs, leg braces or crutches), exercise, physiotherapy, and occasionally orthopaedic surgery. In addition, other supportive treatments such as dietetic advice, prevention and treatment of bone fragility and the management of complications of long-term steroid therapy are required. In the later stages of Duchenne muscular dystrophy, treatments to help improve breathing and increase oxygen levels may be needed if lung function becomes impaired.

The technology

Ataluren (Translarna, PTC Therapeutics) is designed to allow the protein-making apparatus in cells to skip over the nonsense mutation, allowing the cells to produce a full length functional dystrophin protein. It is administered orally.

Ataluren has a conditional marketing authorisation in the UK for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. As part of the conditional marketing authorisation, the company will be required to provide data on the effectiveness and safety of ataluren from an ongoing confirmatory study. It is being studied in a clinical trial compared with placebo in boys aged 7 years and older with Duchenne muscular dystrophy caused by a nonsense point mutation in the dystrophin gene who could walk at least 150 metres during a 6-minute walk test.

Intervention(s)	Ataluren
Population(s)	People aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk
Comparators	Established clinical management without ataluren
Outcomes	The outcome measures to be considered include: • walking ability (ambulation) • muscle function

	• muscle strength • ability to undertake activities of daily living • cardiac function • lung function • time to wheelchair • number of falls • mortality • adverse effects of treatment • health-related quality of life.
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)

Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	None
Related National Policy/information	Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48 http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf Diagnosis and management of Duchenne muscular dystrophy, Duchenne Muscular Dystrophy Care Considerations Working Group, 2011 (NICE Accredited) http://www.nice.org.uk/Media/Default/About/accreditation/accreditation-decisions/Duchenne-Muscular-Dystrophy-Care-Considerations-Working-Group-final-decision.pdf

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene [ID428]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company(ies) • PTC Therapeutics (ataluren) Patient/carer groups • Action Duchenne • Joining Jack • Muscular Dystrophy UK Professional groups • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians Others • Department of Health • NHS England	General • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Welsh Government Comparator companies • None Evidence Review Group • National Institute for Health Research Health Technology Assessment Programme • Warwick Evidence

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against recommendations.

All non-company consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation document for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary).

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the HST Evaluation Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Ataluren (Translarna™) for treatment of nonsense mutation Duchenne muscular dystrophy (in ambulatory patients aged 5 years and older)

26th June 2015

(Specification for manufacturer/sponsor submission of evidence, July 2013)

Contents

Instructions for manufacturers and sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the manufacturer or sponsor to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme' available at: (http://www.nice.org.uk/media/188/49/HST_combined_Interim_Process_and_Methods_FINAL_31_May_2013.pdf). After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional

appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with ‘see appendix X’. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Tables

Figures

Abbreviations

Term	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
AWMSG	All Wales Medicines Strategy Group
BMD	Becker's muscular dystrophy
BSC	Best supportive care
BUN	Blood urea nitrogen
CF	Cystic fibrosis
CHMP	Committee for Medicinal Products
CHF	Congestive heart failure
CI	Confidence interval
cITT	Corrected intention to treat
CK	Creatine kinase
CPAG	Clinical Priorities Advisory Group
CSR	Clinical study report
DH	Department of Health
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDB	Extensor digitorum brevis
EMA	European Medicines Agency
FVC	Forced vital capacity
HDL	High density lipoprotein
HRQL	Health related quality of life
HUI	Health Utilities Index
ITT	Intention to treat
IVR/IWR	Interactive Voice Response/Interactive Web Response
MCID	Minimal clinically important difference
MMRM	Mixed-model repeated-measures
NA	Non-ambulatory
6MWD	6 minute walk distance
6MWT	6 minute walk test
LDL	Low density lipoprotein
LoA	Loss of ambulation
mRNA	Messenger ribonucleic acid
nmDMD	Nonsense mutation Duchenne muscular dystrophy, or nonsense mutation dystrophinopathy in Study 007
nmDBMD	Nonsense mutation Duchenne/Becker's muscular dystrophy
NHS	National Health Service
PBRER	Periodic Benefit-Risk Evaluation Report

PedsQL	Paediatric Quality of Life Inventory
QoL	Quality of Life
RCT	Randomised controlled trial
SAE	Serious adverse event
SAM	Step Activity Monitor
SD	Standard deviation
SMC	Scottish Medicines Consortium
SOC	System organ class
TA	Tibialis anterior
TFTs	Timed function tests
TREAT-NMD network	Treatment of Neuromuscular Diseases network
TSQM	Treatment Satisfaction Questionnaire for Medication
UAA	Uridine-adenosine-adenosine
UAG	Uridine-adenosine-guanosine
UGA	Uridine guanosine-adenosine
UK	United Kingdom
US	United States of America
VA	Ventilation-assisted

Glossary

Six Minute Walk Test and Six Minute Walk Distance

The six minute walk test (6MWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. A subject may stop during the exercise and then continue but they may not sit down.

The 6MWT has been validated for the assessment of general functioning in boys with DMD. It has been found to be sensitive and reliable and shows excellent concurrent validity with other endpoints, such as timed function tests (TFTs) (McDonald, 2013).

In healthy children and adolescents the mean distance walked within six minutes (6MWD) is 618 ± 79 metres. Whereas weight and height steadily increase with age, the 6MWD mainly increases until puberty and then flattens (Ulrich 2013).

The 6MWD has been shown to correlate with the Pediatric Outcomes Data Collection Instrument (PODCI) scale, which is a recognized measure of QoL (Henricson, 2013). Importantly, 6MWD has been accepted by the EMA as a valid endpoint for measuring the efficacy of treatments for DMD (EMA, 2013).

Timed Function Tests

Timed function tests (TFTs) include the time taken to stand from a supine, time taken to run/walk 10 m, time taken to climb 4 standard-sized stairs, and time taken to descend 4 standard-sized stairs. TFTs provide a measure of functional capability in ambulatory patients that is complementary to the 6MWT. The tests are reproducible and simple to administer (McDonald, 2013a).

Ambulation

Ambulation is defined as the ability to walk and in the context of this submission being ambulatory is the ability to take any steps unaided and non-ambulatory is being completely confined to a wheelchair for indoor and outdoor use. Loss of ambulation (LoA) is defined as having become non-ambulant.

Gowers' sign

A manoeuvre performed by a patient with weak knee and thigh flexors on standing from a sitting position on the floor; consists of first flexing the trunk at the hips, then placing the hands on the knees, and then extending the trunk by using the hands to walk up the legs; identified principally with Duchenne muscular dystrophy.

Toe-walking

Toe walking is an abnormality in the way a person walks characterised by an absence of normal heel-to-floor contact (heel strike) by both feet during walking, with the forefoot (ball of the foot) engaging in the majority or all of floor contact.

Corrected Intent-to-Treat

In the ataluren Phase 2b study (Study 007), the pre-specified intent-to-treat (ITT) population included all randomised subjects with a valid 6MWT results available at baseline and ≥1 post baseline visit. The baseline values for 2 patients (1 placebo-dosed and 1 treated with ataluren 80 mg/kg/day) were replaced by their screening values, because their baseline 6MWDs were radically lower than their screening and Week 6 values due to lower-limb injuries before the baseline test. This is referred to as the corrected ITT (cITT) population. Although the cITT population analyses are post-hoc, the Committee for Human Medicinal Products (CHMP) of the EMA considered the approach to be appropriate (Haas, 2015).

Executive Summary

The Technology

Ataluren (Translarna™) is licensed for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (Translarna SPC, 2014). Ataluren received marketing authorisation from the EMA in July 2014 and has been commercially available in the UK since September 2014.

In nonsense mutation DMD (nmDMD) a single base variation in a patient's DNA results in a premature stop codon within the corresponding mRNA, thereby terminating translation before a full-length protein is generated (Translarna SPC, 2014). Ataluren allows ribosomes to read through the premature stop codon, whilst respecting the normal stop codon, to restore the synthesis of full-length functional dystrophin protein (Translarna SPC, 2014) (Section 2.2).

Ataluren is the first specific approved therapy for nmDMD that addresses the underlying cause of the disease ie the loss of dystrophin. Without dystrophin, muscles progressively weaken and deteriorate, leading to complete loss of ambulation, cardiac and respiratory insufficiency and death. Prior to the approval of ataluren for the treatment of nmDMD, the only management options for this devastating disease were supportive in nature.

In a well-conducted international research study of ataluren versus placebo in 172 patients with nmDMD, treatment with ataluren for 48 weeks resulted in a clinically meaningful change in the in the 6MWD, a recognised predictor for the timing of loss of ambulation. Additionally, ataluren was well tolerated with a safety profile similar to that of placebo.

Ataluren is available as granules for oral suspension (125 mg, 250 mg, 1000 mg sachets). The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight) (Translarna SPC, 2014). Ataluren is a long term chronic therapy. The list price for ataluren is £2,532.00 per box of 30 sachets of 125mg (approved by DH on September 4th 2014) which equates to a per mg cost of £0.675 (Section 2.2 and 13).

Nature of the condition

DMD is a severe, progressive and rare genetic muscle wasting disease characterised by a rapid decline in physical functioning starting in childhood with subsequent respiratory and cardiac failure, leading to death in early adulthood.

DMD affects 8.29 in 100,000 males (Norwood 2009). Based on the size of England's population in 2012 (53,865,817) (Office for National Statistics 2013), it is therefore estimated that 2,200 males in England have DMD. Recent data from the TREAT-NMD DMD Global database, which contains over 7,000 mutations, has found that 10% of patients have DMD resulting from a nonsense mutation (nmDMD) (Bladen, 2015). It is therefore estimated that in England there are around 220 patients with nmDMD of which around [redacted].

DMD is an X-linked recessive disorder and therefore predominantly, but not exclusively, affects males. DMD is caused by mutations in the gene encoding dystrophin, a structural protein that stabilises muscle cell membranes.

The most devastating and obvious effect of DMD is on the skeletal musculature causing loss of strength and function resulting in high morbidity, early mortality and reduced quality of life (Bushby, 2010b). Although dystrophin production is affected from birth, symptoms of DMD are often not identified until the age of 3 years (van Ruiten, 2014). The mean age at genetic diagnosis in the UK has been reported as 4.3 years (range of 10–91 months) (van Ruiten, 2014). The mean age of death is between 25.3 and 28.3 years (Eagle, 2002; Rall, 2012; Kieny, 2013).

In the early stages of disease progression children with DMD begin to have difficulties with mobility and show signs typical of DMD such as toe walking, Gower's manoeuver and a waddling type of gait. As the condition progresses the children experience more problems with climbing stairs and getting up from the floor and progressively lose the ability to walk altogether. By the age of 8 years, most boys have difficulty arising from the floor and ascending stairs, and they often fall while walking (McDonald, 2010a). Once children with DMD enter the period of rapid decline they lose walking ability very quickly. In steroid naïve children walking ability is usually lost between 8 to 12 years of age (Biggar, 2006). For those children treated with steroids complete loss of walking ability and permanent wheelchair dependency occurs at around 12 to 15 years of age (Goemans, 2013; Ricotti, 2013).

2010). At this stage they can start to experience respiratory symptoms and are at increased risk of deterioration in cardiac function. As respiratory function starts to decline ventilation support is provided and dependence on night-time non-invasive home ventilation usually occurs before 23 years of age (Ishikawa, 2011; Kieny, 2013). As their condition progresses 24 hour ventilation is required and in some patients invasive ventilation via tracheostomy is needed. Steroid naive children and young adults with DMD can develop scoliosis due to weakening of their back muscles that is exacerbated by wheelchair immobility and which requires major surgical intervention. In the final stage upper-limb function is lost, with subsequent complete loss of independence and increased incidence of medical complications (Section 6.1).

While the muscle involvement and subsequent loss of function described above is inevitable, disease progression and rate of decline is heterogeneous. Even where children receive a similar standard of care, including treatment with steroids, variability has been observed in the rate of disease progression (Goemans, 2013).

In the last 10 years, survival rates for patients in the UK with DMD have improved. Despite this most patients with DMD die from heart or lung failure in adolescence or early adulthood, and patients rarely survive beyond their third decade (Passamano, 2012; Stromberg 2012). When ventilator support is provided the mean age of death has been reported as between 25.3 and 28.3 years (Eagle, 2002; Rall, 2012; Kieny, 2013) (Section 6.3).

DMD has a profound impact on the quality of life of children with the condition, their siblings, parents and other carers. As the condition progresses the quality of life of children with DMD deteriorates, most markedly in the non-ambulatory stage (Uzark, 2012; Landfeldt, 2014; Schreiber-Katz, 2014). When children diagnosed with DMD are young their parents see that they cannot keep up with their peers, have problems walking, running, climbing stairs and fall frequently. Falls can lead to fractures which may even result in permanent wheelchair dependence. Boys with DMD rarely have the chance to fully engage in physical activities normal for their age. The progressive decline in muscle function prevents them from independently performing many self-care activities including, with time, self-dressing, self-feeding, toilet care and personal grooming. Most DMD patients will remain entirely dependent on others for their continued care, although a few will cope with their disabilities until their early adulthood, after which time the accumulation of disease symptoms will force them to become fully dependent on others (EMA, 2015).

The majority of caregivers are the parents of affected boys and help from outside the family is often not available. Although parents value giving care as being important and rewarding, the burden is substantial and many reduce their working hours or stop working completely because of their child's condition (Landfeldt, 2014; Pangalila, 2012). Parents of children with DMD suffer higher levels of anxiety, depression, and guilt and experience the greatest emotional impact of their child's condition around the time of loss of ambulation (Bray, 2011; Dogba, 2014). Overall, physical and mental problems of parents and caregivers increase with the severity of their child's impairment (Schreiber-Katz, 2014, de Moura 2014). Parents themselves may develop medical problems due to the burden of their son's disease, leading to further consumption of medical treatment (Schreiber-Katz, 2014).

Extent & nature of current treatment

Coordinated multidisciplinary care is essential for optimal management of DMD, and includes psychosocial and physical therapy as well as pharmacological interventions.

Other than ataluren, there are no licensed disease-modifying therapies that address the underlying cause of dystrophinopathy. Corticosteroids are the only medication currently available that slow the decline in muscle strength and function in DMD, which in turn helps reduce the risk of scoliosis and stabilise pulmonary function (Bushby, 2010b). However, glucocorticoids are associated with a significant and serious side effect profile that presents significant challenges for long-term use, including excessive weight gain, growth failure, delayed puberty, osteoporosis and vertebral fragility and other fractures, severe behavioural problems, glucose intolerance and hypertension (Bushby, 2010b).

In later childhood and teenage years, inpatient spinal surgery for scoliosis and rehabilitation may be required (more commonly in steroid-naïve patients). There is increased need for inpatient orthopaedic intervention, cardiac and respiratory intervention with potential inpatient admission for treatment of respiratory complications. Dietetic advice (and in some cases gastric feeding), prevention and treatment of bone fragility, and management of complications of long-term corticosteroid therapy are generally also required (Bushby 2010b).

Impact of the new technology

- ***Clinical effectiveness of the technology***

Treatment with ataluren 40 mg/kg/day is associated with clinically meaningful improvements in ambulation and physical function as measured by change from baseline to week 48 in the six-minute walk distance (6MWD) and changes in timed function tests (TFTs) relative to placebo (EPAR, Bushby, 2014, Haas 2014).

Conditional marketing authorisation is an early access mechanism which allows the European Medicines Agency to recommend marketing authorisation for medicines that address an unmet medical need for patients suffering from life-threatening diseases even if comprehensive clinical data are not yet available.The safety and efficacy of ataluren have been demonstrated in a Phase 2b placebo-controlled, randomised, double-blinded, international study, which forms the primary evidence base for this submission (Study 007, Bushby, 2014). Study 007 evaluated ataluren 40 mg/kg/day (N=57) and ataluren 80 mg/kg/day (N=60) vs. placebo (N=57) given orally every day for 48 weeks in males ≥5 years nmDMD. In addition to published data, available data from seven unpublished studies (four of which are on-going) are included in the pooled safety analysis (Table C9.5, and Section 9.7).

Overall, an estimated total of 379 male subjects with nmDMD were treated with ataluren in nine clinical trials that were included in the safety analysis (PTC, 2015). Safety data identified no major concerns. In particular, the ability to co-administer ataluren with corticosteroids, which form part of the current standard of care in DMD, was demonstrated.

- ***Overall magnitude of health benefits to patients and, when relevant, carers***

In Study 007 patients with nmDMD treated with ataluren 40 mg/kg/day demonstrated an average 31.3-metre observed difference in 6MWD (cITT analysis) vs.placebo at 48 weeks compared to baseline (-12.9 metres and -44.1 metres respectively) (Bushby, 2014; PTC Study 007 CSR). In the statistical based model (MMRM) the estimated mean difference between ataluren 40 mg/kg/day and placebo was 31.7m (95% CI 5.1, 58.3; nominal p = 0.0197, adjusted p = 0.0367) (Haas, 2015; Translarna SPC).

Study 007 included a pre-specified analysis of persistent 10% worsening in 6MWD. 26% patients treated with ataluren 40 mg/kg/day experienced ≥10% worsening at Week 48 compared to 44% in the placebo group (nominal p=0.033)(Bushby, 2014). A

≥10% decline in ambulation over 12 months is associated with significantly greater likelihood of lost ambulation over the next 4 years (cited, McDonald 2013b).

Timed function tests (TFTs) have traditionally been used to assess muscle function in DMD and are sensitive to changes in disease status (McDonald 1995, Beenakker 2005a, Mazzone 2011, Mazzone 2013). Ability to climb and descend a short grouping of stairs, ability to run in short bursts, or to walk a short distance unaided, e.g. to a classroom or to the bathroom, reflect the typical activities important in the lives of DMD patients. Importantly, recent data indicated that timed function tests evaluating these abilities are, similarly to 6MWD, predictive of the time for a person with DMD to become non-ambulatory: a time of <6 s on the 10-m run/walk is associated with continued ambulation over the subsequent 12 months, and a time of >10–12 seconds is associated with a high risk of loss of ambulation over 12 months (McDonald, 2013b).

In the secondary endpoints of Study 007, including in TFTs, positive trends favouring ataluren 40 mg/kg/day over placebo were seen across multiple measures of physical functioning. In Study 007 patients treated with ataluren showed less decline in their ability to complete TFTs, with an observed difference of 2.4 seconds, 1.6 seconds and 1.5 seconds compared to placebo in the time taken to climb four stairs, descend four stairs or run/walk 10 metres, respectively (cITT analysis). Again, these positive trends were evident in the overall study population as well as in pre-specified patient subgroups.

The positive trends in the secondary endpoints in Study 007 were considered important by the CHMP to support the data from the primary endpoint of 6MWD.

Treatment with ataluren 40 mg/kg/day was associated with positive trends in physical functioning in the PedsQL (Paediatric Quality of Life Inventory). The physical functioning scale is most directly applicable to the clinical manifestations of DMD. Mean change in physical functioning score at Week 48 was -1.0 for placebo and 2.4 for ataluren 40 mg/kg/day, giving a difference in mean change in physical functioning score at Week 48 of 3.4 favouring ataluren 40 mg/kg/day vs.placebo (Bushby, 2014). Although this is below the minimal clinically important difference it trends in the same direction as a number of other measurements of physical functioning.

Accidental falling is the most common cause of limb fractures in boys with DMD, and 35 to 40% of lower-limb fractures result in permanent loss of ambulation (McDonald,

2002; Vestergaard, 2001). Decreasing the rate of accidental falls and hence the risk of fractures, pain and other trauma, would be of significant benefit to the patients, their carers and the healthcare system. Patients receiving ataluren had fewer falls compared to patients receiving placebo. The number of accidental falls per day decreased by [redacted] in the ataluren group compared to an increase by [redacted] in the placebo (nominal p-value = [redacted])(PTC Study 007 CSR).

As the condition advances, patients who are still ambulatory sometimes require the use of a wheelchair for longer distances or trips. In Study 007, patient reported wheelchair use showed a positive trend favouring ataluren when compared to placebo. At week 48, the mean percentage of days of wheelchair use (95% CI) increased by 11.5% (95% CI: 4.36 to 18.54) for placebo and 4.0% (95% CI: -2.77 to 10.68) for ataluren 40 mg/kg/day (a 7.5% mean difference between groups).

Patient experience indicates that ataluren has a wider effect in terms of improving children's energy levels, overall endurance and independence [Please also refer to patient video 1 provided]:

"*He completely changed, he could do almost anything, he could run down stairs, he could play football, he could get up from the floor without pushing using the Gower's manoeuvre, everything completely changed for him. I can recall one day walking up and down hills for two hours (which he would never have been able to before)… since going back on drug he can jump in the car and put his seatbelt on, no problem at all, which he continues to do to this day." "Gaining his independence means so much to him, to his mental state, and he can now do things on his own, without having to ask for our help.*"

- ***Heterogeneity of health benefits within the population***

A 30-metre change in 6MWD over 48 weeks is considered a clinically meaningful change, based on statistical distribution-based methods as well as the relationship with patient-reported outcomes (McDonald, 2013a, Henricson, 2013). Each 30 metre decrement in 6MWD predicts increasing risk of loss of ambulation over the following 2 years (Mazzone, 2013; Lynn, 2015). Furthermore, depending on an individual's baseline functional status, the minimal clinically important difference in 6MWD could be even lower than 30m (Henricson, 2013).

In the analysis of the pre-specified subgroup of patients with a baseline 6MWD <350 metres patients with nmDMD treated with ataluren 40 mg/kg/day demonstrated

an average 68.2 metre difference in 6MWD vs.placebo at 48 weeks compared to baseline (-39.2 metres and -107.4 metres respectively) (Bushby, 2014; PTC Study 007 CSR) (nominal p=0.0053, corrected ITT analysis).

In a post-hoc analysis of a subgroup of patients defined as being in the "decline phase" of disease progression (based on observed natural history data) patients treated with ataluren 40 mg/kg/day demonstrated an average 49.9 metre difference in 6MWD vs.placebo at 48 weeks compared to baseline (-12.3 metres and -62.2 metres respectively) (nominal p=0.0096, corrected ITT analysis). The selection of this sub-population (>7 years of age, treated with corticosteroids, 6MWD ≥150 m, <80% predicted 6MWD) was considered clinically and scientifically justified by the CHMP, as well as by a convened group of external experts and patient representatives (Scientific Advisory Group [SAG] in Neurology) since a beneficial effect of ataluren on ambulation would be expected to be more readily detectable in these patients (Haas, 2015).

Collectively, these data document a favourable benefit-risk profile for ataluren 40 mg/kg/day in the treatment of patients with nmDMD. Treatment with ataluren allows boys to maintain their ability to walk and carry out everyday tasks such as climbing and descending stairs, thereby improving their independence and their ability to participate in normal activities, attend mainstream school, keep up with their peers, play with friends and keep active. By modifying the course of the disease and delaying the point at which more rapid decline occurs, ataluren will also significantly delay the time to complete loss of ambulation and wheelchair reliance as well delaying the onset of respiratory complications.

- ***Robustness of the current evidence and the contribution the guidance might make to strengthen it***

In Study 007, 40mg/kg/day ataluren demonstrated a significant and clinically meaningful benefit compared to placebo in the change in 6MWD (cITT analysis) (Haas, 2015). Despite limitations in the robustness of the efficacy data presented, ataluren was considered by the CHMP to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need. The majority of the secondary endpoints results directionally supported the results of the primary efficacy analysis. Additional data will be generated post-authorisation via the confirmatory Phase 3 study PTC124-GD-DMD (Study 020) which is expected to report initial results during Q4 2015.

Efficacy of ataluren was observed at the 40 mg/kg/day dose but not the 80 mg/kg/day dose. This was consistent with nonclinical data and a bell-shaped concentration-response curve (Section 9.2).The licensed dose of ataluren is 40mg/kg/day.

There is no clinical data beyond 48 weeks available for this submission. Whilst the assumptions have been validated as much as possible with clinical experts and by a systematic review of the literature, the time horizon of the assessment makes it likely that, at the extremes, there will be a very high level of uncertainty in the results. This may be both in a positive and negative direction.

There are some limitations of the model structure in that it does not allow the full benefit of ataluren to be modelled i.e. increasing survival of ataluren results in fewer QALYs, which is counter-intuitive. This is because the natural history is based on the only available publication that models transition of health states (Humbertclaude et al, 2012). This publication does not allow for extended ambulation beyond 11 years whereas for BSC and ataluren treatment mean age of LoA is 14.5 and 22.6 years respectively. Thus, in using the Humbertclaude data, once a patient has become non-ambulatory they are assumed to be in the worst health state. This is not expected to be the reality and this confounding factor may be addressed by modifying the Humbertcalude data and verifying through clinical experts with subsequent additional analyses (see section 12.8.4).

Evidence from the trial indicates that younger patients will receive greater benefit of ataluren as they will start treatment much earlier in the stage of the condition. Data from the >75% predicted 6MWD group at baseline shows a trend towards improved 6MWD vs.placebo. The current cohort of untreated patients in England, as well as all newly diagnosed patients, are younger than the modelled baseline which was based on the 007 clinical study cohort. However, the natural history data is limited in terms of age thus a variation in cohort age has not been explored. It is therefore expected that incremental costs would reduce and incremental QALYs would increase when modelling a younger age at the start of treatment. In fact, extrapolating the treatment effect seen in a subset of the clinical trial patients who had a baseline 6MWD >350m suggests that they may remain ambulatory for >30 years. Given the mode of action of the drug, this is a clinical possibility. However, we have presented a conservative model; this challenge was discussed at the Scoping meeting and NICE and the ERG are fully aware of the entirety of the limited data availability.

It has not been possible to source data for every important element of the disease that has a significant impact on NHS costs or patients quality of life. For example, ventilation-assistance places a huge burden on patients, carers and NHS costs but no specific cost or quality of life data was available for the DMD patients.

Another weakness is the paucity of Health Utility data in the literature for DMD patients and carers. Landfelt 2014 is a recent publication, but a review of the literature in other similar conditions (involving neurological decline, wheelchair use or ventilatory assistance) suggests that he has underestimated the disutility of being in certain health states both for the patient and carer.

Regarding mortality, there were no deaths in the 48 week study and we have therefore been cautious in our approach to the long-term extrapolation of LoA to extended time of survival, especially knowing that such extrapolations are often heavily criticised. However, the assumptions that have been made are based on available published data and feedback from clinical experts. A long term Registry is being set up that may be able to address this question in its final report.

In addition, increasing the experience of the clinical use through early commercial availability will add to the body of knowledge as is most often the case for treatments of very rare diseases where such data is rarely if ever available at the time a product is granted marketing authorisation.

NHS England is currently in the process of developing a clinical commissioning policy for ataluren which has been ongoing for approximately one year. Due to the delays in a decision from NHS England regarding this policy ataluren has not been commercially available for any eligible children with nmDMD. It is understood that a final decision will be ratified by the NHS England Board on or before June 30th. No matter the outcome, guidance from NICE would serve to remove any uncertainty regarding funding of ataluren and would, in the event of positive guidance, ensure access to treatment for boys who are affected by a devastating disease and are in great need of an effective treatment.

- ***Treatment continuation***

Ataluren should be considered within its marketing authorisation as a treatment for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation (nmDMD). It can be added to existing standard treatment, including use of corticosteroids. In this submission the following continuation rule (stopping criteria) is

proposed: If a patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician should consider stopping ataluren treatment.

Treatment should not be stopped while the patient has any degree of ambulatory ability as it has been shown with other treatments (corticosteroids) that withdrawal of medication at this time can have negative consequences. Patients should not stop treatment until at least 6 months after becoming fully non-ambulant**.**

Cost to the NHS and Personal Social Services

50 boys aged 5 and over who are ambulant and who have nmDMD have been identified (known patients) in England out of a theoretical prevalent population of 66.

The uptake of ataluren in Year 1 is based on the estimates of patients moving from clinical trials and compassionate use supply onto commercial supplies. It also includes 30 patients from the existing pool being initiated on ataluren during 2015 from the point when NHS England guidance is expected to be published (June 30th 2015). If NHS England commissioning commences in July 2015, Year 1 will represent 9 months of a full 12 month funding period.

If 7 new nmDMD patients are diagnosed each year based on published incidence rates and all patients are initiated on ataluren, the total number of patients receiving treatment in year 5 (2019) would be approximately 65 patients taking into account mortality and patients discontinuing therapy due to loss of ambulation in line with the proposed stopping rule.

Based on the median body weight of boys, the number of patients identified in section 13.1 and uptake in section 13.2, the budget impact in year 1 is estimated to be approximately £8.6M rising to around £16.0M in Year 5 assuming uptake by this time is [redacted]

Value for money

- Technical efficiency (the incremental benefit of the new technology compared to current treatment

A semi-Markov model has been used to estimate the long-term costs and consequences of ataluren for the treatment of nmDMD, compared to best supportive

care (BSC). To capture differences in costs and outcomes as patients progress in DMD, health states were defined as: ambulatory, non-ambulatory (NA), NA & ventilation-assisted (VA), NA & scoliosis and NA & VA & scoliosis. The time horizon was the duration of ataluren treatment, which is indicated in ambulatory patients only.

An extrapolation of 6MWD from Study 007 resulted in estimated mean age at loss of ambulation as 14.5 years in the BSC arm and 22.6 years in the ataluren arm (difference 8.1 years). This difference in time to LoA was applied to published BSC data showing comparable median survival of 14 years to generate transition probabilities from the ambulatory to non-ambulatory health state. Published data on time to VA and time to scoliosis were used to generate transition probabilities between the non-ambulatory health states. Death caused by DMD or other causes was assumed possible from every health state, with probabilities derived from published literature. Based on evidence that a delay in LoA leads to a reduced risk of mortality, a relative risk of [redacted] was used for the ataluren arm.

Health state costs, patient utilities and caregiver disutilties for UK DMD patients were obtained from Landfeldt and colleagues (2014) and NHS reference costs.

After applying a discount rate of 3.5%, patients receiving ataluren gained 7.5 years in the ambulatory state compared to BSC, at an additional cost of £4,857,333 per patient. Ataluren patients incurred total costs of £5,092,541, survived for 14.5 years and had 6.152 QALYs. Ataluren patients gained 3.767 additional QALYs compared to BSC patients.

The model was sensitive to the choice of patient utility in the ambulatory state and to the discount rate but insensitive to all other parameters. When incorporating costs relevant to the wider societal perspective, ataluren was associated with cost offsets of £261,180 per patient.

- Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used

It is not anticipated that any additional infrastructure will be required to ensure the safe and effective use of ataluren. Care will be delivered through existing specialist treatment centres and no additional facilities, technologies or infrastructure are required.

Data from Study 007 demonstrate that ataluren has a favourable safety profile with no significant difference in the incidence of adverse events between the ataluren and placebo arms. No costs have therefore been included for adverse events.

- Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)

Based on the median body weight of boys, the number of patients identified in section 13.1 and uptake in section 13.2, the budget impact in year 1 is estimated to be approximately £8.6M rising to around £16.0 in Year 5 assuming uptake by this time is [redacted]

Impact of the technology beyond direct health benefits

- Whether there are significant benefits other than health

As discussed above, DMD has a considerable impact on the quality of life of children with this condition as well as for their families and carers. Ataluren has the potential to significantly improve the lives of boys with DMD and their families. By maintaining their ability to walk ataluren will give boys with nmDMD the chance to live a more normal life and to participate in activities normal for their age enabling them to remain independent, be able to wash and dress themselves, eat and go to the toilet by themselves and enjoy their childhood for as long as possible.

DMD has a considerable societal impact in terms of the lost productivity of both patients and their families and caregivers. Parents of boys with DMD often have to reduce working hours or stop working completely in order to provide the care needed (Landfeldt, 2014). A treatment that stabilises the condition and/or slows disease progression is of considerable benefit for patients with DMD and their carers [please also refer to patient video 2 provided]. It would allow children to maintain a degree of independence for longer and would mean that caring for their children is less intensive for parents/ caregivers and may allow them to stay in paid work for longer. It may also mean that children with DMD can participate in mainstream education for longer, remain more self-sufficient and have an increased chance of higher level educational attainment as well as employment.

- Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services

DMD has a considerable economic burden, of which a large component is incurred outside of the NHS and personal and social services. In the UK, almost 50% of the total per-patient cost is estimated to be made up of the cost of informal care and lost productivity (Landfeldt, 2014). Parents report caring for their children with DMD to be burdensome, costly in terms of time, and contributing to increased social isolation (Dogba, 2014). In addition to helping their children with daily activities such as getting around, dressing and washing, time is spent each day at home on stretching exercises and physiotherapy as well as frequently travelling to visit various members of the multi-disciplinary care team. Families incur significant out of pocket expenses including: days off work, travel costs and the cost of adaptations to the home.

The cost of illness increases with progression from the ambulatory to the non-ambulatory stages of DMD, and almost doubles between the early and late non-amulatory stages when a patient is confined to a wheelchair (Landfeldt, 2014). Ataluren maintains walking ability and therefore will delay progression to the non-ambulatory stage of disease and the associated higher health burden and higher costs, of which a large proportion are made up of costs incurred outside of the NHS and personal social services.

The impact of the technology on the delivery of the specialised service

- Staffing and infrastructure requirements, including training and planning for expertise

The marketing authorisation for ataluren states that treatment should only be initiated by specialist physicians with experience in the management of Duchenne muscular dystrophy. It is expected that ataluren, like many innovative, high cost medicines, will be prescribed only by specialists with expertise in the management of the specific condition. In the case of DMD these specialists are paediatric neurologists with a specific interest in neuromuscular conditions. Ataluren will be delivered in specialist centres as described under the service specification for Paediatric Neurosciences – Neurology (E09/S/b) by NHS England. There are currently 18 centres that specialise in the management of DMD in England and Wales.

The introduction of ataluren is not expected to result in any changes to the way services are delivered nor will it require any additional infrastructure. It is however possible that the introduction of this new technology could focus expertise and optimise services even further.

Genetic testing using the standard genetic tests currently commissioned by NHS England for dystrophin gene mutations is carried out during diagnosis and no additional tests are required to identify patients eligible for treatment with ataluren (Section 8.7). As ataluren is an oral therapy, no additional facilities, technologies or infrastructure need to be used. Unlike many new novel technologies, it will not need patients to come into hospital either as day cases or in-patients to receive treatment and initiation of therapy with ataluren does not require any particular supervision. Minimal monitoring of patients is required. The supply of ataluren can also be arranged as home care delivery if desired thus mitigating any need for patients/ carers to travel to the specialist centre to obtain the prescription and supply of ataluren.

- The potential for long-term benefits to the NHS of research and innovation

The number of large randomised studies in DMD has been limited or non-existent and through the ataluren trial programme PTC Therapeutics have, and continue to, pioneer clinical trial research in this area. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials of treatments for this devastating and life-limiting condition.

Conclusion

Prior to ataluren, there has been no approved drug therapy for patients with nmDMD that addresses the underlying cause of their condition. Ataluren was considered by the EMA to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need and this resulted in the early approval of ataluren for the treatment of nmDMD ambulatory patients aged 5 years and older.

In a degenerative disease with progressive loss of muscle function, usually leading to death before the age of 30, stopping or slowing the progression of the disease is considered meaningful to patients and to healthcare professionals (Lynn, 2015). The ability to walk and maintain independence is of extraordinary importance to children with DMD and their carers. Ataluren has been shown to slow significantly the decline in 6MWD in boys with nmDMD and this in turn is expected to result in delayed wheelchair dependency, delayed time to respiratory complications and subsequently a delayed time to death.

DMD is a very rare disease and the subset of children with nmDMD represents a very small number of patients whose needs are great and for whom the benefit of treatment offers both hope and meaningful clinical improvement. DMD is a devastating condition that has considerable financial impact on the NHS and places a very high personal and financial burden on patients and their carers. These costs increase substantially as the condition progresses and therefore having ataluren available, which maintains walking ability, delays progression and alters the course of the condition over and above current best standard of care, would have minimal budget impact for the NHS and yet provide a very positive impact on quality of life for children with nmDMD and their families.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1.1 Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk	No variation.	
Intervention	Ataluren (Translarna™)	No variation.	
Comparator(s)	Established clinical management without ataluren	No variation.	
Outcomes	• Walking ability (ambulation) • Muscle function • Muscle strength • Ability to undertake activities of daily living • Cardiac function • Lung function • Time to wheelchair • Number of falls • Mortality • Adverse effects of treatment • Health-related quality of life.	No variation.	
Subgroups to be considered	None specified	No variation.	
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	No variation.	
Cost to the NHS and PSS, and Value for Money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the	No variation.	

	other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • Staffing and infrastructure requirements, including training and planning for expertise.	No variation.	
Special considerations, including issues related to equality	A positive review of ataluren by NICE will facilitate and ensure equity of access in a minority group of patients with a genetic disease and ensure that patients with rare diseases are not discriminated against, especially when there are no other treatments available that address the underlying cause of the disease.		

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Translarna™

Approved name: Ataluren

Therapeutic class: M09AX03 (WHO Temporary ATC code)

2.2 What is the principal mechanism of action of the technology?

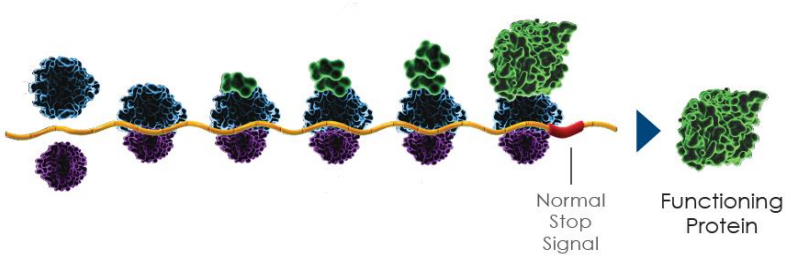
Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (Translarna SPC, 2014).

A nonsense mutation is one in which a single base variation in the patient's DNA results in a premature stop codon within the corresponding mRNA. This premature stop codon in the mRNA causes disease by terminating translation before a full-length protein is generated (Translarna SPC, 2014).

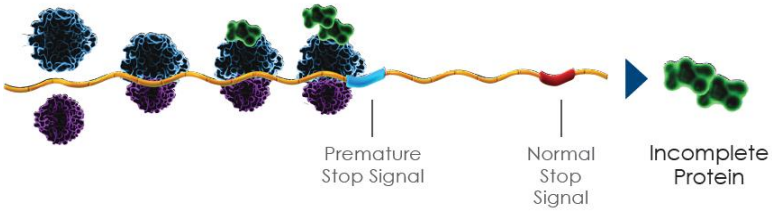
Ataluren belongs to a new class of drugs that target the underlying cause of nmDMD and is the first treatment to be licensed for use specifically in nmDMD. Ataluren allows the ribosomes to read through the premature stop codon, whilst respecting the normal stop codon, to restore the synthesis of full-length functional dystrophin protein (Figure A2.1, Translarna SPC, 2014). Ataluren thus treats the underlying cause of nmDMD, i.e. a lack of functional dystrophin.

Figure A2.1. Translation of mRNA into protein: comparison of normal translation (A), premature termination (B), and treatment with ataluren (C)

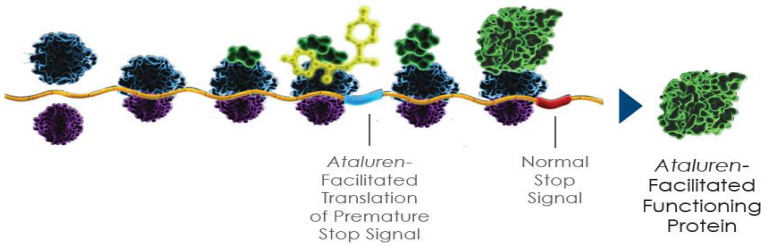
(A) Complete functioning protein



(B) Incomplete protein



(C) Ataluren-facilitated functioning protein



2.3 Please complete the table below.

Table A2.1 Dosing Information of technology being evaluated

Pharmaceutical formulation	Granules for oral suspension (125 mg, 250 mg, 1000 mg sachets)
Method of administration	Oral
Doses	The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).
Dosing frequency	Three times a day (morning, midday, and evening). Recommended dosing intervals are 6 hours between morning and midday doses, 6 hours between midday and evening doses, and 12 hours between the evening dose and the first dose on the next day.
Average length of a course of treatment	Not applicable. Long term chronic therapy

Anticipated average interval between courses of treatments	Not applicable. Long term chronic therapy
Anticipated number of repeat courses of treatments	Not applicable. Long term chronic therapy
Dose adjustments	No studies have been conducted with ataluren in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely. No dosing adjustment is needed for patients who are becoming non-ambulatory.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. Marketing authorisation was received 31st July, 2014.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Ataluren has been commercially available in the UK since 4th September, 2014.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Ataluren is approved in the European Union under the EMA centralised procedure. It is not licensed in any other country outside of the EU.

3.4 If the technology has been launched in the UK provide information on the use in England.

Ataluren has been available in the UK since 4th September, 2014. To date there have been no sales of ataluren as guidance on its use has not yet been issued by NHS England.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A summary of the ongoing ataluren studies is shown in Table A4.1. Although Study 020e is not expected to report until 2017, it has been included for completeness.

Table A4.1. Ongoing ataluren studies in nmDMD

Study Name /Primary study reference	Study design	Population	Intervention/ comparator	Status
PTC124-GD-016-DMD (clinicaltrials.gov)	Open-label Phase 3 safety trial	Ambulatory and non-ambulatory patients who originally participated in Studies 007, 007e, 004, 004e or 008 (USA). Estimated n=110	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration.	Ongoing
PTC124-GD-019-DMD (clinicaltrials.gov)	Open-label Phase 3 safety trial	Ambulatory and non-ambulatory patients who originally participated in Studies 007 and 007e (Europe, Israel, Australia, or Canada). Estimated n=96	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration.	Ongoing
PTC124-GD-020-DMD/ Study 020 (clinicaltrials.gov)	Phase 3, multicentre, randomised, double-blind, placebo-controlled efficacy and safety study	Male patients 7 to 16 years of age with nonsense-mutation dystrophinopathy on systemic corticosteroids for a minimum of 6 months immediately prior to start of study treatment (USA, Canada, Europe, Australia, South America, Korea) Estimated n=220	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for 48 weeks Placebo	Ongoing - estimated primary completion date October 2015
PTC124-GD-020e-DMD (clinicaltrials.gov)	Phase 3, open label extension study	The study will enrol~ 220 boys with nonsense mutation dystrophinopathy who participated in Study 020	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg)for approximately 96 weeks	Ongoing

A registry study (PTC124-GD-025o-DMD) is being performed as a post-approval safety study, per the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA), to gather data on ataluren safety, effectiveness, and prescription patterns in routine clinical practice. This study has just started recruiting patients but no data will be available to inform this submission.

There are no publications anticipated for ataluren in nmDMD during the period of the NICE HST appraisal. PTC124-GD-020-DMD/ Study 020 is expected to report results late 2015/early 2016.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

NHS England is currently developing a clinical commissioning policy for ataluren. This process has been ongoing for approximately one year. On 24 March 2015 NHS England launched a 30-day public consultation (until 23 April 2015) on a proposed number of new products for specialised services, (including service specifications and clinical commissioning policies) including ataluren. There has been extensive engagement on these national specifications and policies and they have been developed with the support and input of lead clinicians and patient and public representatives. NHS England stated that this approach helped ensure that the views of key stakeholders have informed and influenced the development of the policies and specifications so far (NHSE, 2015).

The results of this consultation are awaited but it is understood that the feedback from the consultation will be discussed at the Clinical Priorities Advisory Group (CPAG) meeting on 16th and 17th June and that a final decision will be ratified on or around June 30th.

Scottish Medicines Consortium (SMC) – Ataluren has not been reviewed by the SMC to date.

All Wales Medicines Strategy Group (AWMSG) – Ataluren has not been reviewed by the AWMSG to date.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

It is inequitable that patients with genetic diseases and no lifestyle choice should be disadvantaged by denying access to treatments that can address the underlying cause of their disease in a targeted way and as such delay the accumulation of disability associated with this progressive condition.

Patients with DMD in the UK have significantly greater material deprivation at diagnosis than the average of the population (Bushby, 2001). Patients from deprived backgrounds have less access to health care than people from more affluent areas, and diagnosis of DMD is often delayed. Children with DMD have a lifelong need for the highest quality of care, and the relatively high levels of deprivation associated with the disease may restrict availability of the sustained, high quality, specialised support needed.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Rare diseases have a considerable emotional impact on patients and caregivers, particularly for those where the hope of treatment is minimal (Genetic Alliance, 2013). For those rare disease patients where treatment options are limited, overall they worry more, feel more depressed, interact less, and feel more isolated from family and friends compared to patients with rare diseases for which there are available treatments (Genetic Alliance, 2013).

DMD is a progressive condition that leads to severe disability and wheelchair dependence. This is further compounded by challenges in wheelchair access which severely restricts the mobility of affected children and young adults.

A positive review of ataluren by NICE will facilitate and ensure equity of access in a minority group (approximately 65) of patients with a genetic disease and ensure that patients with rare diseases are not discriminated against, especially when there are no other treatments available that address the underlying cause of the disease.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Duchenne muscular dystrophy (DMD) is a severe, progressive and rare genetic childhood muscle wasting disease characterised by a rapid decline in physical functioning with subsequent respiratory and cardiac failure, leading to death in early adulthood (usually before the age of 30). DMD is an X- linked recessive disorder and therefore predominantly, though not exclusively, affects males.

Aetiology

DMD is caused by mutations in the gene encoding dystrophin, a structural protein that stabilises muscle cell membranes. Over 1000 mutations on the dystrophin gene have been identified in dystrophinopathies. In most cases, those mutations involve a deleted part in the gene, a duplicated part of the gene, or a change of a small number of nucleotides. In approximately 10% of cases, the mutation of the dystrophin gene is a nonsense mutation (Bladen, 2015). A nonsense mutation is a point mutation in a sequence of DNA that results in a premature stop codon in the transcribed messenger ribonucleic acid (mRNA). This premature stop codon halts the ribosome and stops translation, resulting in a truncated protein that is too short and often too unstable to function properly.

Dystrophin is located on the cytoplasmic surface of skeletal muscle cell membranes and plays a central role in protecting the muscles before exercise. Dystrophin works like a "shock absorber" by linking the intracellular matrix of the membrane walls. Dystrophin absorbs the mechanical load that occurs during muscle contraction and ensures that the intracellular matrix remains located accordingly; it provides mechanical reinforcement to the sarcolemma and thereby protects it from the membrane stresses developed during muscle contraction (Petrof, 1993).

DMD mutation leads to the complete absence of functional cytoskeletal dystrophin in skeletal, smooth and cardiac muscle fibres, which gradually causes weakness and atrophy of muscles. DMD results from the constant cycle of degeneration and regeneration in the patient's muscles. During this process, more degeneration than regeneration occurs and much of the muscle is progressively replaced by fat and fibrous tissues, which are not able to compensate for the loss of muscle (Kole 2012).

The most devastating and obvious effect of DMD is on the skeletal musculature with resulting loss of strength and function. The progression of muscle degeneration in DMD is well documented both in terms of pathophysiology and pathokinesiology (with a proximal-to-distal progression of muscle weakness, leading to progressive loss in activities of elevation against gravity with eventual loss of ambulation) (Bushby, 2010b). DMD causes long-term disability: children with DMD lose the ability to walk in childhood followed by progressive loss of upper body and truncal strength. DMD is life limiting because of its effects on the heart and the respiratory muscles.

Natural History

Dystrophin production is affected from birth and symptoms of DMD appear by around the age of 3 years although are sometimes present earlier than this and even in infancy, especially when associated with substantial learning difficulty (range 8 to 72 months) (van Ruiten, 2014). The earliest and most obvious symptom is motor dysfunction, but as the disease progresses major vital organs such as the gastrointestinal tract and heart are affected in turn as well as respiratory muscles leading to breathing difficulties and ultimately the need for ventilation. In DMD, the type of genetic mutation (e.g. deletion, duplication, nonsense) does not appear to correlate with clinical phenotype (Magri 2011).

Five key stages ranging from pre-symptomatic to late non-ambulatory are commonly used to describe disease progression and define appropriate care (Bushby, 2010b). Individual children may go through each of these stages at different rates.

1) In the initial stages prior to diagnosis, children usually have subtle symptoms of delayed walking or delayed speech compared to their peers. Symptoms are present but are usually unrecognised. The mean age of first reported symptoms of DMD has been reported as 32.5 months (2.7 years) with a range of 8–72 months, whilst mean age at genetic diagnosis is 51.7 months (4.3 years) with a range of 10–91 months (van Ruiten, 2014).

2) In the early ambulatory stage, signs typically leading to suspicion and diagnosis of DMD are more noticeable; the following four classical DMD motor signs are major indicators:

- Gowers' manoeuvre: patients need to support themselves with hands on thighs when they get up from the floor.
- Gait characterised by waddling-type walking.
- Toe-walking.
- Typical way of climbing stairs: patients bring the second foot up to join the first rather than going foot over foot.

In some cases, patients also show specific difficulties with learning and behaviour; however, these symptoms appear more often at more advanced disease stages.

3) In the late ambulatory stage, early symptoms get worse and walking becomes increasingly difficult. The children experience more problems with climbing stairs and getting up from the floor and progressively lose walking ability. By the age of 8 years, most boys have difficulty arising from the floor and ascending stairs, and they often fall while walking (McDonald, 2010a). Recent natural history data show that at a certain stage children enter a more rapid decline phase where over a year they experience a substantial decline in walking ability (McDonald, 2013b). Discussed further in Section 7.2 and 9.9.

4) Children lose the ability to walk independently and become permanently wheelchair dependent (early stage of non-ambulation). Wheelchair dependency typically occurs around 12 to 15 years of age in boys on steroids (median 12 years and 14.5 years when treated with intermittent and long-term daily corticosteroids respectively), or between 8 to 12 years in steroid naïve boys (Biggar, 2006; Moxley, 2010; Goemans, 2013; Ricotti 2013). In steroid naïve boys, as the disease progresses and posture worsens, scoliosis develops due to weakening of their back muscles combined with wheelchair immobility. However with steroid treatment posture and arm strength is initially maintained and they are able to wheel the chair themselves for a short time. At this stage patients can start experiencing respiratory symptoms such as poor cough and chest infections and are at increased risk of heart deterioration.

5) In the late stage of non-ambulation, which is the most severe, upper-limb function is decreased and maintenance of good posture is increasingly difficult, and

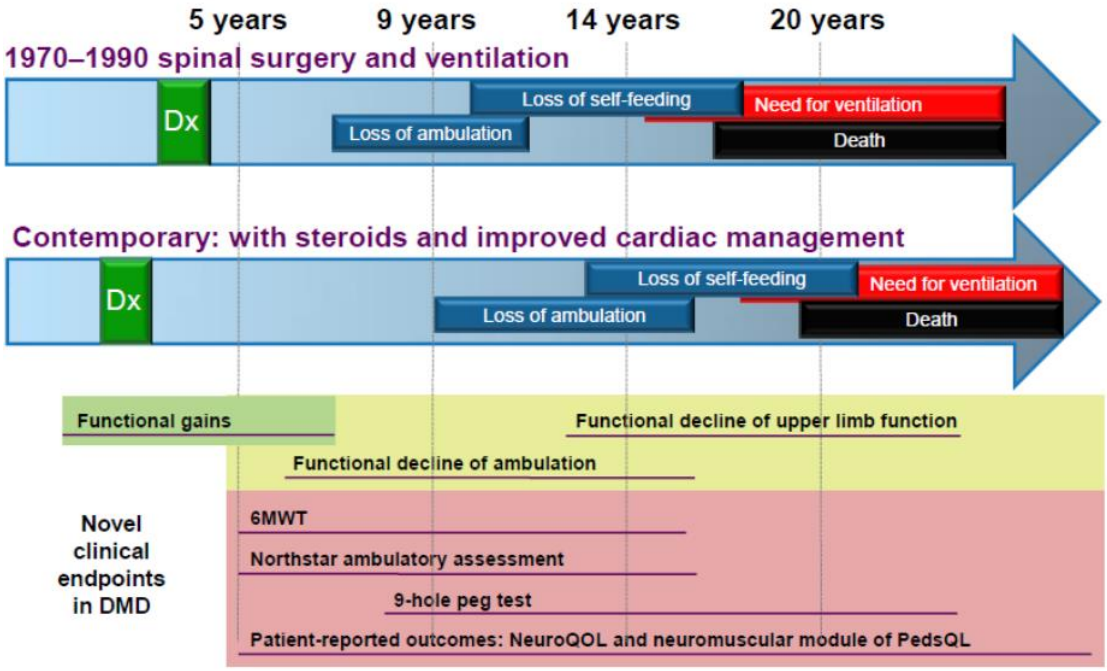
complications are more likely. The risk for respiratory and heart deterioration are high. Usually, patients with DMD die from respiratory or cardiac failure in their late teens or early adulthood despite improvements in care in recent years.

In their late teens, patients with DMD require ventilation support and as respiratory function initially declines ventilation support is provided during the day, usually with a mouth piece. Dependence for permanent ventilation, which may require tracheostomy, usually occurs before 23 years of age (Ishikawa, 2011; Kieny, 2013). In a recent study, mechanical ventilation was seen to be used by 69% of UK adult DMD patients (aged over 18 years), with 47.6 % using intermittent non-invasive ventilation, 16.7 % using continuous non-invasive ventilation, and 4.8 % continuously ventilated via a tracheostomy (Rodger, 2015). Cardiac complications are also seen, especially with disease progression: 52.4% of UK adults with DMD in the study by Rodger et al reported a diagnosis of cardiomyopathy (Rodger, 2015).

Boys with DMD have been found to have decreased bone density and increased risk of fractures. Lower extremity post-fracture recovery often includes prolonged periods of non/partial weight bearing with increased amounts of time spent sitting in wheelchairs, increasing the risk of contractures and disuse weakness. Accidental falling is the most common cause of limb fractures in boys with DMD, and 35 to 40% of lower-limb fractures result in permanent loss of ambulation (McDonald, 2002; Vestergaard, 2001).

The natural history of DMD following the introduction of spinal surgery, ventilation and later steroid use, is shown in Figure B6.1.

Figure B6.1: Changing the natural history of DMD and the application of novel clinical endpoints in 2012



Source: (McDonald, 2013c)

While the muscle involvement and subsequent loss of function described above is well characterised, disease progression and rate of decline can differ greatly from one patient to another. This clinical heterogeneity has to be taken into consideration in the design and interpretation of therapeutic trials. With more data emerging from natural history studies and the placebo arms from DMD treatment studies, many of the causes for variability in outcomes are becoming clearer. The age and stage of disease, steroid use, implementation of standards of care and variable phenotypic expression of dystrophin are factors that contribute to the heterogeneity in disease progression (Bushby 2010b; EMA, 2015). Even where children receive comparable treatment (with steroids) and standard of care, a marked variability has been observed in the rate of progression (Goemans, 2013).

In a degenerative disease with progressive loss of function, eventually leading to death, slowing or stopping the progression of the disease is considered meaningful to patients as this would preserve their physical abilities and delay the next loss of function (Lynn, 2015). The ability to walk and maintain independence is of extraordinary importance to both children with DMD and their carers. Ataluren is the first therapy addressing the underlying cause of nmDMD that has been shown to offer clinically meaningful and statistically significant changes in parameters that

assess ambulation and activities of daily living (Bushby, 2014) thereby changing the course of this devastating condition.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

A 2009 population study of patients with genetic muscle diseases in Northern England estimated that DMD affects 8.29 in 100 000 males (Norwood 2009; Parsons 2002). Based on the size of England's population in 2012 (53 865 817) (Office for National Statistics 2014), it is therefore estimated that 2200 males in England have DMD. [redacted].

Indication	Prevalence	Incidence
DMD	2,200 (Norwood, 2009; Parsons, 2002)	1/5135 male births (Moat, 2013)
nmDMD	10% of DMD (Bladen, 2015)	7 new per annum
Aged 5 and above and ambulatory	[redacted]	
nmDMD aged 5 and over and ambulatory	[redacted]	

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

In the last 10 years survival rates in patients with DMD have improved due to a more comprehensive therapeutic approach. Despite this most patients with DMD die from heart or lung failure in adolescence or early adulthood, and patients rarely survive beyond their third decade (Passamano, 2012). Based on data from the Swedish Cause of Death Registry, the mean age of death in Swedish patients with DMD between 2000 and 2010 was estimated to be 25 years old (range 10 years to 46 years), and death was most commonly caused by cardiac (40%) or respiratory (35%) failure (Stromberg 2012). This compares closely with the mean age of death recorded for UK patients with DMD (25.3 years old) who have received ventilator support (Eagle, 2002). In an Italian case review of 835 DMD patients, the overall mean age for cardiac deaths was 19.6 years, with an increase in survival seen over the past 15 years. The overall mean age for respiratory deaths was 17.7 years in patients without ventilator support, which increased to 27.9 years in patients

benefitting from mechanical ventilation (Passamano, 2012). Similarly, in a study of 119 DMD patients in France the mean age of death was 21.8 years for patients without ventilatory support and 28.3 years for ventilated patients (Kieny, 2013). In a study of 67 DMD patients born in Germany between 1970 and 1980 median survival was 24.0 years (95 % CI 21.3-26.7 years). Again, ventilation significantly prolonged survival: median survival of non-ventilated patients was 19.0 years (95% CI 17.7-20.3 years) compared to 27.0 years for those who were ventilated (95% CI 20.2-33.8 years) (Rall, 2012).

Age of loss at ambulation is associated with time to respiratory failure and age at death in patients with DMD (Rall, 2012; van Essen 1997; Humbertclaude, 2012). Patients who lose walking ability before 10 years have a median survival of 17.3 years (95% CI 16.7–18.0 years) vs. the 20.1 years attributed to those who become wheelchair-bound at or after 10 years (95%CI 19.4–20.9 years)(van Essen 1997). The probability of death due to respiratory failure has also been shown to be significantly higher in patients that lose ambulation at an earlier age ($p<0.03$) (Humbertclaude, 2012).

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

When children diagnosed with DMD are young (~3-14 years) and still ambulant, they cannot keep up with their peers, have problems walking, hopping, running, climbing stairs and fall frequently. Falls can lead to injuries (including fractures). Boys become completely wheelchair dependent between 8 and 15 years of age (Bushby, 2010b; Goemans, 2013). Once ambulation or some other motor functional capacity is lost in an individual with DMD, it cannot be regained. Death can occur without warning, at any moment, even (rarely) in younger boys (<12 years of age) (EMA, 2015). In non-ambulatory boys and young men, there is gradual loss of upper limb, trunk and neck functions, so that grooming, toileting, bathing, dressing, sitting unsupported and

eating become impaired or impossible to perform by oneself - severely affecting the quality of life of patients, their caregivers and families (EMA, 2015).

Nowadays, due to assisted ventilation, adults with DMD typically live into their late twenties. By that time they have hardly any muscle function left with the exception of the facial muscles, which are relatively spared until a late stage of the disease. Muscles needed for chewing and swallowing are also affected, leading to problems with nutrition. In contrast to weight gain problems in younger DMD patients, malnutrition is often seen in older DMD patients.

Boys with DMD consistently report significantly lower quality of life (QoL) than their healthy peers (Uzark, 2012; Bendixen, 2012). In a study that assessed QoL in 117 boys with DMD using the PedsQL mean scores for boys with DMD were significantly lower than those for healthy children for physical and psychosocial scores ($p<0.001$), including emotional, social, and school functioning, by both parent-proxy and child self-report and across all age groups (Uzark, 2012). By self-report, 57% of all children 8 to 18 years of age had Psychosocial Health Summary scores below 66.03, the cut-off point for significantly impaired QoL in the general paediatric population. With respect to physical functioning or symptoms, the most frequently reported problems were not being able to run (68%) or walk more than one block (57%). Anger was the most frequently reported emotional problem reported by the boys (19%) and perceived by their parents (15%). In the teenage boys, 14% also reported frequently worrying about what was going to happen to them. One in 5 boys (19%) frequently worried about their family and about being treated differently from their peers (20%). With respect to Social Functioning, the most common problem was not being able to do things others their age could do (40%). While boys reported frequent problems with paying attention (13%), the most common school problem was missing school to go to the doctor or hospital (20%) (Uzark, 2012).

Quality of life deteriorates as the disease progresses and physical capacity decreases. With advancing age, boys report decreased physical functioning and daily activities (Uzark, 2012; Simon, 2011; McDonald, 2010c). Patients with more severe disease requiring mobility aids or having greater impairment of daily activities do not necessarily perceive worse psychosocial QoL although, not surprisingly, the use of wheelchairs and ventilators has been shown to be significantly associated with lower QoL related to physical functioning (Uzark, 2012; Baiardini, 2011).

A recent study has been conducted with patients with DMD from Germany, Italy, United Kingdom, and United States who were identified through Translational Research in Europe–Assessment & Treatment of Neuromuscular Diseases registries (Landfeldt, 2014). They were invited to complete a questionnaire online together with a caregiver. 770 patient-caregiver pairs completed all sections of the questionnaire (Table B7.1). In this study, patient quality-of-life data were collected using the Health Utilities Index (HUI). In all countries assessed the mean HUI-derived utility decreased through the 4 stages (early ambulatory, late-ambulatory, early non-ambulatory and late non-ambulatory) (Landfeldt, 2014). Similar results were seen in a study that included 363 patient/parent pairs in Germany, with the most prominent loss of QoL following loss of ambulation (Schreiber-Katz, 2014).

Many of the interventions used to manage DMD are associated with new complications, and quality of life often suffers. For instance, adverse events known to be associated with chronic corticosteroid usage include excessive weight gain, growth inhibition, risk of diabetes, behavioural abnormalities, Cushingoid features, severe short stature, delayed puberty and cataracts (Bushby, 2010b). Of particular concern for the DMD community is the issue of weight gain, since DMD is a progressively debilitating disease and weight gain can compound the physical limitations of a patient with impaired muscle function (EMA, 2015). Maintaining the ability to walk and maintain a higher level of physical function should, therefore, help with weight control (DH, 2015).

The burden on parents of boys with DMD is substantial, although parents value giving care as being important and rewarding (Pangalila, 2012). Parents of children with DMD report a high burden of care from an early age, not only compared to healthy children but also compared to children with other chronic disorders. Only parents of children with multiple complex handicaps score higher (EMA, 2015). In addition having to help patients physically with dressing, feeding and lifting, some families have a hard time due to the behavioural issues often seen in DMD patients. It is not unusual that parents of DMD boys and young men have to wake up 6-10 times per night to help to adjust their sons' position in bed, help with ventilation and/or coughing (EMA, 2015). Help from outside the family is often not available. In an Australian study assessing the parent-reported health status of boys with DMD, parents experienced greatest emotional impact of their child's DMD around the time of loss of ambulation (Bray, 2011). The subjective burden reported by parents has

also been shown to be associated with support received, tracheotomy, active coping by the patient and anxiety in patients and parents (Pangalila, 2012).

In the UK, 98% (n=188) of caregivers were the parent and 49% (n=93) of caregivers had reduced their working hours or stopped working completely because of their child's or relative's DMD (Landfeldt, 2014). A recent study which examined the health care burden of DMD in Germany showed that, in addition to a loss of working capacity in DMD parents, more than half of parents themselves developed medical problems due to the burden of their son's disease, leading to further consumption of medical treatment due to parents' physical or mental problems. Overall, physical and mental problems of parents and caregivers increased with the severity of their son's impairment (Schreiber-Katz, 2014).

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Treatment with ataluren allows boys to maintain their ability to walk and carry out everyday tasks such as climbing and descending stairs, thereby improving their independence and their ability to participate in normal activities, attend mainstream school, keep up with their peers, play with friends and keep active.

Boys with DMD progressively lose the ability to walk and most become wheelchair dependent by the age of 12 years to 14 years of age (Bushby, 2010b; Goemans, 2013; Ricotti, 2013). The decline in the 6MWD occurs more rapidly in boys with a lower baseline 6WMD: in particular a threshold of 350 metres seems to be a critical and is associated with a higher rate of decline in the 6MWD (McDonald, 2013b; Pane, 2014). A 330 metre 6MWD or lower is associated with a higher risk of complete loss of ambulation over the following 2 years (Mazzone, 2013). Ataluren has been shown to change the course of disease progression as measured by a lower rate of decline in the 6MWD compared to placebo. Delaying ambulatory decline provides the direct clinical benefit of affording boys with nmDMD a longer period of

self-sufficiency. By slowing ambulatory decline and delaying the point at which more rapid decline occurs, ataluren may also delay complete loss of ambulation and wheelchair reliance. As well as allowing greater mobility and independence this is of further significance since the age at loss of ambulation predicts the age at which subsequent loss of upper limb function occurs and the age at which critical pulmonary milestones are reached (Henricson, 2013a). In addition, maintenance of ambulatory capacity may delay onset or severity of other complications such as scoliosis and the need for major surgery (Yilmaz, 2004; Kinali, 2007).

In a degenerative disease with progressive loss of functions, eventually leading to death, stopping or slowing the progression of the disease is considered meaningful to patients as this would preserve their abilities and delay the next loss of function. Treating children early when they have the greatest amount of muscle to preserve is likely to delay muscle wasting and preserve function for longer. The following quote illustrates the urgency felt by parents for an effective treatment (Peay, 2014):

> "Having Duchenne muscular dystrophy, it's all about the time. Once they are in a chair then everything goes downhill quickly for them far as their health...I just started researching and wanted to be in [the trial]…"

In a study assessing expectations and experiences of investigators and parents involved in the ataluren Phase 2b trial (Study 007), all parents reported some degree of direct benefit for their boys (who were in the ataluren treatment arm), ranging from obvious improvements to subtle changes. These benefits included improved strength, endurance, and cognitive performance. A few parents described being unsure about whether there was benefit until they noted declines following the sudden end of access to the drug (Peay, 2014):

> "It felt like we had seen such tremendous improvement, we had no doubt in our mind that—that he was benefiting from it."

> "I felt like he was working with me and he was stronger. He also felt that way... And I said, well let's be cautious with this subjective type of measure.... about two weeks after he was off the medication he felt he got back to the stage before [the trial started]. So that gives a lot of confidence that the medication does have benefit. And we got the parameters like CK dropping and all these things."

By delaying loss of ambulation, use of ataluren is expected to enable carers and families of boys with nmDMD to continue to work for longer before having to reduce their working hours or give up work entirely to look after their child.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

Standards of Care Guidelines that are NICE accredited (NICE, 2011):

NHS Evidence (provided by NICE) accredited the process used by the Duchenne Muscular Dystrophy Care Considerations Working Group to produce the 'Diagnosis and management of Duchenne muscular dystrophy' guideline in September 2011. (NICE, 2011) The Duchenne Muscular Dystrophy Care Considerations Working Group is an international collaboration of clinicians, researchers and patient groups that was convened by the US Centres for Disease Control and Prevention to develop a guideline covering the diagnosis and management of Duchenne muscular dystrophy. The guideline was published in two parts in Lancet Neurology in 2010.

- Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management (Bushby, 2010a).
- Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care (Bushby, 2010b).

These guidelines provide a framework for recognising the multisystem primary manifestations and secondary complications of DMD and for providing coordinated multidisciplinary care. They outline diagnosis and management of DMD including a detailed discussion on pharmacological intervention for muscle strength and function (corticosteroids) and psychosocial management (part 1). A comprehensive set of DMD multidisciplinary care recommendations for management of rehabilitation, orthopaedic, respiratory, cardiovascular, gastroenterology/nutrition, and pain issues are also provided (part 2). It should be noted that the guidelines were produced before any disease modifying therapy was authorised.

NHS England. Service specification: Paediatric Neurosciences – Neurology (E09/S/b)

This service specification document outlines the aims of paediatric neurology services, a description of services provided and the patient care pathway as well as key outcomes expected for patients.

Aims and objectives of the service

The aim of the service is to ensure that children and young people with serious neurological conditions achieve the best quality of life, through the provision of excellent diagnosis, investigation, intervention, management and information. The NICE Clinical Guidelines note that optimal management improves health outcomes and can also help to minimise other, often detrimental, impacts on social, educational and employment activity. The objectives of the service are:

- To provide accurate diagnosis and cost-effective management including rehabilitation, of children with neurological disorders
- Expert management of life-threatening and potentially treatable disorders
- Avoidance of severe disability by preventing delay in appropriate treatment
- Avoidance of further affected cases by the recognition of a genetic disorder and provision of appropriate counselling
- Effective provision for educational needs by specialist evaluation (e.g. developmental language disorder)
- Avoidance of unnecessary anxiety, hospitalisation, investigation and treatment and provision of appropriate advice and reassurance

Recommended standards in the service specification are those by Bushby (2014) and accredited by NICE as described above.

The service specification states that paediatric neurology services are involved in diagnosis and in collaboration with disability services for long-term management of neuromuscular disorders. Management of complications requires collaboration with spinal services, respiratory services (including non-invasive ventilation) and cardiac

services. End of life care is an important aspect of services for some of these disorders.

NHS England. Manual for prescribed specialised services, Chapter 48: Diagnostic service for rare neuromuscular disorders (adults and children)

This document outlines the commission arrangements for rare neuromuscular disorder diagnostic services.

Department of Health. NHS Outcomes Framework 2014-2015, Nov 2013

The NHS Outcomes Framework are grouped around five domains, which set out the high-level national outcomes that the NHS should be aiming to improve (Department of Health, 2014). For each domain, there is a small number of overarching indicators followed by a number of improvement areas. These improvement areas include both sub-indicators (for outcomes already covered by the overarching indicators but meriting independent emphasis), and complementary indicators (extending the coverage of the domain). The domains focus on improving health and reducing health inequalities, namely by:

Domain 1	Preventing people from dying prematurely;
Domain 2	Enhancing quality of life for people with long-term conditions;
Domain 3	Helping people to recover from episodes of ill health or following injury;
Domain 4	Ensuring that people have a positive experience of care; and
Domain 5	Treating and caring for people in a safe environment and protecting them from avoidable harm.

Ataluren would support the domain of enhancing the quality of life for people with DMD and their carers by enabling them to remain ambulatory for longer, delay the time to when they become wheelchair bound and enable them to participate more fully in society. Generally with the introduction of a new technology, this offers hope and drives innovation in general, thus enabling people with DM and the carers to have a more positive experience of care. It is also anticipated that the introduction of ataluren would in the long term prevent people with DMD dying prematurely as a result of delaying the time in becoming wheelchair bound and its associated complications.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

As the first treatment licensed to treat the underlying cause of DMD, ataluren will be considered as a treatment option for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation. It will be added to existing standard of care in the UK which aims to alleviate disease symptoms as summarised below:

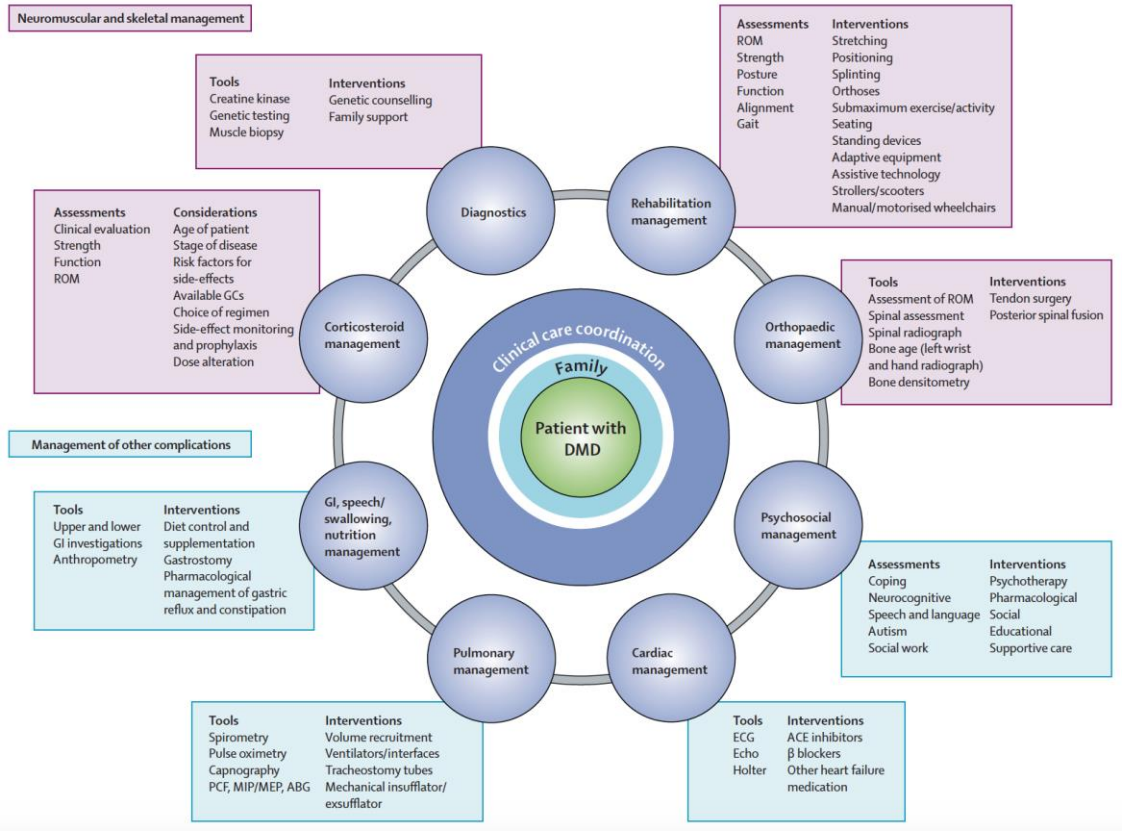
- Early childhood: treatment with corticosteroids; cardiac and respiratory monitoring; occasional inpatient orthopaedic intervention
- Later childhood and teenage years: inpatient spinal surgery and rehabilitation (although this is less common for patients on steroids than steroid-naïve patients); increased need for inpatient orthopaedic intervention; continued cardiac and respiratory intervention; inpatient episodes for treatment of respiratory complications

In addition, dietetic advice (and in some cases gastric feeding), prevention and treatment of bone fragility, and management of complications of long-term corticosteroid therapy may be required, as well as psychosocial support (Bushby 2010b). Genetic counselling and testing with antenatal diagnosis is offered to all families with affected children.

Coordination of clinical care is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort. A coordinated clinical care role can be provided by a wide range of health-care professionals depending on local services, including (but not limited to) neurologists or paediatric neurologists/neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians, and primary-care physicians. It is crucial that the person responsible for the coordination of clinical care is aware of the available assessments, tools, and interventions to proactively manage all potential issues involving DMD (Bushby, 2010b).

The multidisciplinary approach to caring for patients with DMD and the range of expertise required are key features of this process. An overview of the elements that have to be considered in the care of DMD patients is shown in Figure B8.1 below.

Figure B8.1. Interdisciplinary management of DMD

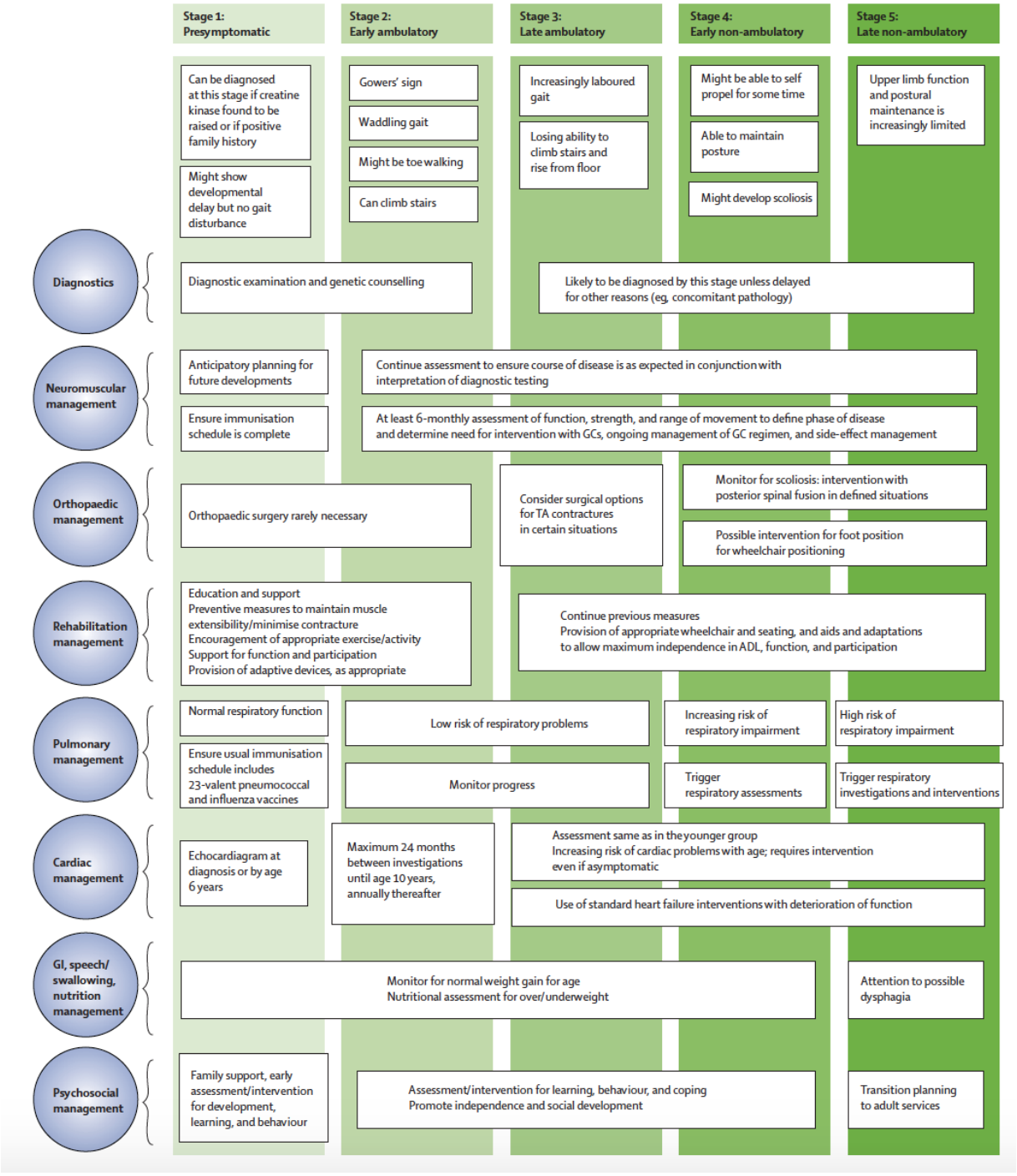


ABG=arterial blood gas. ACE=angiotensin converting enzyme. DMD=Duchenne muscular dystrophy. Echo=echocardiogram. ECG=electrocardiogram. GC=glucocorticoids. GI=gastrointestinal. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. PCF=peak cough flow. ROM=range of motion.

Source: (Bushby, 2010b)

Input from different specialties and the emphasis of interventions will change as the disease progresses (Figure B8.2).

Figure B8.2: Stages of disease and care considerations



ADL=activities of daily living. GCs=glucocorticoids. GI=gastrointestinal. TA=tendo-Achilles
Source: (Bushby, 2010b)

The service specification for Paediatric Neurosciences – Neurology (E09/S/b) by NHS England provides a description of services provided and the patient care pathway as well as key outcomes expected for patients which encapsulates the need for interdisciplinary management and achieve the best quality of life, through the

provision of excellent diagnosis, investigation, intervention, management and information and ultimately outcomes for patients.

As DMD is associated with a high burden of disability for patients, and given the relentless progression of the condition, one of the most important treatment objectives according to patients, caregivers and clinicians is to slow the progression of the disease.

> "*People say it's [Duchenne muscular dystrophy] a slow declining thing….What is slow? To me its fast if [you] lose between 5-7%...that's a lot. If you can't get it back you've just messed with a child's life. Even if it's just 5%, that's 5% of what he has*"
> Father of boy with DMD

Corticosteroids are the only medication currently available that slow the decline in muscle strength and function and their use in patients with DMD has changed the rate of progression of disease manifestations (Manzur, 2008; Moxley, 2010). Despite the benefits of corticosteroids these must be balanced with a side effect profile that presents significant challenges. The adverse effects of steroid use include excessive weight gain, increased risk of bone fracture, behavioural abnormalities, hypertension, cushingoid appearance and excessive hair growth; close management of steroid-related side-effects is crucial once a child has started chronic steroid therapy (Bushby, 2010b). Due to the side effect profile, not all boys are able to tolerate steroids and thus have no effective treatment and therefore a poorer prognosis. have Ataluren at a dose of 40mg/kg body weight per day has shown an effect over and above the use of corticosteroids and is therefore expected to have a meaningful incremental benefit over the use of corticosteroids alone. In addition, following introduction of ataluren, it may be that the use of steroids can be delayed, which would reduce the risks associated with their use (Personal Communication).

Ataluren will be considered as a treatment option for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation. It will be added to existing standard treatment, including use of corticosteroids. Treatment will continue unless the patient meets the stopping criteria described in section 10.1.16.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Prior to ataluren, there have been no approved drug therapies, and otherwise very limited supportive care options for patients with nmDMD. Supportive care options used in clinical practice do not address the underlying cause of the disease.

Although Standards of Care are available, the majority of individuals with DMD do not receive care accordingly, for example although there is a consensus that individuals with DMD should be seen by a multidisciplinary team, this often does not happen. Individuals with DMD often see a wide range of healthcare professionals such as paediatricians, neurologists, neuromuscular specialists, cardiologists, pulmonologists, psychologists, rehabilitation doctors, physiotherapists, orthopaedic surgeons and nutrition specialists. Without a multidisciplinary team in place, DMD patients and parents spend a lot of time at and travelling to and from hospital visits, which keeps them away from school, work, social activities, sports and family life (EMA, 2015).

Steroids are not specifically indicated for use in DMD and there is uncertainty around the appropriate time to initiate, whether to continue their use in non-ambulatory boys, and the use of intermittent of daily dosing (Bushby, 2010b). A widely used regimen in the UK is intermittent dosing, 10 days on/10 days off, which allows drug-free periods, possibly without losing overall benefit. Decisions on dosing regimens used require careful consideration based on the risk benefit profile: whilst daily dosing may be more effective at halting decline in boys with DMD, unmanageable and/or intolerable side-effects may mean intermittent dosing is preferable (Ricotti, 2013). Long-term use of corticosteroids requires much commitment on the part of the family. Essential issues for discussions should include potential side-effects, the obligation to closely monitor and manage any adverse issues that might arise, and the requirement to have the child followed closely by their primary-care physician and specialty health-care team (Bushby, 2010b).

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Ataluren will be considered as a treatment option for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation. It will be added to

existing standard treatment, including use of corticosteroids. Treatment will continue unless the patient meets the stopping criteria described in Section 10.1.16.

Definitions of ambulatory and non-ambulatory status vary and currently there is no clinical consensus. The following definition is used in the draft NHS England Commissioning Policy and is considered to be appropriate: an ambulatory patient is defined as one who can take any steps unaided. Non-ambulatory is defined as patients who have continuous indoor and outdoor wheelchair use (Bello 2014; Pettygrove 2013).

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Ataluren offers a step change in the treatment of nmDMD as there have been no other/previous disease modifying licensed therapies that have been rigorously tested and approved and ataluren therefore represents a brand new paradigm in DMD management.

DMD is a severe, progressive and rare genetic muscle wasting disease in which children suffer a loss of mobility from an early age and are therefore not able to experience a normal childhood. Wheelchair confinement in early adolescence is followed by respiratory failure and cardiac failure, ultimately leading to early death. DMD resulting from a nonsense mutation in the dystrophin gene is a severe ultra-rare disease. There is no current therapy for DMD that treats the underlying cause.

Ataluren is a first in class drug in development for the treatment of genetic disorders due to nonsense mutations and is the first specific approved therapy for DMD that addresses the underlying cause of the disease. Prior to regulatory approval of ataluren for the treatment of nmDMD, the only management options for this devastating disease were supportive in nature and did not address the underlying cause of the condition i.e. the loss of dystrophin. Without dystrophin, muscles progressively weaken and deteriorate, leading to complete loss of ambulation, cardiac and respiratory insufficiency, and death.

- The phase 2b study was the first large-scale, randomised, controlled trial performed in DMD using a new chemical entity targeting the underlying cause of DMD.

- As this was the first study for registration in DMD, there were no established primary or secondary endpoints from a regulatory perspective, and there was limited DMD natural history data available at the time the study was designed. Completion of this trial has provided a better understanding of the natural history of DMD using the 6MWD and has established the 6MWD as a validated primary endpoint in DMD clinical trials; in addition, the data from this trial has helped to identify the best secondary endpoints in DMD trials and lays the clinical trial groundwork for future therapies for this disease.

- The benefit of treatment with ataluren was seen across the disease spectrum. Although efficacy was most prominently shown in the sub-group of patients with more advanced disease, all categories of patients, including milder patients (>70% baseline %-predicted 6MWD), showed a favourable effect for ataluren compared to placebo over 48 weeks (Figure C9.10), indicating the ability of ataluren to change the course of disease independent of severity.

The EMA established that despite limitations in the robustness of the efficacy data presented, ataluren was considered to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need and this resulted in the early approval of ataluren for the treatment of nmDMD ambulatory patients aged 5 years and older. The EMA also acknowledged that whilst the effect was best measured in a sub-population of ambulatory patients in the decline phase of their disease, it was agreed that there should be no scientific reason, nor any safety imperatives, to withhold ataluren from nmDMD ambulatory patients aged 5 years or more who are at an earlier stage of disability progression.

As the first new drug to address the underlying cause of dystrophinopathy, ataluren represents an important advance in personalised, genetic-based treatment in line with Government and NHS strategy.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

The introduction of ataluren is not expected to result in any changes to the way services are delivered. There are currently 18 centres that specialise in the management of DMD in England and Wales.

- Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne
- Leeds General Infirmary
- Sheffield Children's Hospital NHS Trust
- Alder Hey, Liverpool
- Manchester Children's Hospital
- Preston Royal
- Nottingham University Hospital
- Heartlands, Birmingham
- John Radcliffe Hospitals, Oxford
- Southmead Hospital, Bristol
- Southampton General
- Addenbrookes, Cambridge
- The Robert & Agnes Hunt Orthopaedic Hospital, Oswestry
- London (Great Ormond Street Hospital)
- London (National Hospital for neurology & Neurosurgery)
- London (St Thomas's)
- University Hospital Wales, Cardiff
- Morriston Hospital, Swansea

It is possible that the introduction of a more highly specialised service could focus expertise and optimize services even further.

8.7 Describe any additional tests or investigations needed for selecting or patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests are required to identify patients eligible for treatment with ataluren. Genetic testing using the standard genetic tests currently commissioned by NHS England for dystrophin gene mutations is carried out during diagnosis. The first step to genetic diagnosis is to carry out a technique such as multiplex ligation-dependent probe amplification that detects deletions and duplications and covers all exons (Bushby, 2010b). In the UK this is carried out at regional genetic laboratories. If deletion/ duplication testing is negative, then further testing is carried out to look for point mutations or small deletions/insertions, including nonsense mutations. In the UK this is currently conducted at two centres (Guy's and St Thomas' in London and Yorkhill in Glasgow). However a review of the organisation of genetic testing is ongoing.

Minimal monitoring of patients is required. It is recommended that (Translarna SPC):

- Total cholesterol, LDL, HDL, and triglycerides are monitored on an annual basis in nmDMD patients receiving ataluren
- Resting systolic and diastolic blood pressure are monitored every 6 months in nmDMD patients receiving ataluren concomitantly with corticosteroids
- Serum creatinine, BUN (blood urea nitrogen), and cystatin C are monitored every 6 to 12 months in nmDMD patients receiving ataluren

In current practice, blood pressure monitoring and blood tests are carried out on an annual basis during routine visits, regardless of ataluren treatment. As such monitoring of ataluren is not expected to increase the burden of care. Cystatin C is recommended to be used to monitor renal function in DMD since creatinine as a marker of renal function has limited value because of reduced muscle mass.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure are needed. Ataluren is an oral therapy and administration does not require any particular supervision, therefore unlike many new technologies that are injected, initiation and ongoing treatment will not require patients to make hospital visits either as day cases or in-patients. In addition ataluren has no special storage requirements such as refrigerated storage.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Not applicable.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

Methodology

The objective of this systematic review was to evaluate the clinical effectiveness and safety of ataluren compared with best supportive care for the treatment of patients with DMD who are ambulatory and aged 5 years and above. For the purposes of this review, best supportive care includes treatment with corticosteroids, as well as pharmacological therapy for the management of associated cardiac, pulmonary, orthopaedic and gastrointestinal complications.

Literature search strategy

Systematic literature searches were undertaken on 17th July 2014 and were updated on 8th June 2015 to identify published evidence that addressed the research question. The databases and interfaces that were used are presented in Table C9.1.

Publications were restricted to English language but no limits were placed on date of publication. The complete search strategies for each database are presented in Appendix 17.1.

Table C9.1: List of databases searched for the clinical systematic review

Review type	Database	Interface
Clinical evaluations **(July 2014)**	Embase®	Embase.com
	MEDLINE®	
	MEDLINE® In-Process	Pubmed.com
	Cochrane central register of Controlled trials (CENTRAL)	Cochrane library
Clinical evaluations **(June 2015)**	EMBASE	Ovid
	Medline (R)	Ovid
	Cochrane central register of controlled trials (CENTRAL)	Ovid
	Medline complete	EBSCO

Embase®: Excerpta Medica Database; CENTRAL: Cochrane central register of controlled trials
MEDLINE®: Medical Literature Analysis and Retrieval System Online

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Unpublished studies were identified from PTC-sponsored clinical trials as well as clinical trial registries.

9.2 Study selection

Published studies

9.2.1 Complete table C1 [*now renumbered by manufacturer C9.2*] to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C9.2. Selection criteria used for published studies

Inclusion criteria	
Population	Patients with DMD
Interventions	Ataluren Best supportive care, and/ or Any other pharmacological therapy used for the treatment of patients with DMD, and/or Corticosteroids
Outcomes	All available
Study design	Randomised controlled trials, controlled trials, observational studies, retrospective trials, registries
Language	English
Search dates	No limits were put on publication date
Exclusion criteria	
Population	
Interventions	
Outcomes	Studies assessing physical therapies and psychosocial therapy
Study design	
Language	
Search dates	

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Search completed July 2014

The literature search yielded 2449 separate references. 206 duplicates were removed. The remaining studies were screened using their abstracts and 332 relevant citations were identified. Following a detailed evaluation of the full texts, 51 citations were excluded. 281 studies were identified that met the broad review inclusion criteria. Out of these 281 studies, only one RCT evaluating ataluren met the eligibility criteria for the clinical systematic review: PTC124-GD-007-DMD (Study 007; PTC Therapeutics, 2012). The study design and/or data were included in eight publications (McDonald, 2013b; Van Wart, 2013; Barth, 2012; McDonald, 2012; Russman, 2011; McDonald, 2011; Atkinson, 2009; Quinlivan, 2011). A Phase 2a cohort study (PTC124-GD-004-DMD) in patients with nmDMD evaluating treatment with ataluren was also identified (PTC Therapeutics 2011; Finkel 2013). A detailed

PRISMA flow diagram is shown in Figure C9.1. The clinical study reports (CSRs) relating to the studies were provided by the sponsor (PTC Therapeutics).

Search completed June 2015

The literature search update yielded 64 separate references. 17 duplicates were removed. The remaining 47 studies were screened using their abstracts and 6 relevant citations were identified. Following a detailed evaluation of the full texts, 5 citations were excluded. The remaining one publication was the main publication for Study 007 (Bushby, 2014). A detailed PRISMA flow diagram is shown in Figure C9.2.

Figure C9.1. PRISMA flow diagram of study inclusion (July 2014 search)

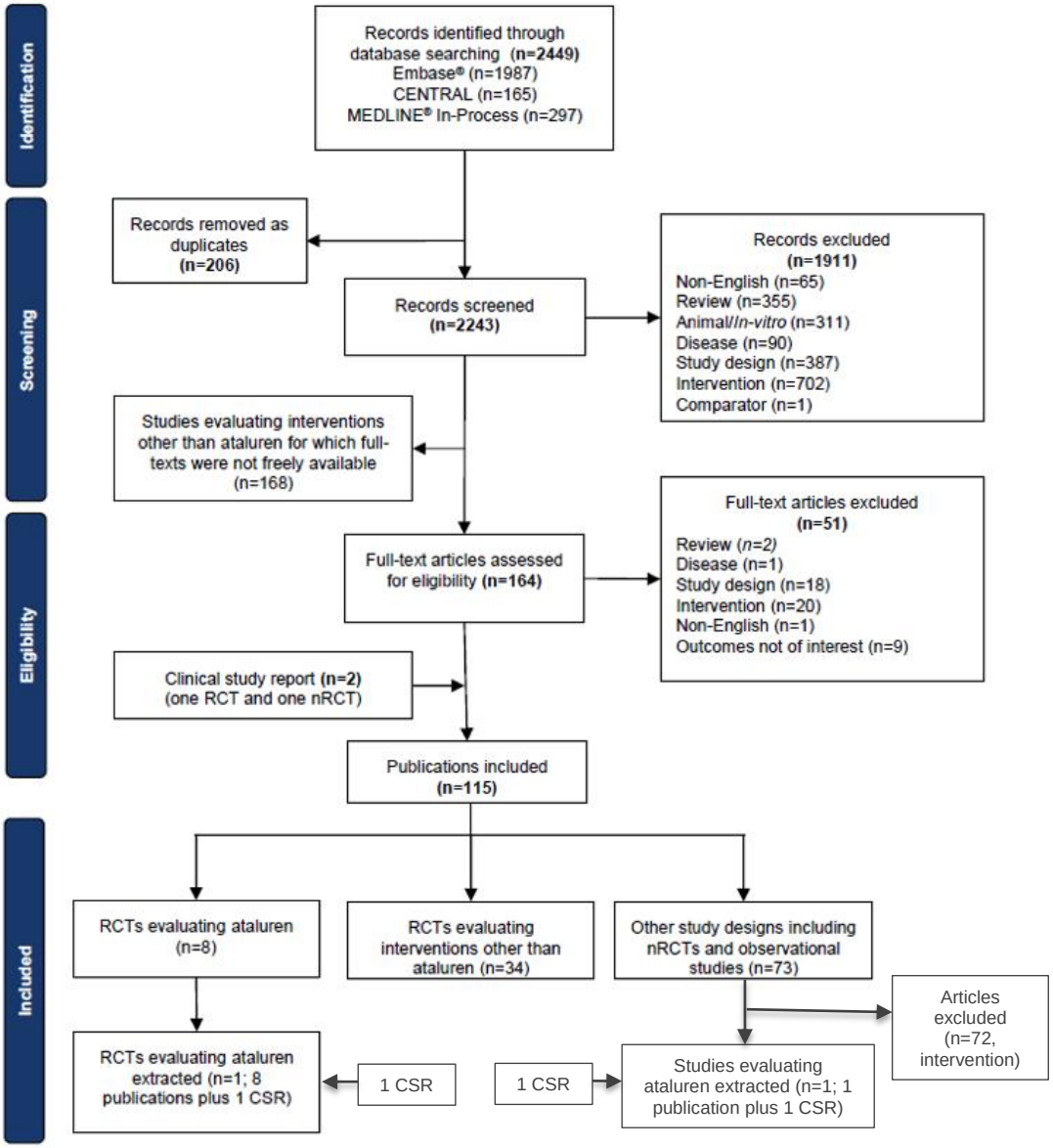
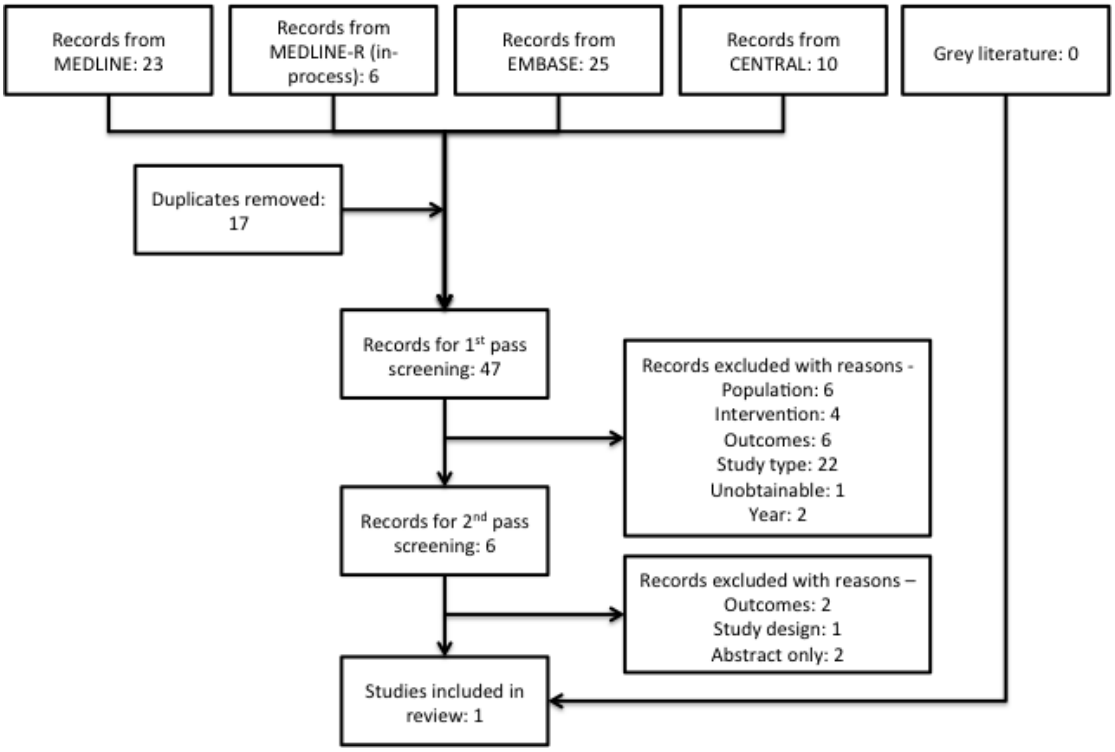


Figure C9.2. PRISMA flow diagram of study inclusion (June 2015 search)



Unpublished studies

9.2.3 Complete table C2 [now C9.3] to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C9.3 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients with DMD
Interventions	Ataluren
Outcomes	All available
Study design	Randomised controlled trials, controlled trials, observational studies, retrospective trials, registries
Language	None
Search dates	No limits were put on publication date
Exclusion criteria	
Population	
Interventions	
Outcomes	Studies assessing physical therapies and psychosocial therapy
Study design	
Language	
Search dates	

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Eleven studies were identified through a search of clinicaltrials.gov. Eight (Study 004, 004e, 007, 007e, 008, 016, 019, 020) are accounted for in Table C9.4 and Table C9.5 and provide evidence for this submission. A retrospective study sponsored by the National Human Genome Research Institute has investigated the experiences of parents, clinician researchers, and industry professionals who were involved in phase 2 clinical trials of ataluren for DMD (Peay, 2014). The remaining two studies do not yet have data to report: PTC124-GD-020e-DMD is an ongoing open label extension due to complete in June 2017. A registry study (PTC124-GD-025o-DMD) is being performed as a post-approval safety study, per the Pharmacovigilance Risk Assessment Committee of the EMA, but has only recently opened for recruitment (clinicaltrials.gov).

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured

abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Efficacy data from two clinical studies are relevant to this submission (Table C9.4). The safety and efficacy of ataluren has been investigated in a Phase 2b placebo-controlled randomised double-blinded study (Study 007, Bushby, 2014), which forms the main evidence base for this submission. Additional data are presented from a Phase 2a proof of concept study (Study 004).

In addition to published data, available data from seven unpublished studies (four of which are on-going) are included in the pooled safety analysis (Table C9.5, and Section 9.7). This includes the original extension studies for Study 007 and Study 004, a Phase 2a open-label study (Study 008) in which patients received ataluren 80 mg/kg/day before the trials were prematurely discontinued due to lack of efficacy of the 80 mg/kg/day dose in Study 007. In addition, data from four on-going studies are included in the safety analysis: two open-label studies assessing the safety of the 40 mg/kg/day dose in patients who originally participated in Studies 007, 007e, 004, 004e or 008 (Study 016 and Study 019), the Phase 3 study (Study 020) and the open label extension of Study 020 (Study 020e).

Table C9.4. List of relevant published studies

Study Name /Primary study reference	Study design	Population	Intervention/ comparator
PTC124-GD-004-DMD/ Study 004 (Finkel, 2013)	Phase 2a, multicentre, open-label cohort, sequential dose-ranging proof of concept study	38 male patients ≥5 years of age with a diagnosis of nonsense mutation DMD	Ataluren 4, 4, 8 mg/kg (total daily dose 16 mg/kg); 10, 10, 20 mg/kg (total daily dose 40 mg/kg), or 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for 28 days
PTC124-GD-007-DMD/ Study 007 (Bushby, 2014)	Phase 2b, multicentre, randomised, double-blind study	174 male patients, ≥5 years of age with a documented nonsense mutation in the dystrophin gene	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) or 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for 48 weeks Placebo

Table C9.5. List of relevant unpublished studies

Study Name /Data source	Study design	Population	Intervention/ comparator
PTC124-GD-004e-DMD (clinicaltrials.gov)/ Periodic Benefit Risk Evaluation Report, April 2015	Phase 2a, multicentre, open-label safety and efficacy study (complete)	36 patients that participated in Study 004	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for up to 96 weeks
PTC124-GD-007e-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 2b, open-label, safety and efficacy extension study (complete)	173 patients that participated in Study 007	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for up to 96 weeks
PTC124-GD-008-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 2a, open-label, safety and efficacy study (complete)	6 patients ≥7 years of age with nonsense mutation DMD/BMD who have been nonambulatory for at least one year	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for 2 to 7 weeks
PTC124-GD-016-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Open-label Phase 3 safety trial (ongoing)	Ambulatory and non-ambulatory patients who originally participated in Studies 007, 007e, 004, 004e or 008 (USA). Estimated n=110	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration.
PTC124-GD-019-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Open-label Phase 3 safety trial (ongoing)	Ambulatory and non-ambulatory patients who originally participated in Studies 007 and 007e (Europe, Israel, Australia, or Canada). Estimated n=96	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration.
PTC124-GD-020-DMD/ Study 020 (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 3, multicentre, randomised, double-blind, placebo-controlled study (ongoing)	Male patients 7 to 16 years of age with nonsense-mutation dystrophinopathy. Estimated n=220	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for 48 weeks Placebo
PTC124-GD-020e-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 3, open label extension study (ongoing)	The study will enrol ~ 220 boys with nonsense mutation dystrophinopathy who participated in Study 020	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg)for approximately 96 weeks

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

No studies reporting efficacy or safety data for ataluren in DMD have been excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Table C9.6. Summary of methodology for randomised controlled trials

Study name	PTC124-GD-007-DMD (Study 007)
Objectives	To determine the efficacy and safety of ataluren in the treatment of patients with nonsense mutation DMD
Location	Patients were recruited from 37 study sites in 11 different countries (UK, US, Italy, Australia, Germany, Canada, France, Sweden, Spain, Belgium, and Israel), including seven patients in each treatment group from the UK.
Design	Phase 2b, multicentre, randomised, double-blind study assessing the efficacy and safety of two doses of ataluren and placebo.
Duration of study	48 weeks
Sample size	A total of 174 patients were randomised
Inclusion criteria	Male, ≥5 years of age with a documented nonsense mutation in the dystrophin gene, onset of dystrophinopathy symptoms by age 9 years, elevated serum creatine kinase (CK), and difficulty ambulating but able to walk ≥75 metres unassisted during a 6MWT at screening. Stable use of concomitant glucocorticoids was allowed. Note: The number of Becker patients in Study 007 was very small in number, estimated to be ~2 patients; estimation based on published criteria, i.e., ambulatory ability at >15 years of age.
Exclusion criteria	• Treatment with systemic aminoglycoside antibiotics within 3 months prior to start of study treatment. • Initiation of systemic corticosteroid therapy within 6 months prior to start of study treatment or change in systemic corticosteroid therapy within 3 months prior to start of study treatment. Note: Increases in corticosteroid dose to adjust for increases in body weight did not exclude a patient from participation. • Any change in prophylaxis/treatment for congestive heart failure (CHF) within 3 months prior to start of study treatment. • Treatment with warfarin within 1 month prior to start of study treatment. • Prior therapy with ataluren. • Known hypersensitivity to any of the ingredients or excipients of the study drug. • Exposure to another investigational drug within 2 months prior to start of study treatment. • History of major surgical procedure within 30 days prior to start of study treatment. • Ongoing immunosuppressive therapy (other than corticosteroids). • Ongoing participation in any other therapeutic clinical study. • Expectation of major surgical procedure (e.g., scoliosis surgery) during the 12-month treatment period of the study. • Requirement for daytime ventilator assistance. • Clinical symptoms and signs of CHF or evidence on echocardiogram of clinically significant myopathy. • Prior or ongoing medical condition, medical history, physical findings, electrocardiogram (ECG) findings, or laboratory abnormality that, in the investigator's opinion, could have adversely affected the safety of the patient, made it unlikely that the course of treatment or follow-up would be completed, or could have impaired the assessment of study results.

Method of randomisation	An Interactive Voice Response/Interactive Web Response (IVR/IWR) system was used to randomise patients. Patients were stratified prospectively by age (<9 or ≥9 years), use of glucocorticoids (yes or no), and baseline 6-Minute Walk Distance (6MWD) (≥350 or <350 metres) and were randomized 1:1:1 to the three treatment groups.
Method of blinding	Double blinding (efficacy and safety data by patients, caregivers, clinic staff, and other study personnel.)
Intervention(s) (n =) and comparator(s) (n =)	40 mg/kg/day dose ataluren (n=57), or 80 mg/kg/day dose ataluren (n=60) Placebo (n=57) Ataluren was administered as three daily doses - morning, midday and evening: • 40 mg/kg/day: administered as 10 mg/kg/day morning, 10 mg/kg/day midday and 20 mg/kg/day evening • 80 mg/kg/day: administered as 20 mg/kg/day morning, 20 mg/kg/day midday and 40 mg/kg/day evening
Baseline differences	There was no significant difference among the 3 arms in any patient characteristic.
Duration of follow-up, lost to follow-up information	One patient discontinued at Week 6 due to noncompliance. The remaining 173 patients completed 48 weeks.
Statistical tests	The hypothesis of this study was that the mean change in 6MWD from baseline to 48 weeks would be 30 metres longer in at least one of the ataluren arms than in the placebo arm. Assuming a common standard deviation of ~50 metres in each arm and a 1:1:1 randomization, 150 patients were required (50 patients in each of the 3 arms) to detect a difference of 30 metres in the 6MWD with >85% power using a 2-sided Dunnett' s t-test at the 0.042 significance level. Assuming a premature discontinuation rate of ~10%, it was planned that ~165 patients (~55 patients in each of the 3 arms) be enrolled. Mixed-model repeated-measures (MMRM) analyses of changes from baseline to Week 48 were performed. The baseline values for 2 patients (1 placebo-dosed and 1 treated with ataluren 80 mg/kg/day) were replaced by their screening values, because their baseline 6MWDs were radically lower than their screening and Week 6 values due to lower-limb injuries before the baseline test. This is referred to as the corrected ITT (cITT) population. The post hoc analysis was performed on the untransformed data with deviations from assumptions addressed by means of a re-randomization test (10,000 iterations) using MMRM. The P-values of the primary and secondary out- come measures were adjusted for comparisons of 2 dose levels against placebo. All analyses were 2- sided at the 0.05 level of significance. Where P-values are described as nominal, they are not adjusted for multiplicity.
Primary outcomes (including scoring methods and timings of assessments)	**The primary outcome measure was the change in 6MWD at Week 48.** Ambulation was assessed via the 6MWT following standardised procedures by measuring the 6MWD in metres.
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary outcome measures of physical functioning included:** • Changes in proximal muscle function measured by Timed Function Tests ([TFTs] - stand from supine, 4-stair ascend, 4-stair descend, and 10 metre run/walk): monitored during screening, at baseline, and every 6 weeks during treatment • Change in activity in the community setting as assessed by step activity monitoring. Patients left the clinic wearing the Step Activity Monitor (SAM, pedometer that continuously records the number of steps per time interval) and were to continue to wear the SAM for ≥9 consecutive days. Step activity parameters were monitored during screening, at baseline, and every 6 weeks during treatment • Change in force exerted during knee flexion and extension, elbow flexion and extension and shoulder abduction as assessed by myometry – monitored during screening, at baseline, and every 6 weeks during treatment

	Patient reported outcome measures: • HRQL measured via the Pediatric Quality of Life Inventory (PedsQL). The generic core module comprises 23 questions and the fatigue-specific module comprises an additional 18 questions. The PedsQL was to be completed at each visit (baseline, and every 6 weeks during treatment) • Satisfaction with treatment measured using the Treatment Satisfaction Questionnaire for Medication (TSQM). The TSQM consists of 14 Likert-scale items. The TSQM was completed at each on-treatment visit (at week 6 and every 6 weeks during treatment) • Change in wheel-chair use and number of accidental falls/day. Patients or parents/caregivers completed a daily diary with information relating to study drug compliance, corticosteroid use, and the frequency of accidental falls occurring during ambulation. Patients or parents/caregivers also completed an activity diary during each day that the SAM was worn (i.e., 9 consecutive days during each 6-week treatment period). The activity diary was employed to collect information about non-disease-related factors that may affect the community ambulation data (e.g., episodes of patient non-compliance, inclement weather, day of the week) and use of assistive devices (e.g., wheelchair, leg braces). **Cognitive function:** • Change in cognitive ability (verbal memory and attention). Basic attention and working memory was measured using the digit span task. The digit span task was completed during screening, at baseline, and every 12 weeks during treatment. **Cardiac function:** • Change in heart rate before, during, and after each 6MWT as assessed by heart rate monitoring. Blood pressure was measured after heart rate monitoring. These parameters were monitored during screening, at baseline, and every 6 weeks during treatment. **Pharmacodynamics:** • Effect of ataluren on muscle fragility as determined by serum CK levels. Blood samples collected at clinic visits for chemistry assays were used to quantify serum CK concentrations. • Effect of ataluren on muscle dystrophin expression as determined by immunofluorescence.

Sources: Bushby, 2014, PTC124-GD-007-DMD CSR, EMA, Translarna EPAR

Table C9.7. Summary of methodology for non-RCTs

Study name	PTC124-GD-004-DMD (Study 004)
Objective	To determine whether ataluren could safely provide pharmacologic activity, as measured by immunofluorescence evidence of an increase in dystrophin production on extensor digitorum brevis (EDB) or tibialis anterior (TA) muscle biopsy. The study also assessed additional markers of disease activity, changes in muscle strength and function, safety, and ataluren pharmacokinetics.
Location	This study was performed at three sites in the US
Design	Phase 2a, multicentre, open-label cohort, sequential dose-ranging proof of concept study.
Duration of study	The duration of treatment was 28 days. Subjects were followed for an additional 28 days post- treatment.
Patient population	Male, ≥5 years of age with a diagnosis of nonsense mutation DMD
Sample size	n=38
Inclusion criteria	• Male, ≥5 years of age with a diagnosis of nonsense mutation DMD based on a clinical phenotype present by age 5, increased serum CK, absent or

	diminished sarcolemmal staining with an antibody to the C- terminal portion of the dystrophin protein on muscle biopsy, and presence of a nonsense mutation in the dystrophin gene (as confirmed by gene sequencing). • Ability to ambulate or, if non-ambulatory, no requirement for ventilator support.
Exclusion criteria	• Prior or ongoing medical condition, medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could have adversely affected the safety of the patient, made it unlikely that the course of treatment or follow-up would be completed, or impaired the assessment of study results. • Clinical symptoms and signs of congestive cardiac failure • Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test. • Haemoglobin <10 g/dL or serum albumin <2·5 g/dL. • Abnormal gamma-glutamyl transferase (GGT) or total bilirubin. • Abnormal renal function. • History of solid organ or haematological transplantation. • Ongoing immunosuppressive therapy with agents other than corticosteroids. • Exposure to another investigational drug within 28 days before the start of study treatment. • Ongoing participation in any other therapeutic clinical trial at the time of enrolment in this study. • Ongoing use of thiazolidinedione peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, e.g., rosiglitazone (Avandia or equivalent) or pioglitazone (Actos or equivalent). • Change in systemic corticosteroid therapy (e.g., initiation of treatment; cessation of treatment; or change in dose, schedule, or type of steroid) within 3 months before the start of study treatment. • Treatment with systemic aminoglycoside antibiotics within 4 weeks before the start of study treatment. Patients were allowed to receive systemic antibiotics as clinically necessary for life-threatening infections during the study; however, use of aminoglycoside antibiotics was to be avoided if possible.
Intervention(s) (n =) and comparator(s) (n =)	Eligible subjects were sequentially assigned to escalating dose levels of ataluren. Ataluren 16 mg/kg/day (n=6), 40mg/kg/day (n=20), 80 mg/kg/day (n=12). Ataluren was administered in three doses across a day - morning, midday and evening: • 16 mg/kg/day: administered as 4 mg/kg/day morning, 4 mg/kg/day midday and 8 mg/kg/day evening • 40 mg/kg/day: administered as 10 mg/kg/day morning, 10 mg/kg/day midday and 20 mg/kg/day evening • 80 mg/kg/day: administered as 20 mg/kg/day morning, 20 mg/kg/day midday and 40 mg/kg/day evening No comparator arm was included in this study.
Baseline differences	Ages and body weights were generally consistent across the dose groups, with a slightly higher range at the 80 mg/kg/day dose level due to inclusion of several older, nonambulatory boys in this cohort.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were actively followed up for a period of 28 days. No patients were lost to follow-up.
Statistical tests	Subjects with both baseline and on-study measurements were included in efficacy analyses. Changes in quantitative dystrophin expression, serum CK, myometry, and timed function tests were analysed using paired t-tests.

Primary outcomes (including scoring methods and timings of assessments)	**The primary outcome was change in dystrophin expression in muscle biopsy samples at Day 28.** The muscle was obtained from one foot at baseline and the other foot on Day 28 of treatment. Immunofluorescence images were analysed qualitatively and quantitatively. For the qualitative analysis, three expert reviewers at Children's Hospital of Philadelphia who were blinded to timepoint (i.e., pre-treatment or post-treatment) and dose level independently compared dystrophin expression in the baseline and post-treatment immunostaining images. If ≥2/3 blinded reviewers observed more dystrophin staining in a subject's post-treatment specimen compared to his pre-treatment specimen, that subject was considered a responder. For the quantitative analysis, the images obtained at the Children's Hospital of Philadelphia were analysed using a custom MetaMorph (Molecular Devices, Inc, Union City, California, USA) script.
Secondary outcomes (including scoring methods and timings of assessments)	**Immunohistological changes.** Dystrophin and dystrophin-associated protein expression in cultured myocytes and dermal fibroblasts; changes in sarcoglycans and dystroglycans in EDB or TA muscle biopsy specimens; presence of dystrophin mRNA in EDB or TA muscle. **Serum CK levels** were monitored at baseline, every seven days during treatment, and at Days 14 and 28 post-treatment. **Motor function.** Muscle strength of upper and lower extremities as assessed through myometry testing; timed function tests (time taken to stand from a supine position, time taken to run/walk 10 metres, and time taken to climb four standard-sized steps). Myometry and timed function tests were performed at baseline, after 28 days of treatment, and Day 28 post-treatment.

Source: Finkel, 2013 (and supplementary appendix S1); PTC124-GD-004-DMD CSR

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Study	Primary publication	Additional data sources
PTC124-GD-004-DMD (Study 004)	Finkel, 2013	CSR: (PTC Therapeutics 2011)
PTC124-GD-007-DMD (Study 007)	Bushby, 2014	CSR: (PTC Therapeutics 2012) Other publications that cited study design and/or data from this study: (McDonald 2013; Van Wart 2013; Barth 2012; McDonald 2012; Russman 2011; McDonald 2011; Atkinson 2009; Quinlivan 2011)

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

The two included phase 2 studies are significantly different in terms of study design. Study 007 was a randomised placebo-controlled study primarily investigating the

clinical efficacy of ataluren (48 weeks treatment) whilst Study 004 was an open-label dose ranging study primarily investigating the pharmacodynamics of ataluren (changes in muscle dysptrophin expression at day 28).

The study populations were similar and both studies investigated doses of ataluren 40 mg/kg/day and 80 mg/kg/day. In study 004 patients also received ataluren 16 mg/kg/day.

Study 004 patient population

The treatment groups were well matched on their baseline characteristics, as shown in Table C9.8. Ages and body weights were generally consistent across the dose groups, with a slightly higher range at the 80 mg/kg/day dose level due to inclusion of several older, nonambulatory boys in this cohort. The majority (71.1%) of patients were receiving corticosteroid treatment (Table C9.9).

Table C9.8. Baseline characteristics of Study 004

	Ataluren dose group		
	16 mg/kg/day (N=6)	**40 mg/kg/day (N=20)**	**80 mg/kg/day (N=12)**
Age (years)			
Mean ± SD	8.3 ± 2.34	8.5 ± 1.70	9.6 ± 3.65
Median	9	8.5	9
Range	5-11	6-12	5-17
Sex, n (%)			
Male	6 (100.0)	20 (100.0)	12 (100.0)
Race, n (%)			
Caucasian	6 (100.0)	15 (75.0)	11 (91.7)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	3 (15.0)	0 (0.0
Hispanic	0 (0.0)	0 (0.0)	0 (0.0
Other	0 (0.0)	2 (10.0)	1 (8.3)
Weight (kg)			
Mean ± SD	29.33 ± 9.895	31.25 ± 10.164	31.95 ± 17.893
Median	30.5	28.95	24.25
Range	17.3 - 39.7	18.5 - 57.5	17.5 - 74.2
Ability to ambulate, n (%)			
No	0 (0.0)	1 (5.0)	3 (25.0)
Yes	6 (100.0)	19 (95.0)	9 (75.0)
Premature stop codon type, n (%)			
UGA	4 (66.7)	11 (55.0)	7 (58.3)
UAG	2 (33.3)	5 (25.0)	1 (8.3)
UAA	0 (0.0)	4 (20.0)	4 (33.3)
Location of mutations on dystrophin gene range of exon numbers	24 to 70	6 to 70	6 to 61
Abbreviations: UAA: Uridine-adenosine-adenosine; UAG: Uridine-adenosine-guanosine; UGA: Uridine guanosine-adenosine			

Table C9.9. History of medication use for DMD

	Ataluren dose group		
	16 mg/kg/day (N=6)	**40 mg/kg/day (N=20)**	**80 mg/kg/day (N=12)**
Prior history of systemic corticosteroid use	6 (100.0)	13 (65.0)	10 (83.3)
Systemic corticosteroid use in study	6 (100.0)	13 (65.0)	8 (66.7)
Steroid type			
Daily deflazacort	2 (33.3)	9 (45.0)	5 (41.7)
Daily prednisone or prednisolone	3 (50.0)	2 (10.0)	2 (16.7)
Weekend prednisone	1 (16.7)	2 (10.0)	0 (0.0)
Prednisolone four times per week	0 (0.0)	0 (0.0)	1 (8.3)
Prior gentamicin Use	0 (0.0)	0 (0.0)	2 (16.7)

Study 007 patient population

Patients were recruited from 37 study sites in 11 different countries (UK, US, Italy, Australia, Germany, Canada, France, Sweden, Spain, Belgium, and Israel), including seven patients in each treatment group from the UK. Groups were well matched on baseline characteristics (Table C9.10).

Concomitant treatment with corticosteroids was balanced with regard to type and frequency of administration at baseline (Table C9.11). Changes during the study were minimal. Similarly, treatment with cardiac drugs such as angiotensin-converting-enzyme inhibitor (ACE) inhibitors, angiotensin receptor blockers (ARB), and beta-blockers was similar across treatment groups.

Table C9.10. Baseline characteristics patients in Study 007

	Placebo (N=57)	Ataluren 40 mg/kg/day (N=57)	Ataluren 80 mg/kg/day (N=60)
Age			
Mean (SD)	8.3 (2.33)	8.8 (2.91)	8.4 (2.53)
Median	8.0	8.0	8.0
Range	5-15	5-20	5-16
Sex, n (%)			
Male	57 (100.0)	57 (100.0)	60 (100.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
Caucasian	54 (94.7)	53 (93.0)	50 (83.3)
Black	0 (0.0)	1 (1.8)	1 (1.7)
Asian	1 (1.8)	1 (1.8)	4 (6.7)
Hispanic	1 (1.8)	1 (1.8)	2 (3.3)
Other	1 (1.8)	1 (1.8)	3 (5.0)
Body height, cm			
Mean (SD)	123.4 (11.8)	124.5 (15.3)	126.2 (13.8)
Median	122.1	121.1	125.9
Range	104-163	99-173	99-173
Body weight, kg			
Mean (SD)	28.6 (9.1)	31.2 (12.1)	31.9 (12.8)
Median	25.6	27.0	27.6
Range	16-55	16-76	17-84
Body mass index, kg/m^2			
Mean (SD)	18 (3.7)	19 (3.5)	19 (4.8)
Median	17.4	18.8	18.2
Range	13-29	14-31	14-41
Sibling pairs	4	1	1
Age at diagnosis			
Mean (SD)	3.9 (2.3)	3.3 (1.8)	3.8 (2.0)
Median	4.0	3.0	3.5
Range	0-10	0-9	0-8
Time from diagnosis to randomization			
Mean (SD)	4.4 (2.5)	5.4 (3.4)	4.6 (3.1)
Median	5.0	5.0	4.0
Range	0-11	0-17	0-14
Phenotype diagnosis, n (%)			
Proximal muscle	50 (88)	49 (86)	52 (87)

	Placebo (N=57)	Ataluren 40 mg/kg/day (N=57)	Ataluren 80 mg/kg/day (N=60)
weakness			
Waddling gait	44 (77)	43 (75)	49 (82)
Gower's manoeuvre	47 (83)	50 (88)	51 (85)
Calf hypertrophy	56 (98)	48 (84)	55 (92)
Other	12 (21)	19 (33)	13 (22)
Stop codon type, n (%)			
UGA	31 (54.4)	29 (50.9)	23 (38.3)
UAG	12 (21.1)	17 (29.8)	19 (31.7)
UAA	14 (24.6)	11 (19.3)	18 (30.0)
Functional characteristics			
Baseline 6MWD, m			
Mean (SD)	359.6 (87.7)	350.0 (97.6)	358.2 (104.0)
Median	354.0	362.1	368.0
Range	159-533	75-525	90-554
%-predicted 6MWD, mean (SD)	61.9 (16.26)	59.6 (18.06)	61.6 (17.78)
Timed function tests			
Climb 4 stairs, s, mean (SD)	6.0 (5.67)	6.9 (6.47)	7.5 (7.46)
Descend 4 stairs, s, mean (SD)	5.5 (5.75)	6.1 (5.98)	6.7 (7.21)
10-m run/walk, s, mean (SD)	6.7 (2.67)	7.4 (4.37)	7.4 (4.36)
Supine to stand, s, mean (SD)	11.5 (11.44)	10.8 (9.92)	12.3 (11.19)
Falls/day* mean (SD)	0.5 (0.94)	0.3 (0.48)	0.4 (0.60)

*Baseline falls/day data were available for 48, 48 and 50 patients in the placebo, ataluren 40mg/kg/day, and ataluren 80mg/kg/day treatment arms, respectively.

Abbreviations: UAA: uridine-adenosine-adenosine; UAG: uridine-adenosine-guanosine; UGA: uridine guanosine-adenosine

Table C9.11. Corticosteroid use at the time of randomisation, as treated population

Corticosteroid Therapy, n (%)	Placebo (N=57)	Ataluren 40mg/kg/day (N=57)	Ataluren 80mg/kg/day (N=60)
Corticosteroid use[a]	40 (70.2)	41 (71.9)	43 (71.7)
Deflazacort use	17 (29.8)	17 (29.8)	20 (33.3)
Daily	14 (24.6)	16 (28.1)	16 (26.7)
Every other day	0 (0.0)	1 (1.8)	2 (3.3)
Other	3 (5.3)	0 (0.0)	2 (3.3)
Prednisolone use	11 (19.3)	14 (24.6)	9 (15.0)
Daily	10 (17.5)	11 (19.3)	7 (11.7)
Every other day	0	1 (1.8)	1 (1.7)
Other	1 (1.8)	2 (3.5)	1 (1.7)
Prednisone use	12 (21.1)	10 (17.5)	14 (23.3)
Daily	6 (10.5)	6 (10.5)	6 (10.0)
Every other day	1 (1.8)	1 (1.8)	0 (0.0)
Other	5 (8.8)	3 (5.3)	8 (13.3)
a: Among patients on a daily regimen, doses ranged from 7.5 mg to 33 mg for deflazacort, 10 mg to 30 mg for prednisolone, and 10 mg to 25 mg for prednisone.			

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

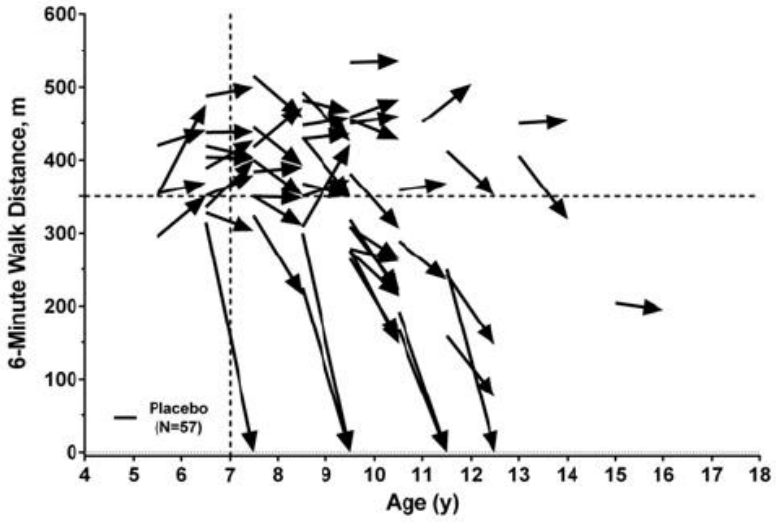
Study 007

Age, corticosteroid use, and baseline 6MWD were pre-specified as stratification factors since these variables were likely to have prognostic significance. The three stratification factors (age [<9 years vs. ≥9 years], corticosteroid use [yes vs. no], and baseline 6MWD [≥350 metres vs. <350 metres]) were included to balance allocation of patients into treatment groups by these potentially important baseline parameters. Age was included as a stratification variable because it is simultaneously predictive for greater extent of disease and for greater developmental capacity; these competing influences were regarded as likely to have substantial effects on the outcome measures (Pradhan, 2006). Corticosteroids have been shown to have positive effects on functional abilities as assessed by strength and TFTs (Biggar, 2006; Pradhan, 2006). Baseline 6MWD was considered likely to have prognostic

significance, both for the primary assessment of ambulation and for secondary assessments of activity, function, muscle strength, and fall frequency. Prior to study start, the estimated mean 6MWD for the study population was ~270 metres; however, early assessment of pre-treatment 6MWD data showed a mean 6MWD of ~350-360 metres. Therefore baseline 6MWD stratification was updated from <270 metres and ≥270 metres to <350 metres and ≥350 metres. Forty-two of the 174 patients were enrolled prior to the implementation the amendment (PTC Therapeutics, 2012). Sub-group analyses were carried out within the 6 subgroups defined by the 3 stratification factors (Bushby, 2014).

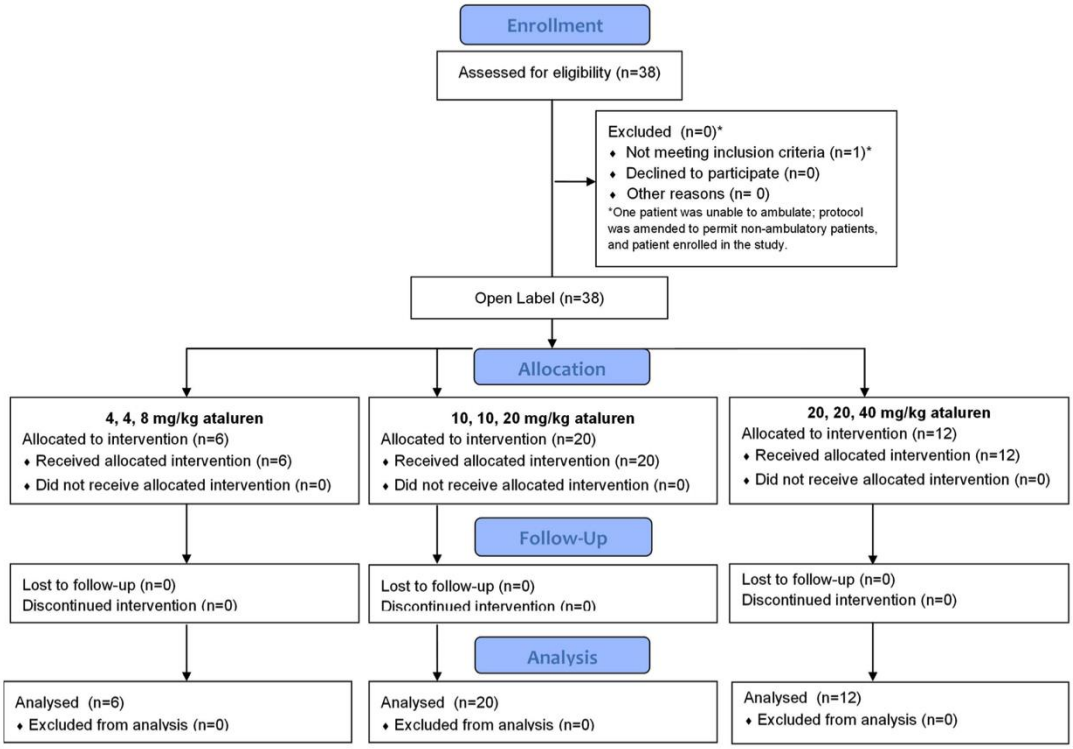
A post-hoc subgroup analysis was conducted after discussion with the CHMP to compare the mean change in the 6MWD from baseline to week 48 measured in placebo treated patients versus those receiving ataluren who were classified as being in the decline phase. Criteria for this subgroup were identified based on the results from the placebo arm, which helped to define the natural history of 6MWD in DMD. Patients younger than 7 years tend to increase their 6MWD over 48 weeks due to maturational improvements. Patients who have higher baseline 6MWD (greater than 350 metres) tend to remain stable over the 48-week period in Study 007, whereas those patients with lower baseline 6MWD (less than 350 metres) show decline in their walking ability over 48 weeks (Figure C9.3). The decline-phase subgroup was thus defined as those aged 7 years to 16 years with a baseline %-predicted 6MWD ≤80%, and to minimise heterogeneity with a baseline of 6MWD ≥150 metres and on a stable dose of corticosteroids.

Figure C9.3. The natural history of DMD as defined by change in 6MWD from baseline to 48 weeks from the placebo group in Study 007



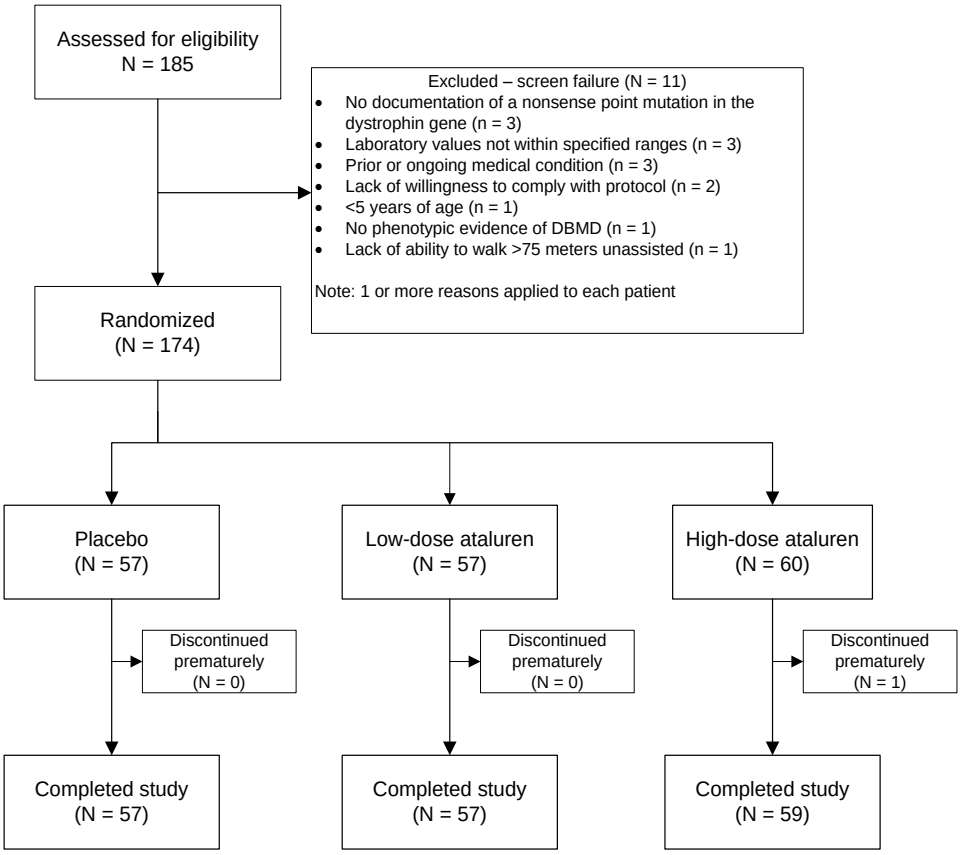
9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Figure C9.4. Consort Flow Diagram, Study 004



Source: Finkel, 2013

Figure C9.5. Consort Flow Diagram, Study 007



Source: Bushy, 2014 (supplement)

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

In Study 004, no patients withdrew or were lost to follow-up.

In Study 007, one patient discontinued at Week 6 due to non-compliance. The remaining 173 patients completed 48 weeks.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Table C9.12 Critical appraisal of randomised control trials

Study name	**PTC124-GD-007-DMD (Study 007)**	
Study question	**Response (yes/no/ not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	An interactive voice response/interactive web response system was used by site representatives to allocate patients. Randomisation was stratified according to age, baseline 6MWD and use of corticosteroids.
Was the concealment of treatment allocation adequate?	Yes	An interactive voice response/interactive web response system was used by site representatives to allocate patients.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Randomisation was stratified according to age, baseline 6MWD and use of corticosteroids and therefore treatment arms were well balanced with respect to these prognostic factors. Treatment arms were also similar in terms of other functional characteristics at baseline.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Double blinding (efficacy and safety data by patients, caregivers, clinic staff, and other study personnel)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The study protocol is available and all outcomes have been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The pre-specified intent-to-treat (ITT) population included all randomised subjects with a valid 6MWT available at baseline and ≥1 post baseline visit. The baseline values for 2 patients (1 placebo-dosed and 1 treated with ataluren 80 mg/kg/day) were replaced by their screening values, because their baseline 6MWDs were radically lower than their screening and Week 6 values due to lower-limb injuries before the baseline test. This is referred to as the corrected ITT (cITT)

		population. All patients completed the study, except for 1 patient in the ataluren 80 mg/kg/day arm who discontinued due to protocol noncompliance at approximately Week 6. The data from this patient were included in all MMRM analyses where this patient had both baseline and Week 6 data. Data for some of the protocol-required assessments are missing for some patients at some of the study visits. None of the missing items was considered to have had an effect on the study conclusions regarding efficacy or safety. As described in the statistical analysis plan, the primary analysis was repeated using a multiple imputation method for missing 6MWDs to check the effect of missing values on the robustness of the primary analysis. A second pre-specified sensitivity analysis to assess robustness of the primary efficacy results to missing data relied on the LOCF concept, by applying an ANCOVA model to the last available post-baseline 6MWD observation.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C9.13. Critical appraisal of non-randomised/ observational studies

Study name	**PTC124-GD-004-DMD (Study 004)**	
Study question	**Response (yes/no/ not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients were enrolled according to pre-specified entry criteria. Eligible subjects were sequentially assigned to escalating dose levels of ataluren. Patients were not to be enrolled at the next higher ataluren dose level until all who had been treated at the previous level had completed the 28-day treatment period and a review of safety and pharmacokinetic data had indicated that dose escalation was appropriate.
Was the concealment of treatment allocation adequate?	NA	None. Patients were sequentially assigned to treatment groups.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	
Were the care providers, participants and outcome	No	This was an open-label study. However, immunoflourescence images to detect in vivo changes in muscle dystrophin expression (the

assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		primary endpoint) were assessed qualitatively by blinded reviewers and therefore are not subject to bias. Quantitative analyses of dystrophin expression and serum CK levels are not expected to be subject to bias. In addition, as this was a dose ranging study there limited scope for bias as compared to a placebo or active intervention controlled study.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The study report is available and all outcomes have been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Although not pre-specified as an ITT analysis, all boys allocated to treatment received treatment and were included in the analysis. No data were missing for the analysis of the primary endpoint.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

Ataluren dose

The licensed dose of ataluren is 40 mg/kg/day (in three divided doses). Therefore, although results for 80 mg/kg/day are presented, they are not discussed in detail. Please see later discussion in Section 9.9.2 regarding the bell-shaped dose response observed with ataluren.

Results Summary

PTC124-GD-007-DMD (Study 007)

Table C9.14. Analysis of 6MWD from baseline to week 48 (Primary endpoint)

Mean change in 6MWD from baseline to week 48							
	Observed					MMRM Model	
Analysis Sub-group	**Placebo** Baseline, mean (SD)	**Placebo** Δ At week 48, mean (SD), n	**Ataluren 40 mg/kg/day** Baseline, mean (SD)	**Ataluren 40 mg/kg/day** Δ At week 48, mean (SD), n	**Observed Difference**	**Difference (95% CI)**	**p-value**
ITT All patients (placebo n=57, ataluren, n=57)	359.6 m (87.7)	-42.6 m (90.1),	350.0 m (97.6)	-12.9 m (72.0),	29.7 m	26.4 m (-4.2, 57.1)	p=0.0905
cITT All patients (placebo n=57, ataluren, n=57)	361.1 m (87.5)	-44.1 m (88.0),	350.0 m (97.6)	-12.9 m (72.0),	31.3 m	31.7 m (5.1, 58.3)	p=0.0197
cITT Decline phase sub-group (placebo n=31, ataluren, n=32)	341.9 m (85.0)	-62.2 m (84.9),	341.0 m (84.8)	-12.3 m (69.4),	49.9 m	45.6 m (11.4, 79.9)	p=0.0096
cITT Baseline 6MWD <350 m sub-group (placebo n=22, ataluren, n=25)	272.6 m (54.1)	-107.4 m (104.0),	262.5 m (71.9)	-39.2 m (84.3),	68.2 m	59.8 m (18.0, 101.6)	p=0.0053

Progression of 6MWD - persistent 10% 6MWD worsening at Week 48 relative to baseline				
Analysis	**Placebo (n=57)**	**Ataluren 40 mg/kg/day (n=57)**	**Hazard ratio**	**p-value**
cITT	26%	44%	0.51	nominal p=0.0326

Source: Bushy, 2014; Ataluren Study 007 CSR

Table C9.15 Timed function tests, cITT analysis set (secondary outcome measures)

Endpoint[a]	Placebo (n=57)		Ataluren 40 mg/kg/day (n=57)		Observed Difference[a]	MMRM Model		
	Baseline, mean (SD)	Δ At week 48, mean (SD)	Baseline, mean (SD)	Δ At week 48, mean (SD)		Difference, mean (95% CI)	% Difference, mean[b]	p-value
Climb four stairs Time, s	6.0 (5.7)	4.8 (7.9)	6.9 (6.5)	2.4 (4.6)	-2.4	-2.6 (-4.8, -0.4)	-49.9	0.0207
Descend four stairs Time, s	5.5 (5.8)	4.1 (7.8)	6.1 (6.0)	2.4 (6.2)	-1.6	-1.8 (-4.2, 0.6)	-39.9	0.1489
Run/walk 10 metres Time, s	6.7 (2.7)	3.2 (6.6)	7.4 (4.4)	1.7 (5.6)	-1.5[c]	-1.7 (-3.7, 0.3)	-45.1	0.1006
Supine to stand Time, s	11.5 (11.4)	3.2 (7.3)	10.8 (9.9)	3.2 (5.8)	-0.01	-0.1 (-2.3, 2.2)	-1.7	0.9613

a For timed function tests, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

b % Difference, mean calculation = ataluren Week 48 Δ - placebo Week 48 Δ / placebo Week 48 Δ

c Corrected figure: please note this is the observed difference based on the cITT population. A calculation error resulted in the 1.4 second difference reported in the publication (Bushby, 2014) and the Translarna SPC

Source: Bushy, 2014; Ataluren Study 007 CSR

PTC124-GD-004-DMD (Study 004)

Table C9.16. Change From Pretreatment in Dystrophin:Spectrin Ratio (primary outcome measure)

	In vivo dystrophin expression[a]		
	Quantitative		Qualitative
	Mean change, proportion positive	p-value	Proportion positive
All dose groups (n=38)	11.0% (61% responders)	p=0.008	38%
16 mg/kg/day dose (n=6)	12.31% (67% responders)	p=0.13	33%
40 mg/kg/day dose group (n=20)	8.42% (55% responders)	p=0.09	40%
80 mg/kg/day dose group (n=12)	14.67% (67% responders)	p=0.15	25%

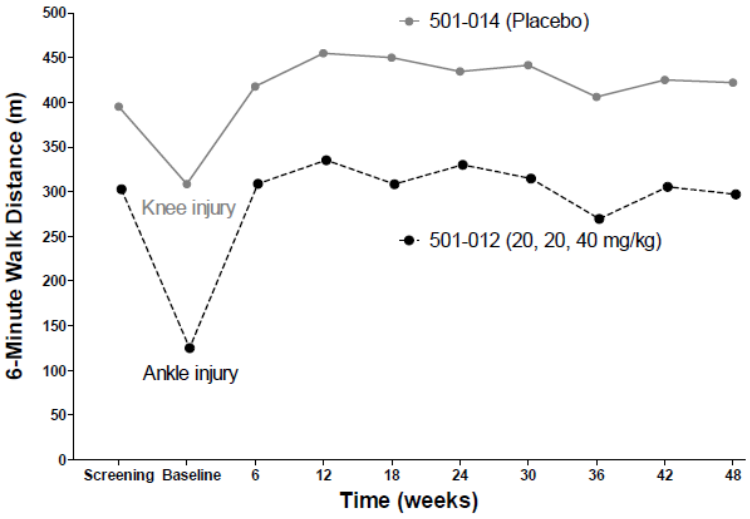
[a]Qualitative: Response = ≥2/3 blinded reviewers observed more dystrophin in post-treatment image compared to pre-treatment image. Quantitative: Change in dystrophin:spectrin ratio from pre-treatment to post-treatment.

PTC124-GD-007-DMD (Study 007)

Data analysis sets

The intention-to-treat (ITT) population included all 174 randomised patients, of whom 57 were assigned to placebo, 57 to ataluren 40 mg/kg/day, and 60 to ataluren 80 mg/kg/day. One patient discontinued at Week 6 due to non-compliance. The remaining 173 patients completed 48 weeks. The baseline 6WMD values for two patients (one placebo-dosed and one treated with ataluren 80mg/kg/day) were replaced by their screening 6WMD values, since these patients suffered lower-limb injuries prior to baseline and therefore their baseline 6MWD was radically lower than their screening and Week 6 values (Figure C9.6). Similarly, corrections were applied to the timed function tests. The updated dataset is referred to as the corrected ITT population (cITT). The cITT dataset is considered to be the most scientifically plausible analysis and although derived post-hoc, was considered by the EMA to be acceptable from a methodological point of view (Haas, 2015).

Figure C9.6. Change in 6MWD from screening baseline to 48 weeks for two patients with lower limb injuries prior to baseline



Change in 6MWD from baseline to 48 weeks (primary endpoint)

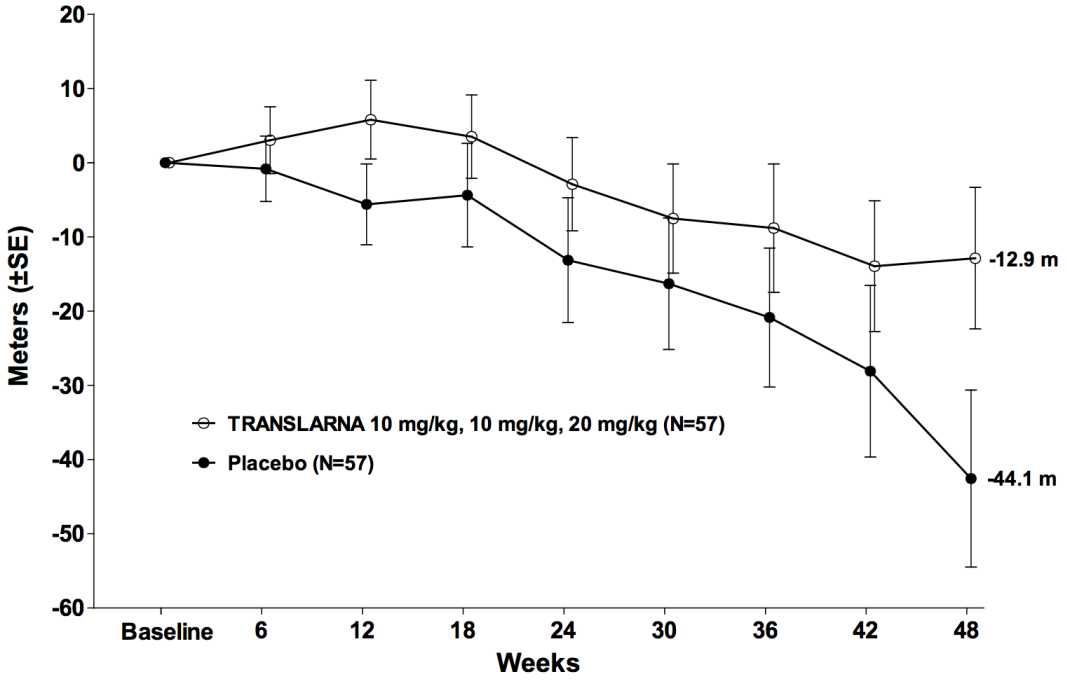
The study hypothesis was that mean change in 6MWD from baseline to 48 weeks would be 30 metres better in at least 1 ataluren arm versus placebo. Thirty metres was selected based on the 6MWD treatment effects seen in trials of drugs which have been approved for the treatment of other rare diseases with neuromuscular

complications (Bushby, 2014). The minimal clinically important difference in 6MWD has since been established as 30 metres (see Section 9.9).

Ataluren 40 mg/kg/day slowed the rate of decline of walking ability and achieved the targeted mean 30 metre difference between ataluren and placebo in 6MWD over 48 weeks in the cITT population. Ataluren 40 mg/kg/day slows the loss of walking ability in patients with nmDMD as demonstrated by a mean observed difference of 31.3 metre in the two groups' change in 6MWD (Figure C9.7). In the statistical based model (MMRM) the estimated mean difference between ataluren 40 mg/kg/day and placebo was 31.7m (95% CI 5.1, 58.3; nominal p = 0.0197, adjusted p = 0.0367) (Haas, 2015).

No effect was observed in the 80 mg/kg/day dose.

Figure C9.7. Mean change in observed 6MWD from baseline to 48 weeks by visit, cITT analysis set

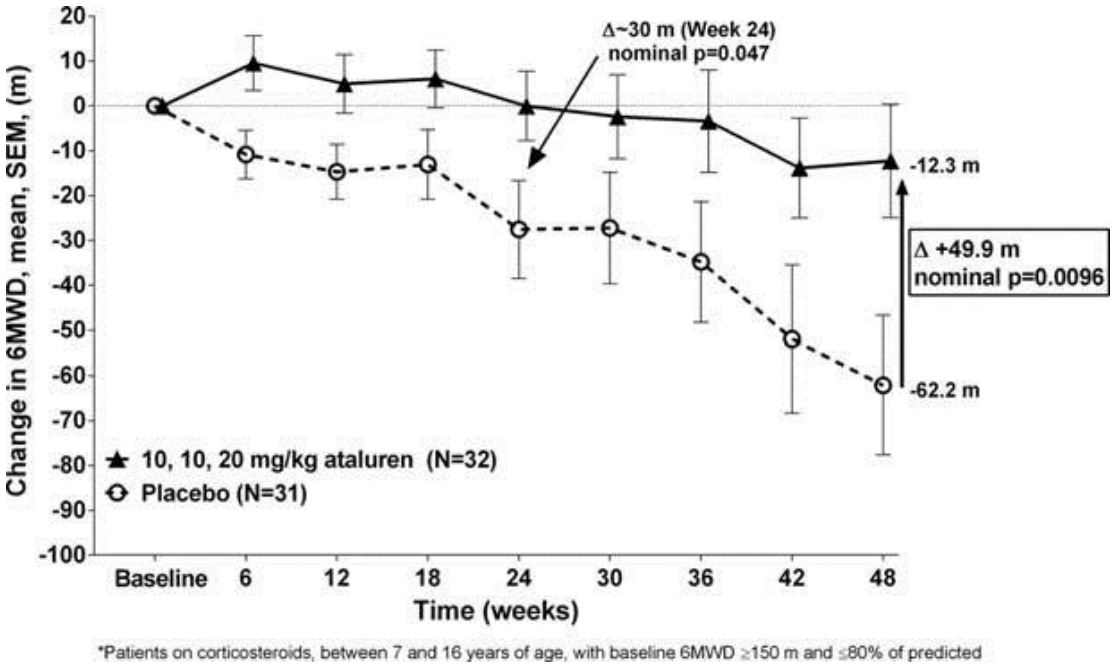


Source: Translarna SPC

A post-hoc subgroup analysis was conducted to compare the mean change in the 6MWD from baseline to week 48 measured in placebo treated patients versus those receiving ataluren who were classified as being in the decline phase (those aged 7 years to 16 years with a baseline of 6MWD ≥150 metres, and 80% of predicted 6MWD and on a stable dose of corticosteroids, as discussed in Section 9.4.4). In this subgroup, the mean reduction in 6MWD from baseline to week 48 was 49.9 metres

greater in the placebo group compared to ataluren 40 mg/kg/day-treated patients (nominal p=0.0096, Figure C9.8).

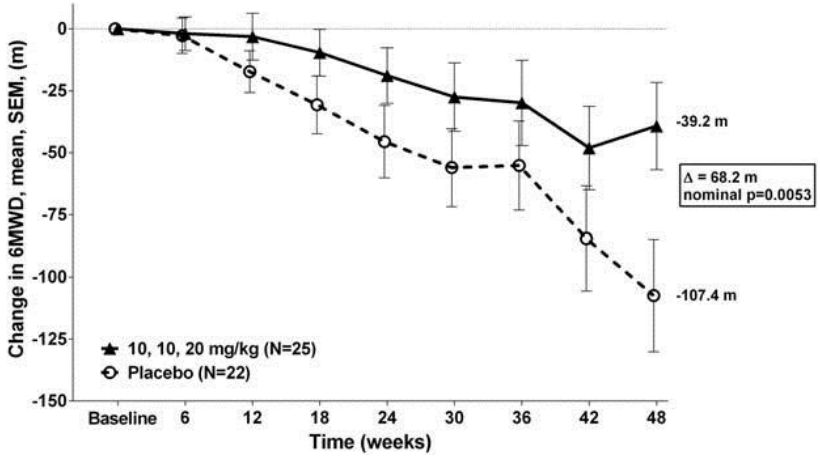
Figure C9.8. Mean change in observed 6MWD from baseline to 48 weeks by visit, cITT analysis set: decline phase subgroup



Source: Bushby, 2014

The natural history of change in ambulation (as measured by the 6MWD) indicates that patients who are able to walk a distance greater than 350 metres at baseline generally do not demonstrate substantial changes in their 6MWD value over 48 weeks, while those achieving less than 350 metres at baseline tend to decline (McDonald 2013b). In the pre-specified subgroup of patients with a baseline 6MWD <350 metres the decline in 6MWD from baseline to week 48 was far greater in the placebo group: mean change in 6MWD was -107.4 in the placebo group (n=22) versus -39.2 in the ataluren 40 mg/kg/day group (n=25), a difference of 68.2 metres (nominal P=0.0053, Figure C9.9).

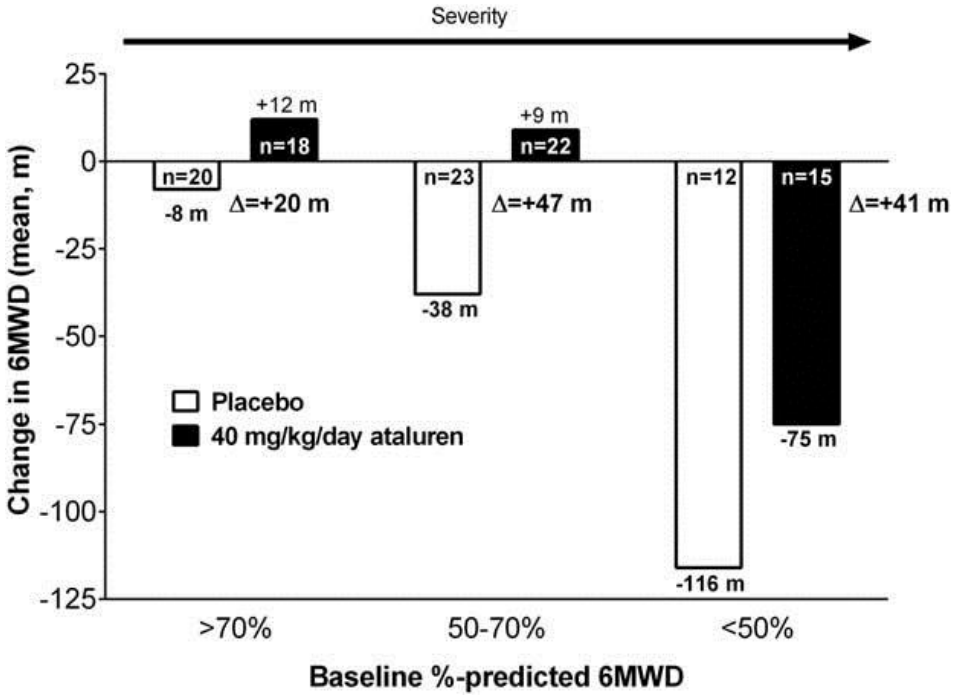
Figure C9.9. Mean change in 6MWD from baseline to week 48 in the < 350 metres 6MWD subgroup



Source: (Bushby, 2014)

The severity of ambulatory compromise can be categorized based on %-predicted 6MWD (relative to a healthy boy of the same age and height) at baseline (Henricson, 2013a; Geiger, 2007). All categories of patients, including milder patients (>70% baseline %-predicted 6MWD), showed a favourable effect for ataluren compared to placebo over 48 weeks (Figure C9.10). Therefore, the activity of treatment with ataluren was seen across the disease spectrum.

Figure C9.10. Percentage predicted 6MWD across disease spectrum as a function of change in baseline score associated with treatment



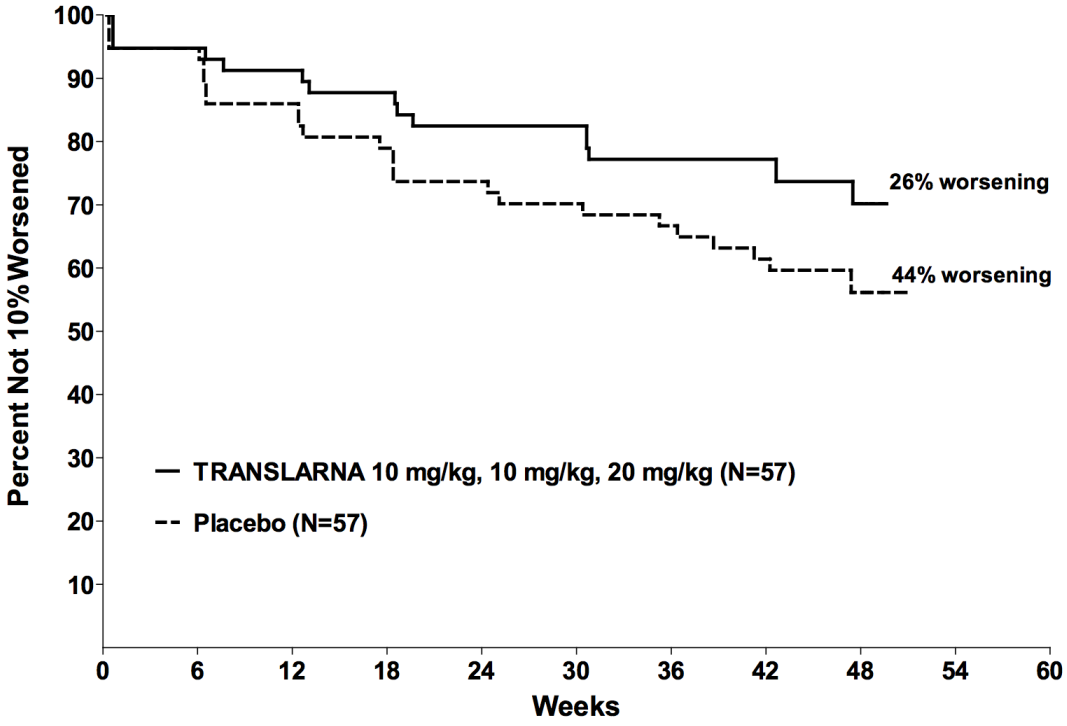
Progressor and time-to-event analyses of persistent 10% 6MWD worsening

Pre-specified analyses on the proportion of patients with a 10% or greater worsening in 6MWD at week 48 compared with baseline were conducted. Twenty-six percent of patients treated with 40 mg/kg/day experienced 10% 6MWD worsening compared with 44% of patients in the placebo arm (Figure C9.11). In the cITT analysis set the hazard ratio for treatment with ataluren 40 mg/kg/day versus placebo was 0.51 (nominal p=0.033), representing a 49% reduction in the risk of 10% 6MWD worsening over 48 weeks.

Similar results were seen in the ITT analysis (hazard ratio of ataluren 40 mg/kg/day vs. placebo of 0.52, nominal p=0.039)(Bushby, 2014).

The proportion of progressors in the ataluren 80 mg/kg/day arm was similar to placebo.

Figure C9.11. Time to persistent 10% 6MWD worsening, cITT analysis set



Secondary Endpoints

Timed function tests

Timed function tests (TFTs) (climbing 4 stairs, descending 4 stairs, running/walking 10 metres) are common outcome measures in DMD. When comparing performance at baseline and after 48 weeks of treatment, the 40 mg/kg/day dose ataluren group showed smaller increases in the time required to walk four steps, descend four steps, and run/walk 10 metres than placebo-treated patients: mean differences for stair climbing, stair descending, and walking/running 10 metres were: 2.4, 1.6, and 1.5 seconds (Table C9.17). Considering that these tests are performed at baseline in 6 to 8 seconds, the magnitudes of the treatment differences are large on a percentage basis.

No clinically meaningful difference was observed in treatment groups' ability to perform the supine to stand test. This was likely due to 23% of all patients being unable to perform the test at baseline, which is presumed to have created a flooring effect.

Consistent with the 6MWD outcome data, larger treatment effects were observed in the ambulatory decline phase and baseline 6MWD < 350 metre subgroups. Mean differences between ataluren and placebo for stair climbing, stair descending, and walking/running 10 metres were: 2.9, 2.9, and 2.8 seconds in the ambulatory decline subgroup; and 6.4, 5.0, and 3.5 seconds in the baseline 6MWD < 350 metre subgroup (Figure C9.12).

Table C9.17 Timed function tests, cITT analysis set (secondary outcome measures)

Endpoint[a]	Placebo (n=57)		Ataluren 40 mg/kg/day (n=57)		Observed Difference[a]	MMRM Model		
	Baseline, mean (SD)	Δ At week 48, mean (SD)	Baseline, mean (SD)	Δ At week 48, mean (SD)		Difference, mean (95% CI)	% Difference, mean[b]	p-value
Climb four stairs Time, s	6.0 (5.7)	4.8 (7.9)	6.9 (6.5)	2.4 (4.6)	-2.4	-2.6 (-4.8, -0.4)	-49.9	0.0207
Descend four stairs Time, s	5.5 (5.8)	4.1 (7.8)	6.1 (6.0)	2.4 (6.2)	-1.6	-1.8 (-4.2, 0.6)	-39.9	0.1489
Run/walk 10 metres Time, s	6.7 (2.7)	3.2 (6.6)	7.4 (4.4)	1.7 (5.6)	-1.5[c]	-1.7 (-3.7, 0.3)	-45.1	0.1006
Supine to stand Time, s	11.5 (11.4)	3.2 (7.3)	10.8 (9.9)	3.2 (5.8)	-0.01	-0.1 (-2.3, 2.2)	-1.7	0.9613

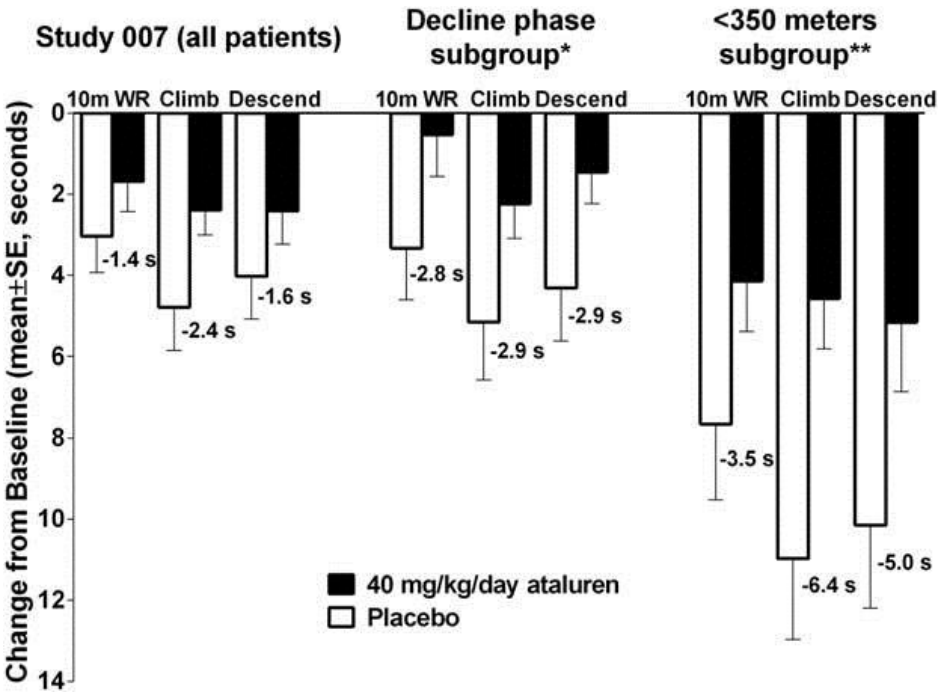
a For timed function tests, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

b % Difference, mean calculation = ataluren Week 48 Δ - placebo Week 48 Δ / placebo Week 48 Δ

c Corrected figure: please note this is the observed difference based on the cITT population. A calculation error resulted in the 1.4 second difference reported in the publication (Bushby, 2014) and the Translarna SPC

Source: Bushy, 2014; Ataluren Study 007 CSR

Figure C9.12. Timed function tests change from baseline to week 48 in Study 007 overall population versus decline-phase subgroup



Frequency of accidental falls

Falling is a common characteristic of DMD patients. The frequency of accidental falls in Study 007 was assessed by the patient or parent/ caregiver in a diary. Over the 48-week study duration, fewer accidental falls were seen in ataluren-treated patients than in placebo-dosed patients (Figure C9.13, Table C9.18). This translated into a relative risk of accidental falls at week 48 of 0.38 (95% CI: 0.16 to 0.94, nominal [redacted]) for ataluren 40 mg/kg/day versus placebo.

Figure C9.13. [redacted]

Table C9.18. Changes in falls per day by treatment group

Treatment arm	Falls / Day (SD)		
	Baseline	**Week 48**	**Change from baseline to week 48**
Placebo	0.54 (0.94)	0.72 (1.28)	[redacted]
Ataluren, 40 mg/kg/day	0.27 (0.48)	0.23 (0.53)	[redacted]

Source: (PTC, Study 007 CSR)

Upper and lower extremity myometry tests

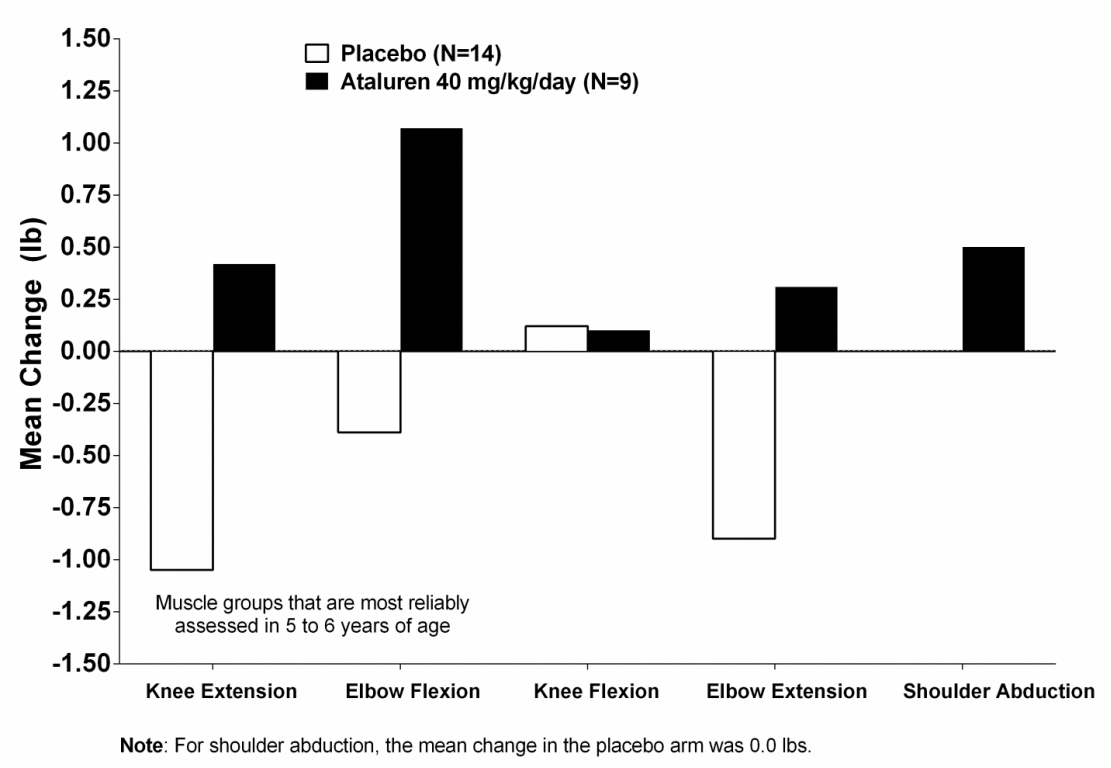
Over 48 weeks, patients treated with ataluren showed less decline in muscle strength relative to patients treated with placebo. These trends were more prominent at the 40 mg/kg/day dose (10, 10, 20 mg/kg/day dose), although the differences were not statistically significant.

Myometric evaluation of limb strength is less sensitive to changes in disease status compared to TFTs, and muscle strength, although severely affected in ambulatory patients with DMD, deteriorates at a much slower rate than muscle function. In the current study, mean changes from baseline to Week 48 in the placebo arm were small, demonstrating that little decline in myometry occurs over this timeframe, thus making it difficult to show a slowing of progression in muscle strength. Nevertheless, most of the myometry parameters showed less mean decline over 48 weeks for ataluren-treated patients versus placebo (Bushby, 2014).

Decrements in muscle strength over 1 year are greatest in younger patients with DMD (<7 years old) (McDonald 2013b; Abresch, 2011). Consequently, for clinical

studies of dystrophin restoration therapy, myometry can only be adequately evaluated in younger patients. Myometry results in patients aged 5 to 6 years of age who are treated with ataluren 40mg/kg/day showed stabilisation of their muscle function (Figure C9.14).

Figure C9.14. Change from Baseline to Week 48 in Myometry, Measured by Force Exerted, in the Study 007 Patients Aged 5 to 6 Years



Note: For shoulder abduction, the mean change in the placebo arm was 0.0 lbs.

Source: (Bushby, 2014)

Step activity monitoring

The difference in mean steps taken from baseline to week 48 favoured ataluren compared to placebo. A trend towards less time spent at no activity (0 steps/minute) and more time spent at medium activity (16 to 30 steps/minute) was observed in the ataluren 40 mg/kg/day dose compared to placebo.

Patient reported wheelchair use

Patient reported wheelchair use also showed a positive trend favouring ataluren (40 mg/kg/day dose) when compared to placebo. At baseline, the mean percentage of days of wheelchair use was 13.2% for placebo and 13.2% for ataluren 40 mg/kg/day. At week 48, the mean percentage of days of wheelchair use (95% CI) increased by 11.5% (95% CI: 4.36 to 18.54) for placebo and 4.0% (95% CI: -2.77 to 10.68) for

ataluren 40 mg/kg/day. This equates to a 7.5% mean difference between groups, which favours ataluren compared to placebo.

Health-related quality of life

Quality of life was assessed using the PedsQL, which contains four scales: physical, emotional, social, and school functioning. Positive trends towards improved quality of life were associated with ataluren treatment; the endpoint scores for physical functioning were numerically higher (indicating higher quality of life) in patients treated with 40 mg/kg/day ataluren than patients treated with placebo. This difference was more pronounced in the ambulatory decline phase subgroup, with a difference of 6.1 in the mean change in physical functioning score, favouring ataluren 40 mg/kg/day over placebo at Week 48.

A more pronounced effect of ataluren on the physical PedsQL domain is consistent with the nature of the treatment, which aims to decrease motor function decline.

Table C9.19. Patient-reported Health-Related Quality of Life, assessed by the PedsQL, ITT analysis set

Endpoint, score	Placebo (N=57)		Ataluren 40 mg/kg/day total (N=57)		
	Baseline, mean	Δ at week 48, mean	Baseline, mean	Δ at week 48, mean	Difference[a], mean (95% CI)
Physical	61.9	-1	59.3	2.4	3.4 (-5.5, 12.2)
Emotional	70.1	4.3	73.7	-1.8	-6.1 (-14.3, 2.1)
Social	63.4	7.8	65.1	3.9	-3.9 (-11.7, 4.0)
School	64.7	4.1	64.6	6.1	2.1 (-6.0, 10.1)
a Positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients					

Treatment satisfaction

Treatment satisfaction was assessed by the TSQM, which comprises 4 scales including effectiveness, side effects, convenience, and global satisfaction with therapy. Because no paediatric version of the TSQM was available, parents/caregivers reported from the perspective of the child. Overall, the results were similar across all treatment arms, including scores relating to side effects, and no statistically significant differences were observed.

Other outcomes

Other outcomes such as digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase expression showed similar results across treatment groups and differences were not statistically significant. Poor sample quality and inadequate methods for quantifying dystrophin expression at the time of the study meant that no reliable data could be obtained from the muscle biopsy samples.

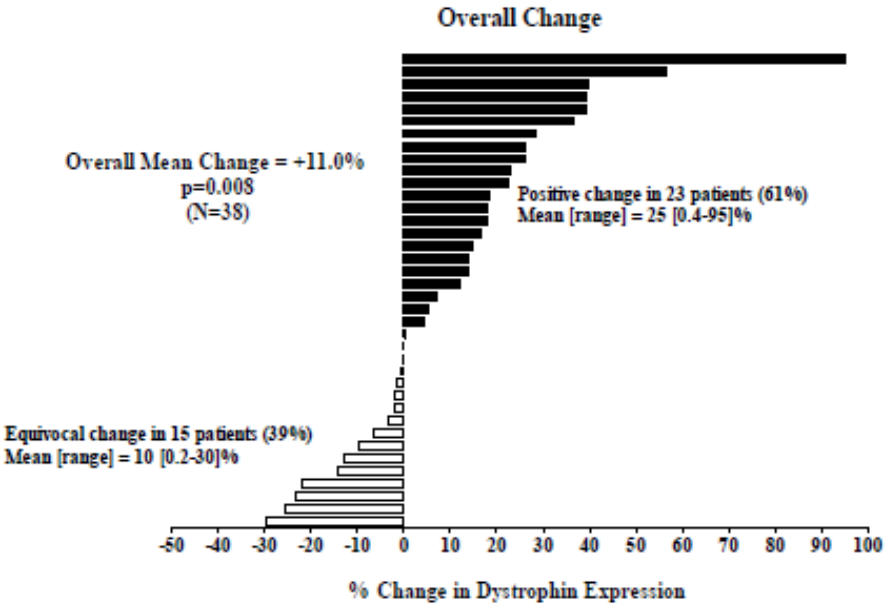
PTC124-GD-004-DMD (Study 004)

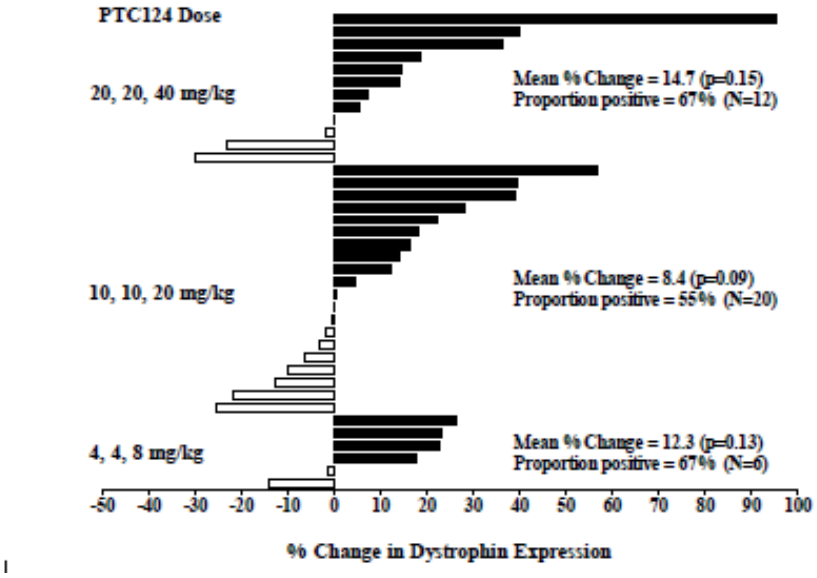
Dystrophin expression (primary endpoint)

At all three dose levels, patients demonstrated qualitative and quantitative increases in the staining for dystrophin.

A quantitative method for assessing the ratio of dystrophin/spectrin expression was developed and became available for this study. Based on this quantitative analysis, a mean change from pre-treatment to post treatment of 11% in dystrophin expression was observed ($p = 0.008$, paired t-test). Of the 38 patients, 23 (61%) showed a positive change in dystrophin/spectrin expression ratio after 28 days of treatment with ataluren (Figure C9.15). Response did not appear to be dependent on age, corticosteroid use, or location or type of nonsense mutation in either method.

Figure C9.15. Percentage change from pre-treatment in dystrophin expression for each patient after 28 days of treatment with ataluren





Secondary Endpoints

Upper and lower extremity myometry

Changes in upper and/or lower extremity myometry scores (for hand grip, elbow flexion, hip abduction, and knee extension) and timed function tests (standing from supine, running 10 metres, climbing four standard stairs) were small and not statistically significant after 28 days of treatment with ataluren. However, although not formally assessed, parents and teachers of several boys anecdotally reported evidence of greater activity, increased endurance, and less fatigue during treatment (Finkel, 2013).

Changes in Serum CK Levels

Due to muscle fragility, serum CK concentrations are universally elevated in subjects with DMD. The majority of subjects in each cohort had decreases in serum CK values when comparing end-of-treatment values to pretreatment values. Although no definite dose-response relationship can be discerned due to small and varying sample sizes, these changes were statistically significant at the 10, 10, 20 mg/kg/day and 20, 20, 40 mg/kg/day dose levels, but not at the 4, 4, 8 mg/kg/day dose level (Finkel, 2013).

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

As discussed in Section 9.6.1, the corrected ITT population (cITT) has been used in the analyses of Study 007 to account for two patients who suffered lower-limb injuries prior to baseline (one placebo-dosed and one treated with ataluren 80mg/kg/day). Their baseline 6MWD were radically lower than their screening and Week 6 values and therefore were replaced by their screening 6WMD values. This was also true for TFTs. While post-hoc, the use of the cITT was considered acceptable by the CHMP.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Identification of studies

The identification of studies reporting safety data for ataluren is described sections 9.1 to 9.5.

Detailed safety data from the Phase 2a and Phase 2b study (Study 004 and 007) is reported. In addition a safety update that includes data from completed and ongoing studies (Tables C9.4 and C9.5) is presented.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

Study 007

The number of adverse events reported was similar between the ataluren and placebo treatment groups in Study 007. The adverse events that were reported in ≥5% of patients in any treatment arm are summarised in Table C9.20. None of the patients discontinued treatment with ataluren or withdrew from the study because of a treatment-related adverse event and there were no deaths reported (Table C9.21).

Only 3.4% of ataluren patients (both doses) reported a serious adverse event compared to 5.3% in the placebo arm treatment group. Importantly, none of these were considered to be related to treatment with ataluren by the investigator. Treatment with ataluren 40 mg/kg/day was generally well tolerated.

Table C9.20. Overview of treatment emergent adverse events in the as-treated population

Parameter, n (%)	Placebo (N=57)	Ataluren 40 mg/kg/day (N=57)	Ataluren 80 mg/kg/day (N=60)
Patients with ≥1 adverse event	56 (98.2)	55 (96.5)	57 (95.0)
Adverse events by severity			
Grade 1 (mild)	21 (36.8)	16 (28.1)	20 (33.3)
Grade 2 (moderate)	26 (45.6)	31 (54.4)	27 (45.0)
Grade 3 (severe)	9 (15.8)	8 (14.0)	10 (16.7)
Grade 4 (life-threatening)	0	0	0
Adverse events by relatedness			
Unrelated	14 (24.6)	8 (14.0)	11 (18.3)
Unlikely	16 (28.1)	17 (29.8)	13 (21.7)
Possible	20 (35.1)	25 (43.9)	29 (48.3)
Probable	6 (10.5)	5 (8.8)	4 (6.7)
Discontinuations due to adverse events	0	0	0
Serious adverse events	3 (5.3)	2 (3.5)	2 (3.3)
Deaths	0	0	0

Table C9.21. Treatment-emergent adverse events with a patient frequency of ≥5%, Study 007

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm		
	Placebo	Ataluren 40 mg/kg/day	Ataluren 80 mg/kg/day
	N=57	N=57	N=60
	n (%)	n (%)	n (%)
Gastrointestinal disorders	37 (64.9)	42 (73.7)	44 (73.3)
Vomiting	22 (38.6)	32 (56.1)	27 (45.0)
Diarrhoea	14 (24.6)	11 (19.3)	17 (28.3)
Abdominal pain upper	9 (15.8)	9 (15.8)	13 (21.7)
Nausea	7 (12.3)	8 (14.0)	10 (16.7)
Abdominal pain	4 (7.0)	7 (12.3)	10 (16.7)
Flatulence	4 (7.0)	5 (8.8)	7 (11.7)
Stomach discomfort	0	4 (7.0)	5 (8.3)
General disorders	21 (36.8)	23 (40.4)	20 (33.3)
Pyrexia	12 (21.1)	14 (24.6)	7 (11.7)
Disease progression	6 (10.5)	4 (7.0)	5 (8.3)
Asthenia	2 (3.5)	3 (5.3)	4 (6.7)
Infections and infestations	43 (75.4)	38 (66.7)	39 (65.0)
Nasopharyngitis	13 (22.8)	13 (22.8)	10 (16.7)
Upper respiratory tract infection	10 (17.5)	9 (15.8)	11 (18.3)
Influenza	8 (14.0)	6 (10.5)	7 (11.7)
Gastroenteritis	4 (7.0)	9 (15.8)	3 (5.0)
Rhinitis	2 (3.5)	6 (10.5)	3 (5.0)
Ear infection	3 (5.3)	3 (5.3)	4 (6.7)
Gastroenteritis viral	3 (5.3)	4 (7.0)	3 (5.0)
Injury, poisoning and procedural complications	26 (45.6)	28 (49.1)	31 (51.7)
Fall	7 (12.3)	11 (19.3)	6 (10.0)
Procedural pain	7 (12.3)	6 (10.5)	8 (13.3)
Contusion	3 (5.3)	6 (10.5)	4 (6.7)
Joint sprain	1 (1.8)	4 (7.0)	4 (6.7)
Investigations	4 (7.0)	10 (17.5)	6 (10.0)
Weight decreased	1 (1.8)	5 (8.8)	3 (5.0)
Metabolism and nutrition disorders	3 (5.3)	7 (12.3)	6 (10.0)
Decreased appetite	2 (3.5)	5 (8.8)	5 (8.3)
Musculoskeletal and connective tissue disorders	19 (33.3)	25 (43.9)	28 (46.7)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm		
	Placebo	Ataluren 40 mg/kg/day	Ataluren 80 mg/kg/day
	N=57	N=57	N=60
	n (%)	n (%)	n (%)
Pain in extremity	6 (10.5)	7 (12.3)	8 (13.3)
Back pain	5 (8.8)	9 (15.8)	6 (10.0)
Arthralgia	2 (3.5)	2 (3.5)	6 (10.0)
Muscle spasms	5 (8.8)	3 (5.3)	1 (1.7)
Muscular weakness	1 (1.8)	3 (5.3)	5 (8.3)
Nervous system disorders	17 (29.8)	25 (43.9)	18 (30.0)
Headache	14 (24.6)	22 (38.6)	15 (25.0)
Dizziness	4 (7.0)	3 (5.3)	3 (5.0)
Respiratory, thoracic and mediastinal disorders	18 (31.6)	20 (35.1)	22 (36.7)
Cough	11 (19.3)	9 (15.8)	13 (21.7)
Nasal congestion	4 (7.0)	5 (8.8)	6 (10.0)
Oropharyngeal pain	4 (7.0)	6 (10.5)	4 (6.7)
Rhinorrhoea	6 (10.5)	4 (7.0)	0
Skin and subcutaneous tissue disorders	18 (31.6)	19 (33.3)	14 (23.3)
Rash	5 (8.8)	4 (7.0)	8 (13.3)
Scar	3 (5.3)	4 (7.0)	5 (8.3)

Abbreviations: MedDRA= medical Dictionary for Regulatory Activities

a Adverse events with a frequency of ≥5% across all three treatment arms are displayed alphabetically by MedDRA System Organ Class and from highest to lowest incidence across all three treatment arms within each System Organ Class. Patients who has the same adverse event more than once are counted only once for that adverse event

Adverse events with a frequency of ≤5% across all 3 treatment arms are not shown.

It should be noted that a very small minority of accidental falls (<0.25%) were reported by investigators as adverse events (7 in the placebo arm and 11 in the ataluren 40 mg/kg/day arm).

Laboratory findings

Data obtained from healthy volunteers suggested that exposure to ataluren might cause elevation of liver enzymes (but not bilirubin), serum cholesterol and triglycerides. However, these changes appeared to be dose-dependent and reversible after exposure to ataluren was stopped.

No significant haematology findings or signals of renal toxicity and effects on adrenal function were seen in studies 007 and 007e. The only finding was hepatic toxicity, which was expected given the data from healthy volunteers. There were ten ataluren-treated patients and one placebo-treated patient with isolated Grade 1 (mild) elevations in gamma-glutamyl transferase (GGT) or total bilirubin. Mean cholesterol and triglycerides levels were in the upper range of normal at baseline and increased to borderline-high or high levels in the ataluren arms and, to a lesser extent, in the placebo treatment arm during treatment, primarily in patients who were receiving corticosteroids.

No clear relationship was identified between the use of ataluren and pulse rate, respiration rate or temperature, but increased blood pressure was observed. This increase was slightly higher in the subgroup using corticosteroids than in the subgroup not using corticosteroids. There was also a slight increase in the diastolic blood pressure in all treatment arms.

Study 004

Adverse events were mild or moderate and showed no dose- dependent increase in frequency or severity. Procedural complications as a result of the muscle biopsy procedures (reported in 29 of the 38 subjects, 76.3%) represented the most frequently reported adverse events, followed by gastrointestinal-related events such as flatulence, diarrhoea, vomiting, abdominal discomfort or pain, and nausea (reported in 22 of the 38 subjects, 57.9%)(Finkel, 2013). No severe (Grade 3) or life-threatening (Grade 4) adverse events were reported. Similarly, there were no reports of deaths and none of the patients discontinued ataluren treatment due to adverse events (Table C9.22).

Table C9.22. Summary of adverse events in Study 004

	Ataluren dose groups		
No. (%) of Patients With:	**16 mg/kg/day (N=6)**	**40 mg/kg/day (N=20)**	**80 mg/kg/day (N=12)**
At least one adverse event	6 (100.0)	19 (95.0)	12 (100.0)
At least one treatment-related adverse event	2 (33.3)	5 (25.0)	10 (83.3)
At least one severe (Grade 3) adverse event	0 (0.00)	0 (0.00)	0 (0.00)
At least one life-threatening (Grade 4) adverse event	0 (0.00)	0 (0.00)	0 (0.00)
At least one serious adverse event	0 (0.00)	0 (0.00)	0 (0.00)
At least one adverse event leading to discontinuation of therapy	0 (0.00)	0 (0.00)	0 (0.00)

Source: Clinical Evidence Review

Safety Update

A Periodic Benefit-Risk Evaluation Report (PBRER) for ataluren presents a summary of safety data received by PTC Therapeutics International Limited collected for the period from 31 July 2014 to 31January2015 (PTC PBRER, 2015).

Cumulatively, an estimated total of 379 male subjects with nmDMD were treated with ataluren in nine clinical trials (four ongoing and five completed, Tables C9.4 and C9.5). This total includes patients who have received blinded study drug (ataluren or placebo) as of 31 January 2015 in the ongoing nmDMD Study 020. Based on the study's 1:1 randomization, it is estimated that approximately 115 patients have received ataluren in this study. It is also estimated that approximately 46 of the 93 patients who are currently enrolled in the nmDMD open-label extension trial (Study 020e) had received placebo in the preceding placebo- controlled study (Study 020).

All nmDMD patients were males and almost all of the subjects in the nmDMD studies were children (5 to ≤11 years) or adolescents (12 to ≤17 years), per their age as of study start. The safety database of unique individuals is described below by actual exposure data from completed and ongoing clinical trials (Table C9.23) and exposure by ataluren dose (Table C9.24).

Table C9.23. Estimated cumulative subject exposure from completed and ongoing trials in nmDMD

Treatment	Number of Subjects[a]
Ataluren	379
Placebo[a]	172

[a]Subject Exposure is estimated that all subjects who receive placebo subsequently receive ataluren.

Table C9.24. Estimated Cumulative Subject Exposure (nmDMD), Unique Patients in Clinical Trials (through 31 January 2015)

Abbreviated Study Number	Study Status	Placebo Naïve subjects (total subjects)	Ataluren 4, 4, 8 mg/kg/day	Ataluren 10, 10, 20 mg/kg/day Naïve subjects (total subjects)	Ataluren 20, 20, 40 mg/kg/day Naïve subjects (total subjects)	Ataluren any dose
004	Completed	0	6	20	12	38
004e[c]	Completed	0	0	0	25	0[a]
007	Completed	57	0	57	60	117
007e[b]	Completed	0	0	0	114 (173)	57[c]
008	Completed	0	0	0	6	6
016[a]	Ongoing	0	0	0 (107)	0	0[a]
019[a]	Ongoing	0	0	0 (93)	0	0[a]
020[d]	Ongoing	~115	0	~115	0	~115[e]
020e[d]	Ongoing	0	0	~46	0	~46[c,e]
nmDBMD Total		172	6	238	217	379

[a] All patients in this study received ataluren at previously administered dose levels, i.e., no new unique patients were enrolled at any dose level. In Study 019, one ataluren-naïve patient was entered via through a special exemption; this patient is not tabulated separately.

[b] Naïve patients who received placebo in the previous controlled trial (Study 007 or Study 020, respectively) and had not received ataluren in any of the previous Phase 2a open-label studies.

[c] Includes 5/6 patients who previously received 4, 4, 10 mg/kg/day in Study 004, and 20/20 patients who previously received 10, 10, 20 mg/kg/day in Study 004. One patient who previously received 20, 20, 40 mg/kg/day in Study 004 did not participate in Study 004e.

[d] Ongoing blinded placebo-controlled study or subsequent open-label extension study; number of patients exposed to ataluren is estimated.

Source: (PTC PBRER, 2015)

Serious adverse events

Cumulative summary tabulations of serious AEs (SAEs) reported in Company-sponsored clinical trials are provided in Table C9.25. The tabulations are organised by MedDRA System Organ Class (SOC) and include blinded and unblinded clinical trial data.

In the ongoing open-label Study 019, there was one event of cardiac failure that resulted in death. The death occurred during hospitalisation for multiple femur fractures, and followed aspiration pneumonia that manifested during surgery. The death was considered by the investigator to be unrelated to ataluren.

Table C9.25. Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials (Until data lock 31 January 2015)

System Organ Class (SOC), Preferred Term	**Count of cases - ataluren**	**Count of cases - placebo**	**Count of cases - blinded**
Cardiac disorders	12	0	1
Cardiac arrest	2	0	0
Cardiac failure	2	0	0
Cardio-respiratory arrest	1	0	0
Myocardial infarction	2	0	0
Myocarditis	0	0	1
Supraventricular tachycardia	1	0	0
Tachycardia	3	0	0
Ventricular arrhythmia	1	0	0
Gastrointestinal disorders	3	1	0
Abdominal pain	1	1	0
Intestinal obstruction	1	0	0
Volvulus	1	0	0
General disorders and administration site conditions	2	0	0
Death	1	0	0
Lethargy	1	0	0
Infections and infestations	9	2	0
Injury, poisoning and procedural complications	28	1	0
Back injury	1	0	0
Compression fracture	1	0	0
Femur fracture	23	1	0
Lower limb fracture	1	0	0
Spinal compression fracture	1	0	0
Tibia fracture	1	0	0
Metabolism and nutrition disorders (dehydration)	2	1	0
Musculoskeletal and connective tissue disorders	1	0	0
Nervous system disorders	3	1	0
Psychiatric disorders	1	0	0
Renal and urinary disorders	1	0	0
Respiratory, thoracic and mediastinal disorders	6	0	1
Vascular disorders	3	0	0
Total	**72**	**6**	**3**

Source: (PTC PBRER, 2015)

Significant findings from clinical trials in the reporting interval

No clinically important emerging efficacy and/or safety findings have been observed from ongoing clinical trials during this reporting period.

Long-term safety data

Information regarding patient survival and the occurrence of any new health conditions unrelated to the patient's underlying condition (e.g., tumours; chronic hepatic, renal, or endocrine disorders; etc.) has been collected from all nmDBMD patients who received at least 1 dose of ataluren, comprising of approximately 379 unique patients. The data indicates no pattern of unexpected new health problems in patients who have received ataluren.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

In clinical trials of patients with nmDMD caused by a nonsense mutation, the most frequent adverse reactions at the recommended dose were nausea, vomiting, and headache. These adverse reactions generally did not require medical intervention, and no patients discontinued ataluren treatment due to any adverse reaction (Translarna SPC). Ataluren requires limited monitoring.

The recent review of data, including long-term data from ongoing studies up to January 2015, revealed no new safety concerns. No changes in characteristics of listed or unlisted adverse drug reactions or increase in reporting frequency associated with ataluren were identified (PTC PBRER, 2015).

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The major goal of intervention during the ambulatory phase of dystrophinopathy is to maintain walking ability for as long as possible (Bushby, 2010b). Loss of ambulation has a profound impact on patients and their carers and is also is significant as it predicts the time at which subsequent loss of upper limb function occurs and the age at which critical pulmonary milestones are reached (Henricson, 2013a).

Maintenance of ambulatory capacity has been associated with prevention or delay of onset and reduced severity of scoliosis and the need for major surgery (Yilmaz, 2004; Kinali, 2007; Humbertclaude, 2012). In addition, the age at loss of ambulation has been shown to be predictive of onset of moderate and severe respiratory insufficiency. In groups of children that lost ambulation before 8 years (mean age at loss of ambulation 7.10), between 8 and 11 years (mean age at loss of ambulation 9.25) and between 11 and 16 years (mean age at loss of ambulation 12.01), the age of severe respiratory insufficiency occurred at a mean age of 14.7 years, 18.1 years and 22.1 years, respectively ($p<0.001$, between group comparison). FVC parameters

were also significantly correlated with the age at loss of ambulation and were statistically different between the groups (Humbertclaude, 2012). Age of loss at ambulation is also with mortality risk. Based on data from 473 Dutch Duchenne muscular dystrophy patients born and diagnosed during 1961-1982, van Essen et al reported that on average patients died 7.9 years after becoming wheelchair dependent (range 2.6-12.4 years)(van Essen 1997). The relative risk (RR) of death associated with becoming wheelchair bound a year earlier was estimated at 1.22 (95% confidence interval [CI] 1.09–1.36); and patients who lost walking ability before 10 years had a median survival of 17.3 years (95%CI 16.7–18.0 years) vs. the 20.1 years attributed to those who became wheelchair-bound at or after 10 years (95%CI 19.4–20.9 years). Furthermore, research by Rall and Grimm has also shown that a significant correlation exists between the age of becoming wheelchair bound and the age of death (p=0.016) in patients with DMD (Rall, 2012). The probability of death due to respiratory failure has also been shown to be significantly higher in patients that lost ambulation at an earlier age (p<0.03) (Humbertclaude, 2012).

Delaying ambulatory decline provides the direct clinical benefit of affording boys with nmDMD a longer period of self-sufficiency. In Study 007 patients treated with ataluren 40 mg/kg/day in the Phase 2b study demonstrated an observed 31.3-metre difference in change in 6MWD relative to placebo. In the statistical based model (MMRM) the estimated mean difference between ataluren 40 mg/kg/day and placebo was 31.7m (95% CI 5.1, 58.3; nominal p = 0.0197, adjusted p = 0.0367) (Haas, 2015; Translarna SPC). A reduction of 6MWD greater than 30 metres is considered clinically meaningful (McDonald 2013a, McDonald 2013b)(see section 9.9.2). Furthermore, each 30 decrement in 6MWD predicts increasing risk of loss of ambulation over the following 2 years (Mazzone, 2013; Lynn, 2015). Therefore by slowing ambulatory decline and delaying the point at which more rapid decline occurs, ataluren may also delay complete loss of ambulation and wheelchair reliance. Importantly, slowing the loss of walking ability may also have beneficial effects that could not be measured within a 48 week timeframe, that is, delayed loss of ambulation, and consequently delayed onset of scoliosis and respiratory insufficiency.

Natural history studies show that patients increase in walking ability in the early years, stabilise, then enter a decline phase, which leads, often rapidly, to wheelchair dependence (McDonald, 2010b; Mazzone, 2010; Mazzone, 2011; Goemans, 2013). The decline in the 6MWD occurs more rapidly in boys with a lower baseline 6WMD:

in particular a threshold of 350 metres seems to be a critical and is associated with a higher rate of decline (Pane, 2014). In one longitudinal study, a 6MWD of less than 330 metres was associated with a high risk of complete loss of ambulation over the following 2 years (Mazzone 2013). This was also observed in placebo arm of Study 007, where children with a higher baseline 6MWD (greater than 350 metres) tended to remain stable over the 48-week period, whereas those patients with lower baseline 6MWD (less than 350 metres) showed decline in their walking ability over 48 weeks (McDonald, 2013b; Figure C9.3). A baseline 6MWD of <325 metres was associated with a greater likelihood of progressing ≥10% in 6MWD and only boys with a baseline <325 metres lost the ability to walk over the 48 week study period (McDonald, 2013b). The efficacy of ataluren was observed across all groups of patients by baseline 6MWD, however the difference in 6MWD was of a greater magnitude in the sub-groups with more severe disease (<350 metre baseline 6MWD and ambulatory decline phase), due to the larger declines observed in the placebo group. This emphasises the need to treat children early, while the disease is more stable, in order to delay entry into the rapidly declining phase and subsequent loss of ambulation. The benefit of treating DMD early is supported by recently reported data from the UK NorthStar Network that showed that the effect of corticosteroid treatment in preserving ambulation is greater when used as an earlier age (Ricotti, 2015).

A ≥10% decline in ambulation over 12 months is associated with significantly greater likelihood of lost ambulation over the next 4 years (cited, McDonald 2013b). Study 007 included a pre-specified analysis of persistent 10% worsening in 6MWD. 26.3% patients treated with ataluren 40 mg/kg/day experienced (at least) 10% worsening at Week 48 compared to 43.9% in the placebo group (nominal p=0.0326).

In the secondary endpoints of Study 007, positive trends favouring ataluren 40 mg/kg/day over placebo were seen across multiple measures of physical functioning, including timed function tests; again, these positive trends were evident in the overall study population as well as in pre-specified patient subgroups. Timed function tests have traditionally been used to assess muscle function in DMD and are sensitive to changes in disease status (McDonald 1995, Beenakker 2005a, Mazzone 2011, Mazzone 2013). Ability to climb and descend a short grouping of stairs, ability to run in short bursts, or to walk a short distance unaided, e.g. to a bathroom, reflect the typical activities important in the lives of DMD patients. There is a strong linear relationship between TFTs and 6MWD and the time taken to complete the functional tests is predictive of a ≥10% decline in 6MWD (McDonald, 2013b). Importantly,

recent data indicated that timed function tests evaluating these abilities are, similarly to 6MWT, predictive of the time for a person with nmDMD to become non-ambulatory: a time of <6 s on the 10-m run/walk is associated with continued ambulation over the subsequent 12 months, and a time of >10–12 seconds is associated with a high risk of loss of ambulation over 12 months (McDonald, 2013b). Data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study demonstrated that a 10% decline in ambulatory function, as measured by the 10-m run/walk, is predictive of the number of months to loss of ambulation over 4 years (McDonald, 2013c). Escolar and colleagues defined the threshold for a statistical difference in TFTs as 0.4 ln (natural log) seconds. In the context of the ataluren 40mg/kg/day Phase 2b results, this was back transformed to ~1.5 seconds. In Study 007 patients treated with ataluren showed less decline in their ability to complete TFTs, with a difference of 2.4 seconds, 1.6 seconds and 1.5 seconds compared to placebo in the time taken to climb four stairs, descend four stairs or run/walk 10 metres, respectively.

Treatment with ataluren 40 mg/kg/day was also associated with positive trends in physical functioning in the PedsQL, reduction in the number of falls, and reduction in wheelchair use versus placebo over 48 weeks, thus allowing patients the possibility to remain self-sufficient for a longer period of time. Accidental falling is the most common cause of limb fractures in boys with DMD, and 35 to 40% of lower-limb fractures result in permanent loss of ambulation (McDonald, 2002; Vestergaard, 2001). Decreasing the rate of accidental falls would decrease the risk of fractures, pain and other trauma and their associated costs, as well as increase the confidence of boys in their walking ability.

Overall, an estimated total of 379 male subjects with nmDMD were treated with ataluren in nine clinical trials. Safety data identified no major concerns. In particular, the ability to co-administer ataluren with corticosteroids, which form part of the current standard of care in DMD, was demonstrated.

Collectively, these data document a favourable benefit-risk profile for ataluren 40 mg/kg/day as a treatment for nmDMD. The EMA established that the benefits of ataluren to public health justified approval by providing a treatment for a serious disease with high unmet need, characterised by inexorable deterioration of the condition and a fatal outcome.

As the first investigational new drug to address the underlying cause of dystrophinopathy, ataluren represents an important advance in personalised, genetic-based treatment of nonsense mutation disease.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The clinical efficacy and safety of ataluren 40 mg/kg/day has been investigated in an international, randomised, double-blind, placebo-controlled, international Phase 2b trial in patients with nmDMD. In order to enable early access by patients to medicines filling an unmet medical need for seriously debilitating or life-threatening diseases, the EMA may recommend the conditional approval of a new medicine with temporarily increased level of acceptable uncertainty over its benefits and risks. Despite limitations in the robustness of the efficacy data presented, ataluren was considered to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need (Haas, 2015).

There have been a limited number of large randomised studies in DMD and through the ataluren trial programme PTC Therapeutics are pioneering clinical trial research in this disease area. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials.

The limitations in the ataluren data do however present challenges for health technology assessment, which are discussed below.

Post-hoc analyses

A methodological limitation of the evidence of efficacy is that it is largely derived from post-hoc analyses from a single phase 2b trial. In the ITT analysis, despite the positive numerical trend for the low dose, the study results did not reach statistical significance for any of the doses tested. The post-hoc cITT analysis, in which baseline values for two patients that had suffered lower leg injuries prior to baseline were replaced by screening values, was considered by the CHMP to be an appropriate analysis. In this analysis, that was considered by the CHMP to be appropriate, a clinically meaningful observed difference of 31.3 metres (nominal p= 0.0197) was observed in the 40 mg/kg/day dose group compared to placebo (Bushby, 2014; Haas, 2015). A further change in this analysis is the inclusion of the baseline by visit interaction term in the MMRM model (discussed below).

Further post-hoc analyses were carried out in a sub-population of ambulatory patients in the decline phase of their walking ability. The selection of this sub-population (>7 years of age, treated with corticosteroids, 6MWD ≥150 m, and <80% predicted 6MWD) was considered clinically and scientifically justified by the CHMP, as well as by a convened group of external experts and patient representatives (Scientific Advisory Group (SAG) in Neurology) since a beneficial effect of ataluren on ambulation would be expected to be more readily detectable in these patients. Whilst the effect of ataluren was best measured in this sub-population, it was agreed by the CHMP that there should be no scientific reason, nor any safety imperatives, to with hold ataluren from nmDMD ambulatory patients aged 5 years or more who are at an earlier stage of disability progression (Haas, 2015).

The variability in the 6MWD over 48 weeks in this disease was unknown at the time the study was designed. Study 007 was powered to detect a 30-metre difference in 6MWD based on an anticipated standard deviation of 50 metres. By Week 48, however, it was evident that there was considerable heterogeneity in the rate of disease progression in nmDMD. This contributed to the higher-than-anticipated standard deviation ranging from 72–90 metres and meant that the study was underpowered (Bushy, 2014).

Further statistical analysis

Adjustment to the MMRM model

In reviewing the results of the MMRM analysis as well as a pre-specified supportive ANCOVA, a marked discrepancy was observed. Only 5/174 (2.9%) patients had missing 6MWD data at Week 48. Consequently, the ANCOVA on the original data (in which the 5 missing values at Week 48 were replaced with the last observation carried forward [LOCF)) and the MMRM analysis on original data at Week 48 would be expected to yield similar results. Instead, the p-values for the difference between ataluren 40 mg/kg/day and placebo that were obtained with the MMRM on original data (0.0905) and with the ANCOVA of original LOCF Week 48 data (0.0445) were at variance.

It was determined in consultation with Gary Koch, PhD, Professor of Biostatistics at the University of North Carolina that a baseline-by-visit interaction term should have been included to account for the varying effects of baseline over time. Inclusion of such a term in the analysis of longitudinal data has recently been described in the drug development literature, and has become a standard practice in the analysis of

such data (Mallinckrodt 2009). The baseline-by-visit interaction term proved to be highly statistically significant ($p<0.001$) and the MMRM analysis result at Week 48 ($p=0.0446$) mirrored the ANCOVA result ($p=0.0445$).

Addressing the non-normal distribution of the 6MWD data

The intent in the statistical analysis plan was to analyse 6MWD on its original scale (metres), unless the original data were non-normally distributed. Normality of changes in 6MWD from baseline was tested using the Shapiro-Wilk W-test at the 0.05 significance level. If there was a significant degree of non-normality, then log-transformed or, if necessary, rank-transformed data were to be used in the analysis.

Because the untransformed data and log-transformed data both exhibited significant non-normality, rank-transformed data were analysed. However, rank-transformation was not the optimal method for addressing the non-normal distribution of the 6MWD data. The resulting nominal p-values for comparisons of mean changes in rank-transformed 6MWD from baseline to Week 48 were 0.1490 for ataluren 40 mg/kg/day vs. placebo.

Dr. Koch also noted that since the protocol already specified a randomization test for addressing the effect of certain deviations from assumptions such as dynamic randomization and heterogeneity, this same test could also be used as a sensitivity analysis to address the effect of non-normality without requiring transformation of the data from its original scale. In this test, 10,000 copies of the Study 007 data are created by re-randomising the 174 patients 10,000 times. The copies are identical except for the random treatment arm a patient is assigned to. The MMRM analysis is then performed for each of the 10,000 data sets and the significance level is determined by the proportion of the 10,000 results that are as extreme as or more extreme than the analysis results of the original data. This was the case in only 281 out of the 10,000 data sets ($p=0.0281$) thus confirming that the deviations from assumptions do not compromise the robustness of primary analysis.

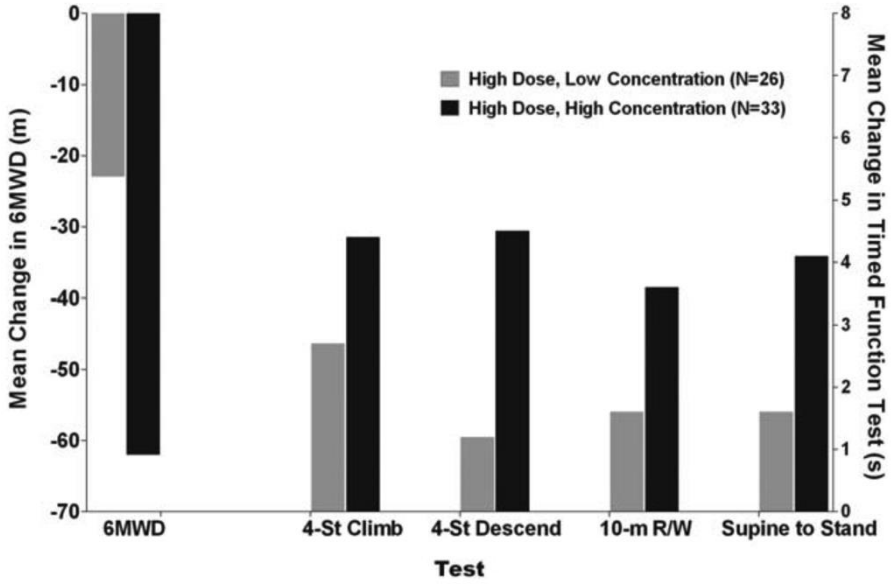
Dose response

Efficacy of ataluren was only observed at the 40 mg/kg/day dose.

The lack of effect on 6MWD of ataluren 80 mg/kg/day is consistent with nonclinical data and the exposure-response analysis. A bell-shaped concentration-response curve for production of dystrophin has been observed in cultured myotubes isolated

from mdx mice and from patients with nmDMD when they were exposed to ataluren (Welch, 2007; Finkel, 2013). In Study 007, an analysis of 6MWD and timed function tests by ataluren C_{2h} showed that ataluren 80 mg/kg/day patients with lower concentrations (i.e., those in the range observed with the 40 mg/kg/day dose) experienced better outcomes than those patients with higher concentrations (Figure C9.16)(Bushy, 2014).

Figure C9.16. Mean change in 6MWD and timed function tests by concentration



Study duration

The 48 week duration of the clinical trial is adequate to investigate the efficacy of ataluren. However, it was noted by the CHMP that the ability to measure a treatment effect in 1 year was more challenging in patients with stable ambulatory ability, as compared to the population of patients in the decline phase of ambulation, which might have impacted the outcome observed in the overall population of the study (EMA, 2014). Long-term safety and effectiveness data beyond 48 weeks are not yet available.

Study population

The population of patients included in the pivotal study (Study 007) was relatively heterogeneous: the distribution of age at study recruitment was wide; the age of diagnosis ranged from 0 – 10 years and the age range of recruited patients ranged from 5 to 20 years and patients with BMD as well as DMD could be enrolled. This heterogeneity may compound difficulties in demonstrating a significant treatment outcome, however given the lack of treatment alternatives and small numbers of

patients eligible it would seem unethical to exclude patients from clinical trials of potentially efficacious new therapies.

6MWT

Prior to Study 007, there was no accepted primary endpoint identified as suitable for evaluating efficacy in clinical trials of patients with dystrophinopathy. Given that ambulatory compromise is a key component of the DMD disease process and that ambulation measures the function of multiple muscle groups as well as cardiovascular activity, ambulation-related outcome measures are the most relevant end-points in DMD patients who are still able to walk. The 6MWT is a well-established outcome measure in a variety of diseases. It is accurate, reproducible, simple to administer, and well tolerated. The distance walked in the 6MWT (6MWD) is considered a valid clinical measurement of ambulatory function in patients of nmDMD (McDonald 2010). Importantly, the 6MWT assesses function and endurance, which are important aspects of DMD patients' disease status. A recently published analysis of data from Study 007 has shown that the 6MWT has high test-retest reliability (Pearson r=0.92) when comparing performance at pre-treatment screening and baseline tests (median length of time between the tests was 42 days, range 0 days - 91 days) (McDonald 2013a).

Several lines of evidence support the clinical relevance of a 30-metre difference in 6MWT in DMD patients. Using two statistical distribution-based methods McDonald et al estimated that a 28.5 to 31.7 metre difference in 6MWD should be considered the minimal clinically important difference (MCID)(McDonald 2013a). Evidence of the clinical relevance of these results comes from a recent report which showed that a 30-metre change in 6MWD over 48 weeks was considered a clinically meaningful change based on the patient/parent-reported Pediatric Outcomes Data Collection Instrument (PODCI), a quality of life measure, in DMD patients with disease status similar to Study 007 (Henricson, 2013). The authors also describe that, from a QoL-based perspective, a "meaningful" change in mobility might be related to small changes in walking distance at lower levels of function: for example even a 6 metre change in 6MWD could represent a clinically meaningful difference for patients at the lower end of the transfer and basic mobility scale. This is also supported by results of longitudinal natural history data in DMD, indicating that each 30-metre decrease in baseline 6MWD predicts increasing risk of loss of ambulation over the following 2 years (Mazzone, 2013; Lynn 2015). A 30-metre difference versus placebo in the 6MWD is in the range in which other drugs have been approved in multiple inherited

conditions, including mucopolysaccharidosis and Pompe disease (McDonald, 2013b).

Secondary endpoints

The majority of secondary endpoints showed positive trends in favour of ataluren versus placebo. The results on TFTs of muscle function indicated positive trends for climbing and descending four stairs and running/walking 10 m, as evidenced by less decline over 48 weeks. Over 48 weeks, ataluren-treated patients generally showed less decline in muscle strength, as evidenced by smaller decreases in most myometry parameters relative to placebo. However, observed differences were considered to be below the level of clinical meaningfulness. The decline in strength in the placebo group was minimal over the course of Study 007 and was lower than the reported MCID (McDonald, 2013b). Thus, in DMD a treatment that produces a therapeutic effect in strength over 48 weeks that would be greater than the MCID would at least need to produce small increases in strength in the functional muscle groups rather than reduction in decline in strength. In the course of DMD there is severe disorganisation within the muscle (at the level of muscle fibres and fibre bundles) as well as fibrosis and aberrant innervation. Therefore, in case of new production of functional dystrophin the regeneration processes and restoration of muscle strength may not be seen in a study of a shorter duration. Decrements in muscle strength over 1 year are greatest in younger patients with DMD (<7 years old) (McDonald 2013b). Myometry results in patients aged 5 to 6 years of age who are treated with ataluren 40mg/kg/day showed stabilisation of their muscle function (Figure C9.14). This is an important result as it demonstrates that treating children at an earlier age has a beneficial effect in terms of preventing loss of muscle strength.

Pharmacodynamics

In Study 004 61% (23 of 38) of patients with nmDMD demonstrated increases in post-treatment dystrophin expression. The dystrophin expression results in Study 007 were difficult to interpret due to generally poor sample quality as determined by the central laboratory pathologist, including freezing artefact, orientation, and fibrotic replacement (Bushby, 2014, Supplementary Appendix). Furthermore, a sensitive and reliable method for quantifying dystrophin is not currently available. This issue has been recognized in the DMD research community, where results of an initiative to develop and validate a reliable dystrophin quantification protocol have only recently been published (Anthony, 2014).

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base is relevant to the scope in both terms of study population and comparator, and is expected to reflect the outcomes that will be observed in clinical practice.

Ataluren at a dose of 40mg/kg body weight per day has shown an effect over and above the use of corticosteroids and is therefore expected to have a meaningful incremental benefit over the use of corticosteroids alone.

Evidence of the effect of ataluren on walking ability (ambulation), muscle function, muscle strength, ability to undertake activities of daily living, cardiac function, adverse effects of treatment and health-related quality of life has been presented. The 6MWT is an established outcome measure reflecting the global status of all the systems involved in walking, including the neuromuscular, pulmonary, and cardiovascular systems. The validity of the 6MWT and meaningfulness of decline in 6MWD in children with DMD are discussed above. Decline in the 6MWD is a highly relevant outcome for children with DMD. The rate of decline in the 6MWD is predictive of time to loss of ambulation. Loss of ambulation is one of the most serious complications of DMD and the age at loss of ambulation is predictive of disease progression and time to significant events such as diagnosis of scoliosis and respiratory insufficiency (Humbertclaude, 2012). TFTs are commonly used in clinical practice to measure muscle function in children with DMD and hence were included as an outcome measure in Study 007. The TFTs (time taken to stand from supine position, time taken to run/walk 10 metres, and time taken to climb and descend 4 standard-sized steps) provide important and established measures of functional capability in ambulatory patients. The tests are reproducible and simple to administer, are widely used to evaluate disease severity, are predictive of clinically meaningful milestones associated with disease progression (as discussed above).

Lung function was not directly measured as an outcome in Study 007. Study 007 was not of sufficient length and was not powered to detect differences in mortality. No deaths occurred during Study 007 in either treatment arm.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The ataluren study populations are comparable to the patients that will be treated in clinical practice. As DMD is an X-linked condition the trial populations only included boys and it is expected that although eligible there will be very few girls treated. Boys in the 40 mg/kg/day ataluren group of Study 007 were on average 9 years old (range 5-20 years). Although this range reflects the age of patients who would be treated in practice, it may be that over time the majority of patients start treatment at the lower end of the range (i.e. closer to 5 years old), with the aim of slowing progression as early as possible.

The randomised phase 2b trial, Study 007, was a placebo-controlled study. The choice of placebo for the reference arm was justified, as ataluren represents a first-in-class approach to DMD treatment where no approved standard therapy exists. During Study 007 all patients continued to receive the best supportive care they were on when they entered the study including, in many cases, corticosteroid treatment. The study therefore provides a comparison of efficacy and safety of ataluren compared to established clinical management without ataluren.

Analysis of the placebo arm of Study 007 has contributed to the understanding of the natural history of the 6MWD in DMD patients. Ataluren's effect appears most pronounced in DMD patients with advanced disease, i.e., patients who have begun a phase of decline in their ambulatory ability. According to experts consulted during the CHMP assessment of ataluren this effect is to be expected, as the decline in function of DMD patients is not linear, and increases with the duration of the disease (EMA, 2014). For these reasons, in a 48-week trial, the efficacy of ataluren in slowing the progression of the condition should be expected to be more notable in patients who already have marked disease progression.

However, it should also be noted that all categories of patients as categorised by baseline %-predicted 6MWD, including milder patients, showed a favourable effect for ataluren compared to placebo over 48 weeks (Figure C9.10). Therefore, although the magnitude of treatment effect of ataluren was more marked in patients in the ambulatory decline-phase, the activity of treatment with ataluren was seen across the disease spectrum. Because dystrophin stabilises muscle function but does not build strength, a dystrophin restoration therapy for DMD patients would be anticipated to preserve muscle function and stabilise or delay disease progression early on in

treatment. The patients and representatives consulted during the CHMP assessment defended the position that at the late stage of the disease even small effects providing longer independent use of arms and hands, or preserving the ability to feed and drink from a cup on their own, would represent a significant and important effect. Therefore treatment with ataluren should be available for all patients across the ambulatory spectrum in order to stabilise their condition and prevent further deterioration of muscle function thereby changing the course of the condition.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Ataluren is suitable within its licensed indication for all children diagnosed with nmDMD who are ambulatory and aged 5 years and older.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

Boys with DMD consistently report significantly lower quality of life (QoL) than their healthy peers (Uzark, 2012; Bendixen, 2012).

In brief, the aspects of the condition that most affect patient's quality of life are:

From a young age, a lowered capacity to engage in physical activity

When children diagnosed with DMD are young (~3-12 years) they cannot keep up with their peers, have problems walking, hopping, running, climbing stairs and fall frequently. Boys with DMD rarely have the chance to fully engage in physical activities normal for their age: running around and playing games with friends, playing football or riding a bike. As disease progresses they experience increasing difficulty walking, and are eventually only able to walk indoors after which time they progress quickly to permanent wheelchair use. Boys with DMD frequently fall over. This can result in fractures, which cause further incapacitation and may even lead to permanent wheelchair dependence (McDonald, 2002; Vestergaard, 2001). Reducing

the number of falls will therefore have both quality of life and improved long-term outcomes.

Learning and behavioural difficulties

Some boys with DMD also have difficulties with learning and behaviour the latter often being exacerbated with corticosteroid treatment. They report lower quality of life in terms of emotional, social, and school functioning across all age groups (Uzark, 2012). Emotional problems include anger and worrying about their future (Uzark, 2012).

Loss of the ability to walk

Losing the ability to walk and permanent dependence on use of a wheelchair is a key milestone in the lives of boys and is associated with a large decrement in quality of life (Landfeldt, 2014).

Losing the ability to walk has an obvious impact on their mobility and ability to carry out daily tasks such as washing and dressing and simply being able to easily get to a toilet. In addition it limits their opportunity for normal social interaction with potential increases in feelings of isolation. The loss of walking ability can also lead to children being unable to continue at mainstream schooling and/or at their local school as many are not wheelchair accessible. The ability to stand and therefore transfer is lost very soon after walking is lost, further impacting their independence. Even such aspects as visiting friends or relations can be severely limited (Contact a family, 2007).

"Being in a wheelchair, you realise things that you've never ever thought about before. This whole other world full of doubts, precautions and barriers opens up to you and results in you having to plan virtually everything you do, often faced by endless restrictions and education was no exception to this rule.

For me I did feel a great deal of social rejection, I'm a confident young person who thrives on social interaction but if the lift was broken I'd often be forgotten by my friends it would seem and spent most break and lunchtimes down the Support Centre as luck would have it the majority of my friends were afraid of lifts, meaning I'd have to go in there alone. Although I was extremely close to all the LSAs and still remain even to this day and they would gladly accompany me, the point I'm making is of that

of independence and the confidence in doing so. Access was also a highly prominent example of restriction to me" Patient with cerebral palsy (Contact a Family, 2007)

Once a child is fully wheelchair bound, home modifications are required. These are both expensive and not always readily available further limiting the child's environment and severely impacting on the quality of life of the family.

Likewise, transport needs are dramatically affected. If a child can no longer walk they are dependent on others in order to have access to their school, friends, and extended family members. The family are highly likely to need to buy a larger car, one that will fit a wheelchair, which has both personal cost and capability implications. Public transport is ill suited to the needs of people in wheelchairs (NHS Choices, 2015) and this can in turn increase the feelings of isolation and dependence for these children and young adults.

Children and young adults with DMD who remain ambulatory are less likely to be develop upper respiratory problems thereby delaying the requirement for ventilator support (Humbertclaude, 2012). In addition to the benefits associated with long-term respiratory function, being able to continue walking for longer enables children to maintain their normal social and school environment and keep a higher level of independence for longer. It is likely that this will enable them to attain a higher level of educational attainment and ultimately to have a higher opportunity to enter the workplace and lead a more normal adult life.

Loss of upper body function

In non-ambulatory boys and young men, there is gradual loss of upper limb, trunk and neck functions, so that grooming, toileting, bathing, dressing, sitting unsupported and eating become impaired or impossible to perform by oneself - severely affecting the quality of life of patients, their caregivers and families (EMA, 2015; Landfeldt, 2014). Boys may also suffer from curvature of the spine and require extensive surgery and physiotherapy in order to attempt to correct this. Even the possibility of maintaining upper limb function for longer means a person with DMD can continue to look after themselves through the ability to feed themselves, transfer to the toilet, bed etc. Also, they are able to continue to use a self-propelled wheelchair for longer which is a lower cost to the NH than an electric wheelchair.

"When the time came for me to have an electric chair none were available and my family had to independently raise the funds for an electric chair as I was in desperate

need of one. A little while later I was given one by the government which is what I use now but we still had to fund my original chair ourselves and the waiting lists for bigger sizes, upgrades etc on the government provided (chair) are absurd" (Contact a Family, 2007)

Loss of respiratory function

Boys with DMD suffer from a progressive decline in respiratory function leading to breathing difficulties and ultimately the need for ventilation, further impacting on their quality of life. As respiratory function initially declines ventilation support is provided during the day, usually with a mouthpiece. Dependence on permanent ventilation, which may require tracheostomy, usually occurs before 23 years of age (Ishikawa, 2011; Kieny, 2013). Maintaining the ability to walk for longer will delay the decline in respiratory function and therefore also delay the time to ventilator support being required (Humbertclaude, 2012).

Loss of independence

As described earlier, in boys with DMD there is a relentless deterioration of muscle function and progressive loss of muscle strength leading at an early age to permanent wheelchair dependence and eventually ventilation assistance. The progressive decline in muscle function prevents patients from independently performing many self-care activities, including self-dressing, toilet care and personal grooming. Most DMD patients will remain entirely dependent on others for their continued care, although a few will cope with their disabilities until their early adulthood, after which accumulation of disease symptoms will force them to become dependent on others.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Quality of life deteriorates as the disease progresses and physical capacity, including walking ability, decreases. Older boys report decreased physical functioning and daily activities (Uzark, 2012; Simon, 2011). A large study has estimated the quality of life of boys with DMD across different stages of ambulation (Landfeldt, 2014, discussed in Section 7). In this study, patient quality-of-life data were collected using the Health Utilities Index. In all countries assessed (Germany, UK, US, Italy) the

mean HUI-derived utility decreased through the 4 stages (early ambulatory, late-ambulatory, early non-ambulatory and late non-ambulatory). In UK children (n=191) the average HUI-derived utility was 0.66 and 0.58 for the early ambulatory and late ambulatory health states, respectively. A prominent reduction in quality of life is observed at loss of ambulation with average HUI-derived utilities dropping to 0.25 and 0.12 for the early non-ambulatory and late non-ambulatory state (Landfeldt, 2014).

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-consequence analysis.
- Results with confidence intervals.

In Study 007, quality of life was measured via the Pediatric Quality of Life Inventory (PedsQL), which contains four scales: physical, emotional, social, and school functioning (Varni, 2007a). The generic core module comprises 23 questions and the fatigue-specific module comprises an additional 18 questions. The PedsQL is available in all languages relevant for this study and was completed by the patient and/or a parent/caregiver. The appropriate age-specific version was completed by patients and it was agreed that a patient would stay with the same age-specific form even if, during the study, an age change made him eligible for a different form. If the patient lacked the ability to complete the PedsQL, the parent/caregiver was still to complete the instrument. If possible, the same parent/caregiver was to complete the instrument each time. The PedsQL was completed at each visit: screening, baseline and every 6 weeks until Week 48 (PTC, Study 007 CSR).

Positive trends towards improved quality of life were associated with ataluren treatment; the endpoint scores for physical functioning were numerically higher (indicating higher quality of life) in patients treated with 40 mg/kg/day ataluren than patients treated with placebo (not statistically significant). A more pronounced effect of ataluren on the physical PedsQL domain is consistent with the nature of the treatment, which aims to decrease motor function decline.

Table C10.1. Patient-reported Health-Related Quality of Life, assessed by the PedsQL, ITT analysis set

Endpoint, score	Placebo (N=57)		Ataluren 40 mg/kg/day total (N=57)		
	Baseline, mean	Δ at week 48, mean	Baseline, mean	Δ at week 48, mean	Difference*, mean (95% CI)
Physical	61.9	-1.0	59.3	2.4	3.4 (-5.5, 12.2)
Emotional	70.1	4.3	73.7	-1.8	-6.1 (-14.3, 2.1)
Social	63.4	7.8	65.1	3.9	-3.9 (-11.7, 4.0)
School	64.7	4.1	64.6	6.1	2.1 (-6.0, 10.1)
Total	64.7	3.2	65.2	2.3	-0.9 (-11.4, 8.6)
* Positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients					

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Although Study 007 measured HRQoL via the PedsQL, it is not possible to estimate health utilities from this instrument, either directly or indirectly. Khan and colleagues have published a study whereby they attempted to map PedsQL generic scale scores to EQ-5D weights (Khan, 2014). However, this mapping exercise was performed in a healthy population of school children; therefore, this mapping algorithm cannot be applied to the patient population from Study 007 as these populations have inherently different characteristics and are incomparable.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

The aim of the search was to identify all studies evaluating the HRQoL of DMD patients and caregivers that could be used generate utility weights for the economic model. There was no restriction on the design of studies.

A search was first conducted in July 2014 and an updated search was conducted for July 2014 to June 2015. The original search strategy aimed to capture all economic and quality of life studies and identified 748 studies from the literature, of which only one reported UK utility values. The update search of quality of life studies identified no further relevant studies.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.

- Results with confidence intervals.

The only study that has evaluated HRQL in DMD patients using a generic instrument is by Landfeldt and colleagues. This study is described in section 7. The study measured HRQL in DMD patients enrolled in registries in the UK, Germany, Italy and the United States. Patient quality of life was measured online using the Health Utilities Index whilst caregiver quality of life was measured using the EuroQol-5D-3L. A total of 2,346 were invited to participate in the study and 770 patient-caregiver responses were received (response rate = 42%). Of these, 191 patients were from the UK and 98% of the caregivers were parents to the patient. No standard errors or confidence intervals were presented in the publication for patient quality of life values by health state.

The resulting patients quality life scores are presented in Table C10.2. Caregivers were found to have a disutility of 0.11 (0.10-0.12).

Table C10.2. HRQL value derived by Landfeldt and colleagues

	Patients in health state	Utility
Early ambulatory (age 5-7)	46 (24%)	0.66
Late ambulatory (age 8-11)	62 (32%)	0.58
Early non-ambulatory (age 12-15)	34 (18%)	0.25
Late non-ambulatory (age 16+)	49 (26%)	0.12
Total	191 (100%)	

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

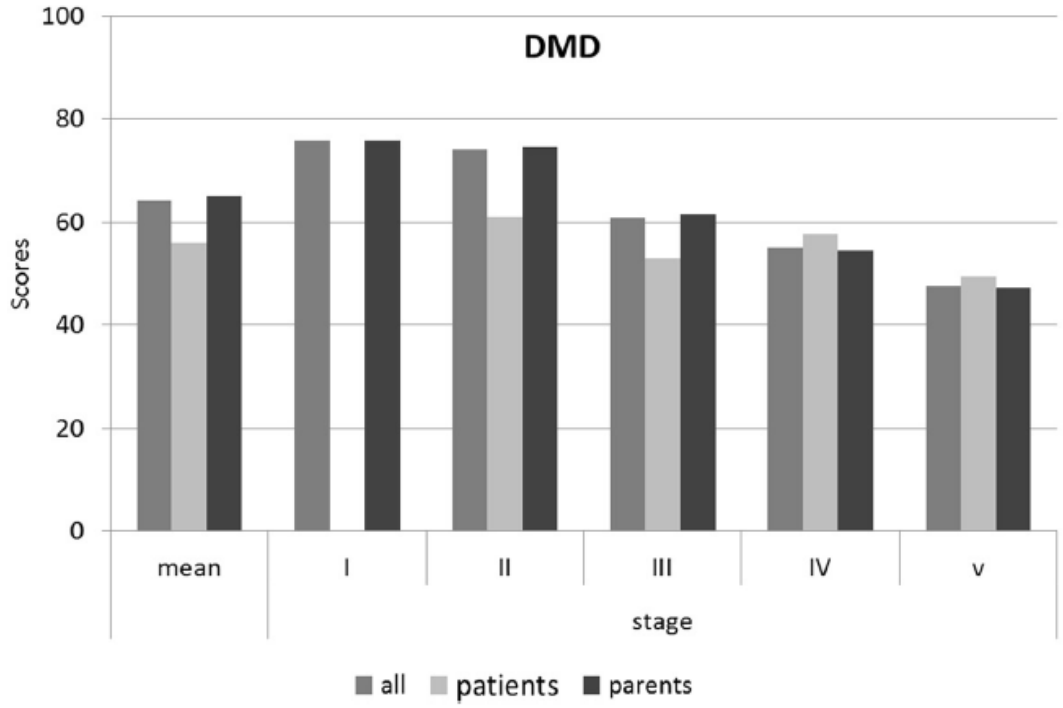
Utilities cannot be generated from the PedsQL instrument used in the clinical trial (section 10.1.14). Consequently, the values reported from the clinical trials cannot be compared to the utilities obtained from the literature search.

However, during the literature search, one relevant study by Schreiber-Katz and colleagues (2014) was identified at the first pass stage that may provide some comparison to the clinical trial data. The mean PedsQL scores for a German DMD population are presented in Figure C10.1. DMD patients assessed their HRQL worse

than their parents did ($p < 0.05$). The response rate for the questionnaires was 43%, with 248 patients included in the analysis.

The mean total PedsQL score across the ataluren and placebo arms in the clinical study was approximately 65, which is lower than the score observed by Schreiber-Katz and colleagues (approximately 75 in the ambulatory stages). This likely due to country variances since quality of life scores in the Landfeldt (2014) paper were also higher in Germany compared to the UK and US.

Figure C10.1. Mean PedsQL scores in a German DMD population



Stage I - Early ambulatory with mild impairment: Gowers' manoeuvre, waddling gait, walking on toes, problems with climbing stairs.

Stage II - Late ambulatory with high impairment: Walking becomes increasingly difficult, more problems climbing stairs and getting up from the floor, part-time wheelchair use.

Stage III - Early non-ambulatory

Stage IV - Late non-ambulatory

Stage V - Non-ambulatory with confinement to bed

Source: (Schreiber-Katz, 2014)

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

As discussed in section 9.7.2, ataluren appears to be well tolerated and the frequency of adverse events were similar in the placebo and ataluren arms of Study

007. It is anticipated that adverse events have a negligible impact on HRQL. No specific HRQL data is available for adverse events.

Quality-of-life data used in cost-consequences analysis

10.1.9 Please summarise the values you have chosen for your cost-consequence analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

The study by Landfeldt and colleagues (2014) provided HUI-measured and EQ-5D-measured utility weights for patients and carers respectively. This study was chosen since it was the only study identified which provided utility values for DMD patients as required by the reference case.

The utility values used in the economic model are outlined in Table C10.3.

Given the inclusion criteria for Study 007, the early ambulatory utility was applied to the ambulatory health state in the economic model. No utilities were available for the impact of ventilation-assistance on HRQL so the late non-ambulatory utility was applied to all the non-ambulatory health state in the economic model. No disutility for scoliosis was available so it was assumed that scoliosis reduces utility by 0.1.

Given that DMD is a condition that generally requires life-long carer support from parents, siblings or other informal carers, it was appropriate to allocate a health-related disutility to the carers of patients with DMD. The base-case analysis does not consider carer disutility in order to meet the NICE reference case perspective of NHS and PSS; however, for the societal perspective, carer disutilities from Landfeldt and colleagues (2014) is applied.

Table C10.3. Health-related quality of life weights used in the model

Health state	Patient utility used in base case	Caregiver disutility	Total utility for heath state	Reference
Ambulatory	0.66		0.66	Landfeldt, 2014
Non-ambulatory	0.12	0.11	0.01	Landfeldt, 2014
Non-ambulatory and ventilation-assisted	0.12	0.11	0.01	Landfeldt, 2014
Non-ambulatory and scoliosis	0.02	0.11	-0.09	Landfeldt, 2014 and assumption
Non-ambulatory, ventilation-assisted and scoliosis	0.02	0.11	-0.09	Landfeldt, 2014 and assumption

Source: (Landfeldt 2014)

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Two clinical experts were consulted. Both are consultant paediatric neurologists with specialist expertise in the management of children with DMD as well as experience with ataluren. The first consultant was consulted during development of the health economic model and ratified the model inputs. The other reviewed the HST submission and model inputs, including utility data and extrapolation of 6MWD data.

Expert opinion cited that the patient utility values applied in the economic model are reasonable. The expert cited the greatest loss of utility in non-ambulatory patients is when they develop the inability of feed themselves. It is not clear from Landfeldt (2014) what level of disability survey respondents had but it is likely that the utility of patients in the latter stages of non-ambulatory disease have a lower utility than published.

Furthermore, the expert cited that the carer disutilities are likely to be drastically underestimating the burden of DMD on caregivers. 95% of DMD patients in the UK live with their families and require 24-hour care, placing a huge burden on time and income of households (Rodger, 2014).

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

There is a limited amount of literature detailing utility data associated with the HRQL of DMD patients. The Landfeldt (2014) study indicates that patients have a decrease in quality of life as their disease progresses in the ambulatory stage (12% decrease in utility between early and late ambulatory) and once they are non-ambulatory (0.13 decrease in utility between early and late non-ambulatory stages) but the biggest decrease in HRQL is between ambulatory and non-ambulatory health states (57% decrease in utility).

Defining health states of ambulatory and non-ambulatory in the cost-consequence model therefore captures the key variances in patients' HRQL throughout the duration of the disease. Since there is slightly more variation in the non-ambulatory stage than the ambulatory stage, it is appropriate to consider the impact of scoliosis on HRQL.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No additional health effects were identified.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed constant within each health state over time.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

No.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.

- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Ataluren will be considered as a treatment for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation. It can be added to existing standard treatment, including use of corticosteroids.

In this submission the following continuation rule (stopping criteria) is proposed:

If a patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to consider stopping ataluren treatment. Treatment should not be stopped while the patient has any degree of ambulatory ability as it has been shown with other treatments (corticosteroids) that withdrawal of medication at this time can have negative consequences. Patients should not stop treatment until at least 6 months after becoming fully non-ambulant**.**

With reference to the following considerations (Table C10.4) this continuation rule is considered to be robust, practical and can be implemented within the existing care pathway.

Table C10.4. Treatment continuation rule

Considerations for ataluren continuation rule	Rationale and how ataluren continuation rule addresses consideration
The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).	It is anticipated that no additional monitoring will be required. Determination of whether the patient is entirely dependent on wheelchair use for all indoor and outdoor mobility will be elicited from routine liaison with primary care and secondary care teams. The decision to stop treatment no later than 6 months after becoming fully non-ambulant will be captured within follow-up clinic appointments which occur at least 6 monthly.
The robustness and plausibility of the endpoint on which the rule is based.	This endpoint is plausible and has been determined based on expert opinion and evidence that treatment should not be stopped while the patient has any degree of ambulatory ability as it has been shown with other treatments (corticosteroids) that withdrawal of medication at this time can have negative consequences
Whether the 'response' criteria defined in the rule can be reasonably achieved.	The response criteria can be reasonably achieved as a patient will either be entirely wheelchair dependent or not.
The appropriateness and robustness of the time at which response is measured.	The suggested time point is a practical one which has been reached following discussion with clinical experts and would allow sufficient time to determine that the patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility.
Whether the rule can be incorporated into routine clinical practice.	The rule can be easily incorporated into routine clinical practice and evaluated on each visit to a specialist.
Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.	The value for money analysis for ataluren is based on the clinical trial data, which evaluated ataluren within its licensed indication of ambulatory DMD patients.
Issues with respect to withdrawal of treatment from non-responders and other equity considerations.	No non-responder criteria have been identified through either Study 007 or subsequent commercial use outside of England. Patients should not have treatment withdrawn while they and they physicians consider that they are benefitting from treatment.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

The aim of the search was to identify all economic studies for DMD that could be used to inform the design of the economic model or provide resource use or cost data for the economic model. A search was first conducted in July 2014 and an updated search was conducted for July 2014 to June 2015. The original search looked for all economic and humanistic (quality of life) studies so identified 748 studies from the literature. Only one study reported relevant data. The update economic search identified one further relevant study.

Table D11.1. Databases searched

Review type	Database	Interface
Economic evaluations (Search July 2014)	Embase®	Embase.com
	MEDLINE®	
	MEDLINE® In-Process	Pubmed.com
	NHS EED	Cochrane library
	EconLit®	EBSCO
Economic evaluations (Search June 2015)	EMBASE	Ovid
	NHS Economic Evaluation Database	Ovid
	Medline (R)	Ovid
	Medline complete	EBSCO
	EconLit	EBSCO

Embase®: Excerpta Medica Database; CENTRAL: Cochrane central register of controlled trials MEDLINE®: Medical Literature Analysis and Retrieval System Online; NHS EED: National Health Service Economic Evaluation Database

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Table D11.2. Selection criteria used for health economic studies

Inclusion criteria	
Population	Duchenne muscular dystrophy
Interventions	Any
Outcomes	Costs, resource use, cost-effectiveness, cost of illness, cost-utility
Study design	Any economic study
Language restrictions	
Exclusion criteria	
Population	
Interventions	None
Outcomes	
Study design	• Animal • Individual case study reports • Letters • Comment articles • Abstracts
Language restrictions	None

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

PRIMSA diagrams for the original search and updated search are provided in Figures D11.1 and D11.2. In the original search, one study met the inclusion criteria specified above (Landfeldt, 2014). In the updated search, 2 economic studies were found that met the inclusion criteria specified above. One of these studies by Landfeldt and colleagues (2014) was the same as identified in the original search (carried out in July 2014). The second study identified in the updated search was a German study by Schreiber-Katz and colleagues (Schreiber-Katz, 2014). In addition, one abstract of interest was found in the updated search and although not a full publication and thus not meeting the inclusion criteria, it is briefly discussed below due the relative lack of economic evidence in DMD.

Figure D11.1 PRISMA for original economic systematic review (up to 8th July 2014)

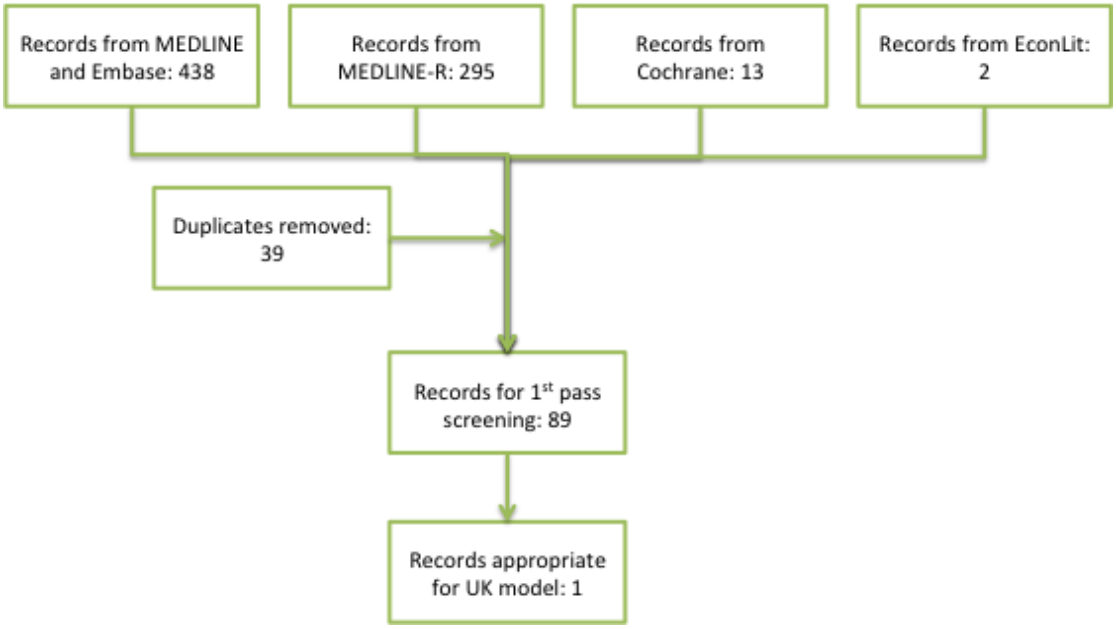
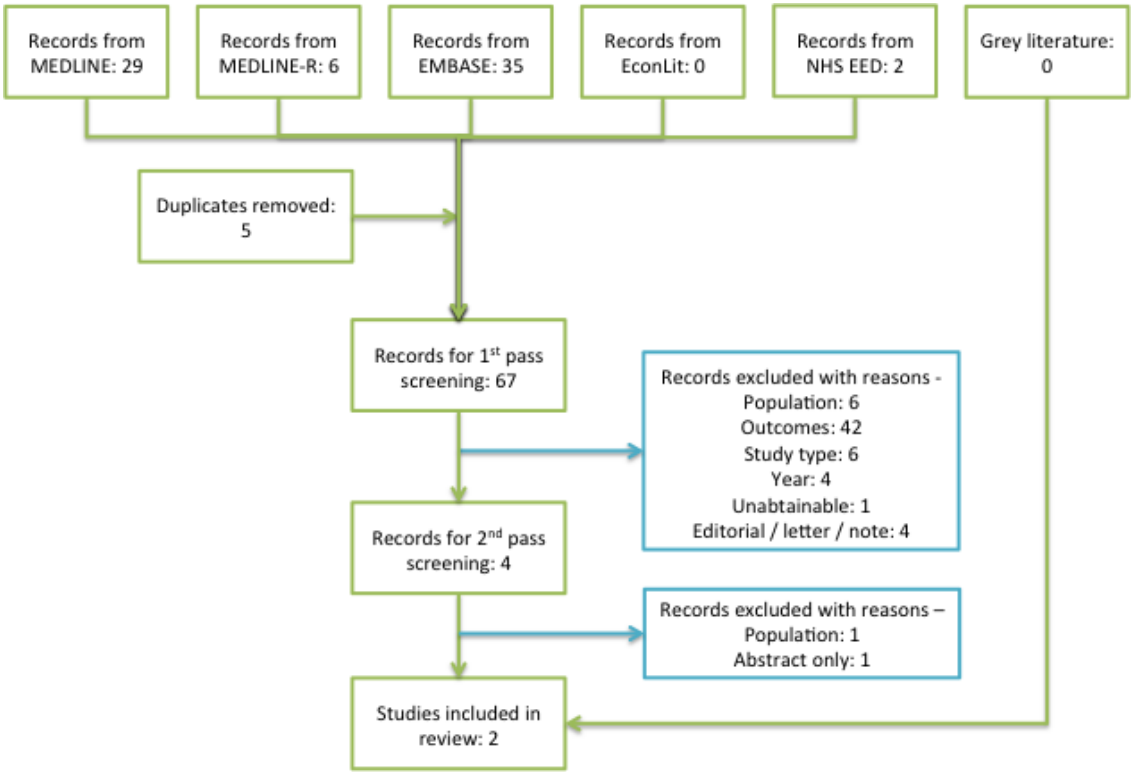


Figure D11.2. PRISMA for updated economic systematic review (July 2014 – June 2015)



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

Table D11.3 Summary list of all evaluations involving costs

Study name (year), Location of study	Patient population	Methods and patient outcomes	Results
Study 1 – Landfeldt et al (2014)[a] Germany, Italy, UK, United States	Male, DMD diagnosis, and age 5 years or older Patients with DMD were identified through national DMD registries, which form part of the global Translational Research in Europe–Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) network. All 4 registries had been in operation for at least 7 years, ensuring good representation across age groups. N= 770 (173 German, 122 Italian, 191 UK, 284 United States) completed the	Eligible patients and one of their caregivers (e.g. parent) were invited to complete a questionnaire online. The questionnaire consisted of questions regarding the patient (demographic information, health status, and DMD-related health care resource use) as well as the caregivers, their households, and DMD-related expenses. Recall periods were specified depending on the frequency of resource use in clinical practice and care guidelines (1 month, 6 months, or 1 year). Patient and caregiver quality-of-life data were collected using the Health Utilities Index and EuroQol EQ-5D instrument, respectively. Study materials were presented in the native language of	*Total cost of illness* The annual total cost of illness (direct and indirect) was estimated to be $72,870 (£53,325) per patient in the UK. Using DMD prevalence the authors estimated the national burden of DMD in the UK was $200,478,000 (£146,705,080). Informal care and indirect costs made up nearly half of the total cost of illness, with hospital admissions, visits to physicians, other healthcare professionals, tests/ assessments and medicines contributing 17% of the total cost of illness. Nonmedical community services made up 27% of costs whilst aids, devices, and investments (e.g. reconstructions of the home for adaptations for wheelchair accessibility contributed 10% of costs. Informal care in the UK was $14,340 (£10,494) per patient on average (20% of cost of illness) and indirect costs were $18,700 (£13,684) per patient

Study name (year), Location of study	Patient population	Methods and patient outcomes	Results
	questionnaire. A total of 2,346 patients were invited to participate in the study. Of those, 18 were not eligible (lived in a different country), 996 provided informed consent and started to complete the questionnaire, and 770 patient-caregiver pairs completed all sections of the questionnaire. The overall study response rate was 42%. In the pooled sample patients had a mean age of 14 years (range 5–43) and a median age of 12 years (interquartile range 9–17). The majority of caregivers were mothers to the participating patients with DMD.	each country and subject to review by the TREAT-NMD coordination team to ensure understandability, accuracy, and completeness. A pilot study was conducted to further establish questionnaire validity. Recruitment started July 2012 and ended July 2013. In addition to direct costs, DMD was also associated with large production losses, for both patients and caregivers. Less than 4% of patients were employed and between 27% and 49% of caregivers had reduced their working hours or stopped working completely, because of their son's DMD. For employed caregivers, the mean overall work impairment (loss in work time and productivity while working) was estimated at 29% (95% confidence interval [CI]: 24%–35%) for the UK sample. The mean activity impairment (ability to perform regular daily activities) due to the son's DMD was estimated at	(26% of cost of illness). The estimated mean per-patient annual direct cost of DMD in the UK was estimated to be $54,160 (£39,633), approximately 16 times higher than the mean per-capita health expenditure and the highest of the countries in the study. Mean per-patient annual cost of illness according to ambulatory status were as follows (approximate, taken from figure 2 of the paper): • Early ambulatory: $52,500 (£38,418) • Late ambulatory: $47,000 (£34,393) • Early nonambulatory: $64,000 (£46,834) • Late nonambulatory: $129,000 (£94,399) Of the direct medical costs, the non-medical community services (home help, personal assistants, nannies, and transportation services) made up 36% of the direct costs. *Household economic burden of DMD* Patients in the late ambulatory, early nonambulatory, and late nonambulatory classes had 38% (relative risk [RR]:1.38, 95% CI: 1.20–1.59), 181% (RR: 2.81, 95%CI: 2.41–3.27), and 191% (RR: 2.91, 95% CI:2.54–3.34) higher annual household economic burden compared with their

Study name (year), Location of study	Patient population	Methods and patient outcomes	Results
		42% (38%–46%) for UK patients. This corresponds to a weekly loss of approximately 44 hours of leisure time.	early ambulatory counterparts.
Study 2 – Schreiber-Katz et al (2014)[b] Germany	All male patients with a confirmed genetic diagnosis of DMD or BMD (n = 733) and/or their caring relatives were approached via the German dystrophinopathy patient registry (www.dmd-register.de). 363 patient/parent pairs were included in the analysis (response rate 50% = 363/733) or which 248 were DMD patients (response rate 43% = 248/571). The age of the DMD patients ranged from 1 to 42 years (median 11y),	A micro-costing method was used to examine the direct, indirect and informal care costs measuring the economic burden of DMD in comparison to BMD on patients, relatives, payers and society in Germany and to determine the health care burden of these diseases. Standardized questionnaires were developed based on predefined structured interview guidelines to obtain data directly from patients and caregivers using the German dystrophinopathy patient registry. To evaluate the direct costs of illness (costs of hospitalization, drug treatment, rehabilitation services such as physiotherapy and occupational therapy) the use of resources was identified and monetarily assessed using the official German price lists of 2013. Incurred costs of health care services were extrapolated to one year, assuming constant use of	Direct medical costs for disease stage I (early ambulatory) to stage V (late ambulatory and confined to bed) were: Early ambulatory €4,220 (£2,996) Late ambulatory €7,629 (£5,417) Early non-ambulatory €11,666 (£8,283) Late non-ambulatory €22,989 (£16,322) Non-ambulatory with confinement to bed €68,968 (£48,967) Including direct non-medical costs and indirect costs increased this to Early ambulatory €28,944 (£20,550) Late ambulatory €33,268 (£23,620) Late non-ambulatory €48,950 (£34,755) Late non-ambulatory €98,601 (£70,007) Non-ambulatory with confinement to bed €164,855 (£117,047)

Study name (year), Location of study	Patient population	Methods and patient outcomes	Results
		resources. A formulas was developed to calculate the economic loss of productivity caused by absenteeism, invalidity or changes in the work situation of patients and parents by analysing patients and parents indirect COI. Compared to the human capital approach, the authors state the developed formula delivers a more precise description of the real-life situation by taking factors such as short-time absenteeism or the actual wage levels into account.	

a Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)
b Converted to GBP using Euro to GBP conversion rate (0.71)

Study 1 – Landfeldt (2014)

This is the only economic publication providing costs for DMD in the UK. Costs are clearly split by type. The NHS relevant costs (17% of the total cost) are relevant to the cost-consequence analysis of ataluren when evaluated from the NHS perspective. The publication also provides indirect costs to be included in the societal perspective analysis. The costs are not split between resource use and unit costs but are nonetheless in line with the NICE reference case. This publication is also used to obtain utility estimates for the cost-consequence model (see Section 10). A disadvantage of the analysis is that outcomes were presented in terms of age groups rather than clinical severity. This means, for example, that patients aged 5 to 7 years may have had a range of disease severity since a patient's age does not exactly represent their stage in the disease.

Study 2 – Schreiber-Katz (2014)

This study is for a German population. The costs are well presented by disease severity and cost category. The results provide an appropriate comparison for the UK costs from Landfeldt (2014) (Table D11.4 and D11.5) but have not been used directly in the cost-consequence model. The distribution between cost categories is similar in the two studies.

When compared to the German population in the Landfeldt study the total direct and indirect costs are much higher in the Schreiber-Katz study and also for most of the different stages of ambulation apart from the late non-ambulatory stage as shown in Table D11.4. It should be noted the different stages of ambulation are described differently in the two papers and so the costs presented in the table for the different stages of ambulation are an approximation.

The differences in the total direct and indirect costs described in the two papers are probably due to the different methodology use for cost estimation, but do seem suggest that the costs from the Landfeldt study which have been used in the health economic model are an underestimation.

Table D11.4. Comparison of costs in German DMD patients by disease stage and Total Direct and Indirect Costs of Illness

	Landfeldt 2012 $	* Landfeldt 2013 €	Schreiber-Katz 2013 €	Difference
Early Ambulatory	36,000	28,717	15,866	-45%
Late Ambulatory	51,000	40,682	18,313	-55%
Early Non-Ambulatory	67,500	53,844	40,904	-24%
Late Non-Ambulatory	90,000	71,792	86,372	20%
Average direct Cost of Illness	42,360	33,790	50,230	49%
Average indirect Cost of Illness	20,770	16,568	28,683	73%
Total COI	**63,130**	**50,358**	**78,913**	**57%**

* costs inflated to 2013 prices and converted to Euros

A study by Fabriani et al (2014) has been excluded from the analyses due to it being only available as an abstract. The objective of this study was to estimate the average annual direct and indirect costs associated with DMD in Italy considering both National Health System (NHS) and a societal perspective. A probabilistic prevalence-based cost of illness model was used to estimate the economic impact of a rare disease such as DMD. All the costs were determined through a survey that families registered with the Italian Muscular Dystrophy Association “Parent Project onlus” completed on-line. NHS and family prospective were analysed by dividing the patients into three age groups (<8 years, 8-16 years and >16 years). The human capital approach was used to determine loss of productivity due to absenteeism, while a bottom up approach was used to calculate direct costs. A probabilistic sensitivity analysis with 5,000 Monte Carlo simulations was performed, in order to test the robustness of the results.

Indirect costs were by far the most significant, total expenditure on the NHS being around €475M [€474,634,836 (95%CI: €300,028,168 - €698,965,090)] per year, while the direct healthcare costs were nearly €7.5M [€7,475,596 (95%CI: €5,124,369,29 - €10,263,785)] and nonmedical costs were nearly €13M [€12,944,879 (95% CI: €7,925,699 - €19,175,331)]. Patients over 16 years old cost more than those between 0 and 7 years old, and more than those aged between 8 and 15 years. In terms of private expenditure, the model estimated €3M [€2,910,506 (95%CI: €345,231,83 - €718,786)] for the direct costs, and around €185M [€185,333,744 (95%CI: €114,177,282 - €273,446,219)] for the nonmedical costs.

The authors concluded that although DMD is a rare disease, its economic impact on NHS was quite remarkable. Furthermore, the most of the impact is on families and society. The Landfeldt study included an Italian population but it is not possible to see how they compare as the Italian study is only available as an abstract and costs per patient were not described.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable – publication resulting from the search were cost studies rather than health economic modelling studies.

12 De novo cost-consequence analysis

Section 12 requires the sponsor to provide information on the de novo cost-consequence analysis.

The de novo cost-consequence analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-consequence analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-consequence analysis?

The cost-consequence analysis of ataluren is conducted within its licensed indication of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (Translarna SPC, 2014). Ambulation is defined as the time during which patients are able to walk some distance (i.e. 6MWD > 0m).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-consequence analysis is different from the scope.

Ataluren is compared to best supportive care, in line with the scope.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

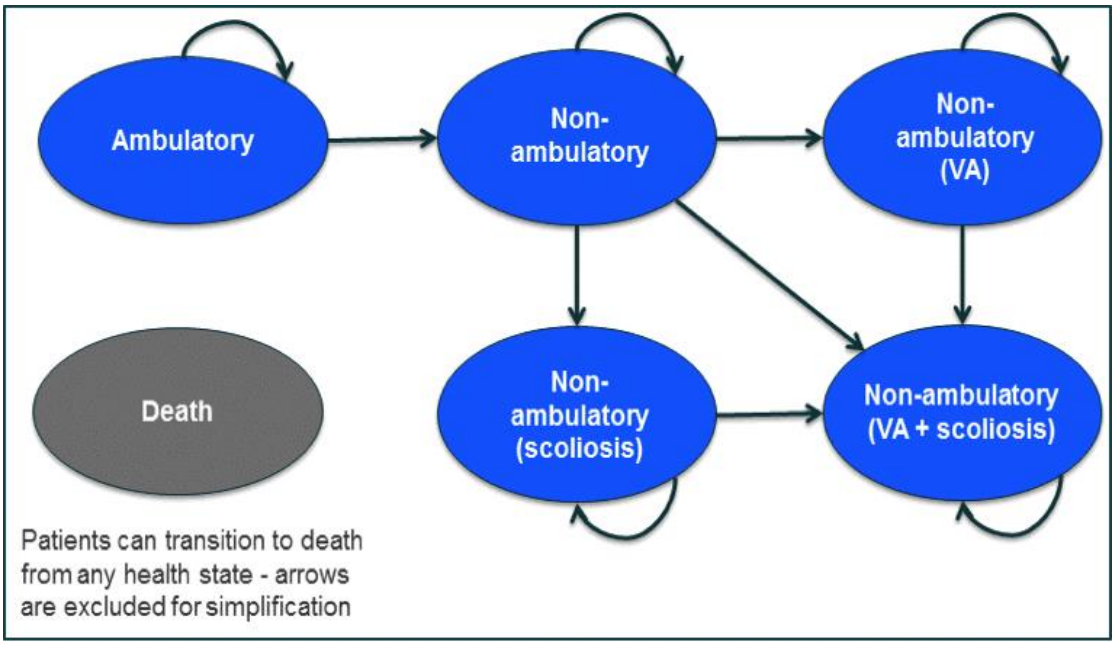
A semi-Markov model structure was used with a cycle length of 3 months. The model tracks patients as they progress through a series of health states. Based on the

natural history of disease progression and variation in resource utilisation, six mutually exclusive health states were identified:

- Ambulatory
- Non-ambulatory (NA)
- Non-ambulatory and ventilation-assisted (NA-VA)
- Non-ambulatory and scoliosis (NA-S)
- Non-ambulatory, ventilation-assisted and scoliosis (NA-VA-S)
- Death

The hypothetical cohort in the model transitions between these health states over the course of the model time horizon. A schematic of the model is presented in Figure D12.1.

Figure D12.1 Cost-consequence model structure



VA = ventilation assisted

At model entry, the entire cohort is ambulatory. As disease symptoms progress patients transition to the NA health state. Patients who are non-ambulatory can either transition to ventilation-assisted, scoliosis, or both. It is possible to transition to death from each health state.

The benefit of ataluren is a delay the transition to loss of ambulation (the non-ambulatory health state), which is then expected to impact on the progression to

subsequent health states requiring either assisted ventilation and/or scoliosis corrective surgery. These health states are specifically considered as they are resource intensive and are associated with decreased utility.

An overview of the properties of the model is provided in Table D12.1.

Table D12.1 Overview of cost-consequence model properties

Aspect	Details	Justification
Analytical method	Multi-state semi Markov model	Most appropriate method for modelling long-term chronic conditions with dynamic deterioration in health status
Software used	Microsoft Excel® 2010	Transparent and widely used software
Model perspective(s)	• Base case: NHS and PSS • Additional scenario: Societal	All relevant perspectives
Cycle length	3 months	nmDMD is a chronic, long-term condition in which disability progression occurs over many years, this cycle length is sufficiently sensitive to capture even the slightest change in patient utility due to treatment
Discounting	3.5% costs and benefits	In line with the NICE reference case
Time horizon	Treatment duration	Patients receive treatment only in the ambulatory stage of the disease thus the chosen time horizon is the latest point at which one on more patients are simulated to the be in the ambulatory state.
Patient population	Ambulatory boys with nmDMD aged ≥5 years	Licensed indication and in line with scope
Health states	• Ambulatory • NA • NA-AV	Based on data availability and expert clinical opinion

	• NA-S • NA-VA-S • Death	
Comparator	Ataluren on a platform of best supportive care (BSC) versus BSC alone	In line with scope

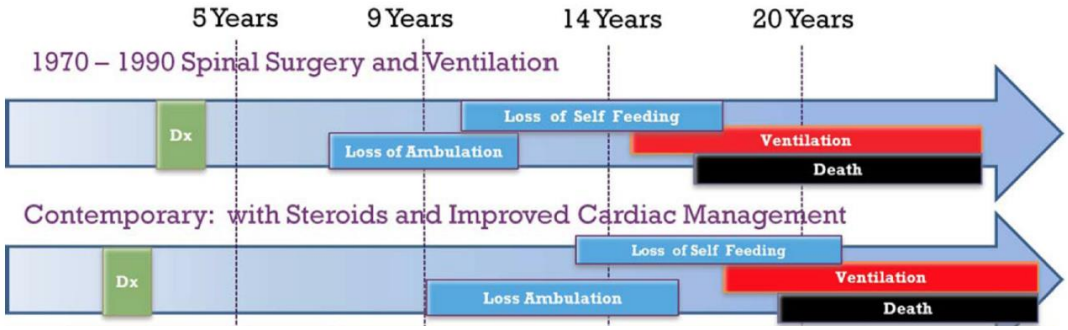
12.1.4 Justify the chosen structure in line with the clinical pathway of care.

DMD is a severe, progressive and rare genetic childhood disease characterised by a rapid decline in physical functioning with subsequent respiratory and cardiac failure, leading to early death (McDonald, 2013). Due to relentless muscle wasting and decline in physical function, DMD causes long-term disability, with patients becoming non-ambulatory and therefore wheelchair dependant at 13-14 years of age or earlier. In late-stage disease, patients with DMD lose the ability to self-ventilate, and some develop scoliosis, which requires corrective surgery and specialist follow-up care. It is possible for patients to develop scoliosis and require assisted ventilation simultaneously.

DMD is life limiting because of its effects on the heart and the respiratory muscles, leading to patients requiring ventilation support and becoming affected by cardiomyopathy (Figure D12.2). Most patients with DMD die from heart or lung failure in adolescence or early adulthood, and patients rarely survive beyond their third decade.

A multi-state semi-Markov model structure was chosen, as it is the most appropriate method for modelling long-term chronic conditions with dynamic deterioration in health status.

Figure D12.2 Schematic of the natural history of DMD (McDonald, 2013)



Dx = DMD diagnosis

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

The assumptions made in the model and the corresponding justification for each is presented in Table D12.2.

Table D12.2 Assumptions made in the cost-consequence analysis

Aspect of the model	Assumption	Justification
Model structure	Ambulation is defined as a 6MWD > 0m	In line with clinical definition and disease characteristics
Model structure	The disease is accurately simulated by transitioning a hypothetical cohort of patients through 6 heath states as defined in section 12.1.3.	There is no universally accepted method of measuring disease progression by severity. The health states used in the model were chosen based on clinical opinion and resource utilisation patterns.
Clinical data	The data from the 48-week study is extrapolated at a linear rate to find the time at which patients lose ambulation	There is no data to suggest otherwise. Clinical opinion supports that the effects of ataluren would continue over the long-term and that there is no reason to suggest that the treatment effect would not persist.
Clinical data	The data form the international study is representative of the UK population	Patients from England and other parts of the UK participated in Study 007.
Clinical data	The time to loss of ambulation observed by Ricotti (2013) is representative of the	Median time to loss of ambulation in Ricotti (2013) was 14 years in those patients receiving daily steroids and in Study 007 74% of patients received daily steroids. The extrapolated data

	placebo arm of the study	from the placebo arm of Study 007 estimates that a patient would lose ambulation 6 years from baseline. The age at baseline was approximately 8 years indicating a mean loss of ambulation of 14 years, in line with the Ricotti data.
Adverse events	The model assumes that there are no adverse effects related to treatment based on clinical trial data, and no additional costs or health effects are included for adverse events	Data from Study 007 suggests ataluren has a very favourable safety profile and there were no significant differences in the incidence of adverse events between the ataluren and placebo arms. Any adverse events that did occur did not have significant impact on the cost of care of quality of life of the patient.
Treatment	There are no treatment discontinuations due to adverse events or other reasons other than loss of ambulation	Very few discontinuations occurred in Study 007 and discontinuations are unlikely to occur in clinical practice
Treatment	Treatment adherence is assumed to be 100%	Adherence in Study 007 was high (over 97%) and non-compliance is unlikely to occur in clinical practice
Treatment	Ataluren is not expected to require any additional resource use over and above standard practice	Expert opinion
Survival benefit	Ataluren delays mortality.	Given that ataluren delays the time to loss of ambulation, it is also expected that ataluren will delay mortality. Given the duration of Study 007 (48 weeks) data on mortality was not captured in the clinical trials thus a risk reduction of mortality following delayed ambulation was obtained from the literature as well as expert opinion
Costs	The cost of scoliosis surgery occurs at the point of scoliosis diagnosis	Expert opinion is that most DMD patients that develop scoliosis in the UK will receive surgery.

12.1.6 Define what the model's health states are intended to capture.

The model heath states are intended to capture the disease progression of an average patient from DMD diagnosis through to death. This includes all points in the disease which have a substantial cost and quality of life impact.

12.1.7 Describe any key features of the model not previously reported.

Please see Table D12.1.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-consequence analysis.

Time to loss of ambulation

Data from Study 007 were used to elicit the decline in 6MWD for placebo and ataluren. Declines per week were estimated using a regression of least squares mean change from baseline from Week 24 to Week 48 from the study.

The regression analysis was performed on the data from weeks 24-48 (see Figure C9.7) since the observations seen in weeks 24 to 48 are expected to be more reflective of the long-term treatment effect of ataluren and the decline seen in best supportive care patients given the disease modifying effect of the drug and the known natural history deterioration as well as in patients receiving best supportive care (BSC). Using only the latter data is a conservative assumption since ataluren clearly has a greater benefit than BSC in improving 6MWD in the first 24 weeks of the study.

The resulting coefficients of 48-week 6MWD changes between placebo and ataluren are presented in Table D12.3. These declines were extrapolated linearly to estimate the time to loss of ambulation (LoA) as defined by a 6MWD=0m.

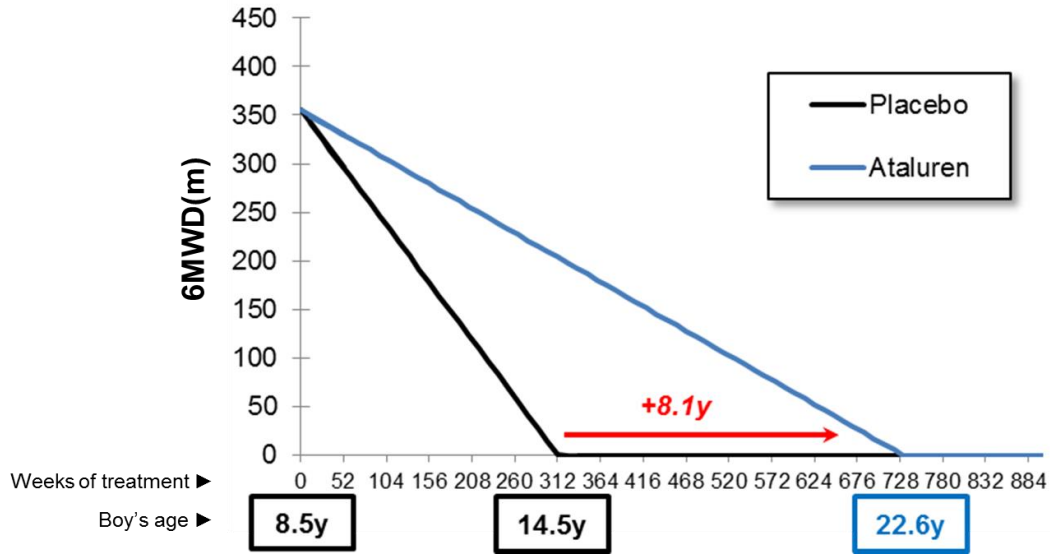
Table D12.3 48-week 6MWD changes extrapolated from the Study 007

Baseline	Placebo	Ataluren	Difference
355.7m	-59.0m	-25.2m	33.8m

The mean LoA was at week 313 (6 years) with placebo and at week 733 (14.1 years) with ataluren, corresponding to a difference of 420 weeks (8.1 years). The mean age at baseline in Study 007 was 8.5 years. Using this as the baseline age in the model, LoA is expected to occur at 14.5 years with placebo compared to 22.6 years for

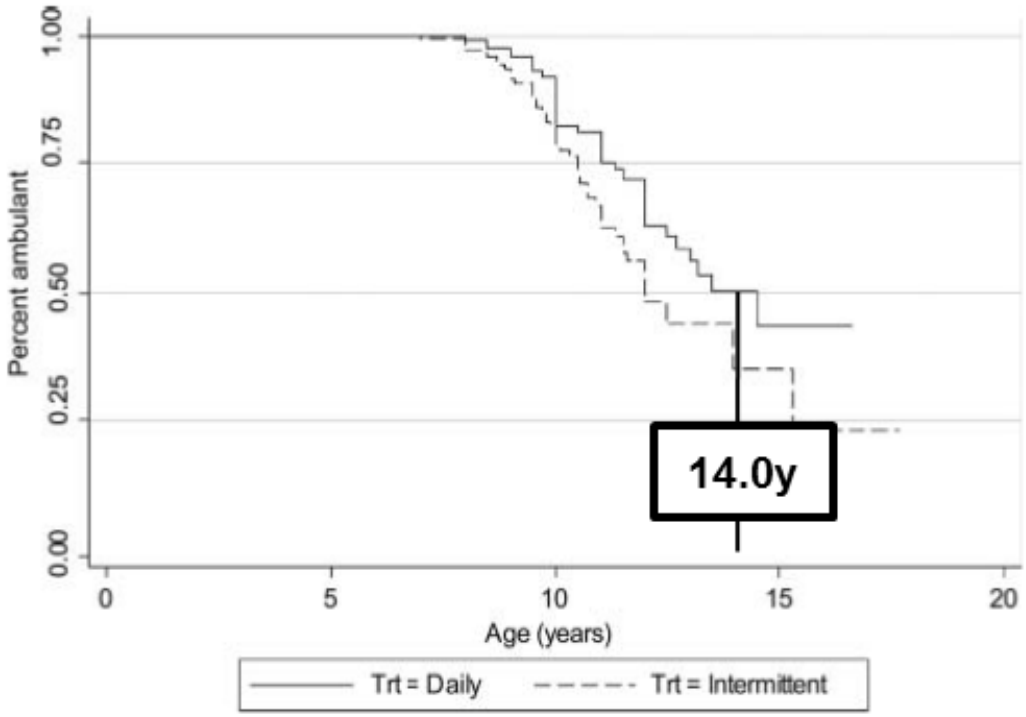
patients treated with ataluren. Figure D12.3 illustrates the extrapolated decline between placebo and ataluren from Study 007 and estimated time to LoA.

Figure D12.3 Time to loss of ambulation used in the model (derived from Study 007)



Whilst this linear extrapolation gives a reliable estimate of the mean time to loss of ambulation, the shape of the curve is unlikely to accurately reflect clinical practice. A search of literature was performed to find Kaplan-Meier estimates of time to loss of ambulation, which found one study. Ricotti et al (2013) reported long-term outcomes of boys with DMD in the UK, comparing daily versus intermittent use of corticosteroids. The Kaplan-Meier survival curve for LoA is presented in Figure D12.4, which shows that LoA occurs at a median age of ~14 years with daily corticosteroid use.

Figure D12.4 Time to loss of ambulation in boys with DMD (Ricotti, 2013)

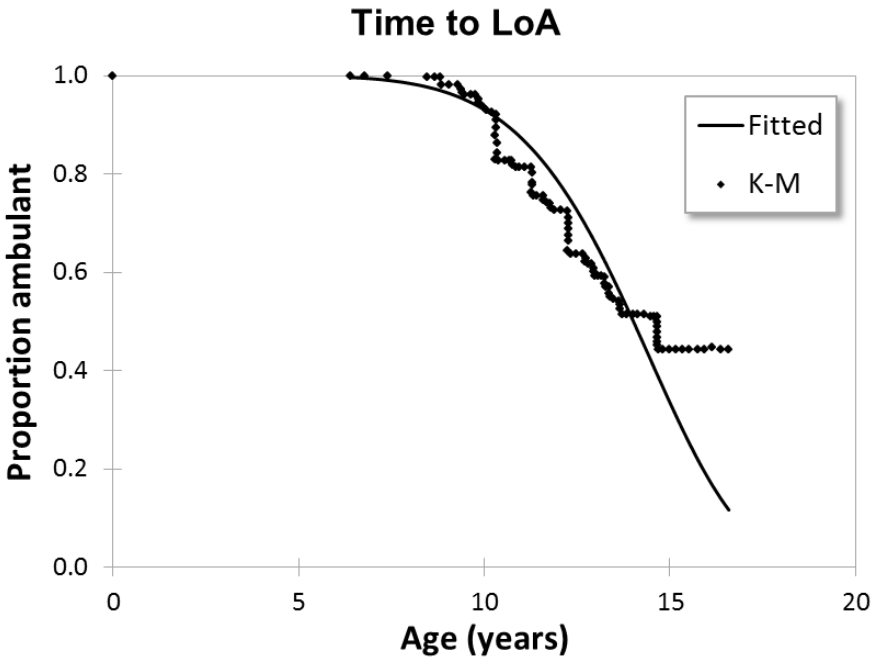


Given the comparability between the mean time to LoA extrapolated from the placebo arm of the Study 007 and the median time to LoA reported in the literature, it is reasonable to assume that the data reported by Ricotti et al (2013) was consistent with, and therefore representative of, the placebo arm of the study. This is also supported by the fact that 74% of patients in Study 007 received daily corticosteroids thus for consistency with the clinical data for ataluren, the daily corticosteroids Kaplan-Meier curve was used for best supportive care.

A clinical expert cited that in the UK, most patients are treated with intermittent corticosteroids rather than daily corticosteroids, due to adverse events. Therefore, using the daily corticosteroids Kaplan-Meier curve for best supportive care may be slightly overestimating the current age of LoA for patients in UK.

A time-to-LoA curve was fit to digitized Kaplan-Meier estimates published by Ricotti et al (2013) in order to obtain time-dependent transition probabilities based on patient age. A Weibull function was the best fit to the data (Figure D12.5).

Figure D12.5 Curve for time to loss of ambulation fit to Kaplan Meier data



To estimate the time to loss of ambulation curve for ataluren compared to placebo, the placebo curve was shifted it to the right until the difference in median time to LoA between ataluren and placebo was the same as predicted by linearly extrapolating Study 007 data (i.e. 8.1 years). The resulting time to LoA curves for ataluren and best supportive care are detailed in Table D12.4 and illustrated in Figure D12.6.

Figure D12.6 Curve for time to loss of ambulation fit to Kaplan Meier data

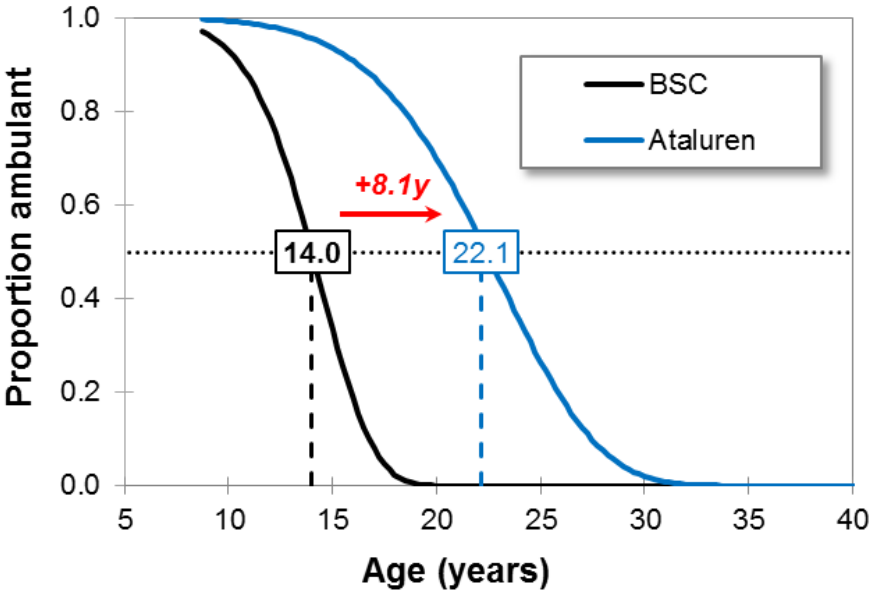


Table D12.4 Weibull function parameters of the time to LoA curves

Treatment group	Weibull parameters		Source
	λ	γ	
Best supportive care	1.3578×10^{-8}	6.7224	Ricotti et al (2013)
Ataluren + BSC	1.0178×10^{-8}	5.8224	Ricotti et al (2013) and Study 007

The fitted curve for ataluren may be considered a conservative estimation of the treatment effect on delaying time to LoA for two reasons:

1. The regression analysis was performed on the data from weeks 24-48 (see Figure C9.7) since the observations seen in weeks 24 to 48 are expected to be more reflective of the long-term treatment effect of ataluren given the disease modifying effect of the drug. However, using only this latter data is potentially a conservative assumption since ataluren clearly has a greater benefit than BSC in improving 6MWD as seen during the first 24 weeks of the study.

2. Data from the study has shown that the long-term treatment effect is likely to be greater when started in younger patients who are still in the maturational stage of their walking capability. Most patients that will be initiated on ataluren in the future would be younger at baseline compared to patients in the clinical study, as they would be initiated on treatment as soon as the license permits i.e. aged 5. Therefore, in younger patients the time to LoA would be greater than estimated in Figure D12.6.

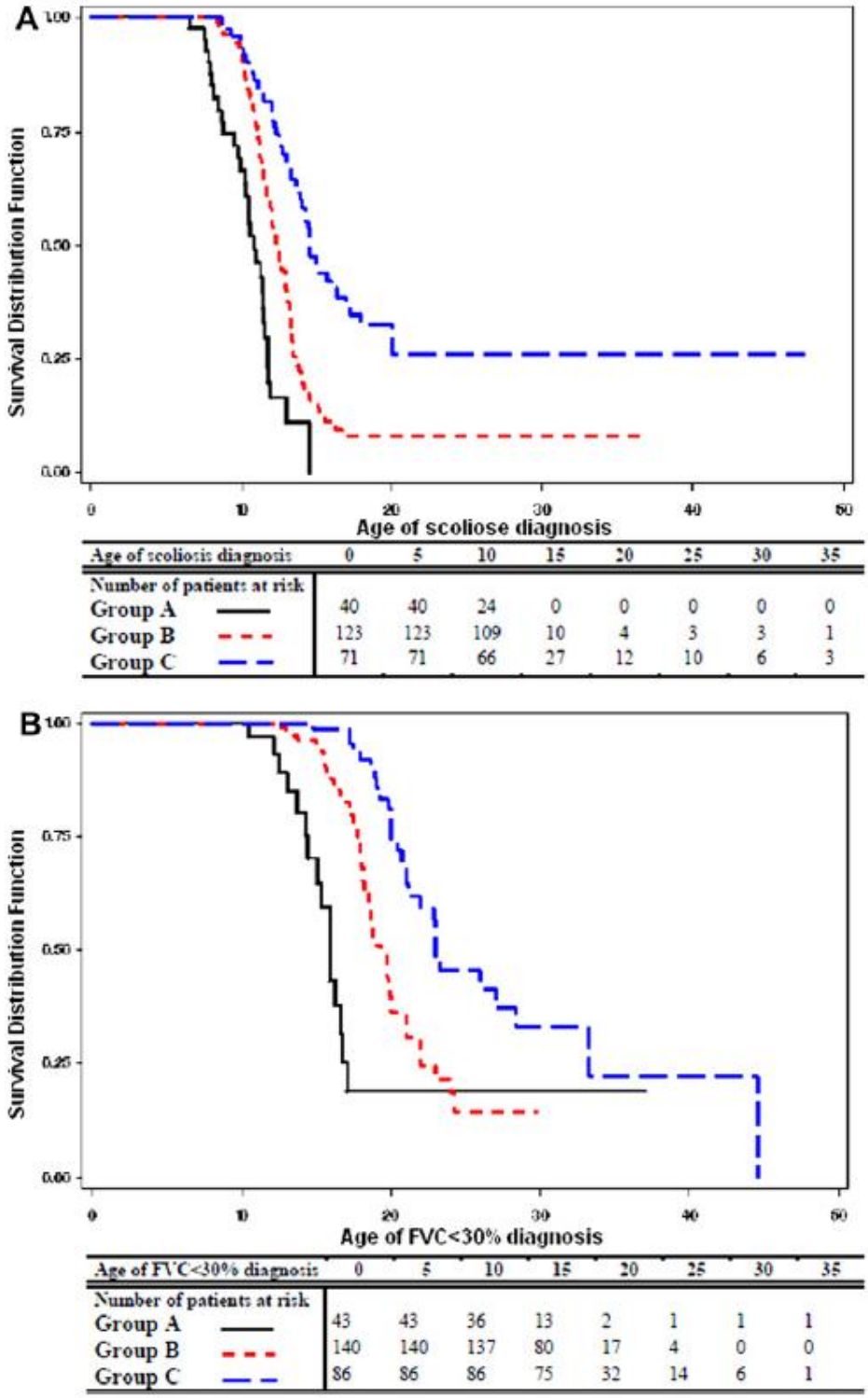
Time to ventilation assistance and scoliosis

Once LoA has occurred, nmDMD patients progress to requiring ventilation assistance (VA), develop scoliosis, or both. The follow-up period of the clinical trial was not long enough to obtain sufficient data on these late and high disease burden stages of transition. Therefore, in the model, transitions from non-ambulatory to VA and scoliosis states were modelled using probabilities obtained from published natural disease history data (Humbertclaude et al, 2012).

A search of the literature for time to VA and time to scoliosis revealed only this one study with Kaplan-Meier estimates. Humbertclaude et al (2012) published data from the French dystrophinopathy database of 278 DMD patients with mean longitudinal follow-up of 14.2 years. The authors found statistically significant relationship in ages

of LoA and diagnosis of scoliosis, as well as age of LoA and age of diagnosis of forced vital capacity (FVC) ≤30% (Figure D12.7). A patient with a FVC ≤30% has severe respiratory insufficiency and therefore the time to FVC ≤30% diagnosis is indicative of time to requiring ventilation assistance. Humbertclaude et al (2012) stratified patients into three groups based on age of loss of ambulation: <8 years, 8–11 years and >11 years.

Figure D12.7 Probabilities to scoliosis and sever respiratory insufficiency from Humbertclaude et al (2012)



Curves were fitted to the Kaplan-Meier plots for each age group published by Humbertclaude et al (2012) to estimate the time from LOA to scoliosis and the time from LoA to requiring ventilation assistance. The Weibull curve was the best fitting function to the data (Figure D12.8 and Figure D12.9). The Weibull function

parameters of the time to ventilation assistance and time to scoliosis once LoA has occurred are detailed in Table D12.5.

Figure D12.8 Transitions from time from LoA to ventilation assistance

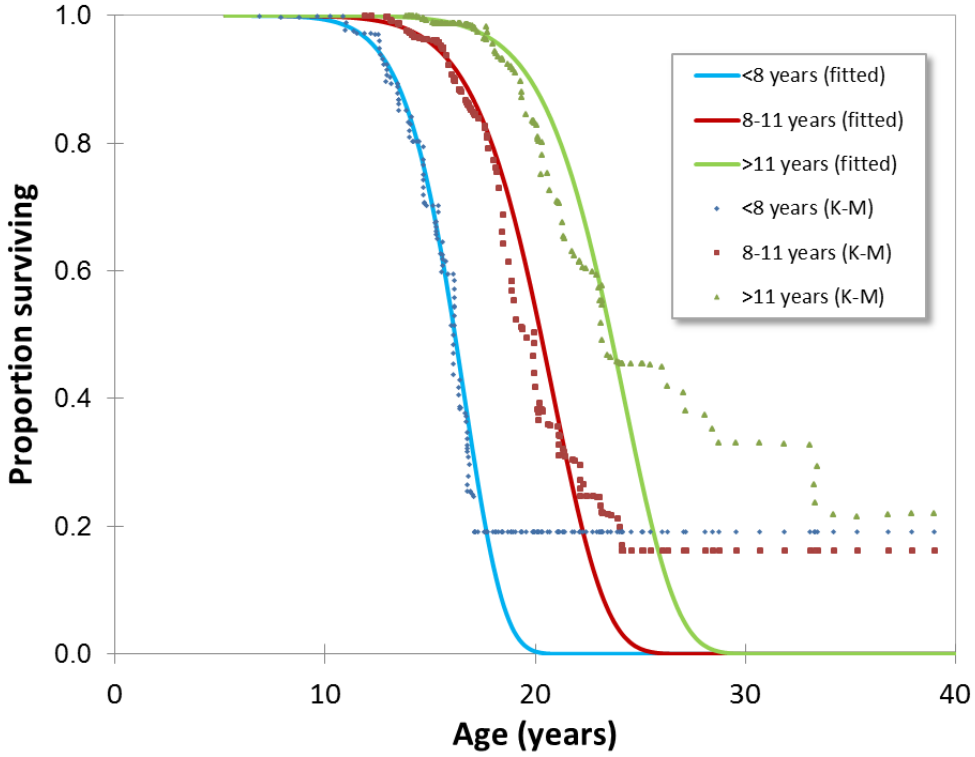


Figure D12.9 Transitions from time from LoA to scoliosis

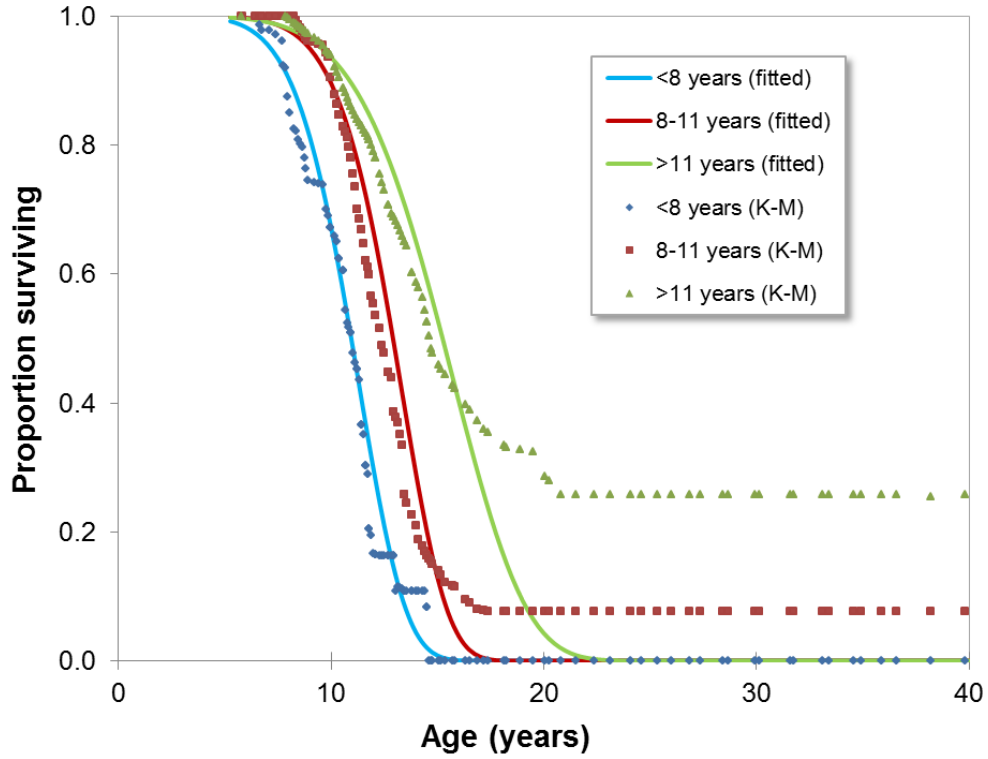


Table D12.5 Weibull function parameters of the time from LoA to ventilation assistance and time from LoA to scoliosis

Age at LoA	Weibull parameters		Source
	λ	γ	
Time to ventilation assistance (VA)			
LoA < 8y	1.0015×10^{-12}	9.7950	Humbertclaude et al (2012)
8y ≤ LoA < 11y	6.0506×10^{-13}	9.2279	Humbertclaude et al (2012)
LoA ≥ 11y	1.9724×10^{-15}	10.5950	Humbertclaude et al (2012)
Time to scoliosis			
LoA < 8y	2.9097×10^{-7}	6.1367	Humbertclaude et al (2012)
8y ≤ LoA < 11y	6.8059×10^{-9}	7.2092	Humbertclaude et al (2012)
LoA ≥ 11y	1.7656×10^{-7}	5.5741	Humbertclaude et al (2012)

As no clinical or observational studies were available on how non-ambulatory patients could progress to both scoliosis and ventilation assistance simultaneously, patient transition probabilities to the 'VA + scoliosis' health state were derived from a combination of the VA and scoliosis transition probabilities.

Mortality

Patients could transition to death from any of the 5 DMD health states. Death could occur due to DMD or other causes.

An age-dependent risk of mortality from any cause was applied to every health-state in the model, based on UK general population mortality (ONS, 2013).

An age-dependent specific risk of mortality from DMD as assessed in a German study (Rall, 2012) was also applied. This study assessed survival patterns in DMD (Figure D12.10). Given all UK patients should have access to ventilation assistance when required, a curve was fit to the Kaplan-Meier curve representing patients with access to ventilation assistance to obtain transitions to death based on patient age over time. The best fitting function for the best supportive care mortality curve was a Weibull function. The final function is given in Table D12.6 and illustrated in Figure D12.11.

Figure D12.10 Kaplan-Meier survival curves for patients with or without ventilation assistance who are diagnosed with DMD

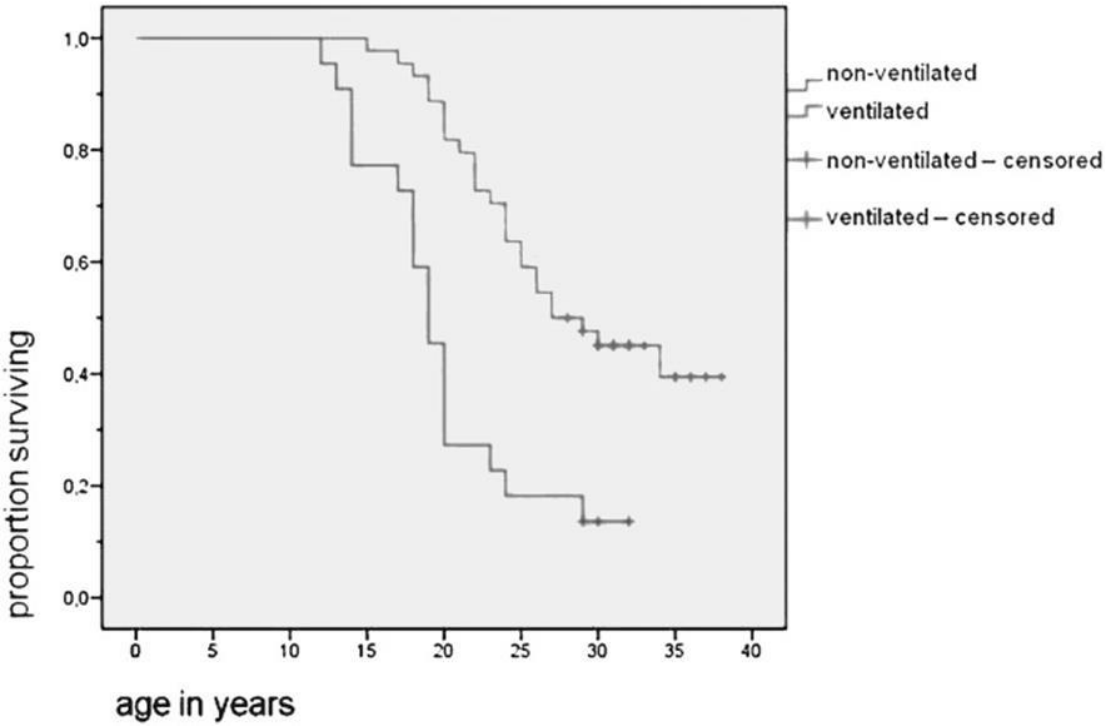
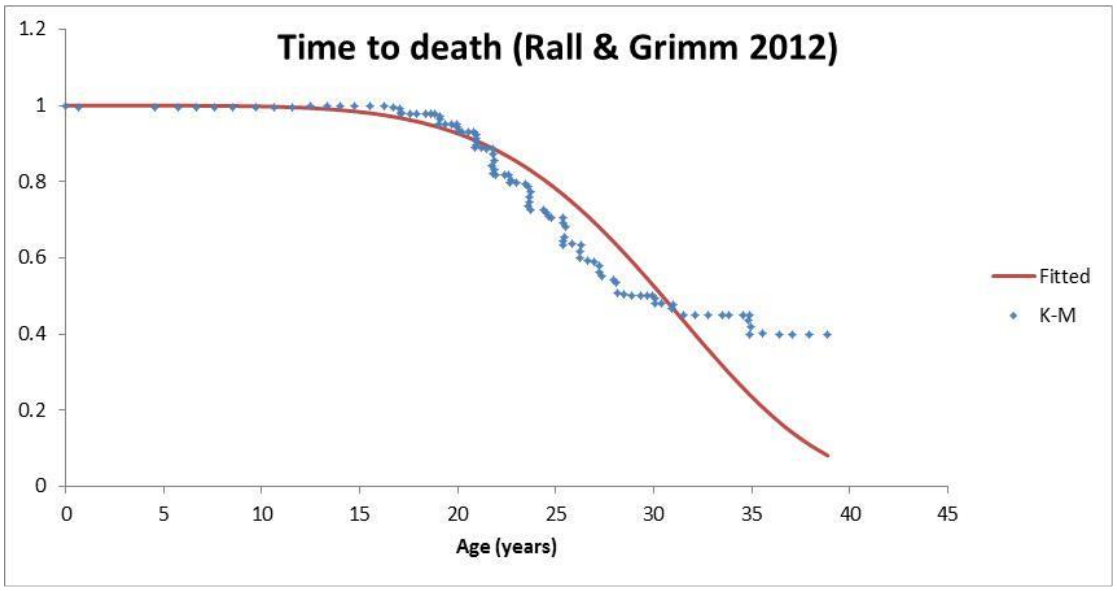


Table D12.6 Survival curve for DMD patients

Weibull parameters		Source
λ	γ	
1.0643×10^{-8}	5.2675	Rall et al (2012)

Figure D12.11 Fitted curve to best supportive care survival Kaplan-Meier curve



Furthermore, there is a correlation between the age of becoming wheelchair bound and age of death (Van Essen 1997; Rall, 2012). Van Essen et al found that the relative risk (RR) of death associated with becoming wheelchair bound a year earlier was estimated at 1.22 (95%CI: 1.09–1.36). In this study, patients who lost walking ability before 10 years had a median survival of 17.3 years (95%CI: 16.7–18.0 years) vs. the 20.1 years attributed to those who became wheelchair-bound at or after 10 years (95%CI: 19.4–20.9 years). Rall and colleagues (2012) have also shown that a significant correlation exists between the age of becoming wheelchair bound and the age of death (p=0.016) in patients with DMD. Furthermore, clinical experts have cited that there is almost a linear relationship between the time to delay LoA and the delay to death.

In light of this, we hypothesized a survival benefit for ataluren-treated patients. A conservative relative risk of death of [redacted] was applied to the best supportive care mortality for the ataluren arm.

There were no deaths in Study 007 and it is therefore meaningless to extrapolate study data to the lifetime of the model. The assumptions we have used have been based on the literature of treatment with steroids and expert opinion. Given the link of LoA to mortality seen in the literature (van Essen, 1997) and with the possible delay to LoA extrapolated from the 48 week treatment effect, modelling a linear effect would provide a life year gain equivalent to that of the benefit on time to LoA. The assumptions that we have included in this submission are therefore a conservative estimate of mortality gain, partly also driven by the unpredictability of modelling at the latter end of the time horizon.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Costs and clinical outcomes were extrapolated beyond the clinical study period of 48 weeks. The decline in 6MWD observed in the study was assumed to linearly decline at the same rate until complete loss of ambulation (0m). Validation of this approach is evidenced by the comparability of the placebo data to published data for best supportive care. Extrapolating the decline for the placebo group in a linear manner resulted in LoA at ~14 years which is the same as the median time to LoA observed

by Ricotti and colleagues (2013) in patients receiving daily corticosteroids. Clinical opinion suggests that based on the results from the 48 week study, the treatment effect of ataluren on LoA would persist over the treatment duration as included in the model.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

It has been found that the age a DMD patient becomes wheelchair bound is significantly correlated with age of death. It can therefore be interpreted that a delay in the time to LoA has a significant impact on reducing the risk of mortality. Consequently, ataluren treatment is assumed to be associated with a reduced risk of death compared to placebo. Only one publication has cited a specific risk reduction but it was only in relation to becoming chair bound 1 year earlier (Van Essen 1997). Ataluren is expected to extend the time to LoA by 8 years thus quantifying the specific risk reduction on mortality from Van Essen (1997) was difficult. Clinical experts have cited that the relationship between time to LoA and time to mortality could be linear, thus a delay in LoA by 8 years could translate to a delay in death by 8 years.

In the absence of exact data, and given the uncertainties associated with long-term extrapolation of 48 week study data, it has been conservatively assumed that the impact of ataluren treatment on reduction in mortality would be more than observed from a 1 year reduction in LoA (RR= [redacted] for ataluren vs. 0.82 in the published data) [redacted]).

12.2.4 Were adverse events included in the cost-consequence analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not included in the cost-consequence model. Data from Study 007 suggests ataluren has a very favourable safety profile and there were no significant differences in the incidence of adverse events between the ataluren and placebo arms. The adverse events that did occur did not have significant impact on the cost of care of quality of life of the patient.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Two experts were consulted to validate assumptions made around the structure and clinical inputs for the model. The questions were asked as part of a telephone interview to validate the approach taken in the economic modelling of ataluren. Please see section 10.1.10 for details on advisors and methods.

The experts were provided with a summary of the modelling approach, the sources of data for transitions and justification for the sources used.

The experts stated that the health state structure of the model was a fair representation and captured most of important elements of disease progression. One stated that the point at which a patient is unable to self-feed is an important marker in the progression of their disease but understood that this is challenging to quantify and is associated with a lack of published data.

The experts cited that the sources of data were reliable and representative of the UK DMD patient population. Specific feedback on each element of the model was received; this feedback informed the model design and is detailed in section 12.2.1.

12.2.6 Summarise all the variables included in the cost-consequence analysis. Provide cross-references to other parts of the submission.

Table D12.7 Summary of variables applied in the cost-consequence model

Variable	Value	Range	Source
Baseline patients characteristics			
Age (years, mean)	8.5	5 - 20	Age at baseline in Study 007
Survival			
Placebo median age	30.4	N/A	Rall, 2012
Relative risk of ataluren vs. placebo	[redacted]	[redacted] - 0.82	*Base case value* – conservative assumption given 48 week data; based on balance between clinical opinion and natural history data *Lower value* – expert opinion based on linear relationship between extension of ambulation and of survival *Upper value* – published natural history data (van Essen, 1997)
Transition probabilities (age, years)			
Time to LoA: BSC	14.0	None	Ricotti, 2013
Time to LoA: ataluren	22.1	None	Study 007
Time to VA if LoA<8 years	16.1	None	Humbertclaude, 2012
Time to VA if LoA 8-11 years	20.2	None	Humbertclaude, 2012
Time to VA if LoA>11 years	23.6	None	Humbertclaude, 2012
Time to scoliosis if LoA<8 years	11.0	None	Humbertclaude, 2012
Time to scoliosis if LoA 8-11 years	12.9	None	Humbertclaude, 2012
Time to scoliosis if LoA>11 years	15.2	None	Humbertclaude, 2012

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The costing of the management of DMD patients varies nationally. Centres negotiate the tariff for DMD patients locally thus it has not been possible for us to quantify the costs of managing DMD patients in terms of the PbR tariff.

The ICD10 code for DMD is G710. This ICD10 code linked to the following HRG codes (HRG4 Code to Group, 2015):

Paediatric activity (Age 18 years and under)

- PA01B – Nervous system disorders without CC (without complications).
- PA01A – Nervous system disorders with CC (if certain comorbidities added)

Non-paediatric activity would be coded to the following HRG codes:

- AA26B – Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury without CC
- AA26A – Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury with CC

The HRG grouper is entirely dependent on the codes entered so it may be that adding additional diagnostic and procedures codes might change the HRGs. If a rehabilitation code is added in the procedure field this does not change the above HRGs for instance.

The 2014/ 2015 tariff for PA01A is £1,299 and for PA01B £965 for an elective spell with a trim point of 5 days which means that for every day following the first five days of an inpatient stay the hospital would get an extra £285 per day. The cost of a non-elective spell for PA01A is £2,020 and for PA01B £726. These tariffs and those for AA26A and AA26B are shown in Table D12.8 below.

Table D12.8 HRG codes and National Tariffs related to DMD

HRG code	HRG name	Combined day case / ordinary elective spell tariff (£)	Ordinary elective long stay trimpoint (days)	Non-elective spell tariff (£)	Non-elective long stay trimpoint (days)	Per day long stay payment (for days exceeding trimpoint) (£)	Reduced short stay emergency tariff applicable?
PA01A	Nervous System Disorders with CC	1299	5	2020	13	294	No
PA01B	Nervous System Disorders without CC	965	5	726	5	294	No
AA26A	Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury with CC	891	5	1191	13	204	No
AA26B	Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury without CC	581	5	666	5	204	No

Source: (National Tariff Payment System 2014/15. Annex 5A: National prices)

This information was verified by an NHS Trust clinical coder in order for PTC to complete this section of the submission as accurately as possible.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic search of resource data was included in the economic review – see section 11.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

Two experts were consulted to validate assumptions made around costs in the model. The questions were asked as part of a telephone interview to validate the

approach taken in the economic modelling of ataluren. Please see section 10.1.10 for details on advisors and methods.

The experts were provided with a summary of the direct and indirect costs per health state and justification for the sources used. The experts cited that the source of costs used was the only one known to them that would be relevant for the submission and was a robust and therefore reliable study.

One expert cited that the costs during the ambulation disease state would progress over time to a greater extent that shown the literature. They stated that ataluren is likely to reduce the costs in the early non-ambulatory phase of the disease as patients are likely to still be able to use a self-propelled wheelchair since they maintained ambulation for so long. Due to the limited data available on costs, it has not been possible to include this factor in the cost-consequence model. Therefore, it is likely that health state costs for ataluren are slightly overestimated by simplifying the health states to simply ambulatory or non-ambulatory.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price for ataluren is £2,532 per box of 30 x 125mg sachets.

Ataluren is also available in higher dose sachets with an equivalent price per mg:

- 30 x 250mg sachets = £5,064
- 30 x 1000mg sachets = £20,256

12.3.5 If the list price is not used in the de novo cost-consequence model, provide the alternative price and a justification.

The list price is used in the cost-consequence analysis results presented in this submission. The results of the cost analysis using the discounted price of ataluren will be presented in the patient access scheme submission (which is currently being approved by the Department of Health).

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequence model. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another

technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The recommended dose of ataluren is 40 mg/kg daily, although this varies by weight range (Table D12.9).

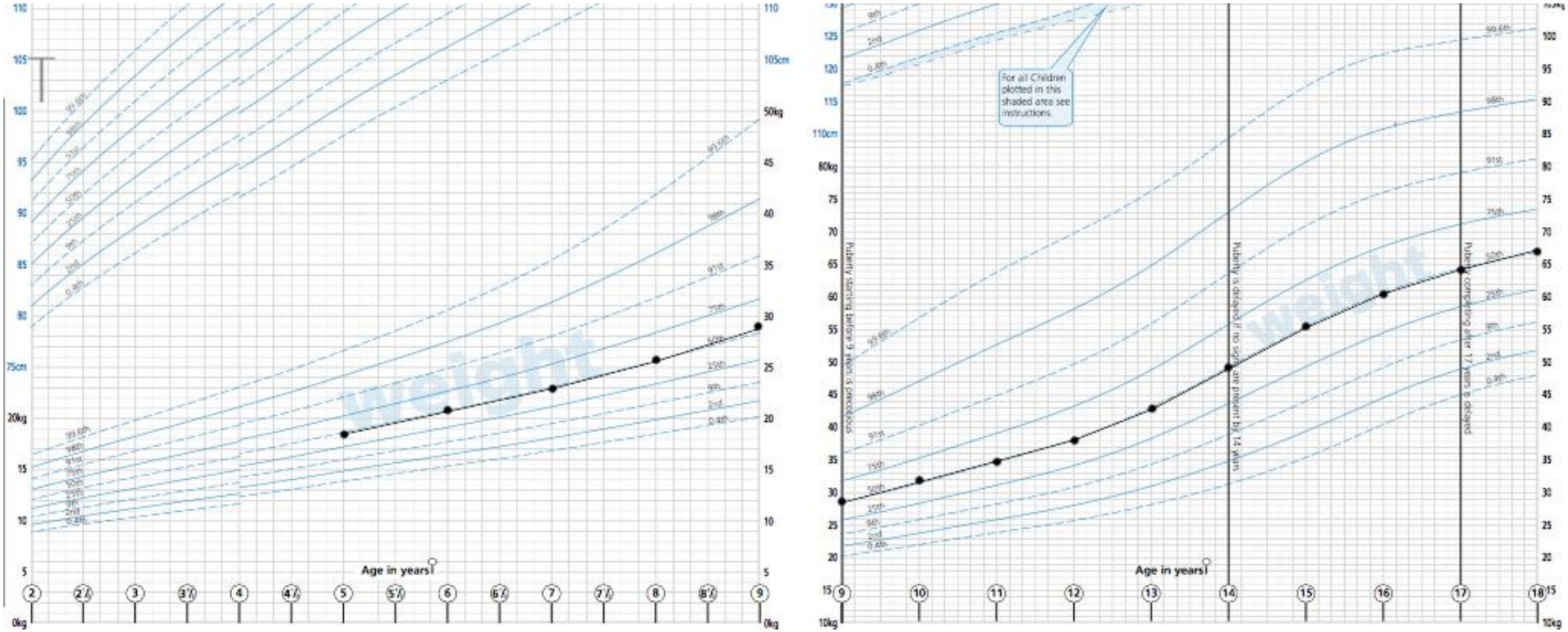
Table D12.9. Recommended dosing by weight (Translarna SPC)

Weight Range (kg)		Number of sachets								
		Morning			Midday			Evening		
		125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	1	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

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. The median age-weight curves for children aged 5-9 and 9-18 (Figure D12.12) were digitized and it was assumed that adults aged 19 and over would have an average weight of 70kg. Experts have verified that DMD patients are typically smaller in stature that healthy children and adults thus treatment costs may be overestimated in the model.

The average age of the cohort, from the baseline of 8.5 years, is looked up on the age weight curve (Figure D12.12.) to give the average weight over time. This weight is then looked up in the SPC dosing table (Table D12.9) to find how many sachets are required daily. The cost per sachet is applied to give a daily cost of treatment, which is then converted to 3-month costs for each cycle.

Figure D12.12. Age weight curve adapted from RCPCH, 2013



No other costs associated with the treatment other than acquisition costs are included in the cost-consequence model. Ataluren is administered orally after being mixed with liquid or semi-solid food by the patients or parents/carers. No specific training is required on how to administer the treatment. Consequently, administration and training costs are null.

The SPC for ataluren recommends the following monitoring:

- total cholesterol, LDL, HDL, and triglycerides should be monitored on an annual basis
- resting systolic and diastolic blood pressure should be monitored every 6 months in patients receiving concomitant corticosteriods
- serum creatinine, BUN, and cystatin C should be monitored every 6 to 12 months

Two experts were consulted on the monitoring requirements of ataluren. They stated that most of the above tests are performed routinely and are associated with a negligible cost. Consequently, no monitoring costs for ataluren were included in the cost-consequence analysis.

A summary of the costs associated with treatment is provided in Table D12.10.

Table D12.10. Costs per treatment/patient associated with the technology in the cost-consequence model

Items	Value	Source
Price of the technology (average 8 year old, weight 26kg)	£675.20 per day £246,448 per year	Translarna SPC RCPCH, 2013
Administration cost	£0	N/A – ataluren administered orally after mixing with liquid
Training cost	£0	N/A – ataluren administered orally after mixing with liquid
Other costs (monitoring, tests etc)	£0	N/A – see text

Health-state costs

12.3.7 If the cost-consequence model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-consequence model.

There is only one source available for UK costs of DMD thus this has been used as the primary source of all health state costs in the model. Costs from Landfeldt and colleagues (2014) were reported in 2012 international dollars thus UK costs were converted using the UK 2012 purchasing power parity (OECD, 2015) and then inflating to 2014 costs using the consumer price index for health (ONS, 2015). NHS reference costs have been used where appropriate, specifically, for costs of scoliosis surgery (Table D12.11).

Table D12.11. List of health states and associated costs in the cost-consequence model

Health states	Items	Value (per cycle)	Reference
Ambulatory	Technology cost		N/A
	Direct costs	£1,633	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Indirect costs	£7,972	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Total	£9,605	
Non-ambulatory	Direct costs	£4,012	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Indirect costs	£19,588	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Total	£23,600	
Non-ambulatory and ventilation-assisted	Direct costs	£4,012	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Indirect costs	£19,588	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Total	£23,600	
Non-ambulatory with scoliosis	Direct costs	£4,012	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Surgery costs	£20,986	NHS reference costs 2013-14. Complex spinal reconstructive surgery with CC score 3+ (code HC40A) - Elective Inpatient cost
	Surgery follow-up costs	£1,458	NHS reference costs 2013-14. Scoliosis or Other Spinal Deformity, with CC Score 3+ (code HC26D): £2915.03 per visit. Assume 2 visits per year.
	Indirect costs	£19,588	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Total	£25,058 - £46,043	
Non-ambulatory and ventilation-assisted with scoliosis	Direct costs	£4,012	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Surgery costs	£20,986	NHS reference costs 2013-14. Complex spinal reconstructive surgery with CC score 3+ (code HC40A) - Elective Inpatient cost
	Surgery follow-up costs	£1,458	NHS reference costs 2013-14. Scoliosis or Other Spinal Deformity, with CC Score 3+ (code HC26D): £2915.03 per visit. Assume 2 visits per year.
	Indirect costs	£19,588	Landfeldt, 2014; OECD, 2015; ONS, 2015
	Total	£25,058 - £46,043	

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost-consequence model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Data from Study 007 demonstrate that ataluren has a favourable safety profile and there were no significant differences in the incidence of adverse events between the ataluren and placebo arms. Any adverse events that did occur did not have significant impact on the cost of care of the patient. The model assumes that there are no adverse effects related to treatment based on clinical trial data, and no costs are included for adverse events.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

The costs of nonmedical community services, aids / devices / home adaptations, informal care and indirect costs (productivity losses) are included within the indirect costs detailed in Table D12.11. Note that for caregiver productivity costs the authors acknowledge that they are likely to be underestimates since they only valued outcomes of the primary caregiver and thus did not capture the burden on additional members of the household e.g. second parent and/or siblings. For this reason, we have conducted a sensitivity analysis increasing the indirect costs by 50% (see section 12.4.1).

Furthermore, Landfeldt and colleagues (2014) identify the additional cost burden on households due to lost income, leisure time, out of pocket payments and intangible costs. This annual cost of £45,038 represents a large burden of DMD so this additional indirect cost is included within the non-ambulatory states in a sensitivity analysis.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Experts cited that the costs during the ambulation disease state would progress over time. They stated that ataluren is likely to reduce the costs in the early stages of a patient being non-ambulant as they are likely to still be able to use a self-propelled wheelchair, which costs considerably less than an electrical wheelchair. Due to the limited data available on specific costs, this factor has not been taken into account in the cost-consequence model. Therefore it is likely that treatment costs are slightly underestimated by simplifying the health states to ambulatory and non-ambulatory.

Furthermore, it was also cited by experts that by delaying the time to loss of ambulation, ataluren is increasing the probability of patients reaching a working age and obtaining a job. Not only would enabling employment increase the mental well being of DMD patients, but they would also be contributing to society through taxation. It has not been possible to quality this benefit due to limited data.

An additional factor that will have costs and consequences that has not been included in the model is the impact of ataluren on the reduction of falls (Figure C9.13). Boys with DMD have been found to have decreased bone density and an increased risk of fractures (Vestergaard 2001). As we have seen in Study 007, falls are common in DMD patients and can lead to a wide range of consequences and subsequent costs for the patient and carer. Loss of function often follows a fracture (32 out of 71 cases) (Vestergaard, 2001). Lower extremity post-fracture recovery often includes prolonged periods of non/partial weight bearing with increased amounts of time spent sitting in wheelchairs, increasing the risk of contractures and disuse weakness. The impact that ataluren has shown in the reduction in number of falls is expected to reduce the number of falls and the subsequent morbidity, and therefore reduce the burden on carers and healthcare system.

12.4 **Approach to sensitivity analysis**

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been

confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-consequence analysis.

A number of scenarios, detailed in Table D12.13, were explored:

1. Experts stated that caregiver disutilities found in the literature do not reflect the true burden of DMD on caregivers (see Section 10.1 for further information). Scenario 1 was explored where all caregiver disutilities were increased to reflect a more realistic burden on parents, siblings and carers.

2. Ventilation-assistance is expected to have a high cost and humanistic burden but the specific costs and utilities for ventilated-assistance in DMD could not be sourced from the literature. In scenario 2, we explore the impact of additional direct costs, reduced patient utility and increased caregiver disutility to ventilation-assisted health states.

3. Inclusion of non-medical direct costs and indirect costs to reflect the true burden of DMD e.g. costs of assisted care, non-medical community services, aids, home modifications for wheelchair accessibility, home help, informal care, production losses.

4. Longer time horizon of model to capture the increased costs and disutilities of patients as they progress to more severe health states.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

One-way sensitivity analysis on discount rates, costs and utilities has been conducted to identify the drivers of the model (Table D12.12). The variation of the relative risk for mortality was between [redacted] (assuming a linear relationship between time to LoA and death) and 0.82 (the natural history value quoted in the literature (van Essen, 1997)). Confidence intervals or ranges for costs and utilities included in the model were not provided in the source so an arbitrary variation of 20% has been applied. In most cases, it is more likely that the true value of costs and disutilities are 20% greater than 20% less than the mean value, but applying a minimum and maximum value will identify the key drivers of the model.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table D12.12 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Relative risk of ataluren vs. placebo on survival	[redacted]	[redacted] to 0.82
Health state direct costs	See Table D12.11	+ / - 20%
Patient utilities	See Table C10.3	+ / - 20%
Caregiver utilities	See Table C10.3	+ / - 20%

Table D12.13 Variables used in multi-way scenario-based sensitivity analysis

Variable	Health state	Scenario			
		Base case	1	2	3
Cost	Ambulatory	£1,633	-	-	£9,605
	NA	£4,012	-	-	£23,600
	NA & VA	£4,012	-	£9,012	£23,600
	NA & S	£5,470	-	-	£25,058
	NA & VA & S	£5,470	-	£10,470	£25,058
Patient utility	Ambulatory	0.660	-	-	-
	NA	0.120	-	-	-
	NA & VA	0.120	-	0.02	-
	NA & S	0.020	-	-	-
	NA & VA & S	0.020	-	-0.08	-
Caregiver disutility	Ambulatory	0	0.05	-	-
	NA	0.11	0.10	-	-
	NA & VA	0.11	0.15	0.20	-
	NA & S	0.11	0.25	-	-
	NA & VA & S	0.11	0.30	0.20	-

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Treatment costs were not included in sensitivity analysis as the price included in the analysis is the list price.

Age was not varied in the sensitivity analysis as the average age of the model cohort corresponded to the average age of the clinical trial population and is expected to be a fair representation of the mean age of the UK patients that could receive ataluren. Although analysis of the trial data indicates that younger patients will receive greater benefit of ataluren and all newly diagnosed patients would have a younger age than the modelled baseline, the natural history data is limited in terms of age thus a variation in cohort age has not been explored.

Best supportive care curves for time to LoA, VA, scoliosis and death were not included in sensitivity analysis since they were based on published estimates and no published variation to this has been identified.

12.5 Results of de novo cost-consequence analysis

Section 12.5 requires the sponsor to report the de novo cost-consequence analysis results. These should include the following:

- benefits
- costs
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean results (costs, QALYs)
- results of the sensitivity analysis.

Clinical outcomes from the model

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The model predicts that for both best supportive care and ataluren treatment, fewer patients lose ambulation at 48 weeks compared to the clinical trial (Table D12.14). This is because the model looks at an average cohort of patients with a moderate baseline 6MWD. The clinical trial included more variability in patients' baseline characteristics thus a proportion were at a much higher risk of losing ambulation within the relatively short duration of the study than the average patient. The low rate of LoA in the first year of the model is consistent with best supportive care patients aged 8-9 in Ricotti (2013).

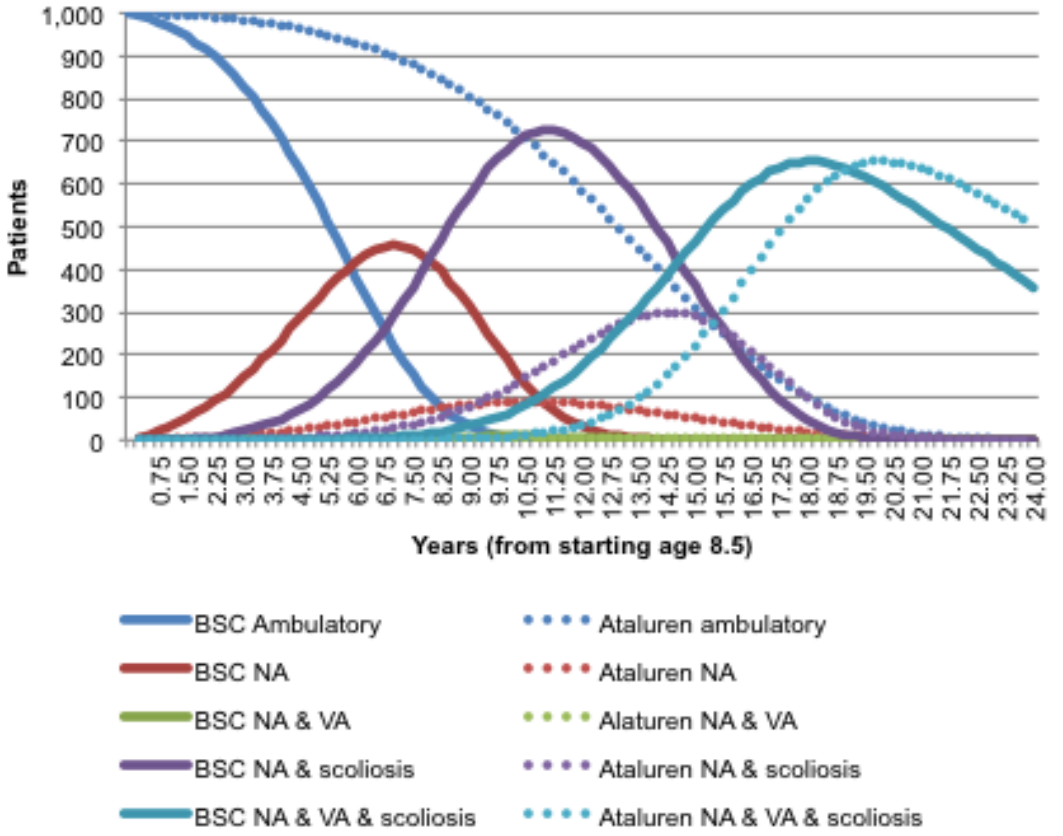
Table D12.14. Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Loss of ambulation at 48 weeks / 1 year: best supportive care	11% (n=6)	5%
Loss of ambulation at 48 weeks / 1 year: ataluren	7% (n=4)	0.5%

12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov trace illustrated in Figure D12.13 clearly shows the treatment effect of delay in time to LoA with ataluren treatment. Patients receiving ataluren transition to the non-ambulatory health states at a slower rate that patients receiving best supportive care. Although expert opinion suggests that the delay in LoA resulting from ataluren will likely reduce the incidence of scoliosis, this treatment effect has not been modelled due to lack of published data. Consequently, the proportion of the cohort entering the NA & VA & scoliosis state is the same between ataluren and best supportive care, although the former is delayed. The proportion of patients entering the NA, NA & VA and NA & scoliosis states is lower in the ataluren group than in the best supportive group because patients spend longer the ambulatory state.

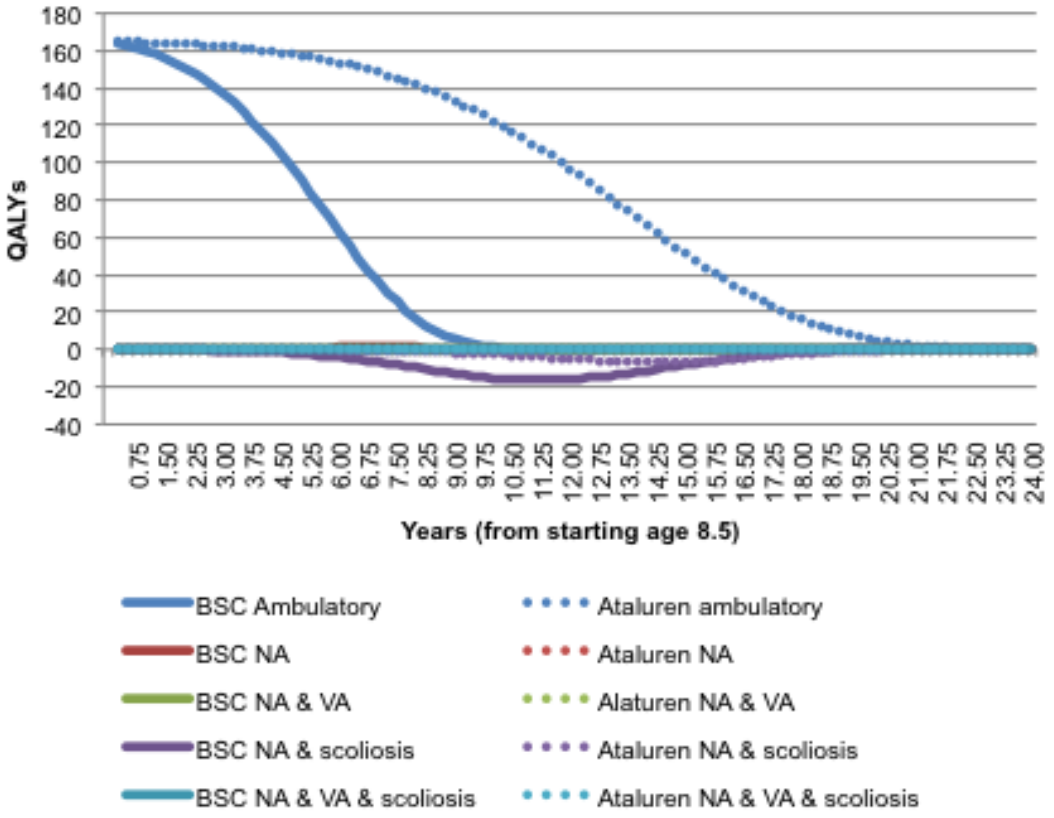
Figure D12.13 Markov trace



12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

In all non-ambulatory states, the total utility per patient, which includes caregiver disutility, is between 0.01 and -0.09 thus very QALYs accrued in these states are negligible or negative. Figure D12.14 shows the majority of QALYs are accrued in the ambulatory state. Since ataluren prolongs the time in which patients are ambulatory, a greater number of QALYs are accrued in the ataluren group.

Figure D12.14 Accumulation of undiscounted QALYs over time



12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Ataluren is indicated for patients that are ambulatory and so the model has patients stopping ataluren treatment when they enter the NA health state. However, because of the way the model is constructed, and in order to be as transparent as possible, the tables below (D12.15 to D12.18) present the LYs, QALYs and costs across all the health states i.e. ambulatory, NA, NA & VA, NA & S, NA & VA & S, both for ataluren and best supportive care (BSC) even though ataluren costs will not apply across the NA health states.

Table D12.15. Model outputs for ataluren by health state (discounted)

Outcome	LY	QALY
Ambulatory	9.857	6.506
NA	0.609	0.006
NA & VA	0.032	0.000
NA & S	1.331	-0.120
NA & VA & S	2.667	-0.240
Total	**14.497**	**6.152**
LY, life years; QALY, quality-adjusted life year		

Table D12.16. Model outputs for best supportive care by health state (discounted)

Outcome	LY	QALY
Ambulatory	4.555	3.006
NA	2.160	0.022
NA & VA	0.032	0.000
NA & S	3.812	-0.343
NA & VA & S	3.329	-0.300
Total	**13.888**	**2.385**
LY, life years; QALY, quality-adjusted life year		

12.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Ataluren is indicated for patients that are ambulatory and so the model has patients stopping ataluren treatment when they enter the NA health state. However, because of the way the model is constructed, and in order to be as transparent as possible, the tables below (D12.15 to D12.18) present the LYs, QALYs and costs across all the health states i.e. ambulatory, NA, NA & VA, NA & S, NA & VA & S, both for ataluren and best supportive care (BSC) even though ataluren costs will not apply across the NA health states.

Table D12.17. Summary of QALY gain by health state (discounted)

Health state	QALY ataluren	QALY best supportive care	Increment	Absolute increment	% absolute increment
Ambulatory	6.506	3.006	3.500	3.500	92%
NA	0.006	0.022	-0.016	0.016	0%
NA & VA	0.000	0.000	0.000	0.000	0%
NA & S	-0.120	-0.343	0.223	0.223	6%
NA & VA & S	-0.240	-0.300	0.060	0.060	2%
Total	**6.152**	**2.385**	**3.767**	**3.799**	**100%**
QALY, quality-adjusted life year					

Table D12.18. Summary of cost by health state (discounted)

Health state	Cost ataluren	Cost best supportive care	Increment	Absolute increment	% absolute increment
Ambulatory	4,984,263	29,752	4,954,511	4,954,511	98%
NA	9,774	34,657	-24,883	24,883	0%
NA & VA	521	520	1	1	0%
NA & S	37,961	96,964	-59,003	59,003	1%
NA & VA & S	60,021	73,314	-13,293	13,293	0%
Total	**5,092,540**	**235,207**	**4,857,333**	**5,051,691**	**100%**

Base-case analysis

12.5.6 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis.

Table D12.19 Base-case results

	Total per patient cost over 24 years (£)
Ataluren	5,092,540
Best supportive care	235,207

12.5.7 Report the total difference in costs between the technology and comparator(s).

The incremental costs between ataluren and best supportive care are £4,857,333 per patient.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost.

Patients receive ataluren whilst they are ambulatory. In the model, based on the extrapolated treatment effect, ataluren patients were, on average, in the ambulatory health state for ~13 years (with a range of 3 months to 24 years) with a technology cost of £4,919,878. Table D12.20 shows ataluren offsets costs of £62,545 per patient by delaying the time to loss of ambulation.

Table D12.20. Summary of costs by category of cost per patient

Item	Cost ataluren	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost	4,919,878	0	4,919,878	4,919,878	99%
Health state cost	172,662	235,207	-62,545	62,545	1%
Total	5,092,540	235,207	4,857,333	4,982,423	100%

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Please refer to Table D12.18.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable. Adverse events were not included in the analysis.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results of the one-way sensitivity analysis are presented in Table D12.21 with illustrations of the QALY results in Figure D12.15 and cost results in Figure D12.16. The tornado diagram of the QALY results shows incremental costs are sensitive to the discount rate and the patient utility in the ambulatory state. Incremental costs are sensitive to the discount rate. Results are insensitive to all other cost and utility inputs.

Table D12.21 Results of one-way sensitivity analysis

Parameter	Value	Incremental QALYs	% difference in QALYs	Incremental costs (£)	% difference in costs
Base case	-	3.767	-	4,857,333	-
Relative risk of ataluren on mortality	[redacted]	3.811	1%	4,997,312	3%
	0.82	3.749	0%	4,811,303	-1%
Ambulatory direct cost	-20%	-	-	4,850,406	0%
	+20%	-	-	4,864,260	0%
Non-ambulatory direct cost	-20%	-	-	4,870,264	0%
	+20%	-	-	4,844,402	0%
Scoliosis surgery cost	-20%	-	-	4,858,093	0%
	+20%	-	-	4,856,573	0%
Scoliosis surgery follow-up cost	-20%	-	-	4,860,946	0%
	+20%	-	-	4,853,720	0%
Ambulatory patient utility	-20%	3.067	-19%	-	-
	+20%	4.467	19%	-	-
Non-ambulatory patient utility	-20%	3.863	3%	-	-
	+20%	3.670	-3%	-	-
Scoliosis patient disutility	-20%	3.704	-2%	-	-
	+20%	3.830	2%	-	-
Non-ambulatory caregiver disutility	-20%	3.678	-3%	-	-
	+20%	3.855	3%	-	-
Discount rate	0%	5.312	41%	6,504,168	34%
	6%	2.994	-21%	4,024,973	-17%

Figure D12.15 Tornado diagram of incremental QALYs illustrating results of one-way sensitivity analysis

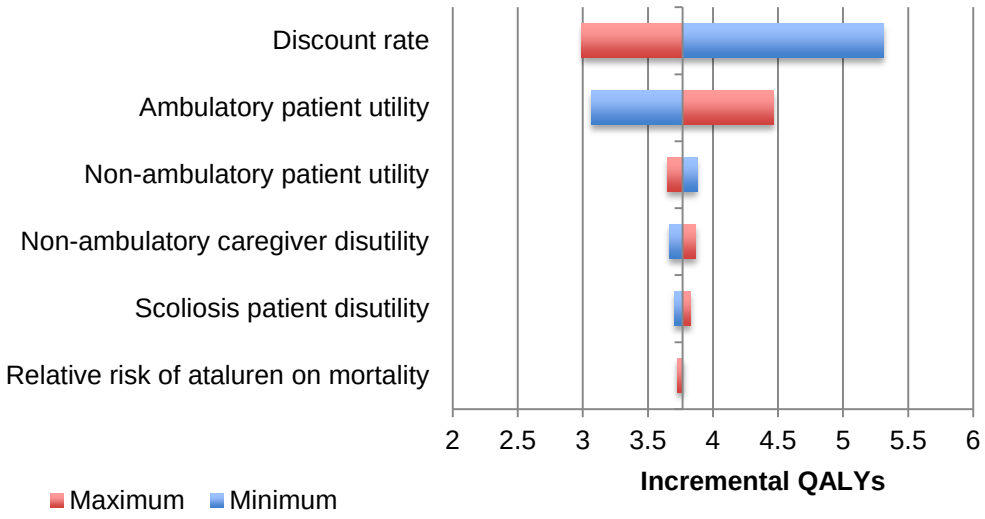
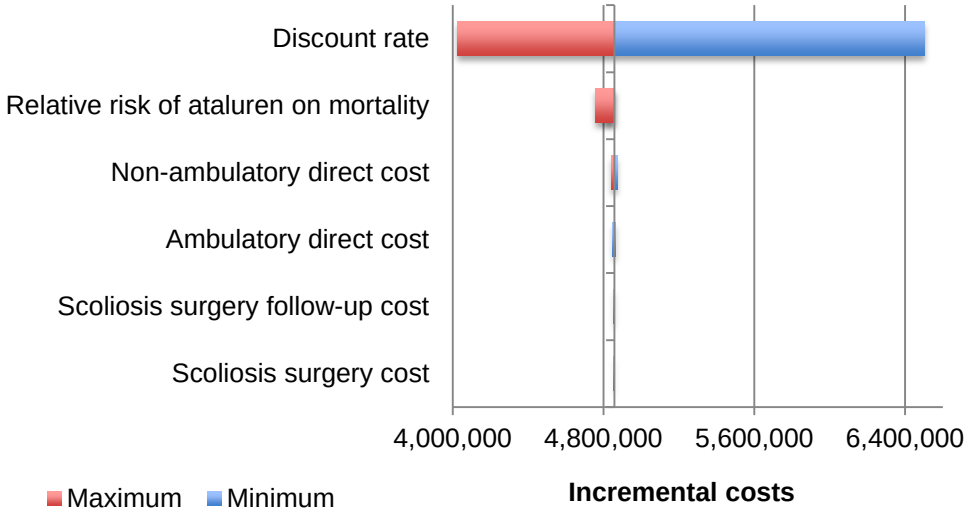


Figure D12.16 Tornado diagram of incremental costs illustrating results of one-way sensitivity analysis



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table D12.22. Results of multi-way scenario sensitivity analysis

Parameter	Incremental QALYs	% difference in QALYs	Incremental costs (£)	% difference in costs
Base case	3.767	-	4,857,333	-
Scenario 1 – increased caregiver disutilities	3.959	5%	-	-
Scenario 2 – increased costs and disutilities for ventilation-assisted state	3.893	3%	4,844,091	0%
Scenario 3 – inclusion of wider societal costs	-	-	4,658,698	-4%
Scenario 4 – Lifelong time horizon	3.728	-1%	4,866,868	0%

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Not applicable.

12.5.14 What were the main findings of each of the sensitivity analyses?

The one-way sensitivity shows the cost-consequence results are most sensitive to discount rates. The results are also sensitive to the patient utility in the ambulatory state. The model is insensitive to all other parameters (<5% change).

The scenario analysis shows the results are insensitive to increasing the costs and disutility associated with ventilation assistance. Increasing caregiver disutilities to more realistically reflect the burden of DMD increases the QALY gain of ataluren. Incorporating the wider impact of DMD on societal costs reduces the incremental costs of ataluren versus best supportive care by 4%. Extending the time horizon of the analysis to a lifetime reduces incremental QALYs by only 1%.

12.5.15 What are the key drivers of the cost results?

Treatment costs were the key driver of cost.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

Not applicable.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

In line with the scope, subgroup analysis has not been conducted.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-consequence analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis).

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

To model has been validated by two health economists to ensure the model is technically accurate. The model design, input and outputs have been ratified by two clinical experts to ensure the assumptions are valid and the timelines for disease progression are reflective of clinical practice.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-consequence analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no relevant literature that the results can be compared to.

12.8.2 Is the cost-consequence analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths of the analysis:

- Model inputs are based on robust systematic reviews of the literature to ensure all information is the best available and the most up to date
- Data on costs and utilities have been sourced from a recent, comprehensive, international publication incorporating UK-specific data
- The model design and inputs have been validated by 2 clinicians with expertise in DMD and knowledge of the ataluren studies so as to ensure the model accurately reflects a patient's progression through the disease heath states as well as appropriate knowledge of the impact of ataluren treatment
- The approach has been highly conservative in nature so as to not over-estimate the long-term effects based on Study 007 data nor therefore to over-inflate the QALY and Life Year gains that could actually be expected
- The pattern of extrapolation has been based on evidence gained from the use of corticosteroids in the treatment of DMD and relating their effect on timing of LoA and mortality to what would be expected with the additive effect of treatment with ataluren
- Efficacy estimates for ataluren are based on data from a 48 week study. However to mitigate against an over-estimate of efficacy for future years, data from the second 24 week period only (i.e. weeks 24-48) have been used as the basis of the overall treatment effect for the duration of the model

Weaknesses of the analysis:

- Due to time limitations, exploration of possible additional benefits of ataluren identified by clinical experts have not been quantified, such as reduction on risk of mortality and reduction on incidence of scoliosis.

- There are some limitations of the model structure in that it does not allow the full benefit of ataluren to be modelled i.e. increasing survival of ataluren results in fewer QALYs, which is counter-intuitive. This is because the natural history is based on the only available publication that models transition of health states (Humbertclaude et al, 2012). This publication does not allow for extended ambulation beyond 11 years whereas for BSC and ataluren treatment mean age of LoA is 14.0 and 22.1 years respectively. Thus, in using the Humbertclaude data, once a patient has become non-ambulatory they are assumed to be in the worst health state. This is not expected to be the reality and this confounding factor may be addressed by modifying the Humbertcalude data and verifying through clinical experts with subsequent additional analyses (see section 12.8.4).

- Evidence from the trial indicates that younger patients will receive greater benefit of ataluren as they will start treatment much earlier in the stage of the condition. Data from the >75% predicted 6MWD group at baseline shows a trend towards improved 6MWD vs. placebo. The current cohort of untreated patients in England, as well as all newly diagnosed patients, are younger than the modelled baseline which was based on the Study 007 cohort. It is therefore expected that incremental costs would reduce and incremental QALYs would increase when modelling a younger age at the start of treatment.

- It has not been possible to source data for every important element of the disease that has a significant impact on NHS costs or patients quality of life. For example, ventilation-assistance places a huge burden on patients, carers and NHS costs but no cost or quality of life data was available.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The ongoing confirmatory study of ataluren will provide additional efficacy results that will validate assumptions made on the extrapolation of treatment effect.

The burden of DMD on caregivers is not accurately captured by the values shown in the literature. 95% of UK DMD patients live with their parents and most parents have to give up work to care for their child. This burden is not accurately reflected when using a caregiver disutility of 0.11 (Landfeldt, 2014), which could be due to the choice of instruments used to capture quality of life.

As stated above in section 12.8.3, Humbertclaude et al (2012) has been used to model the natural history of the disease, i.e. patient progression from LoA to ventilation assistance and scoliosis (see section 12.1.1 on time to ventilation assistance and scoliosis). It was used as it is the only publication identified that modelled the transition of these agreed health states. In this study patients were stratified into three groups based on age of LoA (<8 years, 8–11 years and >11 years). As the starting age of the cohort in the economic model is 8.5 years, and given the impact of BSC and of ataluren on LoA, most of the patients actually lose their ambulation beyond 11 years. As a result, it is the same time-to-VA curve and the same time-to-scoliosis curve from the >11 years group that was applied in the model for both BSC and ataluren arms. This has negatively impacted the QALY gain observed with ataluren as no specific benefit on delaying the time-to-VA or the time-to-scoliosis subsequent to a delayed time-to-LoA were modelled. An update to the Humbertclaude data is therefore required that divides the >11 years group into additional age groups (e.g. 11-16, 17-20, 20-23 and >23) reflecting the changes to LoA seen with ataluren. Such additional analysis would allow the delay in LoA seen with ataluren treatment to be better reflected in health gains during the intermediate and late stages of the condition.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

A 2009 population study of patients with genetic muscle diseases in Northern England estimates that DMD affects 8.29 in 100,000 males (Norwood 2009). Based on the size of England's population in 2012 (53,865,817) (Office for National Statistics 2013), it is therefore estimated that 2,200 males in England have DMD. Recent data from the TREAT-NMD DMD Global database, which contains over 7,000 mutations, has found that 10% of patients have nmDMD (Bladen, 2015). Of these approximately [redacted]% are aged 5 years and over and are ambulatory ([redacted]).

Table D13.1. Calculation of prevalence and incidence estimates

Patient population	Prevalence	Incidence
DMD	8.28 per 100,000 = 2,200 (Norwood, 2009)	1/5,135 male births (Moat, 2013)
nmDMD	10% of DMD (Bladen, 2015)	7 new per annum
Aged 5 and above and ambulatory	[redacted]	
nmDMD aged 5 and over and ambulatory	[redacted]	

In the budget calculation data from the cost-consequence model for the mortality rate and the rate of loss of ambulation have also been applied, [redacted] and [redacted] respectively. This has been derived from the cost consequence model based on a median survival of [redacted] and a median age at LoA of [redacted].

This results in a potential (theoretical) eligible population, i.e. in line with the marketing authorisation for ataluren, of [redacted] patients in Year 1 rising to [redacted] patients in Year 5 (Table D13.2).

Table D13.2. Eligible patients for ataluren over next 5 years in England

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	**66**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	**7**	**7**	**7**	**7**	**7**	**7**
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential (theoretical) available patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

[redacted] boys aged 5 and over who are ambulant and who have nmDMD have been identified (known patients) - [redacted] patients are currently receiving ataluren through clinical trials ([redacted] in study 020 and [redacted] in study 019) and [redacted] have been identified through feedback from specialist centres. This is out of a theoretical prevalent population of 66 in Year 1.

Currently there are no patients in the UK who are prescribed ataluren that is reimbursed/ paid for however [redacted]

The uptake of ataluren in Year 1 is based on the estimates of patients moving from clinical trials and compassionate use supply onto commercial supplies. It also includes [redacted] from the existing pool being initiated on ataluren during 2015 from the point when NHS England guidance is expected to be published (June 30th 2015). If NHS England commissioning commences in July 2015, Year 1 will represent 9 months of a full 12 month funding period.

Expert opinion suggests that the assumptions regarding uptake are reasonable.

Table D13.3. Number of patients treated with ataluren over next 5 years in England

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	**66**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	**7**	**7**	**7**	**7**	**7**	**7**
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential (theoretical) available patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Level of patient identification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Known patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	**35**	**42**	**49**	**57**	**65**	**50**

Genetic testing using the standard genetic tests currently commissioned by NHS England for dystrophin gene mutations is carried out during diagnosis and no additional tests are required to identify patients eligible for treatment with ataluren. This pathway is well established and it is not anticipated that the projected prevalent population will change over time.

The above estimate of uptake might be considered a best case as in reality the actual uptake of a medicine might be lower than that theoretically calculated (see section 13.8).

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

It is not anticipated that any additional infrastructure will be required to ensure the safe and effective use of ataluren as care will be delivered by specialist centres. Genetic testing using the standard genetic tests currently commissioned by NHS England for dystrophin gene mutations is carried out during diagnosis and no additional tests are required to identify patients eligible for treatment with ataluren.

As ataluren is an oral therapy, no additional facilities, technologies or infrastructure need to be used. Unlike many new novel technologies that are injected, it will not need patients to come into hospital either as day cases or in-patients to receive

treatment and initiation of therapy with ataluren does not require any particular supervision. Minimal monitoring of patients is required.

The sachets of ataluren have no special storage requirements such as needing to be stored in a fridge. The supply of ataluren can also be arranged as home care delivery if desired thus mitigating any need for patients/ carers to travel to the specialist centre to obtain the prescription and supply of ataluren.

13.4 Describe any estimates of resource savings associated with the use of the technology.

There are savings to be made in direct costs of fewer surgical procedures, and hence also surgical follow-up costs including physiotherapy, as well as a reduced and/or deferred need for respiratory and palliative care support for a child with nmDMD. However these have not been incorporated into the budget impact calculation as any offsetting of savings cannot be accurately calculated.

As the disease progresses children with DMD can develop scoliosis due to weakening of their back muscles exacerbated by wheelchair immobility. In later childhood and teenage years inpatient spinal surgery and rehabilitation may be required (more commonly in steroid-naïve patients), there is increased need for inpatient orthopaedic intervention, cardiac and respiratory intervention with potential inpatient admission for treatment of respiratory complications (Bushby 2010b).

Loss of ambulation is one of the most serious complications of DMD and the age at loss of ambulation is predictive of disease progression and time to significant events such as diagnosis of scoliosis and respiratory insufficiency (Humbertclaude, 2012).

In addition, maintenance of ambulatory capacity has been associated with prevention or delay of onset and reduced severity of scoliosis and the need for major surgery (Yilmaz, 2004; Kinali, 2007; Humbertclaude, 2012). Corticosteroids slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilises pulmonary function (Bushby, 2010b).

The cost of scoliosis surgery (elective inpatient) is significant £20,985 with post-surgery costs of £2,915 per visit (NHS Reference costs, 2013/14) – see also Section

12.3.1. It is also anticipated that less respiratory support in terms of ventilation may be required but again this is difficult to quantify.

Ataluren could also reduce costs from the use of electric wheelchairs, so that ambulatory people with nmDMD will be able to use self-propelled wheelchairs as they will be older and stronger due to the benefits of ataluren delaying the loss of ambulation and maintaining upper body strength.

Therefore by slowing ambulatory decline and delaying the point at which more rapid decline occurs, ataluren may also delay complete loss of ambulation and wheelchair reliance. Importantly, slowing the loss of walking ability may also have beneficial effects specifically, delayed loss of ambulation, and consequently delayed onset of scoliosis and respiratory and cardiac insufficiency and their associated costs.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is anticipated that resource savings would accrue as described above, but it has not been possible to quantify these with any precision.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

It is anticipated that savings could accrue to the welfare, education and local government budgets. For example ataluren will enable teenagers to stay in mainstream education, attend college/university and reach working age while still ambulatory. Further details are given in section 14.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The recommended dose of ataluren is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight). Ataluren is available in sachets of 125 mg, 250 mg or 1000 mg. Table D13.4 below provides information on which sachet strength(s) to use in the preparation of the recommended dose by body weight range

(Translarna, SPC). This table has also been presented in section 12.3.6 of the submission.

Table D13.4. Recommended dosing by weight (Translarna SPC)

Weight Range (kg)		Number of sachets								
		Morning			Midday			Evening		
		125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	1	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

The median weight of patients used in the budget impact calculation is assumed to be between 24-26kg. Using this bodyweight for a daily dose of 1,000 mg from the table above, the number of patients identified in section 13.1 and uptake in section 13.2, the budget impact in year 1 is estimated to be approximately £8.6M rising to around £16M in Year 5 assuming uptake by this time is [redacted].

Table D13.5. Budget impact of ataluren in England over 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	**66**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	**7**	**7**	**7**	**7**	**7**	**7**
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential (theoretical) available patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Level of patient identifi-cation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Known patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual 12 month cost	**£8,625,680**	**£10,350,816**	**£12,075,952**	**£14,047,536**	**£16,019,120**	**£12,223,821**

NHS England has is a single budget for specialised services of approximately £13 billion, which includes medicines. The budget impact of ataluren in year 1 represents 0.07% of this.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The source used for the prevalence estimates of DMD comes from a detailed population study of patients with genetic muscle disease in the northern region of England (Norwood, 2009). This region comprises the counties of Northumberland, Durham, Cumbria and parts of Yorkshire and Lancashire. The estimated total population according to the last census at the time of the study was 2.99 million. The inclusion criteria were all registered patients with inherited muscle diseases diagnosed and currently seen by the neuromuscular team at the Institute of Human Genetics in Newcastle. All cases of DMD were confirmed to the diagnostic standard of having a deletion, duplication or point mutation within the dystrophin gene.

Another paper from Northern Ireland by Hughes et al (1996) stated that their ascertainment of DMD and other severe cases was probably complete with a low risk

of bias and described a prevalence of 8.2/100 000 which aligns well with the one in the Norwood study.

A recent worldwide systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy reported that the pooled prevalence of DMD was 4.78 (95% CI 1.94-11.81) per 100,000 males respectively and the incidence of DMD was 10.71 per 100,000 (Mah, 2014). The 31 studies included in the meta-analysis differed widely in their approaches to case ascertainment, resulting in significant methodological heterogeneity and varied data quality and so this study was not considered appropriate to use in the budget impact calculations.

Therefore the estimated prevalence of DMD from Norwood et al (8.29 per 100,000) used in the budget impact analysis is believed to be reasonable as it is based on a relatively recent study in an English population, with a confirmed diagnosis of DMD by appropriate methods and having a low risk of bias.

Recent data from the TREAT-NMD DMD Global database, which contains over 7,000 mutations, has found that 10% of patients have nmDMD (Bladen, 2015). This is a new global database for DMD (TREAT-NMD DMD Global database) based on the French UMD-DMD system has been developed with TREAT-NMD collaboration. TREAT-NMD was initially established as an EU funded “network of excellence“ with the remit of „reshaping the research environment“ in the neuromuscular field (http://www.treat-nmd.eu/), 2013; Bushby, 2009). Standardised mutation (DMD mutations) specific data based on TREAT-NMD mandatory and highly encouraged items from the national TREAT-NMD DMD registries (Bladen, et al., 2013) were transferred to the global DMD database in November 2013, in order to provide a single cohort of genetic and clinical variants. Analysis of DMD genetic mutations was then carried out for the 7,149 patient data sets held within the TREAT-NMD DMD Global database. GVS nomenclature was used throughout (http://www.hgvs.org/mutnomen/). It is believed this provides a robust source of information regarding the prevalence of nmDMD.

The proportion of nmDMD patients who are aged 5 and over and ambulatory has been derived from global data from the Cooperative International Neuromuscular Research Group (CINRG) DMD Natural History Study (DMD-NHS) ([redacted]). This involved 20 centres from around the world, collecting the most comprehensive and largest, prospective, longitudinal natural history data to date on a cohort of DMD patients. The study enrolled 340 individuals, aged 2–28

years, with assessments obtained every 3 months for 1 year, at 18 months, and annually thereafter.

The incidence figure in the budget impact calculations is based on a Welsh newborn bloodspot screening programmes for DMD which one of the longest running in the world (Moat, 2013). In this programme newborn bloodspots were collected routinely as part of the Wales newborn screening programme. Specific consent was obtained for this test separately from the other tests. During the 21-year period, 369,780 bloodspot cards were received from male infants, of these 343,170 (92.8%) were screened using a bloodspot creatine kinase (CK) assay following parental consent. DMD was confirmed in 56 cases by genotyping/muscle biopsy studies. The incidence of DMD in Wales of 1:5,136 during this period is lower than that of 1:4,046 before commencement of screening in Wales. It was concluded that screening had reduced the diagnostic delay enabling reproductive choice for parents of affected boys and earlier administration of current therapies. It would mean that one would expect the incidence of DMD to continue to decline over time and thus the figure of 1:5,136 is likely to be an overestimate of the incidence.

An annual background mortality rate of [redacted] has been applied and a rate for loss of ambulation [redacted] based on data from the cost consequence model. There may be a survival benefit with ataluren, as modelled and described in section 12.2.1 but this has not been assumed for the 5 year budget impact calculation.

Compliance is assumed to be 100%. It is expected compliance with treatment will be high as caregivers will be motivated to ensure boys with nmDMD do not miss a dose in order to obtain the full benefits of ataluren in this condition. In Study 007 the compliance rate overall was very high; as calculated per dose, with a median of 97.7% of the doses in the placebo arm, 97.0% of the doses in the ataluren arm being taken as planned (PTC Therapeutics, 007 CSR). PTC Therapeutics has no evidence to believe that compliance in the real world will be any less than this.

The projected uptake is thought to be realistic based on the known number of patients and expert feedback. Experience to date from Germany and France where ataluren has been launched and reimbursed suggests uptake is high and that nearly all known nmDMD patients who are eligible for ataluren are being prescribed the drug.

It is possible the final uptake will be lower than projected as the actual number of patients that are theoretically eligible based on the epidemiology does not always translate into the actual number of patients that are found and diagnosed, especially in very rare diseases. As evidenced by the NICE Innovation Scorecard, the uptake of NICE approved technologies is often less than that predicted from the theoretical prevalent population (HSCIC, 2015).

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

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

Section 15 is aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

A substantial proportion of the benefits of ataluren treatment are incurred outside of the NHS and personal social services. Due to its early onset and rapid progression, DMD results in severe disability and consequent lack of independent living by the early twenties with death usually occurring before the age of 30. As a result, adults with DMD rarely succeed in participating in a working life or contributing to society. Only a very small proportion of patients are reported to be in employment and the burden on caregivers results in substantial losses in productivity. A recent study (described in detail in section 11) has estimated the total economic burden of DMD to society and caregiver households (Landfeldt, 2014). Patients with DMD from Germany, Italy, United Kingdom, and United States were included in the study (770

patient-caregiver pairs). Demographics of caregivers showed that in the UK 98% of caregivers were parents, 79% of whom were female. Informal care (care- givers' nonprofessional paid care and the proportion of caregivers' leisure time devoted to provide informal care) was extensive in all countries. In the UK, 55% of caregivers were employed whereas 49% had reduced working hours or had stopped working completely because of their relative's DMD. For employed caregivers, the mean overall work impairment (loss in work time and productivity while working) was estimated at 29% (95% CI 24%–35%) for the UK sample. Labour-force participation among patients was very low (4%). A further recent study has reported on the demographics and care of adults with DMD in the UK compared to other European countries (Rodger, 2014). In this study 42 patients aged over 18 responded to the survey (18.6% of the total UK respondents). All were non-ambulatory and none were in employment, with 25.6 % still in education (secondary school, special needs school, vocational training, or university). Most of the UK adults were living at home (92.9 %), which was higher than elsewhere in Western Europe (Rodger, 2014).

A treatment that changes the course of nmDMD by slowing disease progression enables children and adults with nmDMD to maintain their independence for longer. This in turn would mean that that caring for their children would be less intensive for parents/ caregivers and may allow them to stay in paid work for longer. It may also mean that children with nmDMD can participate in education for longer, remain more self-sufficient and have an increased chance of employment in adulthood.

Costs associated with DMD-related health care resource use, informal care, and production losses (indirect costs) are presented in Table E14.1. The largest cost component was indirect costs in Germany, Italy, and the US, and nonmedical community services in the UK. The total annual cost of illness of DMD in the UK was estimated as 72,870 US dollars (GBP £53,325) per patient. Of this at least 46% related to the cost of informal care and loss of productivity and therefore not incurred by the NHS/ Personal Social Services. It is also expected that a large proportion of non-medical community care, as well as adaptations to the home is paid for privately by families. The cost of illness (including both direct medical cost, cost of informal care and indirect costs) increases as patients enter the non-ambulatory stages of disease. In the UK the cost of illness almost doubled between the early and late stages of being non-ambulatory (from approximately 66,000 to 129,000 US dollars/per patient/annum). Similar results were seen in a separate study of patients

in Germany where both direct medical and non-medical cost of illness increased with disease severity (Schreiber-Katz, 2014).

Estimates of the total economic burden of DMD, including a monetary value of the loss in patient and caregiver quality of life (intangible costs) were also calculated. Using the most recent DMD prevalence estimates, the national burden of DMD in the UK was estimated at $200,478,000 per annum (GBP £146,705,080)(Landfeldt, 2014).

Ataluren treatment delays loss of ambulation and delaying progression to the non-ambulatory stage of disease would delay the occurrence of the associated higher costs, of which a large proportion are made up of costs incurred outside of the NHS and personal social services.

Table E14.1. Components of annual cost of Duchenne muscular dystrophy (UK)

Component	Percentage of cost of illness	Per-patient cost (US dollars, 2012)	Per-patient cost (GBP 2014)[e]
Hospital visits[a]	3%	2,300 (1,500–3,720)	1,683
Visits to physicians and other health care practitioners	11%	8,230 (6,360–13,150)	6,023
Tests and assessments	2%	1,580 (1,450–1,750)	1,156
Medications	1%	930 (820–1,070)	681
Non-medical community services[b]	27%	19,250 (13,240–28,670)	14,087
Aids, devices and investments[c]	10%	7,520 (5,690–9,790)	5,503
Informal care	20%	14,340 (13,030–15,990)	10,494
Indirect costs (production losses)	26%	18,700 (16,280–21,150)	13,684
Total annual cost of illness	-	72,870 (64,350–84,150)	53,325
Intangible costs[d]	-	46,080 (42,360–50,050)	33,720
Total burden of illness	-	118,950 (108,280–132,710)	87,045

Data presented as mean (95% confidence interval), rounded to nearest 10.

a Including emergency and respite care.

b Home help, personal assistants, nannies, and transportation services.

c Include investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).

d cost (costs due to pain, anxiety, social handicap, etc.) was estimated by assigning a monetary value to the loss in quality of life for patients and caregivers in relation to the age- and sex-specific mean quality of life in the general population.

e Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

Source: (Landfeldt, 2014)

The mean per- patient annual household economic burden of DMD, calculated for households in which the patients with DMD currently lived, is presented in Table E14.2. Patients in the late ambulatory, early non-ambulatory, and late non-ambulatory classes had 38% (relative risk [RR]: 1.38, 95% CI: 1.20–1.59), 181% (RR: 2.81, 95% CI: 2.41–3.27), and 191% (RR: 2.91, 95% CI: 2.54–3.34) higher annual household economic burden compared with their early ambulatory counterparts. By delaying disease progression, ataluren would delay the associated increase in cost to households.

Table E14.2. Per-patient annual household burden of DMD in the UK

	Cost (in 2012 US dollars)	Per-patient cost (GBP 2014)[b]
No. (%) living with caregiver	188 (98)	138
Total out-of-pocket payments	3,490 (2,220–5,570)	2,554
Insurance premiums	10 (0–30)	7
Copayments for medical services	60 (30–140)	44
Copayments for medications	100 (60–140)	73
Copayments for community services	140 (60–290)	102
Out-of-pocket payments for investments[a]	3,180 (2,020–5,710)	2,327
Income loss	750 (440–1,200)	549
Loss of leisure time	13,590 (12,410–14,980)	9,945
Intangible costs	45,770 (42,070–49,670)	33,493
Total per-patient annual household burden	63,600 (58,790–68,370)	46,541

Abbreviation: DMD Duchenne muscular dystrophy. Data presented as mean (95% confidence interval), rounded to nearest 10, if not otherwise stated.

a Include nonreimbursed payments for medical and nonmedical aids and devices, as well as investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).

b Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

Source: (Landfeldt, 2014)

Children with DMD have a higher quality of life in the early stages of disease, which deteriorates with progression through late ambulatory, early non-ambulatory and late non-ambulatory stages (Landfeldt, 2014; Schreiber-Katz, 2014). By slowing the loss of ambulation ataluren will allow children to maintain their quality of life for longer.

The estimation of the impact of ataluren treatment on reduction in societal costs is shown in Section 12.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is anticipated that treatment with ataluren could result in cost savings to the following government departments or budgets:

Education budget – a child with DMD will receive a statement of special educational needs, which will usually involve the cost of classroom assistance and adaptations to the fabric of the school (for example, to widen spaces to accommodate a wheelchair). These costs may be reduced, or postponed, if the patient derives clinical benefit from treatment with ataluren.

Local Government budget – cost savings may accrue (in terms of reduced Disabled Facilities Grant payments, for example) if fewer adaptations need to be made to a patient's home, or if the adaptations needed are less costly.

Welfare budget – the more independent and capable the patient is, the less dependent they – or their caregivers - are on respite care, or on disability and other welfare payments.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Costs borne by patients/ caregivers include:

- Out of pocket expenses, e.g. travel expenses
- Non-reimbursed payments for medical and nonmedical aids and devices, as well as investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility)
- Patient loss of quality of life, leisure time, a normal education and ability to contribute to society
- Patient loss of life
- Caregiver loss of quality of life, leisure time, earnings

- Non-reimbursed payments for home help, personal assistants, nannies, and transportation services

Please also refer to Table E14.2.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

A considerable amount of time is spent by family members in providing care. The majority of caregivers are parents (98%) (Landfeldt, 2014). In addition to helping their children with daily activities such as getting around, dressing and washing, time is spent each day at home on stretching exercises and physiotherapy as well as travelling to visit various members of the multidisciplinary team (MDT). This becomes even more acute when patients transition to adult services when care is generally more fragmented necessitating multiple visits.

In the German study by Schreiber-Katz et al, DMD non-working relatives' total care efforts was estimated at a mean of 9.4 (SD 10.9) hours per day, with a notable increase in more severe clinical stages (Schreiber-Katz, 2014). In this study the cost of informal care was around €8,000 per year in the non-ambulatory stages, which rose to €19,532 in the early non-ambulatory stage, €31,490 in the late non-ambulatory stage and €44,443 when adults were confined to bed (Schreiber-Katz, 2014). This indicates that parents spend at least double the time caring for their children following loss of walking ability and that this again increases substantially in the late non-ambulatory stage as the boys lose upper body function. Since the German health care system provides long-term nursing care insurance, the time spent on care by parents in the UK may be even higher.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Study 007 was the first study for registration in DMD and through its entire pre-clinical and clinical development programme PTC Therapeutics has been a pioneer in this field. At the time of the initial study design there were no established primary or secondary endpoints from a regulatory perspective, and there was limited DMD natural history data available. Completion of this trial has provided a better

understanding of the natural history of DMD using the 6MWD and has established the 6MWD as a validated primary endpoint in DMD clinical trials; in addition, the data from this trial has helped to identify the best secondary endpoints in DMD trials and has provided the clinical trial groundwork for future therapies for this devastating and life-limiting condition.

The EMA established that the benefits of ataluren to public health were substantiated by providing a treatment for a serious disease, characterised by gradual deterioration of the condition, and a fatal outcome.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Innovation, Health and Wealth is the NHS Chief Executive's report on the identification, adoption and spread of innovation in the NHS. Innovation, Health and Wealth defines innovation as "an idea, service or product, new to the NHS or applied in a way that is new to the NHS, which significantly improves the quality of health and care wherever it is applied" (Department of Health, 2011).

Innovation, Health and Wealth describes three reasons why innovation and adoption at pace are important not just to the NHS but to society and the economy as well (Department of Health, 2011):

- Innovation transforms patient outcomes
    - Ataluren has been shown to slow disease progression as measured by a lower rate of decline in six-minute walk distance (6MWD) compared to placebo. A decline in the 6MWD to lower than 330 metres is associated with a high risk of loss of ambulation (Mazzone, 2013), therefore treatment with ataluren is expected to delay complete loss of ambulation and wheelchair reliance. Delaying ambulatory decline provides the direct clinical benefit of affording boys with nmDMD a longer period of self-sufficiency.
- Innovation can simultaneously improve quality and productivity
    - Ataluren can improve the quality of life for both patients and carers by delaying the time to loss of ambulation. The delay in time to loss of ambulation means patients will have the possibility to contribute to

society and for carers to continue to work as normally as possible for longer.

- Innovation is good for economic growth

    - Ataluren is the first medicine that directionally changes the course of the condition. It also changes the management of nmDMD from a purely supportive, palliative care resource investment towards a disease specific, disease modifying treatment and personalised medicine

    - As the first investigational new drug to address the underlying cause of dystrophinopathy, ataluren represents an important advance in personalised, genetic-based treatment of nonsense mutation disease

    - PTC Therapeutics in conducting trials with ataluren has moved forward the understanding of the natural history of DMD and relevant endpoints for trial design. This has led to other companies (including British based ones) investing in developing treatments for DMD. Together this leads to further advances in the treatment of diseases; this has clearly been seen with the number of new treatments that have been developed or are in development for conditions such as idiopathic pulmonary fibrosis where previously, like nmDMD, there had been no hope for patients of any new treatments that could modify the course of the disease.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

A registry study (PTC124-GD-025o-DMD) is being performed as a post-approval safety study, per the Pharmacovigilance Risk Assessment Committee of the EMA, to gather data on ataluren safety, effectiveness, and prescription patterns in routine clinical practice. This study has just started recruiting patients and no data will be available to inform this submission.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Ataluren has received marketing authorization from the EMA. Additional data will be generated post-authorisation in the confirmatory phase 3 study PTC124-GD-020-DMD (Study 020) which is expected to report initial results during Q3 2015.

15 Impact of the technology on delivery of the specialised service

15.1 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The marketing authorisation for ataluren states that treatment should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy. It is expected that ataluren, like many innovative, high cost medicines, will be prescribed only by specialists with expertise in the management of the specific condition. In the case of DMD these specialists are paediatric neurologists with a specific interest in neuromuscular conditions. Ataluren will be delivered in specialist centres as described under the service specification for Paediatric Neurosciences – Neurology (E09/S/b) by NHS England.

15.2 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

It is not anticipated that any additional infrastructure will be required to ensure the safe and effective use of ataluren as care will be delivered by specialist centres. Genetic testing using the standard genetic tests currently commissioned by NHS England for dystrophin gene mutations is carried out during diagnosis and no additional tests are required to identify patients eligible for treatment with ataluren.

As ataluren is an oral therapy, no additional facilities, technologies or infrastructure need to be used. Unlike many new novel technologies that are injected, it will not need patients to come into hospital either as day cases or in-patients to receive treatment and initiation of therapy with ataluren does not require any particular supervision. Minimal monitoring of patients is required. The manufacturer intends to fund the cost of home delivery to the patient if this is required.

The sachets of ataluren have no special storage requirements such as needing to be stored in a fridge. The supply of ataluren can also be arranged as home care delivery if desired thus mitigating any need for patients/ carers to travel to the specialist centre to obtain the prescription and supply of ataluren.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Table 17.1 List of databases searched for the clinical evidence systematic review

Review type	Database	Interface
Clinical evaluations **(July 2014)**	Embase®	Embase.com
	MEDLINE®	
	MEDLINE® In-Process	Pubmed.com
	Cochrane central register of Controlled trials (CENTRAL)	Cochrane library
Clinical evaluations **(June 2015)**	EMBASE	Ovid
	Medline (R)	Ovid
	Cochrane central register of controlled trials (CENTRAL)	Ovid
	Medline complete	EBSCO

Embase®: Excerpta Medica Database; CENTRAL: Cochrane central register of controlled trials
MEDLINE®: Medical Literature Analysis and Retrieval System Online

17.1.2 The date on which the search was conducted.

Systematic literature searches were undertaken on 17th July 2014 and were updated on 8th June 2015.

17.1.3 The date span of the search.

For the search carried out in July 2014, no limits were placed on date of publication. The search carried out in June 2015 was limited to publications from July 2014 to present (or from the Year 2014 for CENTRAL).

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 17.2. Embase.com search strategy for Embase® and MEDLINE® (searched on 17th July 2014)

No.	Search terms	Facet	Hits
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR (duchenne NEAR/3 dystrophy):ab,ti	Disease	13 102
#2	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	Study design (RCT and observational)	5 972 201
#3	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti		5 512 213
#4	#2 OR #3		8 834 196
#5	steroid'/syn OR 'corticosteroid'/syn OR 'prednisolone'/syn OR 'prednisone'/syn OR 'deflazacort'/syn OR 'calcium antagonist'/syn OR 'calcium channel blocking agent'/syn OR 'beta adrenergic receptor stimulating agent'/syn OR 'beta 2 adrenergic receptor stimulating agent'/syn OR 'beta 2 agonists' OR beta NEAR/3 agonist* OR 'beta adrenergic receptor blocking agent'/syn OR beta NEAR/3 (blocker OR antagonist*) OR 'dipeptidyl carboxypeptidase inhibitor'/syn OR 'ace inhibitor' OR 'ataluren'/syn OR ptc124:ab,ti OR 'drug therapy'/syn OR 'therapy'/syn OR treat*:ab,ti OR 'best supportive care'	Intervention	11 285 656
#6	#1 AND #4 AND #5	Limits	3408
#7	#6 AND ([animals]/lim NOT ([animals]/lim AND [humans]/lim)		865
#8	#6 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)		572
#9	#7 OR #8		1421
#10	**#6 NOT #9**	**Final numbers**	**1987**

Embase: *Excerpta Medica* Database; MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.3. Cochrane search strategy (searched on 17th July 2014)

No.	Search terms	Facet	Hits
#1	MeSH descriptor: [Muscular Dystrophy, Duchenne] explode all trees	Disease	64
#2	duchenne muscular dystrophy or duchenne:ab,ti or (duchenne near/3 dystrophy)		251
#3	#1 or #2		251
#4	MeSH descriptor: [Steroids] explode all trees	Intervention	38 190
#5	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees		11 350
#6	MeSH descriptor: [Prednisolone] explode all trees		3455
#7	MeSH descriptor: [Prednisone] explode all trees		2831
#8	MeSH descriptor: [Glucocorticoids] explode all trees		3442
#9	steroid or corticosteroid or prednisolone or prednisone or deflazacort or glucocorticoid		23 716
#10	MeSH descriptor: [Calcium Channel Blockers] explode all trees		2670
#11	calcium channel blocker or calcium near/3 (block* or antagonist*)		6177
#12	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees		4189
#13	'beta 2 agonists' or beta near/3 agonist*		4013
#14	beta near/3 (blocker or antagonist*)		8415
#15	ace inhibitor		1860
#16	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees		3718
#17	ataluren or ptc124		21
#18	drug therapy or therapy* or treat*		504 689
#19	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18		517 569
#20	#3 and #19		195
#21	**#20 in Trials (Word variations have been searched)**	**Final numbers**	**165**

Table 17.4. MEDLINE® in-process search strategy searched via PubMed® platform (searched on 17th July 2014)

No.	Search terms	Facet	Hits
#1	"duchenne muscular dystrophy" or "duchenne"	Disease	8835
#2	#1 AND (pubstatusaheadofprint OR inprocess[sb]))	Final numbers	297

MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.5. Embase via Ovid (searched on 8th June 2015)

Index	Search terms	Search limits	Hits
1	exp ataluren/	Explode	61
2	PTC124	Keyword, abstract, title, drug name, heading word	16
3	translarna		7
4	1 or 2 or 3		64
5	exp "Duchenne muscular dystrophy"/	Explode	690
6	Duchenne	Keyword, abstract, title, drug name, heading word	829
7	5 or 6		829
8	4 and 7		25

Table 17.6. CENTRAL via Ovid (Year 2014 - Current)

Index	Search terms	Search limits	Hits
1	PTC124	Keyword, abstract, title, heading word	0
2	ataluren		10
3	translarna		0
4	1 or 2 or 3		10

Table 17.7. Medline(R)-In Process via Ovid (Year 2014-Current)

Index	Search terms	Search limits	Hits
1	PTC124	Keyword, abstract, title, heading word	11
2	ataluren		20
3	translarna		0
4	1 or 2 or 3		24
5	exp Muscular Dystrophy, Duchenne/	Explode	323
6	Duchenne	All fields	410
7	4 and (5 or 6)		6

Table 17.8. MEDLINE Complete via EBSCO (Date of Publication 01/07/2014 – 08/06/2015)

Index	Search terms	Search limits	Hits
1	PTC124	Title, abstract	61
2	ataluren	Title, abstract	38
3	translarna	Title, abstract	0
4	1 or 2 or 3		79
5	Muscular Dystrophy, Duchenne	Explode major heading	115
6	Duchenne	Title, abstract	7,178
7	1 OR 2		7,197
8	3 or 6		24

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

An additional search was run on clinicaltrials.gov to identify any unpublished studies. The database was searched using the search term ‘ataluren’.

17.1.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Patients with DMD
Interventions	Ataluren Best supportive care, and/ or Any other pharmacological therapy used for the treatment of patients with DMD, and/or Corticosteroids
Outcomes	All available
Study design	Randomised controlled trials, controlled trials, observational studies, retrospective trials, registries
Language restrictions	English
Search dates	No limits were put on publication date
Exclusion criteria	
Population	
Interventions	
Outcomes	Studies assessing physical therapies and psychosocial therapy
Study design	
Language restrictions	
Search dates	

17.1.7 The data abstraction strategy.

Citations were first screened based on title and abstract supplied with each citation ('first pass'). Each citation was screened by two independent reviewers and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded during first pass. Citations with abstracts that were unclear were included during this phase. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded. Full-text copies of all references that could potentially meet the eligibility criteria were obtained through internet search.

The eligibility criteria were then applied to the full-text citations. The list of studies included during the 'second pass' stage was screened for any RCTs evaluating ataluren as an intervention

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable – search outlined in 17.1 was used to identify adverse event data.

17.2.2 The date on which the search was conducted.

Not applicable

17.2.3 The date span of the search.

Not applicable

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

17.2.6 The inclusion and exclusion criteria.

Not applicable

17.2.7 The data abstraction strategy.

Not applicable

17.3 Appendix 3: Search strategy for economic evidence and quality of life data

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Table 17. 9. List of databases searched

Review type	Database	Interface
Economic evaluations (Search July 2014)	Embase®	Embase.com
	MEDLINE®	
	MEDLINE® In-Process	Pubmed.com
	NHS EED	Cochrane library
	EconLit®	EBSCO
Economic evaluations (Search June 2015)	EMBASE	Ovid
	NHS Economic Evaluation Database	Ovid
	Medline (R)	Ovid
	Medline complete	EBSCO
	EconLit	EBSCO

Embase®: Excerpta Medica Database; CENTRAL: Cochrane central register of controlled trials MEDLINE®: Medical Literature Analysis and Retrieval System Online; NHS EED: National Health Service Economic Evaluation Database

17.3.2 The date on which the search was conducted.

Systematic literature searches were undertaken on 21st July 2014 and were updated on 8th June 2015.

17.3.3 The date span of the search.

For the search carried out in July 2014, no limits were placed on date of publication. The search carried out in June 2015 was limited to publications from July 2014 to present (or from the Year 2014 for CENTRAL).

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 17.10. Embase.com search strategy for Embase® and MEDLINE® utility review (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR (duchenne NEAR/3 dystrophy):ab,ti	Disease	13 074
#2	(utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)):ab,ti OR 'health utility index' OR 'hui':ab,ti OR 'hrqol':ab,ti OR 'hqol':ab,ti OR 'quality of life'/exp OR 'quality of life' OR 'quality-of-life'/exp OR 'quality-of-life' OR qol:ab,ti OR utilit* NEXT/1 (score* OR value* OR evaluation*) OR health NEXT/2 utilit* OR ('health'/exp OR 'health' AND state NEXT/1 utilit*) OR hui:ab,ti OR (health NEXT/1 state* AND state* NEXT/1 preference*) OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'quality adjusted life' OR 'quality adjusted' NEXT/1 survival* OR qaly:ab,ti OR qald:ab,ti OR qale*:ab,ti OR qtime*:ab,ti OR 'disability adjusted life' OR daly*:ab,ti OR 'health survey'/exp OR 'health survey' OR hye*:ab,ti OR health*year*equivalent OR health NEAR/2 utility* OR 'wellbeing'/exp OR 'wellbeing':ab,ti OR quality NEAR/2 well*being OR qwb:ab,ti OR willingness NEAR/2 pay OR standard NEAR/2 gamble OR disutili*:ab,ti OR time NEAR/2 trade*off OR tto:ab,ti OR 'discrete choice' NEXT/1 experiment* OR 'short form 36'/exp OR 'short form 36' OR 'sf36':ab,ti OR 'sf-36':ab,ti OR 'sf 36':ab,ti OR 'short form 12'/exp OR 'short form 12' OR 'sf12':ab,ti OR 'sf-12':ab,ti OR 'sf 12':ab,ti OR 'short form 6' OR 'sf6':ab,ti OR 'sf-6':ab,ti OR 'sf 6':ab,ti OR 'euroqol' OR 'euro-qol' OR 'euro qol' OR 'eq5d':ab,ti OR 'eq-5d':ab,ti OR 'eq 5d':ab,ti OR rosser OR (visual NEXT/1 analog* AND analog* NEXT/1 scale*)	Study design (utility)	554 411
#3	#1 AND #2	Limits	463
#4	#3 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)		168
#5	#3 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)		12
#6	#4 OR #5		180
#7	#3 NOT #6	Final number	283

Embase: *Excerpta Medica* Database; MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.11 Cochrane search strategy for the utility review (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	MeSH descriptor: [Muscular Dystrophy, Duchenne] explode all trees	Disease	64
#2	duchenne muscular dystrophy or duchenne:ab,ti or (duchenne near/3 dystrophy)		250
#3	#1 or #2		250
#4	utilit* near/2 (measure* or outcome* or state* or health or score* or weight* or analysis)	Study design (utility)	4102
#5	(utilit* next/1 (score* or value* or evaluation*)) or (health next/2 utilit*)		2126
#6	health and (state next/1 utilit*)		174
#7	hui or (health next/1 state* and state* next/1 preference*) or "health utility index"		1134
#8	MeSH descriptor: [Quality of Life] explode all trees		14 798
#9	quality of life or "quality-of-life" or qol or hrqol or hqol		37 143
#10	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees		3610
#11	quality adjusted life year or "quality adjusted life" or ("quality adjusted" next/1 survival*) or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly*		7038
#12	MeSH descriptor: [Health Surveys] explode all trees		24 324
#13	health survey or hye* or health*year*equivalent or health near/2 utility*		2792
#14	time near/2 trade*off or tto or "discrete choice" next/1 experiment*		136
#15	((visual next/1 analog*) and (analog* next/1 scale*))		17 040
#16	short form 36 or "sf36" or "sf-36" or "sf 36" or "short form 12" or "sf12" or "sf-12" or "sf 12" or "short form 6" or "sf6" or "sf-6" or "sf 6" or euroqol or euro*qol or "eq5d" or "eq-5d" or "eq 5d" or rosser		10 709
#17	wellbeing or quality near/2 well*being or qwb or willingness near/2 pay or standard near/2 gamble or disutili*		2738
#18	Pediatric Quality of Life Inventory or pedsql		98
#19	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18		80 769
#20	#3 and #19		35
#21	#20 in Trials (Word variations have been searched)	Final numbers	11

Table 17.12. MEDINE® in-process search strategy searched via PubMed® platform (searched on 8th July 2014)

No.	**Search terms**	**Facet**	**Hits**
#1	"duchenne muscular dystrophy" or "duchenne"	Disease	8817
#2	**#1 AND (pubstatusaheadofprint OR inprocess[sb]))**	**Final numbers**	**295**

MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.13 Embase.com search strategy for Embase® and MEDLINE® (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	'duchenne muscular dystrophy'/syn OR 'duchenne muscular dystrophy' OR 'duchenne muscular dystrophy':ab,ti OR duchenne:ab,ti OR (duchenne NEAR/3 dystrophy):ab,ti	Disease	13 074
#2	'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use) OR (cost* NEAR/3 (treat* OR therap*)):ab,ti	Study design (economic)	1 040 134
#3	#1 AND #2	Limits	212
#4	#3 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)		7
#5	#3 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)		69
#6	#4 OR #5		74
#7	**#3 NOT #6**	**Final numbers**	**138**

Embase: *Excerpta Medica* Database; MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.14. NHS EED search strategy (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	MeSH descriptor: [Muscular Dystrophy, Duchenne] explode all trees	Disease	64
#2	duchenne muscular dystrophy or duchenne:ab,ti or (duchenne near/3 dystrophy)		250
#3	#1 or #2		250
#4	**#3 in Economic Evaluations (Word variations have been searched)**	**Final numbers**	**2**

NHS EED: National Health Service Economic Evaluations Database

Table 17.15. MEDINE® in-process search strategy searched via PubMed® platform (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	"duchenne muscular dystrophy" or "duchenne"	Disease	8817
#2	**#1 AND (pubstatusaheadofprint OR inprocess[sb]))**	**Final numbers**	**295**

MEDLINE: Medical Literature Analysis and Retrieval System Online

Table 17.16. EconLit® search strategy searched via EBSCO platform (searched on 8th July 2014)

No.	Search terms	Facet	Hits
#1	**"duchenne muscular dystrophy" or "duchenne"**	**Disease**	**2**

Table 17.17. Embase (Date delivered 1/7/14 – 8/6/15)

Index	Search terms	Search limits	Hits
1	exp "Duchenne muscular dystrophy"/	Explode	690
2	Duchenne	Abstract / Title	653
3	1 OR 2		812
4	exp socioeconomics/ or exp "cost benefit analysis"/ or exp "cost control"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ or exp "cost of illness"/ or exp "cost utility analysis"/ or exp "health care cost"/ or exp "economic aspect"/ or exp "health economics"/ or exp "economic evaluation"/ or exp "financial management"/ or exp "health care distribution"/ or exp "health care financing"/ or exp "hospital cost"/ or exp "resource allocation"/ or exp productivity/ or exp absenteeism/ or exp "work disability"/ or exp "work capacity"/ or exp caregiver/ or exp "caregiver burden"/ or exp "caregiver support"/		83,429
5	"resource use" or "resource utilisation" or "resource utilization" or presenteeism or "indirect cost"	Free text: all fields, human	2,279
6	10 or 11		84,367
7	3 and 6		**35**

Table 17.18. Medline(R)-In Process (Date delivered 1/7/14 – 8/6/15)

Index	Search terms	Search limits	Hits
1	exp Muscular Dystrophy, Duchenne/	Explode	325
2	Duchenne	All fields	421
3	1 OR 2		421
4	exp socioeconomics/ or exp "cost benefit analysis"/ or exp "cost control"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ or exp "cost of illness"/ or exp "cost utility analysis"/ or exp "health care cost"/ or exp "economic aspect"/ or exp "health economics"/ or exp "economic evaluation"/ or exp "financial management"/ or exp "health care distribution"/ or exp "health care financing"/ or exp "hospital cost"/ or exp "resource allocation"/ or exp productivity/ or exp absenteeism/ or exp "work disability"/ or exp "work capacity"/ or exp caregiver/ or exp "caregiver burden"/ or exp "caregiver support"/		11,351
5	"resource use" or "resource utilisation" or "resource utilization" or presenteeism or "indirect cost"		13
6	4 or 5		11,363
7	3 and 6		**6**

Table 17.19. Embase (Date delivered 1/7/14 – 8/6/15)

Index	Search terms	Search limits	Hits
1	exp "Duchenne muscular dystrophy"/	Explode	690
2	Duchenne	Abstract / Title	653
3	1 OR 2		812
4	exp "quality of life"/ or exp "quality of life		109,768

	assessment"/ or exp "quality of life index"/ or exp "quality adjusted life year"/ or exp questionnaire/ or exp "rating scale"/ or exp "health survey"/ or exp "health status"/ or exp "outcomes research"/ or exp "scoring system"/		
5	qaly$ or qald or qale or qtime or "disability adjusted life" or daly or hql$ or hqol$ or h$qol or hye$ or "health utilit$"	Free text: all fields	2,142
6	4 or 5		110,351
7	3 and 6		**63**

Table 17.20. Medline(R)-In Process (Date delivered 1/7/14 – 8/6/15)

Index	Search terms	Search limits	Hits
1	exp Muscular Dystrophy, Duchenne/	Explode	325
2	Duchenne	All fields	421
3	1 OR 2		421
4	exp "quality of life"/ or exp "quality of life assessment"/ or exp "quality of life index"/ or exp "quality adjusted life year"/ or exp questionnaire/ or exp "rating scale"/ or exp "health survey"/ or exp "health status"/ or exp "outcomes research"/ or exp "scoring system"/		103,171
5	qaly$ or qald or qale or qtime or "disability adjusted life" or daly or hql$ or hqol$ or h$qol or hye$ or "health utilit$"		874
6	4 or 5		103,407
7	3 and 6		**41**

Table 17.21. NHS EED (Date delivered 1/7/14 – 8/6/15)

Index	Search terms	Search limits	Hits
1	exp Muscular Dystrophy, Duchenne/	Explode	1
2	Duchenne	All fields	2
3	1 OR 2		**2**

Table 17.22. MEDLINE Complete (Date of Publication July 2014 – June 2015)

Index	Search terms	Search limits	Hits
1	(MH "Muscular Dystrophy, Duchenne")	Major heading	115
2	TX "Duchenne"	Boolean search, All text [TX]	643
3	1 OR 2		643
4	(MH "Economics+") OR (MH "Models, Statistical+") OR (MH "Health Care Costs+") OR (MH "Health Resources+") OR (MH "Psychology, Industrial+") OR (MH "Disability Evaluation+") OR (MH "Caregivers+") OR (MH "Patient Care+") OR (MH "Socioeconomic Factors+")	Major heading: Explode	27,996
5	TX socioeconomics or TX economic aspect or TX health care financing or TX health economics or TX resource use or TX resource utili#ation or TX presenteeism or TX work disability or TX work capacity or TX caregiver burden or TX caregiver support or TX indirect cost	Boolean search, All text [TX]	7,666
6	7 OR 8	Boolean search, Limit to Human	34,524
7	3 or 6		**29**

Table 17.23. MEDLINE Complete (Date of Publication July 2014 – June 2015)

Index	Search terms	Search limits	Hits
1	(MH "Muscular Dystrophy, Duchenne")	Major heading	115
2	TX "Duchenne"	Boolean search, All text	643

		[TX]	
3	1 OR 2		643
10	(MH "Quality of life+") OR (MH "Value of life+") OR (MH "Quality-Adjusted Life Years+") OR (MH "Health Surveys+") OR (MH "Health Status+") OR (MH "Health Care Surveys+") OR (MH "Questionnaires+") OR (MH "Health Impact Assessment+") OR (MH "Outcome Assessment (Health Care)+")	Major heading: Explode	35,885
11	TX qald OR TX qale OR TX qtime OR TX disability adjusted life OR TX daly OR TX hql* OR TX hqol* OR TX h#qol OR TX hye* OR TX health * year equivalent OR TX health utility* OR TX rating scale* OR TX scoring system	Boolean search, All text [TX]	13,785
12	10 OR 11	Boolean search, Limit to Human	47,726
13	(9 OR 12) AND 6	Boolean search, Limit to Human	**45**

Table 17.24. EconLit (Published date July 2014 – June 2015)

Index	Search terms	Search limits	Hits
1	Duchenne	All text	**0**

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Not applicable, this was covered in the search strategy shown in section 17.3.

17.4.2 The date on which the search was conducted.

Not applicable

17.4.3 The date span of the search.

Not applicable

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

17.4.6 The inclusion and exclusion criteria.

Not applicable

17.4.7 The data abstraction strategy.

Not applicable

18 Related procedures for evidence submission

18.1 Cost-consequence models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient access scheme evidence submission template

July 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for highly specialised technologies. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a highly specialised technology evaluation, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical effectiveness and value for money of a technology, in the context of a highly specialised technology evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/hst-interim-evidence-submission-template.doc) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the highly specialised technology evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf). The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technology evaluation, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated.

If you are submitting the patient access scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the highly specialised technology and the disease area to which the patient access scheme applies.

Ataluren (Translarna™) for the treatment of Duchenne muscular dustrophy resulting from a nonsense mutation (nmDMD) in the dystrophin gene, in ambulatory patients aged 5 years and older.

3.2 Please outline the rationale for developing the patient access scheme.

This patient access scheme is for provision of Translarna at a discounted price and is the same as the discount already presented to NHS England as part of a proposed Clinical Commissioning Policy. This scheme is being provided to improve Translarna's value for money with the expectation that it will allow a positive recommendation from NICE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a simple discount (fixed price discount which will not vary with any change to the UK list price).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the whole licensed population: Duchenne muscular dustrophy resulting from a nonsense mutation (nmDMD) in the dystrophin gene, in ambulatory patients aged 5 years and older.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Not applicable – the scheme is not dependent on any criteria. All patients will be eligible to enter the scheme in line with the marketing authorisation for Translarna.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The current understanding of both NHS and PTC is that there are 66 patients with nmDMD aged 5 and over and ambulatory.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The fixed price discount will be applied from the list price and *applied to all original invoices* for Translarna.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As the scheme is a simple discount there are no administration requirements. NHS organisations will be provided with a notification document regarding the Terms and Conditions at the start of the scheme for reference.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable - The fixed price discount will be applied from the list price and *applied to all original invoices* for Translarna.

3.10 Please provide details of the duration of the scheme.

As this is a simple scheme it would be in place from the date of guidance publication until NICE next reviews the guidance on Translarna and a final decision has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues have been identified.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

NHS organisations will not be required to complete an agreement from prior to participation in the scheme. They will simply be provided with a notification document regarding the Terms and Conditions for reference.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Value for money

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence'. You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A

4.2 If you are submitting the patient access scheme at the end of the highly specialised technology evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

N/A

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

The cost of a 125mg sachet of ataluren has been amended from the list price of £84.40 to the fixed price proposed under the patient access scheme of [redacted].

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

N/A. The clinical effectiveness data used in the health economic model which includes the access agreement is the same as that presented in the company submission.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

N/A – there are no additional costs envisaged in the implementation and operation of this patient access scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

N/A

Summary results

Base-case analysis

4.7 Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the patient access scheme (Table 1)

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

- the results for the intervention with the patient access scheme (Table 2).

Table 1 Base-case value for money results without patient access scheme

	Ataluren	Best supportive care
Intervention cost (£)	[redacted]	0
Other costs (£)	[redacted]	235,207
Total costs (£)	[redacted]	235,207
Difference in total costs (£)	N/A	[redacted]
LYG	14.497	13.888
LYG difference	N/A	0.609
QALYs	6.152	2.385
QALY difference	N/A	3.767

LYG: life-year gained; QALY: quality-adjusted life-year

Table 2 Base-case value for money results with patient access scheme

	Ataluren	Best supportive care
Intervention cost (£)	[redacted]	0
Other costs (£)	[redacted]	235,207
Total costs (£)	[redacted]	235,207
Difference in total costs (£)	N/A	[redacted]
LYG	14.497	13.888
LYG difference	N/A	0.609
QALYs	6.152	2.385
QALY difference	N/A	3.767

LYG: life-year gained; QALY: quality-adjusted life-year

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

[2] For outcome-based schemes, please see section 5.2.9

N/A

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation. Consider using tornado diagrams.

Incremental cost results from the deterministic sensitivity analysis are presented in Table 3 and Figure 1. Incremental QALY results from the deterministic sensitivity analysis are not presented in this submission, as they do not differ from the submission of evidence for the highly specialised technology evaluation.

Table 3 Deterministic sensitivity analysis results with patient access scheme

Parameter	Value	Incremental costs (£)	% difference in costs
Base case	-	[redacted]	-
Relative risk of ataluren on mortality	[redacted]	[redacted]	3%
	0.82	[redacted]	-1%
Ambulatory direct cost	-20%	[redacted]	0%
	+20%	[redacted]	0%
Non-ambulatory direct cost	-20%	[redacted]	0%
	+20%	[redacted]	0%
Scoliosis surgery cost	-20%	[redacted]	0%
	+20%	[redacted]	0%
Scoliosis surgery follow-up cost	-20%	[redacted]	0%
	+20%	[redacted]	0%
Discount rate	0%	[redacted]	34%
	6%	[redacted]	-17%

[redacted]

4.10 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation.

Four scenarios were presented in the submission of evidence for the highly specialised technology evaluation, one of which related to utilities, which are unaffected by the patient access scheme and are therefore not presented in this submission. Incremental cost results of the remaining three scenarios with the patient access scheme are presented in Table 4.

Table 4 Results of multi-way scenario sensitivity analysis with patient access scheme

Parameter	Incremental costs (£)	% difference in costs
Base case	[redacted]	-
Scenario 2 – increased costs and disutilities for ventilation-assisted state	[redacted]	0%
Scenario 3 – inclusion of wider societal costs	[redacted]	-5%
Scenario 4 – Lifelong time horizon	[redacted]	0%

4.11 If any of the criteria on which the patient access scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

N/A

Impact of patient access scheme

4.12 For financially based schemes, please present the results of the value for money analyses showing the impact of the patient access scheme on the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

The budget impact in year 1 is estimated to be approximately £[redacted] rising to around £[redacted] in Year 5 (Table 5). NHS England has is a single budget for specialised services of approximately £13 billion, which includes medicines. The budget impact of ataluren in year 1 represents [redacted] of this budget, rising to [redacted] in year 5.

Table 5 Budget impact of ataluren in England over 5 years with patients access scheme

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Patients treated	35	42	49	57	65	50
Total annual 12 month cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendices

4.13 Appendix A: Additional documents

4.13.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

The PTC Simple PAS notification to Trusts document has been attached.

4.14 Appendix B: Details of outcome-based schemes

4.14.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A

4.14.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A

4.14.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

N/A

4.14.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A

4.14.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

N/A

4.14.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

N/A

4.14.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A

4.14.8 Please present the value for money results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.14.9 Please present in separate tables the results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

Manufacturer response to ERG clarification questions relating the HST appraisal of ataluren for nmDMD, received 16th July 2015

Section A: Clarification on effectiveness data

A1. Literature searches, inclusion criteria, and study selection:

A1.1. **Priority Question.** Please provide a full list of the excluded studies and the reasons for exclusion. We note that 168 records evaluating interventions other than ataluren were excluded at an early stage if full text was not freely available. If possible, please provide this list too.

Response

Please see the attached Excel spreadsheets that provide the following lists of studies:

- Clinical literature search (July 2014)
    - Studies excluded at 1st pass (duplicates n=206 plus excluded n=1911)
    - Studies evaluating interventions other than ataluren for which full texts were not freely available (n=168)
    - Full text articles excluded at 2nd pass (n=51)
    - RCTs evaluating ataluren (n=8)
    - RCTs evaluating interventions other than ataluren (n=34)
    - Other study designs including non-RCTs and observational studies (n=73)
- Clinical literature search (June 2015)
    - Studies included in 1st pass screening (with details and reasons for excluding publications, n=47)

A1.2. **Priority Question.** *Selection* – In the company submission, the numbers in the text don't appear to match those in the flow chart on page 66 (it says "281 studies were identified that met the broad review inclusion criteria", but the flow diagram (Figure C9.1) says "115 publications" were included). The submission only provides details of the two final included studies (represented by 10 publications and 2 CSRs). Please confirm these numbers.

Response

The figure 281 is incorrect and should have read 115 (113 publications from the literature searches plus 2 CSRs provided by PTC).

A1.3. **Priority Question.** *Search strategy* – Please confirm that the searches were updated for just ataluren on 8th June 2015, this is not made clear in the main text.

Response

Correct, searches carried out in June 2015 were just updated for ataluren.

A2. General questions:

A2.1. **Priority Question.** Please clarify what is meant by "Minimal monitoring of patients is required" (see pages 29, 64, 215)?

Response

Apart from renal function measurement, no specific tests are required to monitor either the efficacy or safety of ataluren treated patients, over and above the standard clinical monitoring of DMD patients. Blood tests are carried out on an annual basis during routine visits, regardless of ataluren treatment (Clinical Expert – personal communication). Therefore the monitoring of lipids and renal and kidney function is not expected to add to the burden of care. Blood pressure monitoring is carried out routinely for those treated with corticosteroids and is not an additional requirement specific to ataluren. The monitoring required for ataluren can therefore be managed easily within routine clinical practice.

A2.2. **Priority Question.** On page 20 of the company submission, it is stated that the "Mean change in physical functioning score at Week 48 was -1.0 for placebo and 2.4 for ataluren 40 mg/kg/day, giving a difference in mean change in physical functioning score at Week 48 of 3.4 favouring ataluren 40 mg/kg/day vs. placebo (Bushby, 2014). Although this is below the minimal clinically important difference it trends in the same direction as a number of other measurements of physical functioning." Please confirm what is the considered "minimal clinically important difference"? What is the minimal clinically important difference for each of the timed function tests?

Response

The physical functioning score is the domain of the PedsQL that could most reasonably be expected to show a response in a condition such as DMD. That being said, it should be emphasized that: 1) The PedsQL is not a sensitive measure of disease progression in DMD; 2) The mapping of EQ-5D utility scores from PedsQL showed higher prediction errors for children in poorer health states (such as DMD). The PedsQL was designed to measure health-related quality of life (HRQL) in healthy children as well as those with acute and chronic health conditions, but it was not designed specifically for use in neuromuscular disease or in DMD. In a

longitudinal study, Henricson et al have determined that the PedsQL is not a sensitive outcome measure of DMD disease progression (Henricson, 2013). PedsQL items are only weakly correlated with clinical outcome measures that have been validated in DMD, such as the 6-minute walk test and 10-metre run/walk velocity. By comparison, a different HRQL instrument, the Pediatric Outcomes Data Collection Instruction (PODCI), strongly correlates with the 6-minute walk test and 10-metre run/walk velocity. Similarly, one-year changes in PODCI scores are more strongly correlated with 1-year change in 6MWD than are PedsQL scores (Henricson, 2013). For these reasons, the DMD community has adopted the PODCI for use in current clinical trials, including the ongoing Phase 3 study of ataluren in DMD, and no longer employs the PedsQL. Further analysis of the PedsQL is therefore not considered justified. [We will also be addressing questions relating to mapping of PedsQL to EQ5D in the response to the additional information request].

MCID is quantified using effect sizes and is defined as the magnitude of change required for an observable difference in function. Expert opinion is that for the timed function tests a difference of 1.5 seconds is the limit of observable difference. Escolar et al (Escolar, 2011) defined the threshold for a statistical difference in TFTs as 0.4 ln (natural log) seconds. In the context of the ataluren 40mg/kg/day Phase 2b results, this was back transformed to ~1.5 seconds. Henricson estimated the MCID (calculated at 1/3 of a measure's standard deviation) of the 10 metre run/walk test to be a velocity of 0.19 m/s in boys with DMD that had a mean velocity of 1.68 m/s at baseline (10 metre walk/run time of 5.95 seconds). This translates to an MCID of 0.76 seconds for the 10 metre walk/run test (Henricson, 2013). Estimates of the MCID for the other TFTs could not be identified.

A2.3. **Priority Question.** The study 007 tested ataluren treatment for 48 weeks. How are patients treated after 48 weeks? Please provide the evidence that supports the statement in the submission which indicates that patients should carry on receiving treatment until at least 6 months after loss of ambulation (page 24)?

Response

Treatment after 48 weeks

Discussions with the EMA led us to design a 48 week study which balanced the ability to show a benefit as soon as possible whilst not subjecting patients to an over burdensome trial. Following the 48 week duration of Study 007, patients were enrolled into an open label extension study, although there was a variable gap between patients stopping Study 007 and restarting the extension study.

As stated below in response to question A8.5.3, the longest continuous exposure to ataluren at 40 mg/kg/day for an individual patient is [redacted] in the ongoing Study 016. The clinical trials of ataluren do not include stopping criteria and the Translarna SmPC states “There were no apparent differences in either steady-state relative bioavailability or apparent clearance due to loss of ambulation. No dosing adjustment is needed for patients who are becoming nonambulatory’.

Given that DMD is a chronic degenerative condition, treatment with ataluren is expected to be given as a chronic therapy. The underlying mechanism of ataluren means that it should stabilise or delay the decline in function of muscles, including those in the upper body. In normal clinical practice one would expect a patient to remain on therapy until such a time as they, in consultation with their physician, agree they are not gaining any clinical benefit.

Stopping criterion

During development of the NHS England Clinical Commissioning Policy a clinically meaningful and 'auditable' stopping criterion was requested. As there were no stopping criteria in the clinical trials it was agreed with NHS England that Clinical Expert opinion could be sought to address this requirement. The timing of 6 months post becoming fully non-ambulatory was therefore based on Clinical Expert opinion of extensive experience from UK clinical practice with corticosteroids. As NICE also requested 'stopping criteria' we have maintained consistency with the draft NHSE England Clinical Commissioning Policy (available on request). Note: the final published policy does not include the stopping criteria because NHS England has decided to not routinely commission ataluren as NICE is to carry out a Highly Specialised Technology Evaluation.

A2.4. **Priority Question.** In the glossary, loss of ambulation (LoA) is defined as having become non-ambulant. Please elaborate on the definition of LoA and confirm whether this definition of LoA is consistent throughout the company submission.

Response

In this submission LoA is defined as the point at which patients become completely confined to a wheelchair for indoor and outdoor use: they are unable to take any steps unaided. This is used consistently throughout the submission including the health economic model where LoA is defined as 6WMD=0m.

Whilst there does not appear to be a clear definition of “ambulatory” patients in the published literature, “non-ambulatory” patients or “loss of ambulation” have been

defined in recent DMD studies as referring to those patients requiring “continuous wheelchair use” (Bello, 2014) or “use of wheelchair full time” (Pettygrove, 2014).

A2.5. Please confirm who were the advisors to the company during the development of the submission (e.g. page 170, page 171)? If possible, please provide an overview of the expert advice they gave.

Response

Two clinical experts were consulted. Dr Rosaline Quinlivan (Consultant Paediatric Neurologist, Centre for Neuromuscular Disease and the National Hospital for Neurology and Neurosurgery, Queen Square) reviewed the HST submission and advised on stopping criteria, and aspects of the clinical management of DMD. The second advisor (Consultant Paediatric Neurologist, UK), who advised on the original pharmacoeconomic model developed in 2014, preferred not to be cited in this submission.

We refer you to various sections of the submission where we have stated the input the clinical experts provided in more detail:

- Treatment continuation & stopping (see response to question A2.3)
- Section 10.1.10 (including Table C10.4)
- Sections 12.2.5, 12.3.3, 12.3.6, 12.4.1 and 12.7.1
- Tables D12.1, D12.2, D12.7

A3. Methods:

A3.1. **Priority Question.** *Outcomes –*

Please provide details of how the Timed Function tests were standardised across centres.

Please provide details of compliance with the diary record for the report of frequency of accidental falls.

Please provide data for the outcomes of 'Step activity' and 'percentage reported wheelchair use'.

Response:

Timed function test standardisation

A Clinical Evaluator (CE) Training Group was responsible for developing standardised procedures for the 6-minute walk test (6MWT), timed function tests (TFTs), myometry, and Step Activity Monitor (SAM) calibration; a CE manual comprising these procedures was distributed to all study sites. The CE Training group oversaw centralised training of site CEs, which included an initial training

session prior to study start and a refresher training session after ~1 year of study conduct (PTC Study 007 CSR, Section 6.3).

Compliance with the diary record

[redacted]

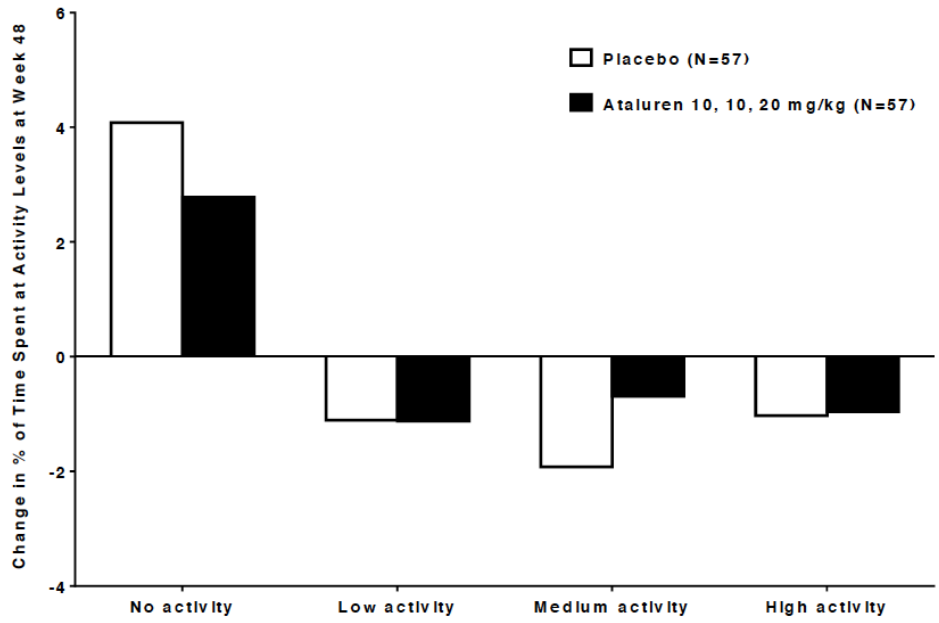
Step activity

Patients wore on the ankle a pedometer-like device that monitors and records the number of steps taken. The proportions of time during which the patient is moving at 0 (no activity), 1 to 15 (low activity), 16 to 30 (medium activity), or >30 (high activity) steps per minute were also assessed.

Differences in changes in mean steps taken from baseline to Week 48 favoured ataluren vs placebo; a difference of -649.86 (SD 1717.550) for ataluren 40 mg/kg/day vs. - 901.70 (SD 2000.530) for placebo.

With regard to patterns of activity, the mean changes at Week 48 between ataluren 40 mg/kg dose and placebo showed trends toward less time spent at no activity (0 steps/minute) and more time spent at medium activity (16 to 30 steps/minute) (Figure 1) (PTC Study 007 CSR).

Figure 1. Change from Baseline to Week 48 in Proportion of Time Spent at No, Low, Medium, and High Activity (ITT)



No activity = 0 steps/minute; low activity = ≤15 steps/minute; medium activity = 16-30 steps/minute; high activity = >30 steps/minute

For no activity, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients. For medium and high activity, positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

Patient-Reported Wheelchair Use

Patient-reported wheelchair use showed a positive trend favouring ataluren 40 mg/kg/day vs placebo (PTC Study 007 CSR).

- At baseline, mean percentage of days of wheelchair use was 13.2% for placebo and 13.2% for ataluren 40 mg/kg/day.
- Mean percentage of days of wheelchair use (95% CI) increased from baseline to Week 48 by 11.5 % (4.36, 18.54) for placebo and 4.0% for ataluren 40 mg/kg/day (-2.77, 10.68).
- Thus, the difference was 7.5% favouring ataluren 40 mg/kg/day vs placebo.

A3.2. Please describe the 'standardised procedures' used for the assessment of the 6MWD (company submission page 74). The 6MWD test is known to be at risk of investigator bias, please explain whether the assessor was blinded (unclear from the details provided in Table C9.12)?

Response

Ambulation was assessed via the 6MWT following standardised procedures as developed at University of California at Davis (McDonald 2010a) by measuring the 6MWD in metres. Patients were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWT (PTC Study 007 CSR, Section 9.5.1.1.1).

The standardised procedures described by McDonald et al are as follows (McDonald 2010a): The 6MWT is performed indoors, along a flat, straight, enclosed, and seldom travelled corridor approximately 8 feet wide with a hard surface. The test area is marked with a tape-line placed in the middle of the corridor and marked at 1-m intervals. A cone is positioned at each end of the course with arrows taped to the floor to indicate the anti-clockwise direction and path of movement.

The Investigator was not the Clinical Evaluator (CE) (see A3.1 above regarding standardisation of testing across centres). All relevant staff were blinded to the treatment allocation, including the CE: patients, parents/caregivers, investigational site personnel, PTC Therapeutics employees, and all other study personnel were to remain blinded to the identity of the treatment assignments until every patient had completed study treatment and the database had been locked (PTC Study 007 CSR, Section 9.4.6).

A3.3. Table C9.10 (page 81) notes the numbers of sibling pairs. Please describe how sibling pairs were accounted for in the randomisation?

Response

Procedures to ensure that siblings participating in the study were to receive the same treatment group designation were added by Amendment 2.0 of the protocol (dated 28 Apr 2008) (Study 007 CSR).

A4. Dose:

A4.1. **Priority Question.** Please explain the dose-response relationship and provide a justification (i.e. biological mechanism rather than statistical) for the lower efficacy with the higher ataluren dose, rather than the higher adverse events that are more usual if patients are being overdosed.

Response

The bell-shaped curve is caused by interactions with the ribosome. Aminoglycosides are known to enable read-through by binding to the ribosome. Ataluren-related compounds also interact with the ribosome and further support for this ribosome interaction comes from *in vitro* studies and clinical trial data in cystic fibrosis showing that aminoglycosides reduce the activity of ataluren (Kerem, 2014). Toxicity is not responsible for the reduced activity in the DMD and cystic fibrosis clinical studies or the *in vitro* studies.

The bell-shaped dose response has been demonstrated in 1) myotube cultures from mice harbouring a nonsense mutation in dystrophin, 2) myotube cultures from a DMD patient harbouring a nonsense mutation in dystrophin, 3) a zebrafish model harbouring a nonsense mutation in the dystrophin gene, 4) DMD patients harbouring nonsense mutations in dystrophin (Ph2b ataluren study 007), 5) fibroblasts from mice harbouring a nonsense mutation in the IDUA gene (encoding alpha-L-iduronidase), and 6) mice harbouring a nonsense mutation in the IDUA gene (EMA, 2014).

A4.2. Page 37 states that “No studies have been conducted with ataluren in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely. No dosing adjustment is needed for patients who are becoming non-ambulatory.” Please provide details of the number of patients that required dose adjustment during the key studies identified in the company submission.

Response

No patients required dose adjustments in Study 004. In Study 007 there were no physician-prescribed dose reductions or interruptions in the ataluren 40mg/kg/day

arm and one dose interruption in the placebo arm due to accidental overdose (Study 007 CSR, Section 11.3.1).

A5. Analysis:

A5.1. **Priority Question.** Age, corticosteroid use, and baseline 6MWD were pre-specified as stratification factors since these variables were likely to have prognostic significance (page 86). Please provide sub-group analyses defined by steroid treatment and age (7 year cut-off) for the ITT and cITT data (e.g. see page 94, Table C9.14) and ITT data for the sub-group analysis by 6MWD.

Response

To follow.

A5.2. **Priority Question.** Use of post-hoc cITT analysis, (i.e. amending the baseline data for 0.9% of the two groups analysed, 1 of 114 patients) has an impact on statistical significance of the primary outcome. Table C9.15 (page 91) presents timed function tests for the cITT analysis set, please also provide the ITT analysis.

Response

To follow.

A5.3. Page 73 states that about two patients in study 07 had Becker muscular dystrophy. Most patients with Becker muscular dystrophy are ambulatory until they are 40-50 years of age (http://www.musculardystrophyuk.org/about-muscle-wasting-conditions/becker-muscular-dystrophy/). Please provide sensitivity analyses of the primary outcome excluding the patients with Becker muscular dystrophy.

Response

All patients met all the criteria for entry to the study including having the presence of a nonsense mutation in the dystrophin gene. The variability in phenotype of patients diagnosed with BMD is wider than that seen with DMD. The diseases may be considered part of the same spectrum, therefore we believe that it is inappropriate to distinguish the results of these two patients from the others.

The results from the ACT DMD Phase 3 study (ongoing Study 020), looking at a larger group with less variability will confirm the treatment effect.

A6. Scope:

A6.1. Table A1.1, page 31, states there is no variation from the scope on outcomes, however, no outcomes on activities of daily living, cardiac function or lung function are presented. Please provide these data if available.

Response

Activities of daily living:

TFTs measure the ability of patients to perform brief activities (McDonald 2013a) that are typical of patients' activities of daily living in a home, school, or community setting: ability to climb 4 stairs, descend 4 stairs, run and walk 10 meters, and rise from a supine position. Timed function tests are the most relevant secondary endpoints that measure physical function and support the robustness of ataluren's efficacy. Timed function tests, which were the most clinically relevant secondary endpoints in Study 007, are well established clinical assessments in DMD. Multiple publications have demonstrated the ability of TFTs to be measures of disease progression that are predictive of the time to loss of ambulation (McDonald 1995, McDonald 2013a).

Cardiac function:

Cardiac complications emerge in the later, non-ambulatory stage of DMD. Nonetheless, heart rate was measured before, during, and after the 6MWT to explore the hypothesis that drug-induced normalization of inappropriate sinus tachycardia might have beneficial long-term effects on cardiac function as a secondary objective of Study 007. Generally, the results were similar across the 3 treatment arms. Please see the CSR, Section 11.4.1.4.3: Heart Rate Monitoring.

Lung function:

As part of the safety assessment, resting vital signs including respiratory rate were monitored during the screening period, before the first dose of study drug on Day 1, every 6 weeks during the treatment period, and at the post-treatment visit in Study 007. No lung function tests were conducted in Study 007.

A7. Quality of Life (QoL):

A7.1. **Priority Question.** Please confirm whether the reported changes in quality of life with ataluren (page 134; e.g. why is 'emotion' worse?) are reported accurately.

Response

Yes, they are reported accurately.

A7.2. Table C9.12, page 88 states that 'data for some of the protocol-required assessments are missing for some patients at some of the study visits. None of the missing items was considered to have had an effect on the study conclusions regarding efficacy or safety.' Please provide details of the missing assessments by

group and describe how these were handled. Please advise if any were due to injuries that may affect outcomes? Were there any missing data for the PedsQL (Table C9.19 provides the ITT data set)?

Response

Details of the missing assessments are not available. The reason we have stated that none of the missing items was considered to have had an effect on the study conclusions regarding efficacy or safety is that the EMA and as the competent authority have granted marketing authorisation based on the MA submission. Data from ACT DMD (Study 020) will further support the robustness of the finding from Study 007.

A7.3. *HRQoL* – On page 103 data are presented in the text for the ambulatory decline phase subgroup for the physical functioning score. Please provide the 95% confidence interval, and data (means and 95% CIs) for the other three scales.

Response

Unfortunately these analyses are not available.

A8. Adverse effects:

A8.1. **Priority Question.** On page 107, it is stated that 'Only 3.4% of ataluren patients (both doses) reported a serious adverse event compared to 5.3% in the placebo arm treatment group. Importantly, none of these were considered to be related to treatment with ataluren by the investigator'. Which criteria were used to determine if a serious adverse event was treatment related and how was this judgement made (and by whom)?

Response

The Investigators determined whether or not a serious adverse event was treatment related (see Study 007 CSR, Section 9.5.1.2.2. Adverse Events).

A8.2. Table C9.20 lists the adverse events by relatedness using a number of categories, please explain which criteria were used for these categories?

Response

These are standard Good Clinical Practice (GCP) wording. We refer you to the ICH standards.

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

A8.3. Table C9.25 provides a count of cases of serious adverse events. The data for ataluren includes 217 participants from the 80mg/kg/day group. Please provide data for the 238 participants in the 40mg/kg/day group.

Response

To follow.

A8.4. In Table C9.25, please clarify which cases in the last column were counted (count of cases – blinded)? Are these cases from the control arm or the ataluren arm?

Response

As these cases are still blinded it is unknown whether they are from the control arm or the ataluren arm.

A8.5. **Priority question:** Please provide the requested data highlighted in pink to Table C9.25: Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials (see revised Table below).

Response

PTC are in the process of completing a revised Table C9.25 and it will be provided as soon as possible. In the interim, the following explanation may assist in the interpretation of listed adverse events.

The Periodic Benefit-Risk Evaluation Report (PBRER) reports cumulative occurrence of adverse events from completed and ongoing studies for ataluren in DMD. It should be noted that more patients were treated with ataluren than placebo; approximately 379 patients were treated with ataluren compared with approximately 172 patients treated with placebo as of 31 Jan 2015 (totals include patients who have received blinded study drug as of 31 January 2015 in the ongoing nmDMD Study 020). Also, based on study designs (open-label extension studies only included ataluren treatment), ataluren treatment duration was longer than placebo treatment duration (Table 1).

Based on the review of the current information presented in the PBRER, the benefit risk evaluation for ataluren remains positive. The review of data revealed no new safety concerns. No changes in characteristics of listed or unlisted adverse drug reactions or increase in reporting frequency associated with ataluren were identified.

Table 1. Estimated duration of exposure in ataluren Phase 2 and 3 studies

A8.5.1. **Priority question:** Please explain whether you are aware of any biological or disease related reasons why cardiac disorders and femoral fractures should occur more frequently as serious adverse events in the ataluren group?

Response

We are not aware of any biological or disease related reason why more adverse events should occur in the ataluren group. As discussed above, since Table C9.25 includes data from open label studies the ataluren and placebo columns are not comparing equivalent populations. Since cardiac disorders and fractures are co-morbidities associated with DMD, their appearance in the cumulative safety databases may be expected over the long duration of follow-up for patients treated with ataluren.

A8.5.2. Are the patients in the different studies (as summarised in table C9.25) comparable, if not – in what ways do they differ?

Response

Table C9.25 includes patients from the following studies: 007, 007e, 004, 004e, 008, 016, 019, 020 and 020e in boys with nonsense mutation dystrophinopathy. These studies are described in Tables C9.4 and C9.5 of the submission. The populations are comparable although there are differences in the included age range and some studies included non-ambulatory boys.

A8.5.3. What is the longest duration of follow-up to date?

Response

As of 31 Jan 2015, the longest continuous exposure to ataluren at 40 mg/kg/day for an individual patient is [redacted] in ongoing Study 016.

A8.5.4. Was follow-up different within and between treatment arms?

Response

Yes. Table C9.25 includes patients from multiple studies including open-label extension studies. Patients originally treated in studies 004 and 007 (either with ataluren or placebo) could enter extension studies where they received open-label treatment with ataluren either at a dose of 80 mg/kg/day (in studies 004e and 007e) or at a dose of 40 mg/kg/day (in studies 016 and 018). The duration of exposure in different studies is shown in Table 2. There is no long-term follow up of placebo patients.

A8.5.5. How is ‘serious’ adverse event’ defined in table C9.25?

Response

A serious adverse event was defined as an untoward medical occurrence, regardless of whether or not it was considered related to the study drug, which resulted in death, was life threatening, required or prolonged hospitalisation, or resulted in persistent or significant disability or incapacity. Important medical events that were not immediately life-threatening or did not result in death or hospitalisation but might have jeopardised the patient or that might have required intervention to prevent one of the other outcomes listed above would have been considered to be serious (eg, intensive treatment at home or in an emergency room for an allergic bronchospasm, new cancers or blood dyscrasias, convulsions that did not result in inpatient hospitalisation, or the development of drug dependency or abuse).

A8.5.6. Were the definitions of the different adverse events used uniformly across the different studies in the table?

Response

Yes, they were.

Section B: Clarification on cost model and value for money

B.1. Literature searches, inclusion criteria, and study selection:

B.1.1. **Priority Question**. Please provide a full list of the excluded studies and the reasons for exclusion for both HRQoL (page 135 and Appendix 3) and economic (Figures D11.1 and D11.2, page 146) searches.

Response

Please see the attached Excel spreadsheets that provide the excluded studies from the original economic/HRQoL search, updated HRQoL search and updated economic search. The reason for exclusion from the original economic/HRQoL search was not available.

B.1.2. Search – The number of records identified in the original 2014 search (748) as reported in the main text (page 135 and page 144) does not match the combined totals of original 2014 searches reported in Appendix 3 (731). Please confirm these numbers.

Response

The number of records stated in the main text (748) is correct. The totals given in Appendix 3 (731) were for a preliminary search that was run 3 weeks earlier and are therefore incorrect.

B2. Priority Question. The clinical trial results reported in Table D12.14 suggest that 11% and 7% of children in the BSC and ataluren arms, respectively, lost ambulation at 48 weeks. However, similar results were not seen in the model at the 48 week time horizon. Please clarify this discrepancy? At the same time point, the model predicts 5% and 0.5% of children in the BSC and ataluren arms, respectively, would lose ambulation.

Response

As stated in section 12.5.1 of the submission, the difference in the proportion of patients losing ambulation between the model and the trial is primarily due to the model being a homogeneous cohort with a moderate baseline 6MWD on average, whilst the clinical trial included a heterogeneous patient population. Given the variability of patients' baseline characteristics in the clinical trial, a small proportion were at a much higher risk of losing ambulation at 48 weeks than the average patient. All patients that lost ambulation in the clinical study were marginally ambulant or had a moderate 6MWD at baseline (Table 2 and Figure C9.3 of the

submission). An individual patient based model would better capture the heterogeneity of the population but given the limited data available and the timeframes of the submission, a cohort-based model was chosen.

Table 2. Characteristics of patients that lost ambulation in the clinical study

	Placebo (n=6 of 57)						Ataluren (n=4 of 57)			
Baseline 6MWD (m)	225	192	300	167	250	215	75	121	95	249
Time to loss of Ambulation (weeks)	22	24	40	42	43	46	4	18	35	37

Although the total proportion of patients that lost ambulation in the model was less than observed in the clinical study, the differences between the BSC and ataluren arms are comparable (4% in both the model and the clinical trial). Furthermore, the clinical trial was not powered to detect differences in loss of ambulation and the result is based on very small numbers of patients: only 6 and 4 in the BSC and alaturen arms, respectively, so should be interpreted with caution.

The low rate of LoA in the first year of the model is consistent with natural history patients of the same age in Ricotti (2013). In addition, of the 71 children aged ≥8 included in a 12 month natural history study, only one lost ambulation at one year (1.4%) (Mazzone et al, 2011) which is much closer to the prediction of the model than observed in the clinical study suggesting the model is more reflective of clinical practice than the clinical trial.

B3. Priority Question. The regression analysis (section 12.2.1) in the company's submission was undertaken using data from weeks 24 to 48, rather than from baseline to 48 weeks, and this is reported as a conservative assumption. However, the 48-week 6MWD change calculated by this method (33.8m, page 160) is greater than the change calculated if the full trial data are used (31.3m, page 18). Please clarify the justification for this assumption, and explain why you consider this assumption to be conservative.

Response

To follow.

B4. Priority Question. It is suggested in the submission that the Ricotti study is a suitable source of natural history data because the median time to loss of ambulation reported in this study was similar to the mean time to loss of ambulation extrapolated from the placebo arm in Study 007. What is the median time to loss of ambulation based on the extrapolation from Study 007, and does the Ricotti study still appear

appropriate when the median time to loss of ambulation is compared between the 2 studies?

Response

The submission should have stated that the Ricotti study is a suitable source of natural history data because the mean time to loss of ambulation reported in this study was the same as the mean time to loss of ambulation extrapolated from the placebo arm in Study 007. The mean time to loss of ambulation in the Ricotti (2013) study was 14.5 years, which exactly equals the extrapolated mean time to loss of ambulation from the placebo arm in Study 007.

B5. Priority Question. It is stated that a Weibull function was the best fit to the data derived from the Ricotti study. Please provide the evidence (statistical or otherwise) on which this judgement was based, as well as the parameters for other distributions fitted during the model selection process, which can be used for sensitivity analyses.

Response

Based on a visual inspection of the data and due to limited time to create the submission, only Weibull curves were fit to the data. Comparing the Weibull model to the published data, it appears the extrapolation is a reasonably good fit and perhaps conservative in the tail.

B6. Priority Question. The Weibull distribution is also listed as the best fit to the Humbertclaude data used to estimate time to ventilation assistance and scoliosis, and the Rall data for mortality. Please provide the supporting evidence to show how this judgement was reached. Please explain why the Weibull distribution is considered to be a reasonable choice of model, given the very poorly fitting survival curves presented (Figures D12.8, D12.9, D12.11).

Response

Based on a visual inspection of the data and due to limited time to create the submission, only Weibull curves were fit to the data. Comparing the Weibull model to the published data, it appears the extrapolation is conservative in the tail.

B7. Priority Question. The submission suggests that individuals would continue to receive ataluren treatment at least six months after losing ambulation. Please justify why these costs were not included in either the economic model or the budget impact analysis?

Response

Patients are eligible to receive treatment with ataluren for up to 6 months following loss of ambulation but it is not expected that all patients will receive treatment in this period. Therefore, despite not including a cost of treatment after loss of ambulation, it is estimated that the treatment costs included in the model are a reasonable reflection of what will occur in clinical practice.
The reason for continued treatment after loss of ambulation is based on clinical expert opinion of UK experience of stopping corticosteroids (see answer to A2.3). We did not estimate how many patients would continue treatment after loss of ambulation and what the duration of treatment would be for the model.

B8. Priority Question. The budget impact analysis assumes an average weight of 25kg for people being treated with ataluren, the weight from the bottom of the eligible treatment age range. Given that ataluren is likely to be offered to patients across all affected age ranges, please explain why the average weight across all eligible patients was not used to inform the budget impact analysis?

Response

The budget impact assumes that boys treated with ataluren will have median weight of between 24-26 kg. The median age in the 007 trial was 8 years in the placebo and ataluren 40 mg/kg arms and the median body weight was 25.6 kg and 27.0 kg respectively. The Royal College for Paediatrics and Child Health (RCPCH), Boys UK Growth Chart Age 2 to 18 Years states boys who are 8 years old will have a body weight of 25.5kg at the 50th percentile. Therefore a median weight of 24-26 kg was used in the budget impact calculations. It will be expected in the first 5 years boys will be initially started on ataluren once they are eligible from the age of 5 years in line with the licensed indication for ataluren. Therefore patients prescribed ataluren will be skewed towards to the 5-year-old age group and according to the RCPCH Boys UK growth Chart their weight is approximately 20 kg at the 50th percentile. In addition, as boys remain ambulant and therefore can be more active and run and play with their friends, they do not gain weight as fast as those patients who are non-ambulatory. Therefore the use of median weight of 24-26 kg in the budget calculations over the next 5 years is reasonable.

B9. Priority Question. In the submission, information from the Ricotti study is used to derive transition probabilities for loss of ambulation in the placebo arm, rather than data from Study 007. In this study, patients were tested using a 10mRT, not the 6MWT of Study 007. Are the definitions of loss of ambulation from these two different

tests interchangeable, and is the choice of different test related to the baseline status of the participants?

Response

Yes, the definitions of loss of ambulation from these two different tests are interchangeable. No, the choice of different test is not related to the baseline status of the participants.

B10. Ataluren is compared to best supportive care in the model. The submission mentions that best supportive care includes treatment with corticosteroids, as well as pharmacological therapy for the management of associated co-morbidities. Please provide a more detailed description of your understanding of what best supportive care represents.

Response

Our understanding of best supportive care is based on the NICE accredited publication from the DMD Care Considerations Working Group 'Diagnosis and management of Duchenne muscular dystrophy' guideline (Bushby, 2010a; Bushby 2010b; NICE, 2011). The guideline provides recommendations for the management of DMD through coordinated multidisciplinary care. This includes (see Figure 1, Bushby 2010b):

- Neuromuscular and skeletal management:
    - Treatment with corticosteroids
    - Rehabilitation management (exercises, stretching, positioning, splinting, orthoses, standing devices, manual/electric wheelchairs)
    - Orthopaedic management (tendon surgery, posterior spinal fusion)
- Management of other complications
    - GI, speech/ swallowing, nutrition management (diet control and supplementation, gastrostomy, pharmacological management of gastric reflux and constipation)
    - Pulmonary management (volume recruitment/ deep lung inflation technique, assisted cough technique, day/nocturnal assisted ventilation, tracheostomy, influenza and pneumococcal vaccination, antibiotics for respiratory infections)
    - Cardiac management (ACE inhibitors, β blockers, other heart failure medication)
    - Psychosocial management (psychotherapy, pharmacological, social, educational, supportive care)
    - Pain management

Input from different specialties and the emphasis of interventions will change as the disease progresses (see Figure 2, Bushby, 2010b).
There is no reason to believe that the care provided to patients in Study 007 deviated from the guidelines by Bushby et al and consequently, the best supportive care arm of the model, which is based on data from Study 007, should be reflective of patients treated with best supportive care in clinical practice in England. In Study 007 patients could receive concomitant treatment with corticosteroids (70.2% in the placebo arm vs 71.9% in the ataluren 40 mg/kg/day arm). Patients could also receive drugs to treat cardiac conditions: ~12% of the study population was receiving a cardiac drug prior to enrolment and usage was similar across treatment groups. Concomitant non-drug treatments included physiotherapy, stretching, exercise, use of knee-ankle-foot orthoses, use of braces, use of a wheelchair, hydrotherapy, psychotherapy, occupational therapy, and speech therapy. Use of such non-drug treatments was balanced across treatment arms in this study.

B11. Table D12.11 provides a list of the health states and corresponding unit costs for occupying these health states. The ERG noted that the unit costs of occupying the non-ambulatory and non-ambulatory and ventilation-assisted health states appear to be the same. Please clarify if this is correct, and if so, why?
Response
This is correct. In the base case analysis, costs for the non-ambulatory state are the same as the non-ambulatory with ventilation-assistance state. As discussed in 12.4.1 of the submission, although it is expected that ventilation-assistance has a high cost, the specific costs for ventilated-assistance in DMD could not be sourced from the literature. As discussed in the response to questions B12, the cost for the non-ambulatory state corresponded to the late non-ambulatory cost from the literature to account for the lack of unit costs specifically capturing ventilation assistance. 18% of UK DMD patients included in the Landfeldt et al (2014) study required ventilation-assistance thus some costs of ventilation-assistance are included in the model. Furthermore, in scenario 2 of the sensitivity analysis presented in Table D12.22, the impact of additional direct costs to ventilation-assisted health states was explored and the incremental costs did not change (0%).

B12. In the submission, resource use and costs were obtained from the Landfeldt et al. (2014) study. In this study the authors have stratified ambulation and non-ambulation and presented resource use and costs separately for these states. However, in the submission, there is one ambulation health state. Please explain

how these costs were derived given that there were two ambulatory states in the Landfeldt study?

Response

In line with the application of utilities from the Landfeldt et al (2014) study discussed in section 10.1.9 of the submission, the early ambulatory cost from Landfeldt et al was applied to the ambulatory health state in the model. No unit costs were available to capture the financial impact of ventilation-assistance, which is expected to be high, so the late non-ambulatory cost from Landfeldt (2014) was applied to all the non-ambulatory health states in the model.

B13. In the submission, utility values were derived based on information obtained from Landfeldt et al. However, it is not clear how utility values were calculated based on this study. Please explain how UK-specific values were derived for these health states (ambulatory, non-ambulatory, non-ambulatory (VA), non-ambulatory (scoliosis) and non-ambulatory (VA and scoliosis))?

Response

Landfeldt et al (2014) captured the HRQoL of patients using the Health Utilities Index and the HRQoL of carers using the EQ-5D. Utilities for UK patients were reported in graphical form by the authors so data used in the model were interpreted from Figure 2 of the publication. The authors state the mean utility of caregivers in the UK was 0.82 corresponding to a disutility of 0.18 if assuming perfect health of the caregivers. However, it is unlikely that all caregivers had a perfect health themselves, so the mean caregiver disutility of 0.11 derived in the study (mean across German, UK, US and Italian caregivers) was applied in the model.

- **Ambulatory:** UK early ambulatory utility from Figure 2 of Landfeldt (2014) = **0.66**.
- **Non-ambulatory; Non-ambulatory and ventilation-assisted:** UK late non-ambulatory utility from Figure 2 of Landfeldt (2014) = 0.12, minus the caregiver disutility from page 3 of Landfeldt (2014) = 0.11, totalling **0.01** (=0.12-0.11).
- **Non-ambulatory and scoliosis; Non-ambulatory, ventilation-assisted and scoliosis:** UK late non-ambulatory utility from Figure 2 of Landfeldt (2014) = 0.12, minus an assumed disutility due to scoliosis = 0.1, minus the caregiver disutility from page 3 of Landfeldt (2014) = 0.11, totalling -**0.09** (=0.12-0.1-0.11).

B14. Table C10.3 provides the HRQL weights used in the model. From this table, a carer disutility of 0.11 is applied. However, in the model the disutility appears to be '0'. Please clarify if a carer's disutility was applied to the non-ambulatory with scoliosis health states?

Response

A carer's disutility was applied to the non-ambulatory with scoliosis health state. In the model the HRQoL values associated with scoliosis are applied as disutilities to the non-ambulatory states. The caregiver disutility is already captured in the non-ambulatory state so applying another caregiver disutility in the scoliosis disutility model inputs would be double counting. See also response to question B13.

Section C: Textual clarifications and additional points

C1. Please remove the commercial in confidence marking from the list price of ataluren in the submission. The list price is in the public domain.

Response

We will remove this commercial in confidence marking, as requested, although we feel it should remain confidential, as it is not been published in the BNF or MIMs.

C2. On pages 15, 45 and 203 in the submission, please clarify why the estimate of [redacted] is marked as commercial in confidence?

Response

The estimate of [redacted] is derived from [redacted]. This estimate has been made based on the interpretation of the data presented in these two papers and to that extent is part of the company intellectual property. As the ERG are probably aware there a several other companies developing medicines for DMD and PTC does not wish to indicate to these companies the potential market that it predicts for ataluren within its licensed indication nor the full details by which the number of patients expected are calculated.

C3. On page 45 in the submission, please clarify why the estimated number of patients eligible to receive ataluren (66) is marked as commercial in confidence? The estimate is based on published prevalence figures.

Response

This figure of 66 is calculated from a breakdown of prevalence in table on page 45 and Table D13.1 on page 203. The prevalence of DMD of 8.28 per 100,000 is from

Norwood et al (2009) and 10% of these patients having nmDMD from Bladen et al (2015) are easily found in the references. However, the estimate for the percentage of nmDMD patients aged 5 years and above who are ambulatory has been interpreted and calculated from the data in the papers by [redacted] by PTC to get to the final figure of 66 patients. This step is CIC in PTC's view for the reasons described in response to question C2 above.

C4. On page 101, please clarify if Figure C9.13 should be marked as academic in confidence? It is noted that Table C9.18 on the same page is not marked academic in confidence and displays the values shown in the figure.

Response

This is a mistake. The entire table should also be marked as academic in confidence.

C5. On page 170, please clarify how the relative risk of mortality was derived and clarify why it is marked as commercial in confidence?

Response

The relative risk of mortality for ataluren was hypothesized based on evidence of correlation between time/age of loss of ambulation and death. The figure was marked as commercial in confidence as it is the intellectual property of the manufacturer. However, we will remove the marking if recommended by the ERG.

C6. On page 171, please remove the confidential marking from the statement relating to clinical opinion. This should not be marked as confidential.

Response

We will remove the CIC marking from the clinical opinion sentence but leave [redacted] as CIC as this remains the intellectual property of the manufacturer.

Section D: Information request

Many thanks for providing the additional information and individual patient data in response to our email dated 7th July 2015. This information is very helpful to the ERG and for the evaluation of ataluren. There are a few outstanding issues relating to the original request that additional information may address, if it is available:

- Ricotti study– We are very grateful for the supplied data. Please provide similar data from the Humbertclaude and Rall studies (P166-169) if available?
  Response – this is attached in Excel and Engauge digitizer 4.1 files.

- 6MWD – We are very grateful for the further information that has been supplied. However, the ERG still believe that in order to rigorously test the analyses in the submission, they still require access to individual patient level data. The ERG consider that even if the correct analysis to undertake is at the group level as you have suggested, patient level data is still necessary for other reasons (e.g. subgroup analysis, sensitivity analyses such as bootstrapping etc.). Please consider whether you are able to provide this information.
  Response: To follow

- PedsQL – Thank you for agreeing to undertake the mapping exercise and supplying us with the data. It will be important to have individual level data for each participant at each time point, not just aggregate group data, so appropriate sensitivity analyses can be undertaken.
  Response: To follow

- Baseline demographics – Even if analyses are going to be undertaken at the group level, individual data is still important for sensitivity and scenario analyses.
  Response: To follow

Without access to the data outlined above, the ERG are concerned that their report could list a large number of uncertainties around key assumptions in the model. They hope to reduce this level of uncertainty using the requested data and provide a more robust critique to assist the Committee's decision-making.

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Manufacturer response to ERG clarification questions relating the HST appraisal of ataluren for nmDMD, received 16th July 2015

Outstanding questions (Part 1)

A5. Analysis:

A5.1. **Priority Question.** Age, corticosteroid use, and baseline 6MWD were pre-specified as stratification factors since these variables were likely to have prognostic significance (page 86). Please provide sub-group analyses defined by steroid treatment and age (7 year cut-off) for the ITT and cITT data (e.g. see page 94, Table C9.14) and ITT data for the sub-group analysis by 6MWD.

Response

The prespecified stratification factors in Study 007 were:

- Age (<9y or ≥9y),
- Concomitant use of corticosteroids at baseline (yes or no) and
- Ambulatory function as determined by 6MWD at baseline (<350m or ≥350m).

The comparison of observed difference for each of these stratification factors are shown in the table below. It should be noted that these are not "subgroups" per se and, as per the scope, should not be analysed as such.

As highlighted by Haas et al, whilst the effect was best measured in a sub-population of ambulatory patients in the decline phase of their disease, it was agreed that there should be no scientific reason, nor any safety imperatives, to withhold ataluren from nmDMD ambulatory patients aged 5 years or more who are at an earlier stage of disability progression.

For the EMA review, further analysis was performed on patients likely to be in the ambulatory decline phase of the disease subsequent to age 7. This subgroup consisted of nmDMD patients aged 7 to 16 with a baseline %- predicted 6MWD ≤80% and, to minimize heterogeneity, who were taking corticosteroids and had a baseline 6MWD ≥150 meters. In this decline-phase group, in patients treated with ataluren 40 mg/ kg/day, the mean change of 6MWD from baseline to Week 48 was 49.9 meters better than placebo-dosed patients (nominal p=0.0096). It is patients with these characteristics that were included in Study 020 (ACT-DMD).

Mean change in 6MWD from baseline to week 48 (cITT)						
	ITT analysis			cITT analysis		
		MMRM Model			MMRM Model	
Analysis Sub-group	**number**	**Difference (95% CI)**	**p-value**	**number**	**Difference (95% CI)**	**p-value**
Corticosteroid use	(placebo n=40, ataluren, n=41)	[redacted]	[redacted]	(placebo n=40, ataluren, n=41)	[redacted]	[redacted]
No corticosteroid use	(placebo n=17, ataluren, n=16)	[redacted]	[redacted]	(placebo n=17, ataluren, n=16)	[redacted]	[redacted]
< 9 years	(placebo n=32, ataluren, n=32)	[redacted]	[redacted]	(placebo n=32, ataluren, n=32)	[redacted]	[redacted]
≥ 9 years	(placebo n=25, ataluren, n=25)	[redacted]	[redacted]	(placebo n=25, ataluren, n=25)	[redacted]	[redacted]
Baseline 6MWD <350 m sub-group	(placebo n=23*, ataluren, n=25)	[redacted]	[redacted]	(placebo n=22, ataluren, n=25)	59.8m (18.0, 101.6)	0.0053
Baseline 6MWD ≥350 m	(placebo n=34, ataluren, n=32)	[redacted]	[redacted]	(placebo n=35, ataluren, n=32)	[redacted]	[redacted]

*One patient randomised to placebo, suffered a knee injury 1 day prior to his baseline visit that affected his walking ability. His baseline 6MWD (309 meters) was incorrectly deemed valid by the clinical evaluator, and he was stratified into the <350 m group. For the cITT analyses, his baseline 6MWD was replaced with his screening 6MWD (395 m), and he was re-stratified into the ≥ 350 m group.

A5.2. **Priority Question.** Use of post-hoc cITT analysis, (i.e. amending the baseline data for 0.9% of the two groups analysed, 1 of 114 patients) has an impact on statistical significance of the primary outcome. Table C9.15 (page 91) presents timed function tests for the cITT analysis set, please also provide the ITT analysis.

Response

The cITT data were used as the basis of the MAA and subsequent license from the EMA. As requested, and for comparison of consistency, the ITT data for the TFTs are shown below.

Timed function tests (ITT)

Endpoint[a]	**Placebo (n=57)**		**Ataluren 40 mg/kg/day (n=57)**		**Observed Difference**[a]	**MMRM Model**		
	Baseline, mean		**Baseline, mean**			**(95% CI)**		**p-value**
Climb four stairs Time, s	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]
Descend four stairs Time, s	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]
Run/walk 10 metres Time, s	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]
Supine to stand Time, s	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]

As highlighted, there was one patient difference between the between ITT and cITT. The details of this patient are as follows:

- The patient was on placebo, age 8, and on steroids.
- The patient's 6MWD and TFTs at screen, randomization and Week 48 are shown in the table below.

Data for placebo patient whose baseline was changed to screening values

	Population	6MWD	10 m Run/walk	Stair climb	Stair descent	Rise from supine
Baseline	ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	cITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A8.3. Table C9.25 provides a count of cases of serious adverse events. The data for ataluren includes 217 participants from the 80mg/kg/day group. Please provide data for the 238 participants in the 40mg/kg/day group.

Response

To follow on Friday 7th.

B3. Priority Question. The regression analysis (section 12.2.1) in the company's submission was undertaken using data from weeks 24 to 48, rather than from baseline to 48 weeks, and this is reported as a conservative assumption. However, the 48-week 6MWD change calculated by this method (33.8m, page 160) is greater than the change calculated if the full trial data are used (31.3m, page 18). Please clarify the justification for this assumption, and explain why you consider this assumption to be conservative.

Response

- The decline observed in the ataluren arm in weeks 0-24 in Study 007 was very small since the average 6MWD improved from baseline before declining (see Figure C9.7 of the submission). We have conservatively assumed that the modelled cohort would not have an improvement in 6MWD after 48 weeks thus it was deemed that the data observed from weeks 0-24 would not be appropriate for extrapolation over the model duration.
- The by-visit data is included in Table B3-1 to enable further exploration of the linear extrapolation. The data are the LS means across visits obtained via the pre-specified MMRM model on the cITT population.
- Figures B3-1 to B3-3 demonstrate that the decline in the first half of the study (i.e., before Week 24) is much slower than that in the second half of the study (i.e., after Week 24) as shown in the regression lines. In the subgroup of baseline 6MWD ≥ 350 meters, the seeming improvement in the first half of the study is much larger than that in the second half of the study. Hence it is inappropriate to fit data with only one linear line for each treatment group.
- Linear extrapolation fits a linear line and extends the linear trend beyond the limit of the known data. It produces a more accurate estimate when the data involved are not too far from the time point of interest due to the higher correlation.
- Considering most new patients (recently identified in the market place) will be younger than the average of the cohort used for projection, and therefore have a lesser degree of muscle

damage, we expect in the long term patients would continue to walk longer than the current model assumes.

Table B3-1
LS Mean Change from Baseline in 6MWD (m) from MMRM
PTC124-007 cITT Population

	All Patients		Baseline 6MWD < 350 m		Baseline 6MWD ≥ 350 m	
Week	**Placebo**	**Ataluren**	**Placebo**	**Ataluren**	**Placebo**	**Ataluren**
0	**0**	**0**	**0**	**0**	**0**	**0**
6	[redacted]					
12						
18						
24						
30						
36						
42						
48						

Figure B3-1

[redacted]

Figure B3-2

[redacted]

Figure B3-3

[redacted]

Additional information

6MWD – We are very grateful for the further information that has been supplied. However, the ERG still believe that in order to rigorously test the analyses in the submission, they still require access to individual patient level data. The ERG consider that even if the correct analysis to undertake is at the group level as you have suggested, patient level data is still necessary for other reasons (e.g. subgroup analysis, sensitivity analyses such as bootstrapping etc.). Please consider whether you are able to provide this information

Response

Thank you for the comment; as mentioned during the teleconference, we believe group level data would provide the level of detail needed for the analysis you have mentioned. Please refer to Table B-3.1 above for such data.

PedsQL - Thank you for agreeing to undertake the mapping exercise and supplying us with the data. It will be important to have individual level data for each participant at each time point, not just aggregate group data, so appropriate sensitivity analyses can be undertaken.

Response

The mapping exercise is being undertaken and will follow on Friday 7th.

Baseline demographics – Even if analyses are going to be undertaken at the group level, individual data is still important for sensitivity and scenario analyses.

Response

The patient demographics are attached

Manufacturer response to ERG clarification questions relating the HST appraisal of ataluren for nmDMD, received 16th July 2015

Outstanding questions (Part 2 of 3)

Section A: Clarification on effectiveness data

A8.3. Table C9.25 provides a count of cases of serious adverse events. The data for ataluren includes 217 participants from the 80mg/kg/day group. Please provide data for the 238 participants in the 40mg/kg/day group.

Response

Please see the table provided for the response to A8.5.

A8.5. **Priority question:** Please provide the requested data highlighted in pink to Table C9.25: Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials (see revised Table below).

Response

Please see Table 1 below which provides the serious adverse event data for ataluren 40 mg/kg/day and placebo. At the data lock of 31st January 2015, the rate per person months of follow up has not been calculated and given the time patients were on each therapy, there are limitations in assessing causality based on this data.

As previously provided, the following explanation may assist in the interpretation of listed adverse events. The Periodic Benefit-Risk Evaluation Report (PBRER) reports cumulative occurrence of adverse events from completed and ongoing studies for ataluren in DMD. It should be noted that more patients were treated with ataluren than placebo; approximately 379 patients were treated with ataluren compared with approximately 172 patients treated with placebo as of 31 Jan 2015 (totals include patients who have received blinded study drug as of 31 January 2015 in the ongoing nmDMD Study 020). Also, based on study designs (open-label extension studies only included ataluren treatment), ataluren treatment duration was longer than placebo treatment duration (Table 2).

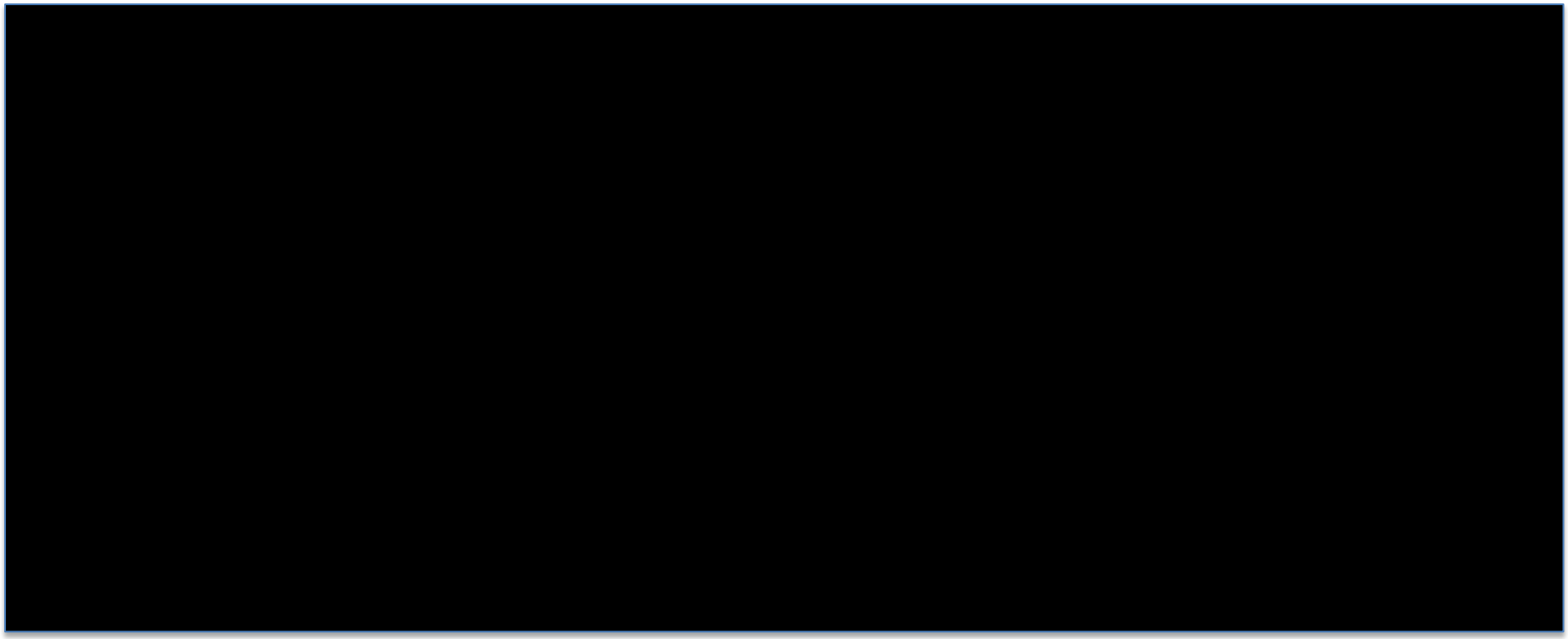
Based on the review of the current information presented in the PBRER, the benefit risk evaluation for ataluren remains positive. The review of data revealed no new

safety concerns. No changes in characteristics of listed or unlisted adverse drug reactions or increase in reporting frequency associated with ataluren were identified.

Table 1. Cumulative Summary Tabulation of nmDMD Total SAEs as of 31 Jan 2015: Ataluren 40 mg/kg/day and placebo

System Organ Class (SOC)	Preferred Term	Count of Cases - Ataluren	Count of Cases - Placebo
Cardiac disorders	Cardiac arrest	2	0
	Cardiac failure	2	0
	Cardio-respiratory arrest	1	0
	Myocardial infarction	1	0
	Tachycardia	3	0
	Ventricular arrhythmia	1	0
	Subtotal	**10**	**0**
Gastrointestinal disorders	Abdominal pain	1	1
	Intestinal obstruction	1	0
	Volvulus	1	0
	Subtotal	**3**	**1**
General disorders and administration site conditions	Death	1	0
	Lethargy	1	0
	Subtotal	**2**	**0**
Infections and infestations	Appendicitis	1	0
	Cellulitis	1	0
	Chicken pox	0	1
	Enterovirus	1	0
	Gastroenteritis	1	0
	Influenza	0	1
	Pneumonia	1	0
	Postoperative wound infection	3	0
	Subtotal	**8**	**2**
Injury, poisoning and procedural complications	Back Injury	1	0
	Compression fracture	1	0
	Femur facture	18	1
	Spinal compression fracture	1	0
	Tibia fracture	1	0
	Subtotal	**22**	**1**
Metabolism and nutrition disorders	Dehydration	2	1
	Subtotal	**2**	**1**
Nervous system disorders	Grand mal convulsion	0	1
	Intracranial pressure increased	1	0
	Loss of consciousness	1	0
	Migraine	1	0
	Subtotal	**3**	**1**
Psychiatric disorders	Mental status changes	2	0
	Subtotal	**2**	0
Renal and urinary disorders	Proteinuria	1	0
	Subtotal	**1**	**0**
	Hypoxia	1	0
	Pneumonia aspiration	1	0
	Pulmonary haemorrhage	1	0
	Pulmonary oedema	1	0
	Respiratory failure	1	0
	Subtotal	**5**	**0**
		Ataluren	**Placebo**
	Total	**58**	**6**

Table 2. Estimated duration of exposure in ataluren Phase 2 and 3 studies



PedsQL - Thank you for agreeing to undertake the mapping exercise and supplying us with the data. It will be important to have individual level data for each participant at each time point, not just aggregate group data, so appropriate sensitivity analyses can be undertaken.

Response

The mapping exercise is being undertaken and will follow on Friday 7th.

Update: the analysis is ongoing and I will have the results later today. I will send this over the weekend.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: Action Duchenne

Brief description of the organisation:

Action Duchenne, initially called Parent Project UK, was set up in 2001 by [redacted] and Dr [redacted] when their son [redacted] was diagnosed with Duchenne Muscular Dystrophy. The charity was the first organisation in the UK dedicated exclusively to Duchenne and Becker Muscular Dystrophy and, with the help and support of friends and supporters and other Duchenne families, developed into a national organisation. In 2006 the DMD registry was set up by Action Duchenne. This was the first patient registry for Duchenne in the UK and one of the first patient registries for Neuromuscular Disease in the World. Action Duchenne's main aim has always been to find a cure for Duchenne and Becker through fundraising and campaigning to raise awareness and develop the necessary protocols. However, we are committed to a dual strategy: searching for a cure whilst, at the same time, ensuring that everyone was gets the standard of care necessary to have the best life possible. Action Duchenne continues to fundraise, campaign and provide support and educational expertise to young people and families affected by Duchenne and we are grateful to all our fantastic families and supporters for making this work possible.

Are you (tick all that apply):

- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

How does the condition impact on patients, their families or carers?

Duchenne muscular dystrophy is the most common fatal genetic disorder diagnosed in childhood, affecting approximately 1 in every 3,500 live male births (around 2500 people have DMD in the UK).

Duchenne results in progressive loss of strength and is caused by a mutation in the gene that encodes for dystrophin. Because dystrophin is absent, the muscle cells are easily damaged. The progressive muscle weakness leads to serious medical problems, particularly issues relating to the heart and lungs. Young men with Duchenne typically live into their late twenties.

Although there are medical treatments that may help slow its progression such as the use of steroids to treat the secondary effects of duchenne, there is no cure. This condition causes the greatest number of deaths amongst genetic diseases in children and young adults.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

This drug will slow the progression of duchenne – enabling those living with the condition to walk and be self reliant for longer. It will crucially decelerate muscle wasting around the heart and lungs and will subsequently improve life expectancy. These improvements will serve to decrease the burden on families and the NHS to

meet the support and care requirements associated with the conditions' degeneration.

There are also huge psychosocial benefits. Positive results on a walk test or stair climb and a stabilising of the degenerative impacts of the condition could be crucial in giving families and patients more freedom, autonomy and stability in their lives.

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Due to the complex nature of duchenne, Translarna will only treat those patients with a specific nonsense mutation: this equates to less than 15% of the UK duchenne population. Eligibility for the treatment has, thus far, only been extended to those patients who are still ambulant. The treatment would provide undoubted benefit to those non-ambulant patients whose Duchenne is engendered by a nonsense mutation.

Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Due to the complex nature of duchenne, Translarna will only treat those patients with a specific nonsense mutation: this equates to less than 15% of the UK duchenne population. Eligibility for the treatment has, thus far, only been extended to those patients who are still ambulant. The treatment would provide undoubted benefit to those non-ambulant patients whose Duchenne is engendered by a nonsense mutation.

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Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted] [redacted]

Name of your organisation: Muscular Dystrophy UK

Brief description of the organisation:

Muscular Dystrophy UK (previously known as the Muscular Dystrophy Campaign) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions.

Founded in 1959, we have been leading the fight against muscle-wasting conditions since then. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 70,000 children and adults in the UK.

We are a member of NHS England's Paediatric Neurosciences and Adults Clinical Reference Groups, and recently helped draft NHS England's draft policy on ataluren.

We represent the approximately 2,300 people living with Duchenne muscular dystrophy in England. We have funded translational research into Duchenne muscular dystrophy through our wide ranging peer reviewed research programme, provide support to the Duchenne North Star Database and fund clinical trials coordinators.

Are you (tick all that apply):

- **an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate.**

Policy and Campaigns Officer

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How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition
and the impact these difficulties have on patients and their families or carers.

Diagnostic delay is a prevalent issue affecting the diagnosis and management of Duchenne muscular dystrophy.

Parents and early years professionals are usually the first to spot developmental delay, such as difficulties in getting up off the floor or an inability to keep up with friends or siblings. This is typically between the ages of 2-3 years old although in some instances symptoms may become apparent earlier.

Average age of diagnosis is 4.5 years old, and diagnosis later than this age is prevalent, indicating a significant delay from first reported parental concerns to diagnosis. In a child aged five years old with Duchenne muscular dystrophy, around 30-40% of muscle mass will already have been lost.

This is primarily due to a lack of awareness of the disease amongst professionals involved in primary care, who may make an incorrect referral or initially misdiagnose the condition.

The diagnosis of Duchenne muscular dystrophy is devastating for families, and can be made all the worse if it follows months and years of such uncertainty.

Diagnostic delay affects subsequent access to the care pathway and implementation of best standards of care. This means there is delayed access to specialist physiotherapy, regular monitoring by specialists and in some cases can mean boys are unable to begin steroid treatment if they have been diagnosed too late.

Lack of diagnosis can also lead to a lack of appropriate support at school, and in other aspects of day to day life. This can have an impact on cognitive and behavioural development.

[redacted], whose son, [redacted], was diagnosed with Duchenne muscular dystrophy aged 7 and a half, said:

"My son, when he was diagnosed, was seven and a half years old. Therefore he missed out on essential steroid treatment– not really bringing into it the enormous distress that was caused by the lack of diagnosis within his schooling and everything else… I can only speak from my own point of view, and having a son diagnosed at seven and a half is horrific. We didn't know why he couldn't walk down the stairs fast enough; the dyslexic problems; the behavioural problems…it was unutterably awful."

Many report a damaging lack of support at the point of diagnosis, and a lack of appropriate information available through the NHS. Many of these families instead turn to Muscular Dystrophy UK and other charities to guide them through the process.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

For children of school age affected by Duchenne muscular dystrophy, significant time may be spent outside of school at various hospital and physiotherapy appointments, sometimes multiple times in a week.

Complexity and costs of care increase as the child becomes older and loses ambulation. A wheelchair is needed typically by the ages of 8-11. As the child enters their teens and during early adulthood, spinal rods and respiratory support, including in some cases a tracheostomy, will be necessary.

Children affected by Duchenne muscular dystrophy will often encounter difficulties at school. This can be as a direct result of the condition, as learning difficulties are associated with Duchenne muscular dystrophy, but can also be because they are struggling to cope with their disability: whilst they see their friends able to do more and more as they grow older, they are able to do less and less. This can result in severe emotional difficulties and behavioural changes, which parents and schools often struggle to deal with.

For these children, prolonging ambulation is crucial, with a longer period of walking life allowing them to keep up with their peers and maintain a greater degree of independence. This also has real world significance, for example the ability to play with a younger sibling or take part in a playground game.

Duchenne muscular dystrophy also places a heavy burden on families. These families, as well as coming to terms emotionally with their child's devastating diagnosis, are forced to make a number of changes to theirs and their family's lives. This may be through having to move to a larger, accessible home, buying new vehicles, or giving up work to fulfil increasing caring responsibilities. This adds to both the emotional and financial burden placed on families.

A recent study by Bushby et al revealed that the costs of Duchenne muscular dystrophy costs the £71,000 every year per patient, with a total nationally of about £120m. The overall figures include medical treatment, as well as the cost associated with loss of employment among caregivers. In the UK, nearly half (49 percent) of

caregivers reduced their working hours or stopped working completely owing to their relative's Duchenne muscular dystrophy.

Gary Hill, whose son, [redacted], has Duchenne muscular dystrophy and is on the ataluren clinical trial at Great Ormond Street Hospital, recently submitted evidence to Muscular Dystrophy UK and NICE:

We have had to move house because our last house was not suitable for a disabled child, the house we bought had to be altered and adapted to suit his needs of today and for the future. We changed our car so it was easier for him to get into. Because of the numerous appointments, [redacted] gave up working at the Infant school and cut down her hours of secretarial work. Trying to be as supportive as possible and attending as many appointments as I can, my business has reduced in size, consequently the turnover and profit have almost halved. These are just a few of the financial costs incurred in our family, they don't take into account the many extra items you take for granted like travel expenses (Taxi bills because he can't walk far), extra heating bills (he feels the cold more), better quality shoes (which help with his walking), more school trousers (because he falls over more often), physio sessions (once a week to keep his muscles supple), Swimming lessons.

Putting the financial impact to one side, let's look at the emotional impact.
Being told your child will probably die before you, has to be the most devastating thing you can tell anyone.
The impact it had on us could not be put into words…We're angry, we look at other families and wonder why us? We blame ourselves, even though we know it wasn't our fault…The emotional effect it is having on [redacted]'s brother is only just becoming apparent, he is struggling at school, he did have a councillor he could talk too but the school have removed that facility. He struggles with concentration, had a breakdown at school last year after googling his brothers condition. When you try to talk to him you feel he doesn't want to talk about it as it will upset us even more. As parents should we feel guilty we can't spend more time helping him?

[redacted] hates to be the centre of attention. At school he has to sit on a chair at assembly rather than the floor with his friends, he is taken out of lessons for physio on a daily basis and other appointment during each month from his speech and language and his occupational therapist he is also driven to and from the sports field this makes him feel he is different. At sports day last year, the school said instead of running in the races would he prefer to hold the finish line tape (talk about patronising).He suffers from extreme mood swings and these are more noticeable towards the end of his 10 days on/10 days off steroid prescription. Every so often he will ask us questions about his condition; does it only affect my legs? Do I always have to take this medicine? Why do I have to wear the night splints? We always try to answer as honestly as possible but try to protect him at the same time.

Below is a brief breakdown of the 'Direct Financial Costs' incurred

Monthly Costs	*£*
Missing 3 days' work (average)	*600.00*
Extra travel expenses (taxi, fuel, parking)	*200.00*

Councillor for [redacted]	*60.00*
Extra for utility bills	*25.00*
Physio (two sessions)	*110.00*
Private swimming lessons	*60.00*
Clothes and shoes	*50.00*
Car repayments (50%)	*250.00*
Extra cost of bicycle (normal-disabled)	*130.00*

One off costs *(Due to* [redacted]*'s condition)*

Moving house	*80,000 (mortgage)*
House alterations	*18,500*
[redacted] *giving up work*	*12,000 p/a*
% profit on business	*??????*

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Ataluren has been shown to prolong walking life for ambulant boys with Duchenne muscular dystrophy.

To fully appreciate the potential benefits of the drug, it is crucial that the impact of loss of ambulation is properly recognised; both the emotional and psychosocial impact it has on boys and their families, but also its correlation with a more rapid progression of Duchenne muscular dystrophy and the severe later functional decline associated with this, including respiratory difficulties.

Costs and levels of care increase once a child has lost ambulation, impacting on all areas of family life, including in many cases parents' earning capacity. Further adaptations to the family's property are likely to be necessary, and the family may have to move home.

For these reasons, evidence reported by Bushby et al (2014) indicates that families of a disabled child, including those with Duchenne muscular dystrophy, are more likely to be financially disadvantaged. By slowing down disease progression for those boys with a nonsense mutation, these families will experience some easing of their caring responsibilities; with the burden of additional costs spread out over a longer timeframe.

Loss of ambulation is also associated with a faster progression of the disease. Therefore, by prolonging ambulation and the onset of the later and costly progression of Duchenne muscular dystrophy, ataluren offers a window of opportunity by which

time treatments currently in clinical trial may emerge to treat, for example, loss of respiratory function.

[redacted] and [redacted], whose son, [redacted], has Duchenne muscular dystrophy, is eligible for Translarna, said:

Translarna is a lifeline with the possibility of more years walking, by which time other drugs may become available, without this drug the window of opportunity to gain the benefits will pass as this drug is only suitable whilst [redacted] is ambulant.

Ambulation is also an important quality of life indicator, with a longer period of walking life allowing boys to keep up with their peers and maintain a greater degree of independence. For a child with Duchenne muscular dystrophy, this may mean including walking independently to the toilet or getting from the car park into school.

One mother whose son has Duchenne muscular dystrophy told Muscular Dystrophy UK that: *"we have a three year old son, and as things are now he will never remember the times when his older brother walked and played with him."*

Another mum, [redacted], whose son, [redacted], is eligible for ataluren, describes a longer period of ambulation as allowing [redacted] to '*just be one of the boys'*.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and outcome of the condition

Early loss of ambulation is associated with a faster overall progression of the disease. Consequently, ataluren offers the prospect of delaying the later devastating decline in physical, cardiac and respiratory function that occurs during the late teens and early adulthood.

- physical symptoms and level of disability

Ataluren would slow the severity in progression of physical symptoms and keep boys walking for longer. Thus it would have an impact on overall level of disability, and spread physical decline out over a longer period of time.

- mental health

Loss of ambulation is one of the most difficult and devastating points of disease progression in Duchenne muscular dystrophy, for the children affected and their families. Delaying this could have an impact on mental health, with boys in the ambulatory decline stage not losing ambulation at such a rapid rate and having longer to adjust to a more gradual loss of function.

- quality of life (lifestyle, work, social functioning etc.)

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By keeping boys walking for longer, ataluren reduces costs of care in the short term, and ensures that costs are spread out over a longer period of time. Prolonging ambulation also lifts some of the heavy burden that caring for a child who is a full time wheelchair user places on families. For the children themselves, there is a strong psychosocial benefit derived from being able to walk for longer, which can impact on interaction with peers, performance at school and overall quality of life and wellbeing.

[redacted], whose son, [redacted], is eligible for ataluren, said:

"Decision makers need understand the impact on children of even a small change. It gives them more time to run and play football with their friends. It's really buying precious time. [redacted] will have to deal with very difficult mental and physical challenges as his condition progresses. Translarna is buying time for [redacted] just to be a kid."

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

We are not aware of any disadvantages relating to the taking of the technology, its impact on others, its financial impact on the patient and families or any associated side effects.

Currently, ataluren has only been tested on ambulant and outcome measures have been focused on walking ability.

Whilst ataluren's mechanics of action suggest it could improve other aspects of physical function, not solely related to walking, there have been no clinical trials as of yet to confirm this.

There is no indication that the drug would have adverse effects on other aspects of the condition.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

We are not aware of differences in opinion on the 'usefulness' of the technology amongst patients. However, ataluren is designed to treat ambulant boys aged five and over whose condition is caused by a nonsense mutation. It would therefore not be able to treat all those affected by the condition.

5. Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Under the terms of the drug's conditional licence, it could be administered to boys who are aged five and over and who are still ambulant. Patients not meeting these licensing criteria do not currently stand to benefit from the treatment.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Treatment options for Duchenne muscular dystrophy in the UK are very limited, with no targeted therapies available for the condition. Ataluren is unique in this respect, as it is the only licensed drug to address an underlying genetic cause of Duchenne muscular dystrophy.

The current standard course of treatment for ambulant boys is steroid treatment, which is typically administered from the age of five.

Whilst giving short term benefits in walking ability, there are severe side effects, including mood swings, weight gain and thinning bones. For this reason, some families opt out of this course of treatment.

Ataluren, however, has been shown in clinical trial to be safe and well tolerated. In the recent Phase 2b trial, after 48 weeks, boys on 40 mg/kg per day were able to walk a clinically meaningful 31 metres further than boys who received a placebo.

Clinical trial data also indicates that the physical function stabilised in boys aged seven and under, who were treated with ataluren 40mg/kg/per day.

We note that ataluren would be taken alongside steroids.

With regard to other available treatments, specialist physiotherapy and cardiac and respiratory monitoring would continue in the event that ataluren is granted approval.

(ii) If you think that the new technology has any advantages for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall

- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Clinical trials show that ataluren is safe and well tolerated. It is simple to administer, via powdered solution mixed with liquid, and can be taken at home.

Data from the recent Phase 2b clinical trial for ataluren shows a clinically significant reduction in the decline in walking ability of boys taking the product. Patients would therefore derive benefit from a longer time spent ambulant and enjoy associated benefits in health and overall quality of life.

Steroid treatment compares unfavourably in this respect. Whilst there is some clinical benefit, there are serious side effects associated with this drug's use. It also only addresses the symptoms of the condition, rather than address the underlying genetic cause.

(iii) If you think that the new technology has any disadvantages for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We are not aware of any specific disadvantages associated with use of ataluren compared to current practice.

The drug is easy to administer and swallow and can be taken at home. There are no reported side effects.

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

We are in contact with parents whose children are currently receiving ataluren following completion of a clinical trial.

These patients' testimonies corroborate the clinical trial data, and indicate a benefit both in walking ability and other physical function, such as hand and arm movement.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

We are not aware of any adverse effects that have become apparent following clinical trials.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

For further information, please see:

The Burden of Duchenne muscular dystrophy – an international cross sectional case study' (Bushby et al 2014)
Improving recognition of Duchenne muscular dystrophy: a retrospective case note review (Bushby et all 2014)
Access to high-cost drugs for rare diseases (All Party Parliamentary Group for Muscular Dystrophy, 2013)
Newborn screening for Duchenne muscular dystrophy (All Party Parliamentary Group for Muscular Dystrophy, 2014)
Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis and pharmacological and psychosocial management (Busby et al, 2009)
Diagnosis and management of Duchenne muscular dystrophy, part 2: Bushby et al, 2009

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Patients would benefit from access to this first licensed treatment for Duchenne muscular dystrophy through:

- a slower decline in physical function
- a reduction in some of the burden the disease places on families
- a spreading out of costs of care
- improved quality of life, through a longer period spent ambulant
- a potential lessening of emotional and behavioural difficulties amongst children experiencing rapid loss of ambulation

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(ii) What implications would it have for patients, their families or carers if the technology was not made available?

If the technology was not made available, patients would:

- have a lack of available alternative treatment options
- have to deal with the emotional and financial impact of loss of ambulation at an earlier stage
- experience a faster progression of the disease, which could be avoided whilst they were prescribed ataluren

(iii) Are there groups of patients that have difficulties using the technology?

Within the group of patients meeting the terms of the drug's licence, we are not aware of any patients who would have difficulties using the technology.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Duchenne muscular dystrophy affects 8.29 per 100,000 males, which equates to approximately 2,300 people in England. 10-15% of these cases are caused by a nonsense mutation. In England, we understand that 24 patients are currently on a clinical trial for ataluren, leaving a further 33 patients who meet the terms of the drug's licence and are not on the trial.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ataluren is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

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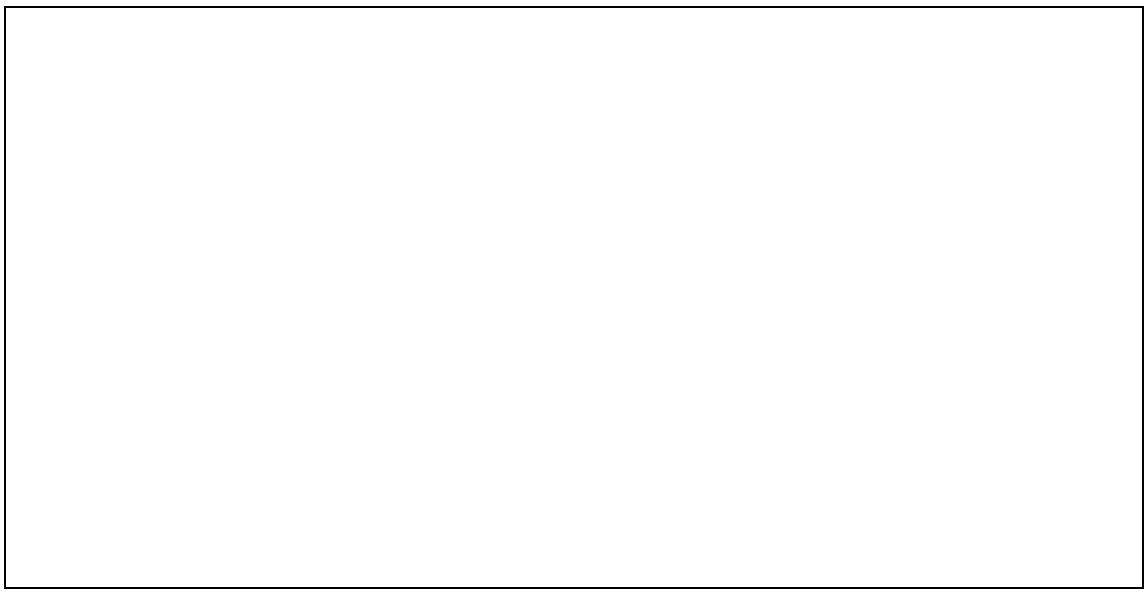

Appendix G - professional organisation statement template

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Dr [redacted]

Name of your organisation: National Hospital for Neurology, UCLH, London
Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

X other? (please specify) I have acted as a medical expert for PTC bio

Appendix G - professional organisation statement template

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What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Approximately 2200 DMD patients in the UK, 66 of whom will be eligible for the new treatment.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The condition is treated with corticosteroids, either daily of 10 days on 10 days off, there is some regional variation for steroid regimen. However, the evidence for which regimen provides optimal benefit is not available. The 'forDMD' trial is currently underway to answer this question. Other management strategies include physiotherapy, cardiomyopathy treatment (ace inhibitors and beta blockers) and spinal surgery for scoliosis, home ventilation -BIPAP, cough assist.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

A small number of children who develop early cardiomyopathy have a poorer prognosis and die at an earlier age.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

The new technology is not likely to impact on the current level of patient care or services

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

The drug is currently available to some patients in the UK enrolled in a phase three study. It is available in other European countries for prescription

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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There is a NICE accredited guideline for the management of DMD, also published in the Lancet. It is an international consensus document which used a DELPHI approach.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I was involved in the phase 2b study of this drug and now the phase 3 study. It is well tolerated by patients with few significant side effects. At this stage, I cannot comment on quality of life because data are not yet available from the phase 3 studies, however, there was a trend for improvement in the phase 2b study. No new side effects have been reported by my patients in the phase 3 trial. The drug has been used with steroids and cardiac medications in both trials without any interactions.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Results of a Phase 2b, dose-ranging study of ataluren (PTC124®) in nonsense mutation Duchenne/Becker muscular dystrophy (nmDBMD)
Cited in Scopus: 0
R. Finkel, B. Wong, K. Bushby, A. Reha, G.L. Elfring, L.L. Miller, J. Babiak, M.A. Morsy, and others
Neuromuscular Disorders, Vol. 20, Issues 9-10, p656–657
Published in issue: October, 2010

Bushby K; Finkel R; Wong B; Barohn R; Campbell C; Comi GP; Connolly AM; Day JW; Flanigan KM; Goemans N; Jones KJ; Mercuri E; Quinlivan R; Renfroe JB; Russman B; Ryan MM; Tulinius M; Voit T; Moore SA; Lee Sweeney H; Abresch RT; Coleman KL; Eagle M; Florence J; Gappmaier E; Glanzman AM; Henricson E; Barth J; Elfring GL; Reha A; Spiegel RJ; O'Donnell MW; Peltz SW; McDonald CM; PTC124-GD-007-DMD STUDY GROUP.
Ataluren treatment of patients with nonsense mutation dystrophinopathy
Muscle & Nerve. 50(4):477-87, 2014 Oct.

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The relationship of ataluren plasma concentration and response across clinical studies in nonsense mutation dystrophinopathy
Neuromuscular Disorders, Vol. 21, Issues 9-10, p707
Published in issue: October, 2011

European Medicines Agency review of ataluren for the treatment of ambulant patients aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene
Manuel Haas, Viktor Vlcek, Pavel Balabanov, Tomas Salmonson, Serge Bakchine, Greg Markey, Martina Weise, Gabriele Schlosser-Weber, and others
Neuromuscular Disorders, Vol. 25, Issue 1, p5–13
Published online: November 24, 2014

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Currently, consultants in 3 specialist neuromuscular centres in the UK are experienced in prescribing and monitoring Ataluren (Professor [redacted], Newcastle. Professor [redacted] Great Ormond Street Hospital, Dr [redacted], Great Ormond Street Hospital and The National Hospital Queen Square). These clinicians could either be responsible to prescribing and monitoring treatment within their teams and/or they can disseminate knowledge through the North Star Network of Neuromuscular centres.

No additional facilities or equipment are required

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ataluren is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Appendix G - professional organisation statement template

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If funding of this drug is CCG based it is highly likely that there will be variations in prescribing across the UK because of its cost.

Centralised funding should not pose a problem with equality of access

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Commissioner's perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: E G Jessop

Name of your organisation: NHS England

Please indicate your position in the organisation: Public health adviser

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Current treatment is supportive. Historically there has been some evidence of geographical differences in median survival of patients with Duchenne muscular dystrophy but it is believed that these differences have been reduced by widespread adoption of protocols for spinal surgery and for ventilation.

To what extent and in which population(s) is the technology being used in England?

Ataluren is currently only used by trial and ex-trial patients.

- is there variation in how it is being used across England?

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Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Variation arises from the nature of trial recruitment.

- is it always used within its licensed indications? If not, under what circumstances does this occur?

- what is the current total budget for specialised and highly specialised services?

T*he budget for specialised and highly specialised services is £14bn per annum.*

- what is the scale of the NHS investment in areas of medicine comparable to duchenne muscular dystrophy with nonsense mutation in the dystrophin gene?
- *This information is not available, and depends heavily on what areas are considered 'comparable'. We will be happy to discuss this further during the committee meeting if you wish.*

- what is the impact of the current use of the technology on resources?

Ataluren is currently provided free of charge to trial and ex-trial patients so there is no direct impact on NHS resources.

- what is the outcome of any evaluations or audits of the use of the technology?
- *None available.*

- what is your opinion on the appropriate use of the technology?

The appropriate use of the technology is for patients within the licensed indication.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

Guidance will permit the development of uniform clinical policy for patients of the NHS in England.

In what setting should/could the technology be used – for example, expert centres only, homecare? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Initiation and monitoring of treatment should take place within expert centres but administration of the drug can take place at home. The main requirement for additional resources will be in the monitoring of treatment.

Appendix G – NHS England statement template

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Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

We believe the budget impact of treating all eligible (i.e. within the licensed indication) patients will be about £15m - £20m per annum, depending on various assumptions about uptake.

What considerations relating to the management of the highly specialised commissioning budget should be taken into account when formulating a recommendation?

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

The main resource implication is the opportunity cost of high spend on the drug. The specialised services budget, though large, is already over committed. There may also be some cost from genotyping patients whose mutation is currently unknown, and extra staff costs for clinic time in monitoring the effect of treatment.

Would there be any need for education and training of NHS staff?

Some additional training may be needed to allow for careful monitoring of the effect of treatment, particularly if loss of ambulation is a stopping criterion.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not think there are any relevant considerations under this heading.

Appendix G – NHS England statement template

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Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Other Issues
Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

[redacted] Hill and our family as told by [redacted] Hill - July 2014

In 2008 our lives were easy with two young boys enjoying a happy family life. [redacted], the youngest was a normal 3 year old boy, and then everything changed on January 8th 2009.

In Mid-November 2008 [redacted]'s nursery pointed out he was having trouble getting to his feet, holding onto table legs or things he could find to help him rise from the floor. We took him to our G.P and didn't think much of it. Our G.P sent us to our local Hospital to have some blood tests done to rule out anything sinister. A few days later we were called back and sent straight to another local hospital to see Dr [redacted] head of Paediatrics. I then became worried that something was not right; never did I think it would be something so devastating. An appointment was then made at Great Ormond Street Hospital (GOSH) on 8th January 2009. We met with Dr Manzur who was the main consultant Paediatric Neurologist at the Neuromuscular Department. We were told it may be something called "Duchenne Muscular Dystrophy". He strongly advised us not to go home and Google it on the internet, but like most people we ignored his advice. I remember coming into the room and looking at Gary sitting on the bed with his head in his hands, his face was as white as a sheet. He just said "God I pray it's not!!"

The following week we were back at GOSH and [redacted] was being prepared for a General Anaesthetic for a muscle biopsy which would confirm if it was Duchenne or not. We then had to wait 6 agonising weeks for the results. I can't begin to tell you the emotions we were going through during this time. The only way to describe it was, we felt as though we were grieving as though we had lost something so perfect. His blood test results came bac, and it was confirmed he had Duchenne.
All I can remember being told from [redacted]'s consultant were the devastating few words, that our beautiful perfect son may stop walking between ten and twelve and his life expectancy may only be into his twenties. We both felt our lives just crumble beneath us.

If I'm honest the next few months (even years) were a blur. As a family we turned from being very socialable, to one that just shut the door and stayed at home. We almost tried to pretend it was a big mistake and we would wake up and it was just a horrible nightmare. I stayed in a lot, Gary did most of the school runs, I didn't want to see other mothers in the playground moaning about mundane things like having to make packed lunches or that the playground hadn't had salt put on during the icy months. I certainly wasn't ready to start explaining things to people. We had lots of appointments with [redacted] at various hospitals, bearing in mind I still had to try and keep things together for my elder son [redacted] who was seven at the time. [redacted] never moaned during this time (except when there were blood tests !!)
We booked several holidays to different places. [redacted] and his older brother [redacted] have always got on well, but on holiday they really have fun. We have never hidden anything from [redacted] and he is a very loving and caring brother towards [redacted].

About 18months after [redacted] was diagnosed, Gary and I realised we couldn't carry on as we were.
We realised how important family was and who our real friends were. I had always enjoyed running, so I signed up to run the London Marathon. Gary is lucky enough to be a member of a very nice Golf Club, so we decided to organise a Charity Golf Day. The first year we raised between us about £14,000.
Unfortunately I was injured for the next London Marathon, but really set to getting bigger and better prizes for our second Golf Event. . (It has gone from strength to strength and so we are about to hold our 5th Golf Event this year.)
I must send about 150 emails to different companies asking for anything they can offer. We have received donated flights to New York, Holidays in Madeira and the Caribbean, Boxes at Ascot and rounds of golf at Wentworth, Sunningdale and St Andrews.

I have now run 4 Marathons for Duchenne Muscular Dystrophy. This year I did the 'London2Brighton 100k challenge' and walked continuously for 27hours from London to Brighton and helped raise another £6,500.

Over the past 4 years we have raised over £75,000.00. We have donated money to the Muscular Dystrophy Campaign and Action Duchenne. We were then told about the 'Duchenne Research Breakthrough Fund, it was a new research fund of the Muscular Dystrophy Campaign. We presented an £8000 cheque to the new fund at our Golf Day which was the first official donation. We were proud to be nominated as 'ambassadors' to the charity. This way we get to help all children with Duchenne.

We were also so proud to be invited as a family by Arsene Wenger, the Arsenal Football Club manager to spend a day at the club's training ground meeting the players including [redacted]'s hero Jack Wiltshire and getting signed shirts, photographs and for [redacted] and [redacted] to get a pair each of Robin Van Persie's football boots.
More recently we were asked by the Muscular Dystrophy Campaign to represent them at the 'BGC Annual Charity Trading Day' at Canary Wharf London, we met Roy Hodgson and Sir Alex Ferguson who is one of the Ambassadors of MD. [redacted] was also lucky enough to meet Jack Wiltshire again along with other celebrities.

Our lives will never be the same again, have we coped well? I don't know, Are we happy? As happy as we can be. Are there things we would change? Absolutely!!!
I've learnt to use a switch in my head, turn it on when I need to; during appointments, physio sessions, questions about [redacted] etc… and turn it off and continue with normal family life, which is so important to us as a family. [redacted] is one amazing little boy who shows such courage and determination. Right now at the age of nine he is now more aware of his condition but he is one extremely happy boy who is doing fantastically well, and we are all very proud of him.

In August 2014 [redacted] was accepted onto the Translarna trial which was fantastic news. This involved lots of base line tests (6 minute walk tests. blood tests and ECG'S etc...) even flying back from our summer Holiday in Portugal for 2 days so not to miss appointments.
The trial is double blind so we don't know if [redacted] is taking Translarna or not, but hope by helping with the trial it will soon be available for [redacted] and all boys with Duchenne, to gain a few more years.

Overall we are a closer family now, Gary, [redacted] and [redacted] are the most important people in the world to me. Sometimes I wonder what life would be like if [redacted] hadn't been diagnosed, but then I realise he was, and that's the way it is and you just have to carry on.

A very good friend of mine, who has been battling Cancer for many years, always says to me 'one day at a time [redacted], one day at a time'. Life has to go on and all I want is for our boys to be as happy as they can be, and to grow up knowing we will always be there for them, just like my parents have been for me no matter what life throws at you. Nobody realises how strong they are until they have to go through something so difficult.
I never thought 5 years ago a family from Chalfont St Peter would be talking on live radio stations being interviewed by Channel 5 news, talking with MP's, attending 10 Downing Street and giving a talk in front of 60+ parents at [redacted]'s old school….. How wrong I was!!!
One day I hope [redacted] will look back and be proud of his parents and know we did everything we could for him and never gave up.

Duchenne and its impact on the Hill family

7th February 2015

Trying to explain the impact Duchenne has on a family is difficult, trying to do the same about your own family is almost impossible. Those effects don't just have an Impact on the immediate family they stretch much further along the family tree and also have a ripple effect on friends. The impact it has is not just an emotional one either, self-esteem, financial, relationships, mental and physical health are other facts that need to be taken into account.

[redacted] was diagnosed in 2008; I had a small construction business employing five staff. [redacted] worked as the company secretary and helped in the local infant school. Everything seemed good, little did we know. After several months of tests we got the news that we were dreading, [redacted] had Duchenne. The next few months were a bit of a blur, I stayed at home to support [redacted] and [redacted] was there for me. Over the next couple of years we became very reclusive, barely getting out the car at school drop off, avoiding friends in the supermarket, sometimes not even answering the phone. In hindsight maybe we should have let those people help, but at the time we wanted to grieve on our own (grieving is not too strong a word).

Here are some of the effects of having a child with Duchenne.
We have had to move house because our last house was not suitable for a disabled child, the house we bought had to be altered and adapted to suit his needs of today and for the future.
We changed our car so it was easier for him to get into. Because of the numerous appointments, [redacted] gave up working at the Infant school and cut down her hours of secretarial work. Trying to be as supportive as possible and attending as many appointments as I can, my business has reduced in size, consequently the turnover and profit have almost halved.
These are just a few of the financial costs incurred in our family, they don't take into account the many extra items you take for granted like travel expenses (Taxi bills because he can't walk far), extra heating bills (he feels the cold more), better quality shoes (which help with his walking), more school trousers (because he falls over more often), physio sessions (once a week to keep his muscles supple), Swimming lessons. I have attached a brief breakdown at the bottom of this letter.
Putting the financial impact to one side, let's look at the emotional impact.
Being told you child will probably die before you, has to be the most devastating thing you can tell anyone.
The impact it had on us could not be put into words. Both our personalities have changed; we are less compassionate, probably more selfish with our time, if we want to do something, we will generally do it and not worry too much about the consequences. We're angry, we look at other families and wonder why us? We blame ourselves, even though we know it wasn't our fault. We are more negative towards others; often letting people down because we would rather have a quite night in with the boys instead of going out.

The emotional effect it is having on [redacted]'s brother is only just becoming apparent, he is struggling at school, he did have a councillor he could talk too but the school have removed that facility. He struggles with concentration, had a breakdown at school last year after googling his brothers condition. When you try to talk to him you feel he doesn't want to talk about it as it will upset us even more. As parents should we feel guilty we can't spend more time helping him?
[redacted] never ceases to amaze us; he is academic, enjoys school and loves playing with his friends. He still enjoys playing football with his mates at school and on a Saturday morning.
His friends accept he is much slower than them, so protect him from other teams (they are amazing friends). [redacted] hates to be the centre of attention. At school he has to sit on a chair at assembly rather than the floor with his friends, he is taken out of lessons for physio on a daily basis and other appointment during each month from his speech and language and his occupational therapist he is also driven to and from the sports field this makes him feel he is different.

At sports day last year, the school said instead of running in the races would he prefer to hold the finish line tape (talk about patronising).
He suffers from extreme mood swings and these are more noticeable towards the end of his 10 days on/10 days off steroid prescription. Every so often he will ask us questions about his condition; does it only affect my legs? Do I always have to take this medicine?
Why do I have to wear the night splints?
We always try to answer as honestly as possible but try to protect him at the same time. Nonetheless, [redacted] carries on and always has a smile on his face. In time I hope that smile everyone remembers him for doesn't fade away.

[redacted]'s condition has had a large effect on our relationship, not only to each other but to others as well. It has tested our relationship, we are permanently tired, often up early to give physio to [redacted] and up late catching up with household chores. During the day there are always doctors, Physio, orthotic appointments to attend or sort out. Both our patience levels are low so often row over trivial things. There has been an effect on other members of the family too. [redacted]'s grandparents all struggle to accept his condition. His uncle, Aunts and cousins are all supportive but have their own families to worry about. We have some amazing friends who are always there for us but you sometimes feel they try to protect us as a family. Recently, [redacted] was excluded from a friend's birthday party, because 'skiing' would have been to dangerous for him! How do you think that made him feel?

We are always conscious of the clock ticking, we try to do as much as [redacted]'s condition will allow. We have an imaginary bucket list that we keep adding too.
Having a son with Duchenne has made us do things we may not have done if not for this awful condition. We have raised lots of money for research into Duchenne, been to amazing places on holiday, places we may not have visited and met people that others would only dream of meeting. It has made us stronger and more determined to give our boys every possible opportunity to be happy.

There have been times that have very dark, finding it hard to carry on.
[redacted] especially has had lots of help through councillors. As a mum there have been times she has been at rock bottom, been emotionally unstable which can be very difficult to cope with, our children should not have to witness this as they haven't done anything to deserve it.

Translarna is the first drug that has given us and the whole of the Duchenne community real hope. We understand it is not a cure but it will slow the progression down and give [redacted] and other boys with Duchenne more time to enjoy playing with their Brothers, sisters, friends and family, something most of us take for granted. As parents we would do anything for our children, all we are asking you is to help us to help them…….

Thank you for taking the time to read our story.

Warm regards

Gary and [redacted] Hill

[redacted]

Tel: [redacted]
Email: [redacted]@[redacted].[redacted]

Below is a brief breakdown of the 'Direct Financial Costs' incurred

Monthly Costs	£
Missing 3 days' work (average)	600.00
Extra travel expenses (taxi, fuel, parking)	200.00
Councillor for [redacted]	60.00
Extra for utility bills	25.00
Physio (two sessions)	110.00
Private swimming lessons	60.00
Clothes and shoes	50.00
Car repayments (50%)	250.00
Extra cost of bicycle (normal-disabled)	130.00

One off costs (Due to [redacted]'s condition)	
Moving house	80,000 (mortgage)
House alterations	18,500
[redacted] giving up work	12,000 p/a
% profit on business	??????

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Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene [ID 428]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name:
Bernie Mooney

Name of your organisation:
Action Duchenne
Brief description of the organisation:
Action Duchenne, initially called Parent Project UK, was set up in 2001 and was the first organisation in the UK dedicated exclusively to Duchenne and Becker Muscular Dystrophy. With the help and support of friends and supporters and other Duchenne families, developed into a leading national organisation dedicated to improving care and research.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology? ✓
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

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How does the condition impact on patients, their families or carers?
Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis, appropriate treatment, helpful information about the condition and the impact these difficulties have on patients and their families or carers:

Diagnosis was difficult. We knew something was wrong but were told several times over the course of a year that we were being paranoid and over – protective. Despite our concerns nothing could have prepared us for diagnosis.

At diagnosis we were told that our son would be in a wheelchair by the age of 11, and that life expectancy was at best early 20's and most devastating of all we were told there was no cure. Like many [Duchenne] parents we were told to enjoy our time with him, because there was not a lot we could do.

At the time we were expecting our second child. Due to the genetic nature of the condition we were inundated with specialist investigations and discussions about the long term prognosis and the need to check the gender of our unborn child. Thankfully our second son doesn't have Duchenne.

The most difficult thing to contend with is the progressive nature of the condition. In early years apart from the missed milestones and a lack of strength when climbing and doing distances life is pretty normal. That word normal seems like heaven compared to the progression of the condition in how it destroys mobility. Early treatment is fairly easy to contend with. Night splints to keep ankles stretched and regular checks at a variety of 'specialists'. Steroids are next at 5 or 6, and although these bring many problems, the alternative is too difficult to face. Information from experts – the Newcastle team in our case who we heard at the Action Duchenne conference -is vital, and just not available at a local level.

'Normal' becomes regular hospital visits, both near and far, with time off work. It becomes round –the –clock care and waiting for inevitable questions about why friends can do more. As parents you begin to dread birthdays – a year closer to the inevitable. Everyday life is full of challenges. A trip to the park is difficult. A school trip is a problem. A children's party becomes nearly impossible. Seeing a football field with your Duchenne son is a nightmare. Stairs and steps become a major issue. Family life is strained. Normality seems a distant memory.

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Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Duchenne has a massive effect on families.
For the child with Duchenne every day becomes a mountain to climb, but with heavy weights attached to each part of your body. You never get to the top though; you've just got to climb another the next day. Days begin with the tablets. Steroids to help him stay strong, but another to prevent bone fragility. Another to stop his heart from deteriorating, another to ensure he can go to the toilet regularly. Another prevents acid attacking his stomach. School can be difficult – especially if there are learning needs too. Because a Duchenne child's mobility is limited, their social development is limited too. The condition means that there is increasing dependence on others, and decreasing self-esteem as a result. The psychological effects on the child as they see themselves become more dependant are huge. Anger issues are frequent.

Parents become carers. As normal children grow up they become more independent. With a child with Duchenne the opposite is true. You become more reliant on help from elsewhere (if there is any). Work begins to take a back seat. One of us has had to go part time. Even then we take time off for meetings and appointments. Work isn't your main focus when you are wondering whether your child will stop walking today. Career prospects and related earnings are limited – there's just too much to deal with to have a full impact on your chosen career, and this makes us resent the horrendous condition even more. Sleep is precious. Often disturbed because of uncomfortable splints or trips to the toilet. You know this will increase with deterioration. That promotion is way out of reach, even worse it means reducing working hours to cope. Another burden to carry.

Siblings have to cope with major outbursts from [redacted]. Important events in our second son's life are always overshadowed. As a parent you worry about his loss of childhood. Even the smallest trip out becomes either impossible or a major event. There is nothing 'care free' about life with Duchenne. Siblings learn very quickly that their needs have got to come second. We have been told by school that he has been upset at school. It's devastating to realise that your 11 year old second son feels the need to protect his parents from further upset.
This means every day, for all the family, is draining emotionally and physically

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What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages

Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers:

From soon after the beginning of the trial [redacted] had the ability to keep going for longer. He could not necessarily go faster but he didn't stop so soon. [redacted] has never really performed under pressure. In the original trial we were never aware of the results of his six minute walk distance. However in real life he wouldn't necessarily go any further in six minutes, but he would be able to walk for twelve minutes which wasn't tested. When he stopped to rest he previously wouldn't want to continue. This changed. For the first time we had what we had always imagined to be 'normal' family days out. On one particular day in summer, when [redacted] had been taking Ataluren for a few months, we went to a farm with an indoor soft play area. We arrived at the farm when it opened at 10.30 and we did not leave until 3.30pm. [redacted] played in the soft play area at the beginning of the day and seemed to cope more easily with the obstacles. Throughout the day [redacted] walked around the farm – a huge incentive for [redacted] – but even keeping this in mind he did keep mobile. At the end of the day [redacted] went back into the play area and was able to, again, play with his brother. We had previously been to many similar places and [redacted] had never done as much or stayed as mobile for as long.

We hoped that the drug would prolong ambulation. When looking at [redacted] in comparison to his peers we can see that this has happened. Prolonging ambulation means delaying the most devastating aspects of the condition.

Life with Ataluren is better because [redacted] is still walking. He can leave the sofa when he needs to go to the toilet he can go into friends' houses and he can walk around his classroom. As a direct result of this his self-esteem is maintained as is his muscle function and related general health. Additionally our self-esteem as parents is improved because we have increased our son's independence. Additionally we haven't seen any evidence of any loss of upper body function in our 14 year old son.

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Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

As mentioned elsewhere the aim of Ataluren is to delay the loss of ambulation. By delaying this, the quality of life for our son is maintained and his self-esteem is also maintained. He doesn't have to ask for ***everything*** to be done for him. Anger issues are reduced and this in turn enables our son to deal with the ravages of the condition. The delay in loss of ambulation also has many longer term benefits:
-Weight gain due to steroid use is managed more easily
-Respiratory problems are delayed
We also hope that Ataluren will delay loss of upper body muscle function and extend heart and lung function. The most obvious outcome is walking, but we hope and pray that it also has benefit on all muscles in the body

Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Ataluren has not had any disadvantages for us. The only impact has been to take the chalky drink 3 times a day at 6 hour intervals. We have seen no side effects.
Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

No difference in opinion as far as I am aware
Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?
Ataluren only works for those 13% of Duchenne boys with a nonsense mutation.

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Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

There are no other alternative treatments available apart from steroids and other care such as physio and night splints. Obviously steroids only treat the secondary effects of the condition, not the underlying cause of it, and the side effects cause major problems in themselves. A chubby face, short stature, the list goes on. This is the first and only form of hope to the Duchenne community. Although as previously stated Ataluren will only work for 13% of those affected.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

As there are no alternative treatments; Ataluren is the **only** option.

If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

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Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

We are aware that the intention of Ataluren is to maintain muscle structure integrity. As we understand it this is not about repairing muscle, but about ensuring that it doesn't break down as quickly. Better oil, not a new shock absorber is how we describe it to friends. For us, this is exactly what it does. [redacted]'s condition has not progressed at the predicted rate. He is much more mobile than boys who are of a similar age but do not take Ataluren. We hope that all [redacted]'s muscles are benefitting from Ataluren and that he his heart and lungs last longer too.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

None.

Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

We are asked at each visit to comment on progression from visit to visit. We don't have access to any reports.

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Highly Specialised Technology Evaluation

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

With Ataluren [redacted] has maintained the ability to walk. He is able to take himself to the toilet, get out of bed in the morning, feed himself, and is able to take his own medicine. Friendships are easier to maintain because he is mobile. Although he experiences moments of anger and upset we know that his prolonged ambulation has helped his emotional well-being. He's able to hug his brother and younger family members.
As parents we are both still in employment as teachers. We can leave the room and know that [redacted] is safe and able to perform simple daily tasks. Ataluren has given us time. Ataluren has also given us the chance to have a more balanced family life – our second son has at least a chance of being 'as important'.

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

When we see other Duchenne boys of a similar age, some of whom we have known for many years and who were physically stronger than [redacted] before Ataluren, we see a devastating difference.
A day for a boy without Ataluren begins with being hoisted from their bed to a wheelchair, being hoisted from the wheelchair to the toilet, being hoisted from the toilet back to the chair. [redacted] gets himself up, and goes to the toilet.
A boy without Ataluren spends the day in his wheelchair. Immediately the world is a smaller place. Houses and classrooms are inaccessible. Friends and family are problematic. [redacted] can still choose where he wants to go. Whilst a Duchenne boy's house will be adapted with time, those of his friends will not. The shrinking world occurs much faster for a non-ambulant boy.
Because we know that loss of ambulation is linked to a faster progression of the condition [the devastation caused to vital organs] we hope that Ataluren will oil all muscles and thus prolong life. Ataluren gives us more time.

Are there groups of patients that have difficulties using the technology?

Not to our knowledge.

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Highly Specialised Technology Evaluation

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

Is it equality to exclude non-ambulant boys from being given the drug if the results show that it does "oil" muscle function and thus can prolong mobility – a young man who is wheel-chair bound still needs upper body strength prolonging. If the drug is stopped at loss of ambulation this may exclude part of the population that can benefit by prolonging upper body strength.

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

Not aware.

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Not aware.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Unsure.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology
This is the first drug to come to market for the Duchenne community that treats the underlying cause of the condition – to deny its funding would rip any hope away for the entire Duchenne community that when the next drug comes along, that may also only treat a small percentile of the community, that that too will not be funded.....this drug will give treatment to some (and relieve the burden on the NHS) and give hope to the whole.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Kate Bushby

Name of your organisation: Newcastle University and NUTH
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

About 100 boys are born every year with DMD in England. Around 10-13% of them might be expected to benefit from the drug during the time they are above 5 years old and before they lose ambulation (as per label)

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

DMD is managed mainly by doctors and MDTs at centres who participate in a charity funded clinical network the North Star (MDUK). These centres are mainly trying to be compliant with the DMD standards of care which have been published in Lancet Neurology and which are the basis of the Neurology specialised service annex for neuromuscular diseases. However there are some variations in practice where different aspects of the service are not met in various areas.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The subset of DMD patients likely to benefit from the drug are those with nonsense mutations. They are not known to be different in any way from the general group of DMD patients

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

No.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

N/A

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

The Lancet Neurology published care considerations for DMD in 2010 in two parts (Bushby et al). these have been NICE process accredited. An update is currently underway led by the CDC in Atlanta and supported by international patient organisations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There are no currently licensed drugs for DMD. Current treatment includes corticosteroids. It is hoped that the side effect profile for ataluren might be favourable to steroids long term but this would need to be confirmed by long term studies.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The label suggests terminating the drug at loss of ambulation. I am not sure this completely makes sense as it is possible the drug could also benefit non ambulant boys but it reflects lack of trials in the non ambulant population.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

There were quite a lot of UK children enrolled in the clinical trials and their overall conduct reflects our practice generally.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As the drug is only newly available there are no new data on side effects, but the drug did not appear to have major side effects in the trials available to date.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The drug has not been available for long enough to be able to generate these datea

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

It could be provided within the current clinical structure for managing DMD without further need for support.

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Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene [ID 428]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ataluren is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

The DMD population is an example of a rare disease group. The population who are eligible to receive ataluren and who might benefit from it due to the specific mutation type is an even rarer subgroup. No other interventions are currently licensed for this disease and it is uniformly progressive and leads to premature death. It is really important not to discriminate against this patient group by not taking full notice of the beneifts of slowing disease progression. We have seen with steroid use that slowing disease progression in short term studies has a long term benefit on highly patient relevant disease milestones such as independent ambulation, self feeding, need for overnight ventilation and development of scoliosis. It could be extrapolated for ataluren that the slowing in disease progression seen in the trials might have a similar long term effect. The current population of DMD patients in England will be discriminated against compared to patients in other EU countries if they are not allowed access to the drug at the current level of risk/ benefit which was enough for the regulators to come to a positive opinion. Once skills are lost in DMD they are gone and in the context of a lifespan of maybe 30 years, a couple of years is a significant chunk to await a decision on the use of a drug which might have a beneficial effect.
However there is not additional evidence beyond watching how the drug behaves in practice to be able to answer these imponderables- the only way is by approving the drug and watching how it performs with strict guidance on withdrawal if efficacy in the longer term cannot be established. It is to me discriminatory that for drugs for rare

diseases the high cost of drugs means that inevitably they have a very high threshold to reach. That is not these patients' fault and we have to find a way to square this difficult balance without the patients losing out.

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Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene [ID 428]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Dr Adnan Manzur

Name of your organisation : Great Ormond Street Hospital, London

The views on this document the present primarily my views, and an informal consensus with the other four consultant colleagues on the neuromuscular team. This should not be taken as official position from the GOSH trust perspective, but treated as a clinical opinion primarily from Dr Manzur, and following discussions from his neuromuscular consultant colleagues.

Are you (tick all that apply):

- Yes -a specialist in the treatment of people with the condition for which NICE is considering this technology?

- Yes - a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- Yes - an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? :
- Clinical lead for the UK Northstar clinical network for Duchenne muscular dystrophy. (This is not a paid or salaried post. It is undertaken as a clinical activity within the framework of CPD)

- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Duchenne muscular dystrophy is treated in line with the published standards of care, which have also been approved by NICE.
Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.
Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C; DMD Care Considerations Working Group.
Lancet Neurol. 2010 Feb;9(2):177-89. doi: 10.1016/S1474-4422(09)70272-8. Epub 2009 Nov 27. Review. Erratum in: Lancet Neurol. 2010 Mar;9(3):237.
Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management.
Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C; DMD Care Considerations Working Group.
Lancet Neurol. 2010 Jan;9(1):77-93. doi: 10.1016/S1474-4422(09)70271-6. Epub 2009 Nov 27.

Boys with Duchenne are treated with oral corticosteroids, with benefit, but also considerable side-effects. Steroid's alone are not an alternative to the use of ataluren but may complement this role.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The group of boys with nonsense mutation DMD, in particular, are treatable and have potential benefit from Atalauren

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

We already have established age specific Duchenne muscular dystrophy clinics. The use of this medication will not impose significant additional burden. Optimally, we would like to introduce six minute walk this as testing as a part of a physiotherapy assessment, though this is not essential.

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There are some boys with subsequent to the clinical trial I getting the medication provided free by the pharmaceutical manufacturer.
The manufacturer has also agreed to provide the medication to unaffected siblings on compassionate grounds, and it has been provided to one child to our service

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The evidence for clinical use of Atalauren in ambulant nonsense mutation DMD patients is based on the following article:
Ataluren treatment of patients with nonsense mutation dystrophinopathy.
Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, Connolly AM, Day JW, Flanigan KM, Goemans N, Jones KJ, Mercuri E, Quinlivan R, Renfroe JB, Russman B, Ryan MM, Tulinius M, Voit T, Moore SA, Lee Sweeney H, Abresch RT, Coleman KL, Eagle M, Florence J, Gappmaier E, Glanzman AM, Henricson E, Barth J, Elfring GL, Reha A, Spiegel RJ, O'donnell MW, Peltz SW, Mcdonald CM; PTC124-GD-007-DMD STUDY GROUP.
Muscle Nerve. 2014 Oct;50(4):477-87.

The methodology used in this study, in particular the randomised placebo-controlled control, and using six minute walking distance as outcome measure, is appropriate

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The Bushby et al 2014 study (Muscle Nerve. 2014 Oct;50(4):477-87.) Was for a treatment period of one year. The longer term outcomes are not known.
Another clinical trial of Atalauren is currently being concluded, with the aims of confirming the beneficial response seen in the first study.
There is optimism that they will be cumulative long-term benefit, not only on the skeletal muscle, but potentially also on the axial muscles (preventing or delaying scoliosis) and respiratory muscle (preventing or delaying respiratory failure and the need for ventilatory support). This however remains unproven for now.

The side-effects reported up to la have been minor, especially when compared with the currently use standard of care of management of corticosteroids.

A practical protocol of the use of Atalauren is as follows:
Translarna (Atalauren) protocol. (in development. AM 6th July 2015)
Indications: nmDMD above 5 yrs and ambulant. (non-ambulant boys who are sibs of nmDMD boys on PTC124 clinical trials as compassionate use, with drug provided by PTC Therapeutics)
Dose as per prescribing sheet according to body weight.

PTC recommended monitoring:
6 monthly BP for those on steroids
Annual: U&E and LFT, total Cholesterol, Triglyceride, LDL, HDL
Caution: Not to be given concomitantly with GENTAMYCIN

Clinic visit monitoring: Age and functional stage appropriate evaluation + the following translarna specific monitoring:
Ambulant: (the main indication)
Clinic visits monitoring (3 months to start with, then 6 monthly)
- Vital signs (BP)
- Blood tests (Annual: U&E and LFT, total Cholesterol, Triglyceride, LDL, HDL)
- Urinalysis
- (ECG)
- FVC
- Physio assessment – 6MWD + Rising time, 10m time, NSAA

Non-Ambulant: (currently, 2015, compassionate use in siblings with medication provided by the manufacturer)
Clinic visits monitoring (3 months to start with, then 6 monthly)
- Vital signs (BP)
- Blood tests (Annual: U&E and LFT, total Cholesterol, Triglyceride, LDL, HDL)
- Urinalysis

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Highly Specialised Technology Evaluation

- (ECG)
- FVC
- PUL (upper limb function as possible)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The additional results required is not significant. The boys with nonsense mutation DMD are already being followed up in our and other neuromuscular/neurology clinics, usually on a six monthly basis.
For doctors, learning the protocol for this new drug is relatively easy. The registration with the individual trusts drug and therapeutics committee/boards, takes some work but is routine.
For physiotherapy assessment of these patients, additional routine testing for six minute walk distance will be highly desirable to monitor long-term efficacy. Also the

recommendation would be to set up local audits, and audits through the Northstar clinical network for benefits and adverse effects of Atalauren, used on a long-term basis. These facilities are in place in most NHS services caring for boys with DMD.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; -
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts

I do not anticipate problems in the equality and diversity aspects.

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

Produced by ERG: Warwick Evidence

Authors: Peter Auguste, Research Fellow, Warwick Evidence, University of Warwick
Jill Colquitt, Partner/Senior Researcher, Effective Evidence LLP
Karoline Freeman, Research Fellow, Warwick Evidence, University of Warwick
Emma Loveman, Partner/Senior Researcher, Effective Evidence LLP
Andy Clegg, Partner/Senior Researcher, Effective Evidence LLP
Joshua Pink, Assistant Professor in Health Economics, Warwick Evidence University of Warwick
Martin Connock, Senior Research Fellow, Warwick Evidence, University of Warwick
Rachel Court, Information Specialist, Warwick Evidence, University of Warwick
Aileen Clarke, Professor of Public Health & Health Services Research, Warwick Evidence, University of Warwick
Paul Sutcliffe, Associate Professor, Warwick Evidence, University of Warwick

Correspondence to: Aileen Clarke
Director of Warwick Evidence
Head of Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry
CV4 7AL
02476 150189

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This report should be referenced as follows: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. A Highly Specialised Technology. Warwick Evidence, August 2015.

Contributions of authors: Paul Sutcliffe (Associate Professor) co-ordinated the project. Peter Auguste (Research Fellow in Health Economics) and Joshua Pink (Assistant Professor in Health Economics) conducted, reviewed and evaluated the cost-effectiveness evidence. Jill Colquitt (Senior Researcher) and Emma Loveman (Senior Researcher) co-ordinated and conducted the evaluation of the clinical effectiveness evidence. Karoline Freeman (Research Fellow) conducted the evaluation of the clinical effectiveness. Rachel Court (Information Specialist) conducted the evaluation of the Company searches. Martin Connock (Senior Research Fellow) undertook the survival analyses. Aileen Clarke (Professor of Public Health and Health Services Research) and Andy Clegg (Senior Researcher) contributed in peer review, summaries, conclusions and editing. All authors contributed to the writing of the report.

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Rosaline Quinlivan, Helen Roper and Kate Bushby provided clinical advice on the topic. Hannah Fraser and Pam Royle provided advice and input on formatting and referencing respectively.

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are [redacted]

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List of Abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse event
ANCOVA	Analysis of covariance
BiPAP	Bilevel positive airway pressure
BMD	Becker's muscular dystrophy
BSC	Best supportive care
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
cITT	Corrected intention to treat
CK	Creatine kinase
CS	Company Submission
CSR	Clinical study report
DH	Department of Health
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
ERG	Evidence Review Group
EU	European Union
GCP	Good clinical practice
GOSH	Great Ormond Street Hospital
HDL	High density lipoprotein
HRQoL	Health-related quality of life
HST	Highly specialised technology
HUI	Health Utilities Index
ICH	International Conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICTRP	International Clinical Trials Registry Platform
IPD	Individual patient data
ITT	Intention to treat
Kg	Kilogram
LDL	Low density lipoprotein
LoA	Loss of ambulation

LOCF	Last observation carried forward
LYG	Life-years gained
MCID	Minimal clinically important difference
MDUK	Muscular dystrophy UK
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MMRM	Mixed effect Model Repeat Measurement
mRNA	Messenger ribonucleic acid
6MWD	6 minute walk distance
6MWT	6-minute walk test
NA	Not applicable
NICE	National Institute for Health and Care Excellence
NUTH	Newcastle Upon Tyne Hospitals
nmDMD	Nonsense mutation Duchenne muscular dystrophy, or nonsense mutation dystrophinopathy in Study 007
nmDBMD	Nonsense mutation Duchenne/Becker's muscular dystrophy
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
ONS	Office of National Statistics
PedsQL	Paediatric Quality of Life Inventory
PPP	Purchasing power parity
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PTC	PTC Therapeutics Limited
QoL	Quality of Life
RCT	Randomised controlled trial
SAE	Serious adverse event
SAG	Scientific Advisory Group
SAM	Step Activity Monitor
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
TFTs	Timed function tests
TREAT-NMD network	Treatment of Neuromuscular Diseases network
TSQM	Treatment Satisfaction Questionnaire for Medication

UAA	Uridine-adenosine-adenosine
UAG	Uridine-adenosine-guanosine
UCL	University College London
UCLH	University College London Hospitals
UGA	Uridine guanosine-adenosine
UK	United Kingdom
US	United States of America
VA	Ventilation-assisted
WHO	World Health Organisation

1. SUMMARY

1.1. Background

Duchenne muscular dystrophy (DMD) is a severe, progressive, rare genetic childhood muscle wasting, X-linked recessive disorder affecting mainly boys. Prevalence data indicate that there are approximately 2200 patients in England diagnosed with DMD which results from various mutations in the gene encoding dystrophin. Patients with DMD have a rapid decline in physical function with subsequent gastrointestinal tract, respiratory and cardiac failure. Wheelchair use is needed from about 12 years of age in the majority of patients. The loss of use in the upper limbs causes complete loss of physical function by teenage years resulting in increased reliance on carers for tasks of daily living, feeding and personal care. Disease progression usually leads to death by the third to fourth decade of life.

Dystrophin is the main component of a complex set of proteins important for force transduction from muscle fibres and membrane stability. In DMD the production of dystrophin is affected from birth and symptoms appear by around the age of 3 years, although they may present earlier than this, even in infancy. The burden on parents of boys with DMD is substantial and this can lead to physical and mental problems in parents and caregivers. Quality of life of patients with DMD deteriorates as the disease progresses and physical capacity decreases.

The Duchenne Muscular Dystrophy Care Considerations Working Group have developed guidelines covering the diagnosis and management of DMD which recognises the different body systems affected and the secondary complications of DMD and describes provision of coordinated multidisciplinary care (involving diagnosis, treatment management (such as corticosteroid treatment and management of its side effects), orthopaedic management, psychosocial management (especially for behavioural disorders such as autism and ADHD), rehabilitation management, cardiac and respiratory management). Over the last few decades the treatment of DMD has been mainly supportive in nature.

More recently new treatment methods have emerged including read-through strategies for stop codons, exon skipping, and, although more experimental in nature, cell as well as gene therapy.

Nonsense mutation Duchenne muscular dystrophy (nmDMD) is a specific sub type of DMD and represents approximately 13% of the whole DMD patient population (286 children in England). The specific point mutation results in a premature stop codon within the dystrophin

gene and subsequently in premature termination of protein synthesis and production of non-functional protein. Ataluren (brand name Translarna™, Therapeutic class: M09AX03, WHO Temporary ATC code) is the first treatment to be licensed for use in nmDMD. Ataluren allows the ribosomes to read through the premature stop codon, whilst respecting the normal stop codon, to restore the synthesis of functional dystrophin protein.

Marketing authorisation was received on 31st July 2014. Ataluren has been commercially available in the UK since 4th September 2014. Ataluren is approved in the European Union under the European Medicines Agency centralised procedure. It is not licensed in any other country outside of the EU. To date there have been no sales of ataluren as guidance on its use has not yet been issued by NHS England. There are currently 18 centres that specialise in the management of DMD in England and Wales.

1.2. Critique of decision problem in the Company's submission

The decision question in the Company's submission (CS) matches broadly the question described in the scope. There are some minor variations of the CS from the NICE scope but the ERG has no concerns in terms of the intervention, the nature of the condition and the impact of the technology. There were slight concerns around the comparator as the main evidence is from a single multinational trial with expected heterogeneity in established clinical management. One outcome listed in the scope (lung function) was not measured in the trial as no measurable effect was expected in the patient group over the short time frame of the trial. Limited assessment was made of some other outcomes, such as ability to undertake activities of daily living, cardiac function, and time to wheelchair use. Monitoring and training were thought by the ERG to have been underestimated in terms of impact for implementation into clinical practice and cost to the NHS. However, the main concerns relate to the included patient population. Bias may have been introduced in the CS assessment due to different thresholds of ambulation used in the clinical and cost-effectiveness assessments and due to the inclusion of two patients with Becker's muscular dystrophy, a milder version of muscular dystrophy with a different rate of progression.

1.3. Summary of ERG critique of clinical effectiveness evidence

Despite some inadequacies in the searches undertaken and poor reporting of the study selection process to identify evidence, it was felt that the approach was generally appropriate and no studies meeting the selection criteria should have been missed. Eligible studies for the systematic review of clinical effectiveness included one RCT (study 007) and one cohort study (study 004).

The CS reported the efficacy of ataluren (40mg/kg/day) compared to placebo (or best supportive care) on the outcomes of 6MWD, timed function tests, accidental falls, myometry tests, step activity monitoring, wheelchair test, HRQoL and treatment satisfaction, digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase. The populations assessed were boys aged ≥5years with a diagnosis of nmDMD and an ability to walk at least >75 metres unaided. The clinical and statistical significance of results varied depending upon the outcome and statistical approach taken (i.e. type of ITT analysis). On the primary outcome of a change in 6MWD from baseline to 48 weeks, the benefit of ataluren compared to placebo only became statistically and clinically significant when a post-hoc corrected (cITT) approach was taken (ITT: difference 26.4m (p=0.09); cITT: difference 31.7m (p=0.02)). In the cITT analysis the baseline value for the 6MWD test was replaced with the screening values for two patients (one in the control group and one in the intervention group) due to ineligible baseline 6MWD values because of lower limb injury. This adjustment had substantial implications on the outcomes, moving results from statistically not significant to statistically significant. Subgroup analyses and secondary outcome analyses were based on this corrected (cITT) group.

Post-hoc sub-group analyses focusing on patients with a more severe condition (i.e. decline phase of DMD or a baseline of <350m 6MWD) identified that ataluren conferred a statistically significant benefit in limiting the reduction in the mean change in 6MWD compared to placebo. (Difference in reduction - decline phase: 45.6m (p=0.0096); baseline <350m 6MWD: 59.8m (p=0.0053)). However, the effects on patients with less severe disease were not reported and, as a consequence, the findings should be viewed with caution.

The evidence on secondary outcomes was more equivocal. Only time to climb 4 stairs (2.4 seconds vs. 4.8 seconds; p=0.02) and frequency of accidental falls (RR 0.38; 95% CI 0.16, 0.94; p=[redacted]) appeared to benefit significantly from ataluren compared with placebo. For all other outcomes, no statistically significant differences were reported.

Some uncertainty was identified around the completeness of reporting of outcome measures and estimates of statistics. Limited data or no data were presented for outcomes that were not statistically significant, for example: step activity monitoring, treatment satisfaction, cognitive ability, heart rate monitoring, serum creatinine kinase expression and dystrophin expression. In addition, a number of post-hoc adjustments to statistical methods and post-hoc analyses were undertaken which, despite being appropriately conducted, all appeared to favour ataluren compared to placebo.

Similar rates of adverse events were experienced by patients receiving ataluren and placebo. Data were not reported on safety and tolerability of the treatments and no deaths were reported from either study. A cumulative summary of serious adverse events from four ongoing and five completed company-sponsored clinical trials appeared to suggest that serious cardiac disorders, infections and infestations, injury poisoning and procedural complications and total number of serious adverse events are more common with ataluren than placebo, however it is not clear from the information provided whether this is due to longer exposure in the ataluren group.

Outcomes from the six patient submissions and the patient organisations Muscular Dystrophy UK and Action Duchenne were highly positive in nature and no known disadvantages to the treatment were reported. However, a reverse of benefits after stopping treatment was observed in one case. Key themes identified by the ERG included the emotional and social impacts of DMD, the anticipated effects of treatment, and the importance to carers of self-reliance and reduced burden No details on how generalisable these views are to the wider UK nmDMD community were reported.

1.4. Summary of evidence submitted on value for money

The Company's submission included a decision analytical semi-Markov model to compare the costs and benefits of ataluren with best supportive care versus best supportive care for people with nonsense mutation Duchenne Muscular Dystrophy. The model starts with a hypothetical cohort of children age 8.5 years and weighing approximately 25kg and simulates the clinical pathway for people with nmDMD. In each three-monthly cycle people incur costs and benefits depending on their health state and the cost consequences are assessed. The model time horizon was set at the time at which the last individual leaves the ambulant health state. The discount rate was 3.5% per annum. Results are presented in terms of mean costs and mean benefits, measured in QALYs. Information required to populate the model was obtained from various sources, with data on the treatment benefit of ataluren versus best supportive care mainly drawn from Study 007. One-way sensitivity analyses and scenario analyses were undertaken to determine the impact of changes in parameter values and assumptions on the base case results.

The initial model submitted by the Company estimated mean costs for ataluren and best supportive care of £5,092,540 and £235,207, with equivalent mean QALYs of 6.152 and 2.385, giving incremental costs and QALYs of £4,857,333 and 3.767. A revised model was subsequently submitted by the Company, which included improvements in the distributions used to extrapolate data forward over time. This model was found to have an error, but after

adjustment this 2nd model gave cost and QALYS estimates of £4,784,895 and 6.178 for ataluren, and £229,396 and 2.269 for best supportive care, with incremental costs and QALYs of £4,555,499 and 3.909.

Sensitivity analyses applied with a ±20% applied to variation in costs, utility values and discount rates were robust to changes except for the utility value for the ambulatory health state and changes made to the discount rate. The Company highlighted that the main driver of cost differences in the economic model was ataluren treatment costs.

1.5. Summary of ERG critique of value for money evidence

The ERG considered that the economic model developed by the Company included the appropriate health states and transitions, representing the natural disease progression of nmDMD. The ERG has concerns regarding deviation from the scope in the age of children entering the model (5 in the scope, 8.5 in the model) and the derivation of transition probabilities used for time to loss of ambulation, time to scoliosis, requirements for ventilation and time to death. The ERG were also concerned about the derivation of health state utilities and resource use assumptions particularly in relation to use of ventilatory assistance. Some of these concerns were addressed by the ERG in development of a preferred revised base case model, but others were not possible to assess quantitatively. These include:

- The assumption that the treatment benefit with ataluren is permanent, with the advantage over best supportive care found between weeks 24 and 48 of Study 007 continuing until people lose ambulation.
- The use of a linear extrapolation of mean difference in 6MWD, which relies on the assumption of a homogeneous population following the same trajectory of progression. Such an approach is not valid if this assumption is not met.
- The model assumes that no treatment effects occur with ataluren that would generate either costs or consequences.
- Treatment adherence to ataluren is assumed to be 100%, with no-one discontinuing treatment for any reason other than loss of ambulation.
- There are no additional costs for administration, training or monitoring related to ataluren treatment.

1.6. Summary of exploratory sensitivity analyses undertaken by ERG

We undertook further analyses exploring some of the assumptions that were made in the company model and checked the findings from the revised company model sent as part of clarifications. Modifications made to the company's model were:

- A lifetime horizon rather than until the last individual losses ambulation.

- The inclusions of the costs of 6 months of ataluren treatment post loss of ambulation, in line with clinical advice.
- Refitting of survival curves to the various sets of Kaplan-Meier data, using a log-normal distribution for time to loss of ambulation, and flexible parametric distributions for other transitions.

The ERG ran a number of different models, using different assumptions for the distributions used to extrapolate trial results over time. These generated incremental cost estimates ranging from £4,295,464 to £5,544,981 with a range of associated QALY estimates of 1.722-3.924. The ERG's best estimate of cost and QALYs, which uses a log-normal distribution for loss of ambulation, and the statistically best fitting models for all other events, includes treatment with ataluren for 6 months post loss of ambulation and a life time horizon, giving incremental mean costs of £5,544,981 and associated QALYs of 3.049. The ERG undertook additional analyses of budget impact taking account of the expected weight of patients with nmDMD likely to be eligible for ataluren use leading to estimates of an average annual budget impact of £19,069,166, as compared to the £12,223,821 reported in the initial Company submission.

1.7. Effects of technology beyond direct health benefits and on provision of specialised services

The ERG considered that the company presented appropriate wider societal costs and some potential savings for ataluren. However the ERG were concerned about the heavy reliance on the Landfeldt study for this and were concerned that these wider societal costs might be either under- or overestimated. Because of the uncertainty it was not possible to assess quantitatively which, if any, of these costs would be alleviated by the use of ataluren. The likely impact of ataluren on the delivery of the specialised services for DMD and for nmDMD in particular is not yet clear in a number of respects. The most important potential impact is the likely need for clinical input for additional monitoring and decisions on continuation and stopping of treatment.

A key criterion for the appraisal, and for the evaluation undertaken in the RCT and the CS was the definition of loss of ambulation. The NICE scope does not provide a clear definition. The RCT states that for inclusion in the study, a loss of ambulation relates to the ability of the patient to walk ≥75 metres. However, the Company's economic model adopted a different definition of loss of ambulation. Inevitably the different definitions may influence the outcomes of the assessment and it remains unclear which definition should be used in clinical practice. This is of importance as the suggested stopping rule for ataluren is based on the

definition of LoA. In addition, the ERG have been advised that the 6MWD test is not currently used in clinical practice. Consistency in applying the stopping rule would require implementation of, and training in the use of a standardised 6MWD test across the centres treating children and adults with nmDMD.

1.8. Summary of conclusions

The ERG consider that, given the immature evidence and the small size of the population, the Company submission presents a good report of available evidence and of the relevant trial. The evidence presented shows that ataluren appears to have some effect in limiting the loss of ambulation, however some uncertainty remains around whether it is statistically or clinically meaningful. On other measures, results were more equivocal due to a lack of transparency in the presentation of results or statistical significance. Patients, the public and consultees in general were very strong in their support of the introduction of ataluren and its perceived benefits. An appropriate model was provided by the Company and this (after corrections) suggested that total mean discounted costs were £4,784,895 for ataluren with best supportive care and £229,396 for best supportive care alone. At the treatment time horizon, ataluren produced 6.178 QALYs compared to best supportive care which produced a mean of 2.269 QALYs, giving incremental costs and QALYs of £4,555,499 and 3.909.

The ERG's preferred scenario model revision estimates resulted in total mean discounted costs of £5,744,175 for ataluren and £199,194 for best supportive care, and total mean discounted QALYs of 6.853 and 3.804. Mean incremental costs were therefore £5,544,981, and mean incremental QALYs 3.049. The ERG considered that there were a number of areas of remaining uncertainty in relation to assessment of the costs and consequences of the technology as well as in assessment of its likely impact beyond direct health effects.

2. BACKGROUND

2.1. Introduction

This chapter presents an overview of the treatment and management of nonsense mutation Duchenne muscular dystrophy (nmDMD) in ambulatory patients aged 5 years and older. The content of this chapter is taken from relevant literature, information provided by advisors (both clinical and NHS England specialist commissioners) to the Evidence Review Group (ERG) and information presented in the background sections of the Company Submission (CS). The European Medicines Agency (EMA) report (2015)[1] for ataluren for the treatment nmDMD and a summary of this report by Haas (2015)[2] both also provide helpful background. The chapter concludes with a critique of the background information provided in the Company's submission.

2.2. Nature of the condition

2.2.1. Duchenne muscular dystrophy

DMD is a rare, severe, progressive, wasting, genetic disorder of childhood affecting mainly boys.[3, 4] The main characteristics of DMD are a rapid decline in physical functioning with subsequent gastrointestinal tract, respiratory and cardiac failure.[5, 6] DMD causes progressive muscle weakness from early childhood, resulting in the loss of lower and then upper body function.

As decline in physical functioning progresses, wheelchair use is most often needed between ages 8-13.[7] Loss of walking ability (ambulation) tends to have a significant impact on quality of life (QoL) and is followed by increased deterioration in the loss of upper-limb mobility and self-feeding, as well as the need for breathing assistance. A more complete loss of physical function occurs from about mid teenage years of age, during this time patients become increasingly dependent on carers for tasks of daily living, feeding and personal care. The disease progression affects the respiratory muscles leading to breathing difficulties and ultimately the need for night time home ventilation[7] with most of those affected dying by their third to fourth decade of life.[8, 9]

DMD is caused by mutations in the gene encoding dystrophin, (deletions, duplications or point mutations in the dystrophin DNA). Dystrophin is the main component of a complex set of proteins important for force transduction from muscle fibres and for membrane stability.[10-12] A range of different mutations are found in affected patients with DMD. Some have a specific type of mutation termed a nonsense mutation which causes a single-point alteration in deoxyribonucleic acid (DNA), and which results in the presence of a premature stop codon in the protein-coding region of the corresponding messenger ribonucleic acid (mRNA). This premature stop codon causes the production of a shortened protein with loss of dystrophin protein function and consequently to disease.

The lack of production of dystrophin starts from birth and symptoms of DMD appear by around the age of 3 years although sometimes present earlier, especially when associated with substantial learning difficulty (range 8 to 72 months).[13]

In the initial stages prior to diagnosis, children usually have subtle symptoms of delayed walking or speech compared to their peers. Symptoms are often present but unrecognised. Mean age of first reported symptoms of DMD is reported as 32.5 months (2.7 years) with a range of 8–72 months, whilst mean age at genetic diagnosis is 51.7 months (4.3 years) with a range of 10–91 months.[13] A significant proportion of patients have learning difficulties, which may initially manifest as global developmental delay; these are non-progressive.[14]

From their late teens, patients with DMD will require ventilation support, initially at night. As their respiratory function continues to decline, ventilation support may be needed during the day. In the UK, ventilation is usually delivered by non-invasive ventilators..[15, 16] Cardiac involvement with cardiomyopathy is common and requires regular monitoring from diagnosis, with use of heart protection medication, usually from teenage years. In a recent study in the UK, a diagnosis of cardiomyopathy was reported in 52.4% of adults with DMD[17], while clinical expert opinion suggests this figure to be as high as 100% by 18 years of age (Dr Rosaline Quinlivan personal communication).

Boys with DMD tend to have increased risk of fractures and decreased bone density. A common cause of limb fractures is through accidental falling. Around 35 to 40% of lower-limb fractures are reported to result in permanent loss of ambulation (LoA).[18, 19] There is no clinical consensus about definitions of ambulatory and non-ambulatory status. Currently the NHS England Commissioning Policy considers an ambulatory patient to be one who can take any steps unaided. Non-ambulatory is defined as patients who have continuous indoor and outdoor wheelchair use.[20, 21]

Death usually occurs before the age of 30 years of age in patients with DMD.[22] The Swedish Cause of Death Registry suggested the mean age of death in Swedish patients with DMD between 2000 and 2010 was around 25 years (range 10 to 46 years), and death was mostly related to respiratory (35%) or cardiac (40%) failure.[23] Similarly, the mean age of death reported for patients in the UK with DMD who have received ventilator support was 25.3 years.[22]

In section 6.1, pages 43-45 of the CS, “five key stages” are described starting with pre-symptomatic to late non-ambulatory to define the disease progression and care.[9] It is recognised that children may progress through these stages at different rates. A summary of these stages reported by the Company are provided in Box 1.

Box 1. Five key stages defining the disease progression and care of DMD

1) *Initial stages prior to diagnosis:* Subtle symptoms of delayed walking or delayed speech compared to their peers. Symptoms are often unrecognised. Mean age of first reported symptoms of DMD is about 32.5 months (standard deviation (SD) 2.7 years; range 8–72 months). Mean age at genetic diagnosis is about 51.7 months (SD 4.3 years; range 10–91 months).[13]

2) *Early ambulatory stage:* Signs of DMD become more noticeable; these include four classical DMD motor signs that are major indicators: i) Gowers' manoeuvre: boys support themselves with hands on thighs when raising from floor; ii) Waddling-type of walking; iii) Toe-walking; and iv) Climbing stairs by bringing the second foot up to join the first rather than going foot over foot. Some patients may show specific difficulties with learning and behaviour although these symptoms tend to occur at more advanced stages of the disease.

3) *Late ambulatory stage:* Early symptoms get worse and walking becomes increasingly difficult. Children have more difficulties with getting up from the floor, climbing stairs and progressively lose their ability to walk. By the age of 8 years, most boys have difficulty arising from the floor and ascending stairs, and they often fall while walking.[24] Boys can enter a more rapid decline phase where over a year they have a substantial decline in walking ability.[25]

4) *Early stage of non-ambulation:* Children lose the ability to walk independently and become entirely wheelchair dependent (around 12 to 15 years of age in boys on steroids, median 12 years and 14.5 years when treated with intermittent and long-term daily corticosteroids, respectively; or between 8 to 12 years in steroid naïve boys).[5, 26-28] In steroid naïve boys, with disease progression and problems with posture, scoliosis develops as the back muscles weaken combined with wheelchair immobility. The boys receiving steroid treatment, posture and arm strength is initially maintained and can usually wheel the chair themselves for short periods of time. At this stage, patients start experiencing respiratory symptoms (e.g. poor cough and chest infections) and have an increased risk of heart deterioration.

5) *Late stage of non-ambulation:* Upper-limb function is decreased and maintenance of good posture is difficult, and complications are more common. Risks of respiratory and heart deterioration are high. Patients with DMD often die from respiratory or cardiac failure in their late teens or early adulthood.

2.2.2. Epidemiology

Prevalence data indicate approximately 2200 patients in England diagnosed with DMD[29, 30] with an overall estimated prevalence of 5/100,000 and a birth prevalence of 14.3/100,000 in the European Union (EU).[31] There are however considerable differences in the reported prevalence rate across different geographic regions.[32] Patients with nmDMD represent between 10 and 13% of the whole DMD patient population; which equates to around 2400 patients with nmDMD in the EU[2] and

approximately 286 patients in England. Based on this prevalence and according to the licensed indication for ataluren the CS estimated that current eligibility equates (page 47) to approximately "*66 people*". Supplementary information from NHS England[32] suggests that the incidence of nmDMD represents about 10 new cases per year in England with a total nmDMD population of approximately 250 patients. However, recent estimates based on actual numbers suggests a slightly smaller number - about 8 new cases per year. NHS England estimated that the number of patients in England for whom ataluren treatment might be indicated is approximately 80; but also noted this as a possible slight overestimate.[32]

The CS reports that: *'in the last 10 years survi*val rates *in patients with DMD have improved'* due to more comprehensive therapeutic approaches. They also state that, "*age at loss of ambulation is associated with time to respiratory failure and age at death in patients with DMD* (page 48)'.

NHS England provide a concise summary of the epidemiology of DMD in their recent publication: "Clinical Commissioning Policy: Ataluren for the treatment of nmDMD"[32] They also provide more information on girls and adults with DMD including that girls carrying the mutation rarely have phenotypic symptoms "*except in very rare cases (8%) of female carriers who show progressive muscle weakness in adult life (Barkhaus 1989)"* and that ambulation (a predictor of disease progression) varies according to age: *"Up to age 9 years around 95% of patients will be ambulatory whereas after age 20 around 95% of patients will be non-ambulatory (Henricson 2013; Ricotti 2011)."*[32]

2.2.3. Aetiology

As stated previously DMD is caused by mutations in the gene encoding dystrophin, a structural protein that stabilises muscle cell membranes and is responsible for healthy muscle structure and function. These mutations can involve deletions, duplications or point mutations in the dystrophin DNA. In nmDMD these point mutations produce a premature stop codon which causes termination of protein synthesis resulting in truncated, non-functional proteins. Muscles in patients without dystrophin are exposed to stresses during muscle contraction and are not protected from degeneration which leads to muscle weakness and atrophy (wasting).

2.2.4. Diagnosis

Children are usually diagnosed at around 3-4 years of age, but diagnosis can be earlier if delays in meeting developmental milestones are noted (e.g. speech and walking alone). Once DMD is suspected on the basis on these developmental delays, diagnosis of DMD is made using genetic testing in a two-staged process. The first step looks for deletions and duplications in the dystrophin gene using multiplex ligation-dependent probe amplification (in about 70% of DMD patients) (K. Bushby

personal communication). If this is negative, gene sequencing is undertaken in order to identify single point mutations including nonsense mutations. In the UK genetic sequencing is currently conducted at two centres (Guy's and St Thomas' in London and Yorkhill in Glasgow). This second line test is required to identify patients for whom ataluren might be indicated. First and second line tests are usually undertaken on the same sample and no tests additional to standard management would be required to identify eligible patients for ataluren treatment. There are programmes to increase awareness to allow earlier diagnosis of DMD, permitting earlier potential treatment and genetic counselling for families.

Furthermore, it was been reported that DMD is often diagnosed late, which in turn has a negative effect on access to potential recruitment into clinical trials, genetic counselling and standards of care.

2.2.5. Current standard of care

Standards of care for the diagnosis and management of DMD are available and have been produced in two publications by Bushby et al. accredited by the National Institute for Health and Care Excellence (NICE) (2010).[8, 9] The standards focus on the importance of multidisciplinary care for patients with DMD and provide care recommendations for coordination by a neuromuscular consultant (with input from e.g. a respiratory paediatrician, paediatric cardiologist, physiotherapist, psychologists, neuromuscular specialists, community paediatricians, orthopaedic and spinal surgeons, dieticians, speech and language therapists, neurologists, pulmonologists, nutrition specialist, physiotherapists, and cardiologists).

Very broadly the standards require:

- Precise genetic diagnosis should be actively sought in all cases for diagnosis of DMD
- Pharmacological management of DMD is by use of glucocorticoids following the provided framework to allow greater consistency
- Psychosocial care should be placed at the centre of management
- Complications of the gastrointestinal tract should be proactively managed
- Timing, level of expertise and type of interventions listed for physical therapy, nutritional, swallowing, and speech / language management should be followed
- Clearly staged assessments and interventions to address cardiac and respiratory complications should be followed to allow a structured, proactive approach

Despite the availability of standards many patients with DMD in the EU do not receive the desired care.[33]

Patients with DMD are required to see a large number of healthcare professionals (e.g. psychologists, neuromuscular specialists, paediatricians, orthopaedic surgeons, neurologists, pulmonologists, nutrition specialist's, physiotherapists, and cardiologists).[33] The EMA (2015)[33] reports that without adequate coordination of the multidisciplinary team, patients with DMD and their parents can waste time travelling to and from hospital, impacting on work, social activities, sports and their families. Furthermore, it has been reported that DMD is often diagnosed late.[13]

In the UK care for DMD patients is fairly standard. All paediatric centres belong to the North Star Network (see section 2.5 for more detail) and provide a similar standard of care. All North Star centres provide access to psychology support and specialist physiotherapy support but in other centres this is variable. On the other hand there are reported to be substantial deficiencies in the comprehensiveness of treatment for adults with DMD in the UK (Dr Rosaline Quinlivan personal communication).

2.2.6. Impact of the disease on carers' quality of life

Since there is no cure for DMD, current management focuses on prevention and management of complications.[2] Carers of children with DMD witness the increasing needs of those affected due to symptoms of muscle weakness and the decline in ability to walk. Maintenance of independence is likely to be of substantial importance to both children with DMD and their carers, since in the UK, 98% of caregivers of DMD patients are the parent and 49% of caregivers had reduced their working hours or stopped working completely to care for a family member with DMD.[34]

Section 7 of the CS (page 48) describes the burden on the parents and carers of boys with DMD. It states that: "*Parents of children with DMD report a high burden of care from an early age, not only compared to healthy children but also compared to children with other chronic disorders. Only parents of children with multiple complex handicaps score higher (EMA, 2015).*" And that *"it is not unusual that parents of DMD boys and young men have to wake up 6-10 times per night to help to adjust their sons' position in bed, help with ventilation and/or coughing (EMA, 2015)".*

In addition, those affected may also suffer from behavioural issues resulting in high levels of stress in parents of boys with DMD[35] and psychosocial challenges for the family.[36] The CS also reports that *"parents experienced greatest emotional impact of their child's DMD around the time of loss of ambulation (Bray, 2011)."*

2.2.7. Impact on patients' health-related quality of life

The CS (section 7.1, page 47) summarises the health related quality of life for patients with DMD as follows:

"Boys with DMD consistently report significantly lower quality of life (QoL) than their healthy peers (Uzark, 2012; Bendixen, 2012). In a study that assessed QoL in 117 boys with DMD using the PedsQL mean scores for boys with DMD were significantly lower than those for healthy children for physical and psychosocial scores ($p<0.001$), including emotional, social, and school functioning, by both parent-proxy and child self-report and across all age groups (Uzark, 2012). By self-report, 57% of all children 8 to 18 years of age had Psychosocial Health Summary scores below 66.03, the cut-off point for significantly impaired QoL in the general paediatric population. With respect to physical functioning or symptoms, the most frequently reported problems were not being able to run (68%) or walk more than one block (57%). Anger was the most frequently reported emotional problem reported by the boys (19%) and perceived by their parents (15%). In the teenage boys, 14% also reported frequently worrying about what was going to happen to them. One in 5 boys (19%) frequently worried about their family and about being treated differently from their peers (20%). With respect to Social Functioning, the most common problem was not being able to do things others their age could do (40%). While boys reported frequent problems with paying attention (13%), the most common school problem was missing school to go to the doctor or hospital (20%) (Uzark, 2012).

Quality of life deteriorates as the disease progresses and physical capacity decreases. With advancing age, boys report decreased physical functioning and daily activities (Uzark, 2012; Simon, 2011; McDonald, 2010c). Patients with more severe disease requiring mobility aids or having greater impairment of daily activities do not necessarily perceive worse psychosocial QoL although, not surprisingly, the use of wheelchairs and ventilators has been shown to be significantly associated with lower QoL related to physical functioning (Uzark, 2012; Baiardini, 2011)."

QoL is also affected by complications due to treatment with corticosteroids. These include the usual anticipated complications of steroid treatment including for example central abdominal weight gain, psychological sequelae, short stature, disruption to normal pubertal maturation, Cushingoid facial signs, cataracts and propensity to increased likelihood of infection.[8]

2.2.8. Extent and nature of current treatment options

In the recent Clinical Commissioning Policy document produced by NHS England (2015)[32] current treatment options are summarised as limited and mainly supportive.

Life expectancy and clinical outcomes in patients with DMD have significantly improved over the last 10–15 years through nocturnal ventilation, steroid treatment, and cardiac support, as outlined by the

NICE accredited Care Standards for DMD.[8, 9, 22] A boy diagnosed with DMD today and managed according to these Care Standards has a good chance of living well into his 30s.[13]

According to the CS, one of the most important treatment objectives identified by patients, caregivers and clinicians, is to slow the progression of the disease. Box 2 provides a summary of the current supportive treatments, interventions and additional options for DMD affected children and their families.

Box 2 Current supportive treatments, interventions and additional options for DMD affected children and their families

Current supportive treatments, which aim to alleviate symptoms and manage complications, are:

- Corticosteroids
- Orthopaedic devices
- ACE inhibitors and beta blockers for cardiomyopathy
- Surgery
- Ambulatory assistance
- Mobility assistance – e.g. wheelchairs
- Artificial ventilation

Current interventions by age and stage can be summarised as follows:

- Early childhood:
  - treatment with steroids
  - cardiac and respiratory monitoring
  - occasional inpatient orthopaedic intervention
- Later childhood and teenage years:
  - inpatient spinal surgery and rehabilitation for some patients (this is less common for those on steroids than steroid-naïve patients)
  - increased need for inpatient orthopaedic intervention
  - continued cardiac and respiratory intervention
  - inpatient episodes for treatment of respiratory complications.

In addition, dietetic advice and, in some cases, gastrostomy feeding, prevention and treatment of bone fragility and management of complications of long-term steroid therapy are all required, as well as psychosocial support. Genetic counselling and testing with antenatal diagnosis are offered to all families with affected children.

Source: Adapted from the CS

Even though steroids are the main pharmacological management option in DMD, there is reported to be uncertainty around the appropriate time to initiate corticosteroids, whether to continue their use in

non-ambulatory boys, and the use of intermittent or daily dosing.[8] Furthermore, because of side effects, corticosteroids are not tolerated by all patients for which no effective treatment is currently available.

In summary, over the last few decades the treatment of DMD has been mainly supportive in nature. In addition to ataluren other treatment options which aim to restore the expression of dystrophin may be on the horizon.[37] Intravenous or subcutaneous drugs are being tested which aim to restore the expression of dystrophin by a process called exon skipping (for patients who carry a deletion in the gene and will therefore not be effective for patients with a nonsense mutation) which involves skipping over the DNA region that contains the mutations and results in a truncated but functional dystrophin protein.[37] Gene therapy works by introducing the missing dystrophin gene into the patient. However, several issues still remain before clinical trials are feasible. These include immunogenicity of the viral vector that carries the gene into the system, the size of the dystrophin gene as well as targeting the gene to all muscles.[38]

Cell therapy uses stem cells that have the potential to restore dystrophin production in DMD patients. These come either from DMD patients following genetic modifications in vitro or from individuals with functional dystrophin. Similar challenges remain including targeting of muscles either by injection or via the circulatory system as well as immunogenicity. These technologies are still at an early stage of development and require further research into feasibility and safety.[37] To date exon skipping and suppression of stop codons appear to offer the most promising approaches for increasing dystrophin expression in patients with DMD.[37]

2.3. Description of the technology under assessment

Ataluren is an orally administered small-molecule compound that is considered as a treatment for all ambulatory patients aged 5 years and older with nmDMD resulting from a nonsense to be added to existing standard treatment. Ataluren is dosed according to the patient's weight achieve a final daily dose of 40 mg/kg which is divided into three doses across each day.

shows the dosing instructions for the drug. The ERG provides a full evaluation of the trials involving ataluren in section 4.2. Further consideration of the expected place of ataluren in current practice, the advantages and disadvantages of the technology, relevant evidence, and implementation and equality issues can be found in the summary of the expert submissions in section 4.5.5.

Table 1 Dosing instruction for ataluren

Pharmaceutical formulation	Granules for oral suspension (125 mg, 250 mg, 1000 mg sachets)
Method of administration	Oral
Doses	The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).
Dosing frequency	Three times a day (morning, midday, and evening). Recommended dosing intervals are 6 hours between morning and midday doses, 6 hours between midday and evening doses, and 12 hours between the evening dose and the first dose on the next day.
Average length of a course of treatment	Not applicable. Long term chronic therapy
Anticipated average interval between courses of treatments	Not applicable. Long term chronic therapy
Anticipated number of repeat courses of treatments	Not applicable. Long term chronic therapy
Dose adjustments	No studies have been conducted with ataluren in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely. No dosing adjustment is needed for patients who are becoming non-ambulatory.

Reproduced from CS Table A2.1 page 36

2.3.1. What is the principal mechanism of action of the technology?

Ataluren (brand name Translarna™, Therapeutic class: M09AX03, WHO Temporary ATC code) is the first treatment to be licensed for use in nmDMD. Ataluren allows ribosomes to read through the premature stop codon diagnostic of nmDMD, whilst respecting the normal stop codon, thus restoring synthesis of functional dystrophin protein.

2.4. Current usage in the NHS

Marketing authorisation was received on 31 July 2014. Ataluren has been commercially available in the UK since 4th September, 2014. Ataluren is approved in the EU under the EMA centralised procedure. It is not licensed in any other country outside of the EU. To date there have been no sales of ataluren as guidance on its use has not yet been issued by NHS England. According to the CS, there are currently 18 centres that specialise in the management of DMD in England and Wales (see Appendix 1 for a list of centres).

In section 8.7, page 64 of the CS, the Company discuss whether any additional tests or investigations are needed for the selection of patients, or particular administration requirements, associated with using the technology over and above usual clinical practice. In summary no additional tests are believed to be required to identify patients eligible for treatment with ataluren.

Monitoring of ataluren treated patients is considered in section 8.2.3.

Currently NHS England[32] has a policy statement which suggests that since ataluren is being considered by NICE as a Highly Specialised Technology Evaluation to test the benefits and costs, it will not be commissioned until the outcome is known. NHS England also state that '*Where an individual's clinician believes that there may be exceptional clinical circumstances that might warrant consideration of funding outside of this policy, an application can be made under NHS England's Individual Funding Request (IFR) procedure'.*

2.5. Critique of background information provided in the CS

The ERG consider the background information provided by the Company to be fair, comprehensive and appropriate, and the ERG clinical advisors agree that this is an accurate overview of the condition relevant to the decision problem.

The Company provide a detailed coverage of the underlying nature of DMD, the prevalence as well as the epidemiology of DMD and a concise coverage of the underlying aetiology of DMD.

The provided information directly related to nmDMD was limited and it is unclear whether at times the terms DMD and nmDMD were being used interchangeably due to limited evidence on nmDMD.

The CS did not discuss diagnosis of DMD in the background but touches on the benefits of early diagnosis to maximise the treatment effect of novel treatments, i.e. ataluren if approved.

The CS provided some relevant information about the impact of the DMD on the carers' QoL. The specific impact on carers' quality of life in nmDMD specifically remains unclear. No QoL data for carers was presented.

A concise overview of the impact of DMD on the health related quality of life (HRQoL) in boys was provided. However, it is unclear whether the impact of DMD on the QoL in girls, which make up a more diverse group with a variable degree of disability, is the same to that reported in boys with this condition and whether this can be extended to patients with nmDMD.

Finally, the Company could have referred to the North Star Clinical Network which was set up in 2003 to help improve services and set national standards of care for children living with DMD.[39] The North Star Project aims to optimise the care of young people with DMD through consensus on best clinical management, with agreed assessment and treatment protocols, regardless of which clinical centre is attended. The North Star Clinical Network consists of lead consultants, senior physiotherapists and other allied health professionals from paediatric tertiary centres across the UK. Many hundreds of children with DMD are registered with these centres. A national database was established in October 2006 by Professor Francesco Muntoni (Head of the Dubowitz Neuromuscular Centre, Institute of Child Health [ICH], University College London [UCL]) and Dr Adnan Manzur (Dubowitz Neuromuscular Centre, Great Ormond Street Hospital [GOSH] to collect data from children with Duchenne muscular dystrophy followed in all the major paediatric neuromuscular centres in the UK. The data base provides standardised clinical data for patients with DMD and enables novel insight on the current natural history of DMD[40] and facilitates audits to improve the standards of care.[5]

3. CRITIQUE OF INTERPRETATION OF THE DECISION PROBLEM

3.1. Introduction

The objective of this section is to critique to what extent the CS adheres to the final NICE scope. The scope aimed to evaluate the benefits and costs of ataluren within its marketing authorisation for treating DMD resulting from a nonsense mutation in the dystrophin gene. The critique will consider the intervention, population, comparators, outcomes, nature of the condition, impact of the new technology and the cost to the NHS and Personal Social Services addressed in the CS.

3.2. Adherence to the decision problem

The CS states in its statement of the decision problem (Table A1.1, pages 31-32) that the submission does not deviate from the NICE scope in any of its factors. Table 2 presents a summary of the decision problem as set out in the NICE scope and some comments from the ERG considering the CS. It should be noted that the table presented within the CS differs slightly from the factors included in the final NICE scope. Factors added included "subgroups to be considered". 'Impact of the new technology' was omitted from the CS table and 'other considerations' were rephrased to 'special considerations including issues related to equality'.

Table 2 Comments on the adherence of the CS to the NICE decision problem

	Final scope issued by NICE	**ERG comments on submission in relation to the scope**
Intervention(s)	Ataluren	The CS focuses on the 10, 10, 20 mg/kg/day dosages of ataluren as the higher doses of 20, 20, 40 mg/kg/day failed to achieve a clinical effect. (This inverse dose-response relationship was explained by a bell-shaped dose response of ataluren).
Population(s)	People aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk	As DMD is an X-linked recessive disorder affecting predominantly males, the submission only included boys in the assessment. The effect on girls with the same condition was not considered. Ability to walk for trial inclusion was defined as ≥75 metres unassisted in 6MWD test, while ability to walk in the

		Company's model was defined as >0 metres in the 6MWD test. The cost-consequence model submitted used a cohort of children beginning at age 8.5, rather than age 5.
Comparators	Established clinical management without ataluren	The main trial 007 was a multinational trial, therefore the established clinical management is expected to be very heterogeneous
Outcomes	The outcome measures to be considered include: walking ability (ambulation) muscle function muscle strength ability to undertake activities of daily living cardiac function lung function time to wheelchair number of falls mortality adverse effects of treatment health-related quality of life	The main trial 007 did not measure lung function, hence there is no evidence on this outcome available which is more closely associated with mortality than walking ability and muscle function. However, this would possibly require longer follow up than 48 weeks. At home activity and heart rate were measured in the main trial 007, but results were not reported in the CS. No data on mortality is available from the trial 007. This needed to be extrapolated for modelling.
Nature of the condition	Disease morbidity and patient clinical disability with current standard of care. Impact of the disease on carer's quality of life Extent and nature of current treatment options	Carers' quality of life was not measured formally, but utility decrements for carers were included in the cost-consequence model.
Impact of the new technology	Clinical effectiveness of the technology Overall magnitude of health benefits to patients and, when	No variation

	relevant, carers heterogeneity of health benefits within the population Robustness of the current evidence and the contribution the guidance might make to strengthen it treatment continuation rules (if relevant)	
Cost to the NHS and Personal Social Services (PSS), and Value for Money	Budget impact in the NHS and PSS, including patient access agreements (if applicable) Robustness of costing and budget impact information Technical efficiency (the incremental benefit of the new technology compared to current treatment) Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	Monitoring of ataluren treatment was stated to be minimal and costs were therefore not included**.**
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	Whether there are significant benefits other than health Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services The potential for long-term benefits to the NHS of research and innovation staffing and infrastructure requirements, including training	Training of staff not fully covered in the CS

	and planning for expertise	
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The CS noted: *"A positive review [will] ensure that patients with rare diseases are not discriminated against, especially when there are no other treatments available that address the underlying cause of the disease."*

3.3. Detailed critique of adherence to the decision problem

3.3.1. Population

The population in the clinical section of the CS considers boys aged 5 years or more with the ability to walk at least 75 metres unassisted which is based on trial 007. In contrast the cost-consequence analysis included patients aged 5 years and older with an ability *"to walk some distance (i.e.6MWD > 0)"* (page 154).

In terms of gender the decision to include girls in the cost-consequence analysis appears clinically justified as it seems unlikely that girls should not be affected in a similar way as boys even though there is no evidence on the effectiveness of ataluren treatment in girls. However, manifesting carriers are milder forms of nmDMD and patients are likely to be older.

The NICE scope does not provide a definition for 'ability to walk'. In the CS there is inconsistency between the clinical (at least 75 metres unassisted) and cost consequence (walk some distance) assessments concerning the definition of 'ability to walk'. Clarification received from the Company on the definition of LoA confirmed that:

"LoA is defined [in the submission] as the point at which patients become completely confined to a wheelchair for indoor and outdoor use: they are unable to take any steps unaided)" and that *"there does not appear to be a clear definition of "ambulatory" patients in the published literature".*

In summary, the clinical evidence section uses a higher threshold for defining ability to walk (>75m 6MWD unassisted) compared to the cost effectiveness section (>0m 6MWD). This will potentially result in an overestimation of outcomes for those with a 6MWD of more than zero but less than 75m

as although this patient group was not included in the trial they are assigned equal benefit in the model. It is unclear how ability to walk should be defined in clinical practice if ataluren is approved.

The CS table states that the NICE scope does not specify any subgroups and that the CS does not deviate from the scope. However, it should be noted that age is an important covariate and that the submission identifies boys under 7 year old as the ones with the greatest potential to benefit, whilst boys > 7 years who have entered the 'decline phase' as those who experience the greatest measurable effect. In fact, the submission relies heavily on a post-hoc subgroup analysis of the latter group for the argument of a statistically significant treatment effect of ataluren. The Company has initiated a Phase 3 randomised, placebo controlled trial of patients in the 'decline phase' (trial 020) to be completed by the end of 2015. The 7-year cut-off for this analysis was directly derived from analysing the data of study 007. This is notably different to the more arbitrarily 9-year cut-off chosen for the pre-specified sub-group for stratification and sub-group analyses to investigate the impact of age on the study outcomes. (See also section 4.2.3) This was explained in the CS by the fact that this pivotal study contributed knowledge on the natural history of nmDMD which was not available before the trial.

The main evidence provided in the Company Submission is based on a single pivotal multinational RCT (study 007)[41] which evaluated the efficacy and safety of ataluren in two doses compared to best supportive care in boys 5 years and older with DMD and the ability to walk at least 75 metres. The trial recruited from 11 different countries including the UK, US, Italy, Australia, Germany, Canada, France, Sweden, Spain, Belgium, and Israel. 14/114 (12%) patients included in the ataluren 40mg/kg/day and placebo groups were from the UK. The submission was unclear about the proportion of patients from the additional countries. It stated that trial 007 included seven patients in each treatment group from the UK (page 75). It is therefore difficult to assess to what extent the studied patient population reflects the patient population in England and Wales. Clarification received from the Company included the make-up of the nationalities and ethnicity of the included subjects which is summarised in Table 3 below.

Table 3 Demographics of included patient in the ataluren 40mg/kg/day versus placebo trial

Country	**Number of subjects**
Australia	8
Canada	5
Israel	3
US	51
Europe	47
Belgium	2

Ethnicity	**Number of subjects**
Caucasian	107
Asian	2
Black	1
Other	2
Hispanic	2
Total	114

France	5
Germany	7
Italy	6
Spain	5
Sweden	8
UK	14
Total	114

Overall, it appears that the study population largely reflects the population in the UK but applicability to minority ethnic groups might need to be viewed with caution.

It is also noted that Trial 007 included patients with Becker's muscular dystrophy (BMD). In Table C9.6, page 75 of the CS they state: *"The number of Becker patients in Study 007 was very small in number, estimated to be ~2 patients; estimation based on published criteria, i.e., ambulatory ability at >15 years of age."*

It remains unclear which trial arm these "~2 patients" with BMD were assigned to. This is of concern as these two conditions differ in severity (the condition is generally milder and more varied in Becker's MD), age of onset, and rate of progression. A clarification question posed to the Company asking for a sensitivity analysis which excludes those two patients received the following response from the Company:

"All patients met all the criteria for entry to the study including having the presence of a nonsense mutation in the dystrophin gene. The variability in phenotype of patients diagnosed with BMD is wider than that seen with DMD. The diseases may be considered part of the same spectrum, therefore we believe that it is inappropriate to distinguish the results of these two patients from the others.

The results from the ACT DMD Phase 3 study (ongoing Study 020), looking at a larger group with less variability will confirm the treatment effect."

This response contrasts with the opinion of clinical experts who stated that patients with Becker's MD should not have been included in the trial (K. Bushby personal communication). The ERG has concerns that the inclusion of patients with milder symptoms and slower progression of disease may not fully reflect the scope and could also have the potential to bias results in favour of ataluren.

3.3.2. Interventions

There is no variation between the technology as described in the submission and in the NICE scope which is also in line with the licence agreement.

"Ataluren (Translarna™) is licensed for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (Translarna SPC, 2014). Ataluren received marketing authorisation from the EMA in July 2014 and has been commercially available in the UK since September 2014. Marketing authorisation was received 31st July, 2014." (page 15).

Please refer to

in section 2.3 for dosing information of ataluren.

3.3.3. Comparators

The comparators described in the CS match those described in the final scope. The ERG recognise that the Company have consulted with clinical experts. Clarification received from the Company confirmed that one of whom (Dr Rosaline Quinlivan, Consultant Paediatric Neurologist) advised on aspects of the clinical management of DMD. It is noted by the CS in section 9.1.1, page 66 that *"for the purposes of this review, best supportive care includes treatment with corticosteroids, as well as pharmacological therapy for the management of associated cardiac, pulmonary, orthopaedic and gastrointestinal complications."* The main trial 007 was a multinational trial therefore clinical management is expected to be heterogeneous.

3.3.4. Outcomes

The outcomes in the CS match broadly those described in the scope. The 6MWD is the primary outcome in the main trial 007. Prior to this trial there had been no established primary or secondary endpoints for studies in DMD patients. A 30 metre change in the 6MWD test versus placebo has been used in other trials for other conditions and is generally accepted as clinically relevant.[2] In section 9.9.2, page 130 the Company state *"Given that ambulatory compromise is a key component of the DMD disease process and that ambulation measures the function of multiple muscle groups as well as cardiovascular activity, ambulation-related outcome measures are the most relevant end-points in DMD patients who are still able to walk."*

The CS states on page 132: *"Evidence of the effect of ataluren on walking ability (ambulation),*

muscle function, muscle strength, ability to undertake activities of daily living, cardiac function, adverse effects of treatment and health-related quality of life has been presented." However, in terms of 'ability to undertake activities of daily living' and 'cardiac function' the Company only states on page 108: *"Other outcomes such as digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase expression showed similar results across treatment groups and differences were not statistically significant."* The ERG consider that this provides insufficient detail on these outcomes. Clarification received from the Company indicated that the timed function tests (TFTs) measure physical function and are approximate measures of the ability of patients to perform brief activities. Clarification also referred the ERG to the CSR, Section 11.4.1.4.3 for the outcomes of the heart rate monitoring.

Number of falls was reported.

No outcomes on lung function were considered as these were not measured in the trial as this outcome is not likely to change significantly in ambulant patients.

There appears to be potential evidence of selective reporting of outcomes.

[redacted] is reported in the CSR p. 95, but not in the CS. For more details on outcomes and appropriateness of outcome measures see section 4.2.4.

3.3.5. Cost to the NHS and PSS, and value for money

The training of staff that will be required for assessing patients on ataluren was not fully covered in the CS. As noted by the specialised commissioning expert, training will form an important part of the implementation of ataluren in order to measure 6MWD accurately, reliably and consistently across centres if it is going to be used as a stop criterion (E. Jessop personal communication).

The 6MWD test is currently not used in the assessment of ambulation in clinical practice. Approval of ataluren would also require the implementation of a standardised method of assessment of ambulation in clinical practice.

3.4. Summary of critique of Company's interpretation of decision problem

In summary, there are some minor variations of the CS from the NICE scope. Bias may have been introduced in the CS assessment due to different thresholds of ambulation in the clinical and cost-effectiveness assessments and due to the inclusion of two patients with Becker's MD.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

This chapter evaluates the presented evidence of the clinical effectiveness in seven sections. Section 4.1 assesses the appropriateness of the methods employed for the systematic review in the CS in terms of searches, study selection, data extraction, quality appraisal and evidence synthesis. Section 4.2 evaluates the available trial evidence in terms of baseline characteristics, quality of included studies, the statistical methods employed by the trials, the outcome measures selected in the trials and the reported results. It also considers unpublished studies as well as ongoing trials. Sections 4.3 and 4.4 provide a summary and critique of the Company's Submission and reported results. Section 4.5 presents evidence from other submissions, namely NHS England, patient organisations, carers and patients, and experts. Section 4.6 reports additional work undertaken by the ERG on the clinical effectiveness evidence and section 4.7 concludes the entire chapter.

4.1. Critique of the methods of review(s)

This section assesses the appropriateness of the methods employed for the systematic review in the CS in terms of searches, study selection, data extraction, quality appraisal and evidence synthesis.

4.1.1. Searches

The Company's main set of searches were very broad and aimed to find both RCTs and observational studies of ataluren, corticosteroids or other pharmacological therapies for the management of DMD. Searches were limited to English and were undertaken on 17th July 2014 in the following medical databases: MEDLINE and Embase (via EMBASE.com); MEDLINE In-process (via PubMed); and CENTRAL (via the Cochrane Library). One term for best supportive care was included, but no synonyms. The search terms and lines appear to have been combined appropriately. The searches were updated on 8th June 2015 in the same databases, but via different interfaces (Ovid and EBSCO) and just for ataluren in DMD. This was confirmed through clarification. While this is highly likely to have resulted in more recent (published post 17th July 2014) studies of corticosteroids or other pharmacological therapies being missed, these update searches were appropriate for retrieving studies on ataluren in DMD. The Company searched one trial register (clinicaltrials.gov) and Company sponsored trials were also checked for ongoing studies. It is unclear when these additional searches were undertaken, but an independent search for unpublished trials conducted by the ERG on 4th August 2015 via the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) found no additional trials on ataluren in DMD. No other supplementary search techniques or sources are reported.

4.1.2. Inclusion Criteria

The inclusion criteria for the review were appropriate but somewhat broad. The population

appropriately consisted of patients with DMD. However, both ataluren and best supportive care were listed in the selection criteria as interventions rather than intervention (ataluren) and comparator (best supportive care). Therefore no comparator was listed in the selection criteria. The ERG believes that this resulted in the broad search and the high number of full texts needed to be screened (n=332) and the resulting 281 studies "*that met the broad review inclusion criteria"* (page 66). (Clarification received from the Company stated that this number should read 115 [113 studies from search plus 2 CSRs] because 168 studies were excluded that were not available for a full text screen). The CS was not clear about why such a broad view was taken. All outcomes available were considered and eligible study designs were very inclusive. The review restricted study inclusion to English language studies and did not place any restriction on publication date. The review excluded studies assessing physical and psychosocial therapies.

The study selection process was not transparent and was poorly reported. The provided PRISMA diagram (Figure C9.1 on page 68) showed several inconsistencies and the ERG felt the need to request excluded full texts for spot checking. The main issues were:

1. the high number of records excluded on the basis of study design (n=405) even though according to the inclusion criteria, study designs included spanned RCTs, controlled trials, observational studies, retrospective trials and registries.
2. A number of RCTs (n=34) and non-RCTs (n=72) were excluded on the basis of the intervention after they had been included once full-texts had been assessed.
3. Inconsistencies in the reason for exclusions and reported inclusion/exclusion criteria.

Clarification provided by the Company listed the following categories with corresponding numbers of excluded studies, which contradicted the PRISMA flow diagram in terms of the 8 RCTs evaluating ataluren. Clarifications also provided full lists of excluded studies for each category.

"Clinical literature search (July 2014)

- *Studies excluded at 1st pass (duplicates n=206 plus excluded n=1911)*
- *Studies evaluating interventions other than ataluren for which full texts were not freely available (n=168)*
- *Full text articles excluded at 2nd pass (n=51)*
- *RCTs evaluating ataluren (n=8)*
- *RCTs evaluating interventions other than ataluren (n=34)*
- *Other study designs including non-RCTs and observational studies (n=73)"*

The ERG spot checked the lists with particular focus on the 'RCTs evaluating ataluren (n=8)' which

were in fact composite/duplicate publications of the RCT published by Bushby et al. (2014)[41] (see below) and did not identify any additional studies that should have been included in the assessment of clinical effectiveness.

Even though 281 (115 following clarification) studies met the broad inclusion criteria, the final included studies eligible for the clinical systematic review consisted of one RCT (study 007 reported in Bushby et al., 2014[41] and 8 additional publications) and one cohort study (study 004). The subsequent clinical effectiveness review concentrated on the publication of study 007 trial results by Bushby et al. (2014)[41] and the publication of the Phase 2a cohort study by Finkel et al. (2013).[42] The additional 8 studies consisted of one full text by McDonald et al. (2013)[25] which reported the experience of using the 6MWD test in nmDMD patients and 7 abstracts [43-49] reporting on the clinical outcomes of the 007 trial. These 8 studies did not provide information on trial outcomes that is additional to what was reported in the included study by Bushby et al. (2014)[41] according to the CS.

In summary, while the exclusion of 168 studies for which full texts were not freely available is a methodological shortcoming of the selection process, the ERG believes that the flaws in this section of the CS are mainly due to poor reporting rather than due to insufficiencies in the search and selection process. The ERG is reasonably confident that all relevant evidence has been identified and reported in the CS.

4.1.3. Critique of data extraction

The data extraction in the CS appears appropriate. Please refer to section 4.2.1 for more detail.

4.1.4. Quality assessment

The quality appraisal of the included trials was appropriate using criteria recommended by NICE. Please refer to section 4.2.2 for more detail.

4.1.5. Evidence synthesis

In two sections of the CS (9.8.1 and 9.8.2, p. 122) concerning the techniques used and rationale for evidence synthesis undertaken, the Company replied "*not applicable*". The Company could have stated that they undertook a narrative review of the included RCT (study 007) and the non-randomised trial (study 004) and that a meta-analysis was not appropriate. The Company might also have reported the methods to account for their quality assessment of the included studies in the interpretation of results.

4.2. Critique of trials of the technology of interest: analysis and interpretation

This section evaluates the available trial evidence presented in the CS in terms of baseline

characteristics of trial participants, quality of included studies, the statistical methods employed by the trials, the outcome measures selected as well as the reported results and considers unpublished studies as well as ongoing trials.

4.2.1. Summary of studies included in the Company Submission

The CS identified one RCT (study 007) and one non-randomised trial (study 004). The RCT (study 007) compared two doses of ataluren (40 mg/kg/day or 80 mg/kg/day) versus placebo for 48 weeks, and the non-RCT evaluated three doses of ataluren (16 mg/kg/day, 40 mg/kg/day and 80 mg/kg/day) for 28 days. The 80mg/kg/day dose is discussed in section 4.3.2. The 16mg/kg/day is not further considered. Both studies were sponsored by the Company.

Summary details of the RCT were submitted, including methodology (CS Table C9.6, p. 73), baseline characteristics (CS Table C9.10, p. 81), subgroup analyses (CS p. 83) and a participant flow chart (CS figure 9.5, p. 86). Electronic copies of the trial publication and the clinical study report (CSR) were provided. The ERG considers that the CS provides an adequate level of detail about the characteristics of RCT study 007.

Baseline participant characteristics in the RCT are provided in CS Table C9.10, p. 81. The CS states there were no significant differences between groups (CS p. 74 and 80). Based on observation of data of the two groups relevant to the decision problem (ataluren 40 mg/kg/day versus placebo), the ERG notes that calf hypertrophy is lower in the 40 mg group; there are some different proportions of stop codon type; and the number of sibling pairs is higher in placebo group (but unlikely a prognostic factor). These differences could be due to chance.

In addition, the CS presents the corticosteroid use at randomisation for each group. On observation of the data it appears that the ataluren 40mg/kg/day group and the placebo group are similar in the proportion using corticosteroids at baseline (71.9% ataluren, 70.2% placebo) but the choice of corticosteroid differed between groups on the use of prednisolone or prednisone. The ERG does not consider that this would have an effect on prognosis as they are similar in effectiveness.

The CS states on page 78 that the populations of the two studies were similar. Some differences in patient characteristics between RCT study 007 and the 40 mg/kg/day arm of study 004 were noted by the ERG. Study 004 had a higher proportion of Asian (study 004: 15%; study 007: 1.8%) and 'Other' (study 004: 10%; study 007: 1.8%) patients. Fewer were on corticosteroids at baseline (study 004: 65%; study 007: 71%). One patient (5%) in the 40 mg/kg/day group in study 004 did not have the ability to ambulate (outside licensed indication). A number of characteristics reported in the RCT population were not reported for the study 004 population (e.g. time from diagnosis, phenotype

diagnosis, 6MWD) and therefore the ERG are unable to check for any key differences between the studies. Key baseline characteristics of the relevant studies are summarised in Table 4.

Table 4 Summary of relevant studies (CS Table C9.10;page 81)

Study	**Study 007**		**Study 004**
Design	RCT		Non-randomised
Sample size (relevant arms)	114		20
Length of follow-up	48 weeks		28 days
Relevant intervention	Ataluren 40 mg/kg/day		Ataluren 40 mg/kg/day
Relevant comparator	Placebo		None relevant
Relevant outcomes	Primary: 6 MWD Secondary: muscle function, activity, muscle strength, HRQoL, treatment satisfaction, wheelchair use, falls, cognitive function, cardiac function		Secondary: Motor function
	Placebo n=57	**Ataluren n=57**	
Mean age (SD), years	8.3 (2.33)	8.8 (2.91)	8.5 (1.70)
Race, %:			
Caucasian	94.7	93.0	75.0
Black	0.0	1.8	0.0
Asian	1.8	1.8	15.0
Hispanic	1.8	1.8	0.0
Other	1.8	1.8	10.0
Ability to ambulate, %:			
No	0	0	5
Yes	100	100	95
Corticosteroid use, %	70.2	71.9	65.0
Time from diagnosis to randomisation, mean (SD) ***(units not reported)***	4.4 (2.5)	5.4 (3.4)	Not reported
Stop codon type, %			Not reported
UGA	54.4	50.9	
UAG	21.1	29.8	
UAA	24.6	19.3	

In this and following sections the ERG present the data from the CS, focusing on the data of relevance to the decision problem. All data have been checked with the CSRs and publications where available.

4.2.2. Quality assessment of included studies

The CS assessed the included RCT (study 007) using criteria recommended by NICE. The ERG quality assessment mostly agrees with the Company assessment of study quality. However the ERG note that both intention to treat (ITT) analysis and post hoc 'corrected ITT' (cITT) were used for the primary outcome, and that only cITT analysis was used for the secondary outcomes. The post hoc use of cITT analysis, whereby the baseline data are replaced with screening data for 0.9% of the two relevant groups analysed (1 of 114 patients), has an impact on the statistical significance of the primary outcome (see section 4.2.3 for further details).

[redacted]

[redacted] is reported in the CSR p. 95, but not in the CS. Also, limited data or no data were presented for outcomes that were not statistically significant (e.g. step activity monitoring, treatment satisfaction, cognitive ability, heart rate monitoring, serum creatinine kinase expression, dystrophin expression). This suggests the possibility of selective reporting which may introduce bias in the CS.

The study is reported as double blind, although no details are provided in the CS or the trial publication of blinding. In response to clarification the Company confirmed that outcome assessors (clinical evaluators) were blinded to treatment allocation.

The CS states there were no significant differences in baseline characteristics between groups, between the ataluren 40 mg/kg/day and placebo group. Please refer to section 4.2.1 for more detail.

The CS also assessed the included non-RCT (study 004). On the whole the ERG agrees with the assessment of study quality; however notes that only one of the three arms in the study is relevant to the decision problem. The ERG also completed some additional quality criteria checklists, and notes that only limited information (text but no data) was presented on upper and lower extremity myometry, and limited details on the methods for myometry were presented. It was unclear whether the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.

The CS does not provide a narrative summary of the quality of these studies, or refer to the quality of the studies in their consideration of the study results in any way. The ERG considers that overall the RCT is of low risk of bias (based on the risk of selection bias). For the non-RCT (Study 004) the ERG considers that study quality was reasonable. Table 5, 6 and 7 detail the CS and ERG quality

assessment checklist results and associated ERG commentary.

Table 5 RCT: Quality assessment

NICE QA Criteria for RCT	CS response	ERG response	ERG comments
1. Was the method used to generate random allocations adequate?	Yes	Yes	
2. Was the allocation adequately concealed?	Yes	Yes	
3. Were the groups similar at the outset of the study in terms of prognostic factors,	Yes	Yes (including 6MWD)	States no significant differences. Based on observation of data of the two groups relevant to the decision problem: calf hypertrophy lower in the 40 mg group; different proportions of stop codon type; sibling pairs higher in placebo group (but unlikely a prognostic factor). These differences could be due to chance.

e.g. severity of disease?			
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	
5. Were	No	No	

there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?			
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes	[redacted] is reported in the CSR p. 95, but not in the CS. Also, limited data or no data are presented for outcomes that were not statistically significant, for example: step activity monitoring, treatment satisfaction, cognitive ability, heart rate monitoring, serum creatinine kinase expression, dystrophin expression.
7. Did the analysis include an intentio	Yes	Unclear	The CS presents ITT analysis for the primary outcome (change in 6MWD) only. The CS also presents 'corrected ITT (cITT) analysis for this outcome and other outcomes, whereby the baseline values for 2 patients (1 placebo-dosed and 1 treated with ataluren 80 mg/kg/day) were replaced by their screening values, because their baseline 6MWDs were radically lower than their screening and Week 6 values due to lower-limb injuries before the baseline test. The CS states

n to treat analysis ? If so, was this appropriate and were appropriate methods used to account for missing data?			that the CHMP considers the approach to be reasonable. However the use of this post hoc analysis, (i.e. amending the baseline data for 0.9% of the trial population (1 of 114 patients in the two groups analysed) has an impact on statistical significance of the results. Methods to account for missing data for secondary outcomes unclear.

Table 6 Non RCT: Quality assessment

Study question	CS Response	ERG response	ERG Comments
Was the cohort recruited in an acceptable way?	Yes	Yes	NA
Was the concealment of treatment allocation adequate?	NA	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	NA	Only one of the three groups is relevant to the decision problem
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	No	Low risk of bias for objective outcomes. No subjective outcomes assessed
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	All patients were followed and analysed.
Is there any evidence to suggest that	No	No	NA

the authors measured more outcomes than they reported?			
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	NA
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination			

Table 7 Non RCT: additional questions from modified Downs and Black checklist

Quality criteria for the assessment of uncontrolled studies in the CS	ERG response	ERG Comments
Are the characteristics of the patients included in the study clearly described?	Yes	NA
Are the interventions of interest clearly described?	Yes	NA
Are the main findings of the study clearly described?	No	Although discussed in the CS, data on myometry not presented in CS (muscle strength is relevant to the scope)
Were the subjects in the study representative of the entire population from which they were recruited?	Yes	Considered to be representative by the clinical expert. A higher proportion of Asian and 'Other' than study 007 is noted. 65% were on corticosteroids at baseline. One (5%) of 40 mg group did not have ability to ambulate (outside licensed indication).
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unclear	NA
Were the statistical tests used to assess the main outcomes appropriate?	Yes	NA
Were the main outcome measures used accurate (valid and reliable)?	Unclear	The outcome relevant to scope is myometry, but limited details on methods are presented.

4.2.3. Evaluation of statistical methods in submitted evidence

This section focuses on the statistical methods employed by study 007 the pivotal RCT of ataluren

versus placebo. For clarity on the statistical methods used and post-hoc analyses undertaken, the ERG considered the study by Bushby et al. (2014)[41] additionally to the CS. Statistical advice was sought. The ERG checked the tabulated data and the narrative reflected the data in the included studies.

a) Sample size

"The hypothesis of this study was that the mean change in 6MWD from baseline to 48 weeks would be 30 metres longer in at least one of the ataluren arms than in the placebo arm. Assuming a common standard deviation of ~50 metres in each arm and a 1:1:1 randomization, 150 patients were required (50 patients in each of the 3 arms) to detect a difference of 30 metres in the 6MWD with >85% power using a 2-sided Dunnett's t-test at the 0.042 significance level. Assuming a premature discontinuation rate of ~10%, it was planned that ~165 patients (~55 patients in each of the 3 arms) be enrolled." (Page 74)

Due to underestimation of the standard deviation of the 6MWD scores over the 48 week trial duration the trial was underpowered. This could explain the lack of a significant effect observed in the trial.

b) Pre-specified sub-group analyses

The CS reported three important baseline patient characteristics, namely age (<9 years versus ≥ 9 years), corticosteroid use (yes versus no) and baseline 6MWD (≥350 metres versus < 350 metres), that were used as stratification factors in study 007 (please refer to section 3.3.1 for details on difference in age cut-off for pre-specified and post hoc sub-group analyses). On page 84 the CS reports that: "*Prior to study start, the estimated mean 6MWD for the study population was ~270 metres; however, early assessment of pre-treatment 6MWD data showed a mean 6MWD of ~350-360 metres. Therefore baseline 6MWD stratification was updated from <270 metres and ≥270 metres to <350 metres and ≥350 metres. Forty-two of the 174 patients were enrolled prior to the implementation of the amendment*".

Sub-group analyses were pre-specified for the subgroups defined by the stratification factors. However, only one subgroup analysis for the cITT population was reported in the CS (baseline 6MWD ≥350 metres versus < 350 metres). (p 90) The Company provided the additional subgroup analyses during clarification.

c) Intention to treat analysis

Intention to treat (ITT) analysis was pre-specified to include all randomised boys with a valid 6MWD test at baseline and at least one post baseline visit according to study 007.[41] One boy discontinued before the first follow-up at 6 weeks and was reported as having 'discontinued prematurely' and was therefore excluded from the analysis. Furthermore, two subjects had invalid baseline 6MWD test

results due to lower limb injuries. These considerably lower baseline 6MWD were replaced with the appropriate screening values and included in the post-hoc corrected ITT (cITT) analysis. One of the boys was randomised to the control arm and the other to the 80mg/kg/day treatment arm (which was not considered in the analysis in the CS). While this decision was classed as appropriate by the CHMP according to the CS (page 121), it needs to be considered that a higher revised baseline 6MWD in the control arm is in favour of a difference when compared to ataluren and that this single measurement had a huge impact by changing the difference in treatment arms from non-significant (ITT) to statistically significant (cITT). The supplementary information for the Bushby et al. (2014) paper reports that similar results were obtained when both patients were excluded from the study.[41] The cITT population formed the basis of all reported primary and secondary outcomes in the CS. During clarification outcomes based on the ITT population were provided by the Company.

d) Missing values

The analysis was pre-specified to impute missing values using the Analysis of Covariance (ANCOVA) on the original data in which missing data points were replaced with the last observation carried forward (LOCF) method and with the Mixed effect Model Repeat Measurement (MMRM) method. The latter is the preferred method as it assumes missing at random while LOCF methods assumes data to be missing completely at random which is rarely the case. The MMRM analysis included the following terms in the model: treatment, baseline 6MWD, age (<9 or ≥ 9 years), glucocorticosteroids (yes or no), visit and treatment-by-visit interaction. 5/174 patients had missing values for the 6MWD test at week 48. The time point the data was missing for was not reported in the CS. The expectation of similar outcomes using the two methods was not met (p-value for difference in trial arms for MMRM, p=0.0905 and for ANCOVA/LOCF, p=0.0445). A post-hoc correction to the MMRM model was undertaken by including a baseline-by-visit interaction term, which adjusted the p-value to p=0.0446 for ataluren 40mg/kg/day versus placebo which was in accordance with the ANCORA / LOCF method, which was also the more favourable outcome. The ERG believes that the cITT population was used for the MMRM analysis.

e) Non-normal distribution of the 6MWD scores

Rank-transformed data were used for the analysis following the Shapiro-Wilk W-test to test for normality as pre-specified. However, it was reported that use of the rank-transformed data was not the optimal method to address non-normality of the 6MWD data as it is less sensitive to treatment difference since it uses relative ordering of distances walked and the magnitude of distances walked is not considered. The permutation test, which was pre-specified to address the possibility of a biased coin randomisation effect, was therefore also used to address non-normality of the data. The supplement appendix of the Bushby paper 2014, [41] states that: *"For these reasons the permutation test provides a more accurate assessment than the pre-specified rank test of the treatment differences in*

this study".

f) Post-hoc analysis

Additional analyses were carried out in a sub-population of subjects in the decline phase (>7 years of age, treated with corticosteroids, 6MWD ≥150 m, <80% predicted 6MWD) as this group of patients was believed to be the most likely to display the greatest measureable effect with ataluren treatment. While this analysis was believed to be clinically and scientifically justified according to the CHMP, the EMA also noted that: "…*the patients in the decline phase of their ambulation constituted of a subset of the study 007 population and the analysis should be seen as exploratory*."

g) Adjustment for multiplicity

"*The p-values of the primary and secondary outcome measures were adjusted for comparison of two dose levels against placebo*"[41] (p. 479). The method for adjustment was not reported. Reported nominal p-values were not adjusted for multiplicity. The ERG noted that the reported nominal p-values were generally lower than the adjusted values and that the values for the MMRM analyses were lower than for the observed data. The outcomes table C9.14 on page 90 in the CS does not report any p values for the observed differences, but reports p-values for the MMRM model which for all comparisons except the ITT analysis suggests that the difference was statistically significant. The analysis does not state whether these are nominal or adjusted p-values, but the text on page 94 clarifies that these are nominal p-values. Notably, the p-values reported for the cITT MMRM analysis (the corrected analysis reporting a 31.7m (95% CI 5.1, 58.3) treatment effect of ataluren) in the CS (nominal p=0.0197, adjusted p=0.0367) do not match the values reported in the EMA report (nominal p=0.0281, adjusted p=0.0561). This appears to be the only adjusted p-value reported in the CS.

Summary

The statistical methods used in the 007 trial were appropriate, however, a number of post-hoc adjustments as well as post-hoc analyses were undertaken all of which appeared to favour the intervention (ataluren) arm of the trial. Both trial 007 and the CS were transparent about adjustments and justifications; however, the ERG considers that the reporting of outcomes was selective. The ERG would have expected clear reporting of outcomes separately according to pre-specified analyses using rank-transformed data with post-hoc analyses using permutation. The ERG would have also expected reporting of both adjusted and nominal p-values throughout with p-values for differences of observed data in table C9.14 on page 90 of the CS. While the observed difference between ataluren and placebo might be clinically significant, the statistical significance of some reported outcomes should be viewed with extreme caution as this was derived following several post-hoc adjustments. The adjustments seem to be methodologically appropriate but reporting as sensitivity analyses might have been more appropriate. This should be considered when assessing the evidence of the reported

treatment effect in the primary and secondary outcomes in section 4.2.5.

4.2.4. Summary of selected outcomes measures

The NICE scope listed 11 outcome measures to be considered. Some of these outcomes were not adequately measured or reported by the CS (described below). The relevant results are all from the single eligible RCT (trial 007), other than for adverse effects. The CS refers to outcomes of myometry and timed function tests from study 004 but no data are reported.

4.2.4.1. Ambulation

The primary outcome in the CS is 6MWD, a measure of ambulation, which was also the primary outcome in the 007 trial. The CS states on p. 62 and 125 that prior to this trial there were no established primary or secondary endpoints for studies in DMD patients.

The 6MWD test is a measure of exercise tolerance and functional status where the individual is asked to walk on a flat surface for 6 minutes. It is a reliable measure and shows only small variation at individual level over short periods of time. However a recent systematic review looking at nine chronic paediatric conditions, which included three studies in DMD, found evidence that the measurement properties of the 6MWD test varied between studies.[50] The authors concluded that caution is recommended in the interpretation of changes in 6MWD in children with chronic conditions. The CS states on p.125 that a 30 metre change in 6MWD versus placebo is in the range in which other drugs have been approved in multiple inherited conditions. However, the 6MWD test is known to be at risk of inter-operator bias through encouragement,[51] and it is not clear in the CS whether the assessor was blinded. In response to a clarification question the Company confirmed that the clinical evaluator was blinded to allocation. In addition, de Groot et al (2011)[52] discuss potential variations that can occur in the administration of the 6MWD test, for example differences in the distance between turning points, the choice of circuit layout (e.g. circle, squares or use of a treadmill), and instructions given. They note that guidelines for the standardised administration of the test are available. Standardisation between different centres is therefore important. In response to a clarification question the Company provided details of the standardisation of the 6MWD test across study centres, which appear appropriate.

The CS also reported the proportion of patients who experienced at least 10% worsening in 6MWD compared with baseline. The rational for the 10% cut-off was not provided.

[redacted] This indicates selective reporting of results.

The results of the 6MWD test from trial 007 were used as for the measure of time to loss of

ambulation in the CS economic evaluation.

4.2.4.2. Muscle function

Muscle function was measured by four timed function tests, stand from supine, 4-stair ascend, 4-stair descent, 10 metre run/walk. The CS states that timed function tests are established clinical assessments in DMD. The CS does not report details of these tests or how these were standardised between centres. However the ERG consider that standardised administration of the test between different centres is an important consideration. The ERG is not aware of any evidence for the validity of these tests as measures of muscle function. Minimal clinically important differences (MCIDs) have been published for these outcomes, based on trial 007.[53] In response to a clarification question the Company confirmed that a clinical evaluator training group developed standardised procedures for timed function tests and training and a manual were provided to all study sites, including refresher training after approximately one year.

In the North Star group, standard annual assessment of ambulatory patients with DMD includes measurement of 10m walk/run, time to stand from supine and stair climb. These tests have been validated by the North Star group for use in clinical monitoring and their measurements are included in other trials. The ERG requested information on the MCID for the timed function tests. The Company response stated that for the 10 metre walk/run the MCID is 0.76 seconds,[54] but that estimates of the MCID for the other timed function tests could not be identified.

4.2.4.3. Muscle strength

Force exerted during knee flexion and extension, elbow flexion and extension, and shoulder abduction was measured using myometry. The CS states on p. 101 (Results section) that "*myometric evaluation of limb strength is less sensitive to changes in disease status compared to TFTs, and muscle strength, although severely affected in ambulatory patients with DMD, deteriorates at a much slower rate than muscle function.*" The CS also justifies the inclusion of post hoc subgroup analysis in patients aged 5 to 6 by stating that "*myometry can only be adequately evaluated in younger patients*" (CS p. 102). The validity of myometry in the trial population is therefore uncertain.

4.2.4.4. Ability to undertake activities of daily living

'Activities of daily living' were not evaluated by a specific validated tool, however the CSR states that the timed function tests (stand from supine, 4-stair ascend, 4-stair descent, 10 metre run/walk) measure the ability of patients to perform brief activities that are typical of patients' activities of daily living in a home, school, or community setting (CSR p.124, also confirmed in the response to clarifications). The ERG notes that there are other activities of daily living that are not captured in these timed function tests (e.g. washing and dressing, toileting). Activity in the community was also

measured using a pedometer to assess step activity. Further details of the step activity monitoring were provided in response to a clarification request. The Company states that participants wore an ankle pedometer-like device that monitors and records the number of steps taken. The Company also state that the proportions of time during which the patient is moving at 0 (no activity), 1 to 15 (low activity), 16 to 30 (medium activity), or >30 (high activity) steps per minute were also assessed.

The CS provides a statement (CS p. 102) regarding 'time spent at no activity (0 steps/minute)' and 'time spent at medium activity (16 to 30 steps/minute)', but data and the time period over which this is calculated are not reported. In response to a clarification question the Company provided data on the change in mean steps taken from baseline to Week 48, and a figure displaying the proportion of time spent at no, medium and high activity. The validity and reliability of this outcome is unclear.

4.2.4.5. Cardiac function

Change in heart rate was measured before, during and after the 6MWD test. A statement was made in the CS (p.104) regarding non statistical significance of the results but data were not reported. Blood pressure was also measured (CS p.77 and p.116) but data were not reported. The Company state in their response to clarifications that "*Cardiac complications emerge in the later, non-ambulatory stage of DMD. Nonetheless, heart rate was measured before, during, and after the 6MWT to explore the hypothesis that drug-induced normalization of inappropriate sinus tachycardia might have beneficial long-term effects on cardiac function as a secondary objective of Study 007. Generally, the results were similar across the 3 treatment arms*". The response refers the ERG to Section 11.4.1.4.3 of the CSR. This confirms the use of the heart rate monitoring and refers to relevant tables in the CSR for the results (discussed in section 4.2.5).

4.2.4.6. Lung function

Lung function was not measured in trial 007. This outcome may be more closely associated than walking ability and muscle function with mortality.

4.2.4.7. Time to requirement for a wheelchair

Time to requirement for a wheel chair is not reported by the CS, although the CS does report change in wheelchair use (percentage of days of wheelchair use) assessed by diary record. The time period for calculating the 'percentage of days' was not reported. Compliance with the diary record, and validity and reliability are unclear from the CS. Response to a clarification request show that diary record compliance was '[redacted] In addition, the Company reported in clarifications [redacted]

4.2.4.8. Number of falls

Number of accidental falls per day was assessed by diary record.

4.2.4.9. Mortality

Number of deaths within the 48 week trial (007) was reported. However, the study was not powered to detect differences in mortality (as stated on CS page 132).

4.2.4.10. Adverse effects of treatment

The CS reports adverse effects from trial 007 and ongoing studies, however data were not clearly reported. The ERG requested details of the definition used for a serious adverse event. The Company response was that "*A serious adverse event was defined as an untoward medical occurrence, regardless of whether or not it was considered related to the study drug, which resulted in death, was life threatening, required prolonged hospitalisation, or resulted in persistent or significant disability or incapacity. Important medical events that were not immediately life-threatening or did not result in death or hospitalisation but might have jeopardised the patient or that might have required intervention to prevent one of the other outcomes listed above would have been considered to be serious (egg, intensive treatment at home or in an emergency room for an allergic bronchospasm, new cancers or blood dyscrasias, convulsions that did not result in inpatient hospitalisation, or the development of drug dependency or abuse).*"

The ERG also requested clarification over the criteria used to determine if a serious adverse event was considered to be related to treatment and how this judgement was made. The response from the Company was not very informative, stating that "*Investigators determined whether or not a serious adverse event was treatment related (see Study 007 CSR, Section 9.5.1.2.2. Adverse Events)*". The CSR does not provide any further information about how this judgement was made, but states that the relationship of the event to the study drug as 'probable', 'possible', 'unlikely', or 'unrelated' was recorded by the investigator. The ERG also requested details of how relatedness of an adverse event to treatment (as seen in CS Table C9.20, p.108) was ascertained. The Company response stated that these are standard Good Clinical Practice (GCP) wording and the ERG was referred to ICH standards. The link provided is to a general page of the ICH efficacy guidelines and refers to a large number of publications of which the ERG have been unable to source the information on definitions of relatedness.

4.2.4.11. Health-related quality of life

HRQoL was measured using the Paediatric Quality of Life Inventory (PedsQL). Age appropriate versions were used. The PedsQL was completed by the child unless they lacked the ability to complete it when the parent or caregiver completed it (CS page 138). It is not clear how many parents

completed the questionnaire on behalf of their children, or whether there were any occurrences of a change in who completed the PedsQL during the 48 week study period. A clinical expert stated that this instrument is not sensitive for use in DMD and that other instruments would be preferable. (K. Bushby personal communication). The CS states on page 20 that the physical functioning scale of the PEDsQL is most directly applicable to the clinical manifestations of DMD. In response to clarifications the Company emphasized, however, that the PedsQL is not a sensitive measure of disease progression in DMD[54] and that although it has been designed to assess HRQoL in healthy children and those with acute and chronic health conditions, it was not designed specifically for use in DMD. In ongoing trials a different measure of HRQoL is currently being used. The Company were asked to quantify the MCID for PedsQL further to a statement in the CS on page 20 that "*Although this* [physical functioning score] *is below the minimal clinically important difference it trends in the same direction as a number of other measurements of physical functioning*". No response was provided. The results from the PEDsQL were not applied in the economic evaluation.

Other measures not listed on the NICE scope but assessed in the CS were as follows.

- Statements were made in the CS (p.103-4) regarding statistical significance of the results but data were not reported. Treatment satisfaction (Treatment Satisfaction Questionnaire for Medication). This was completed by the parent/caregivers from the perspective of the child, as there is no paediatric version of the questionnaire.
- Cognitive function measured by the digit span task.
- Pharmacodynamics (serum CK levels, muscle dystrophin expression).

4.2.5. Summary of primary outcome results

4.2.5.1. Change in 6 minute walk distance

ITT analysis demonstrated no statistically significant difference between ataluren and placebo in the change in 6MWD from baseline to 48 weeks.

Error! Reference source not found. shows this. A statistically significant difference was, however, found using a post hoc cITT analysis. Concerns regarding the cITT raised by the ERG in section 4.2.3 should be noted. The CS notes that this difference (31.7 metres) is clinically important.

Table 8 Analysis of 6MWD from baseline to week 48

	Observed, mean (SD)	**MMRM Model**

Analysis	Placebo Baseline	Placebo Δ At week 48	Ataluren 40 mg/kg/day Baseline	Ataluren 40 mg/kg/day Δ At week 48	Difference between groups	Difference between groups (95% CI)
ITT All patients Placebo n=57, ataluren, n=57	359.6 m (87.7)	-42.6 m (90.1)	350.0 m (97.6)	-12.9 m (72.0)	29.7 m	26.4 m (-4.2, 57.1) p=0.0905
cITT All patients Placebo n=57, ataluren, n=57	361.1 m (87.5)	-44.1 m (88.0)	350.0 m (97.6)	-12.9 m (72.0)	31.3 m	31.7 m (5.1, 58.3) p=0.0197

Reproduced from CS Table C9.14 p. 90. Δ: change from baseline; MMRM: Mixed Model Repeated Measures; cITT: corrected intention to treat (post hoc analysis); ITT: Intention to treat.

Statistical significance can only be inferred for the modelled difference using MMRM from Table 8. P-values for the observed difference are not reported in the CS. The ERG was unclear why the reported p-values for the modelled difference (MMRM column) in the CS are different to the p-value for the same modelled difference in the EMA report (p= 0.0281) for the nominal (unadjusted) p value. The EMA also reported the adjusted p-value = 0.0561 which suggests lack of statistical significance of the difference between ataluren and placebo in 6MWD. The CSR was consulted to investigate this discrepancy. The following table (Table 9) was reproduced from Table 28 on page 100 of the CSR with the following outcomes reported for the ataluren 10, 10, 20 mg/kg vs placebo comparison.

Table 9 Post hoc MMRM Analysis of Change in Untransformed 6MWD Based on

Analysis	**Ataluren 10, 10, 20 mg/kg vs Placebo**			
	Difference		**p-value**	
	mean	**95% CI**	**nominal**	**adjusted**
MMRM[a]	31.7	5.1, 58.3	0.0197	0.0367[b]
Permutation test[c]	--	--	0.0281	0.0561[d]

[a] MMRM model: 6MWD = baseline 6MWD (covariate) + arm + visit + visit*arm + baseline 6MWD*visit + age group (<9 vs =9 years) + corticosteroid (yes vs no); unstructured variance/covariance matrix.
[b] Dunnett's test was applied to adjust for the comparison of 2 dose levels vs placebo.
[c] Permutation test of 10,000 re-randomizations. For each re-randomization, patients were dynamically re-randomized in the same order as they originally entered the study (starting seed = 14576).
[d] Based on the proportion of the 10,000 permutations in which the maximum effect size among the 2 comparisons (10, 10, 20 mg/kg vs placebo and 20, 20, 40 mg/kg vs placebo) exceeded the observed maximum

effect size
Reproduced from CSR Table 28 p. 100

The CSR concludes on page 142: *The difference in the mean change in 6MWD from baseline to Week 48 between ataluren 10, 10, 20 mg/kg and placebo was 31.3 meters in the overall cITT population, consistent with the targeted 30-meter difference (nominal p=0.0281); multiplicity-adjusted, p=0.0561 (post hoc refined MMRM analysis).* This questions the appropriateness of the reported p=0.0197 in the CS for the cITT population and the statistical significance of the modelled difference because the permutation test provides a more accurate assessment than the pre-specified rank test of the treatment differences in this study as reported in section 4.2.3.

4.2.5.2. Ten per cent worsening of 6MWD: time to event

Pre-specified analyses evaluated time to persistent 10% 6MWD worsening (defined a priori as the last time that 6MWD was not 10% worse than baseline) (Figure 1). Twenty six percent of patients treated with ataluren 40 mg/kg/day experienced at least 10% worsening at Week 48 compared with 44% in the placebo group (cITT hazard ratio 0.51, nominal p=0.033; ITT hazard ratio 0.52, nominal p=0.039). The ERG notes that in Table C9.14, p. 90 of the CS the proportions have been switched in error.

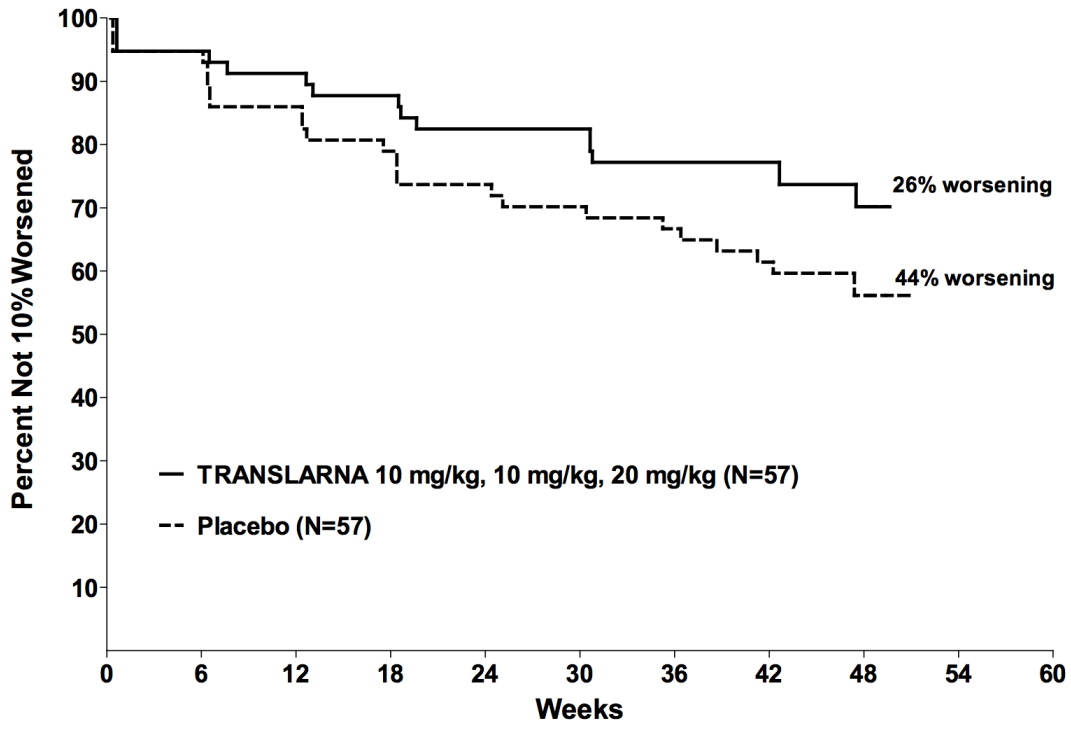


Figure 1 Time to persistent 10% 6MWD worsening, cITT analysis set (pre-specified analyses)
Reproduced from CS Figure 9.11 p. 97

[redacted]

4.2.6. Summary of secondary outcome results

4.2.6.1. Timed function tests

Smaller increases between baseline and 48 weeks in the time required to climb four stairs were found with ataluren compared with placebo [2.4 seconds (SD 4.6) versus 4.8 seconds (SD 7.9), p=0.0207 cITT analysis set]. No statistically significant differences were found for descending four stairs, run/walk 10 metres, or supine to stand time.

The ERG requested details of the ITT analysis results for the timed function tests. These were provided by the Company, although change from baseline for each group was not provided. This shows similar results to the cITT analyses,

[redacted]. (Tables 10 and 11). The Company note that the cITT was used for the marketing authorisation to the EMA. Further details are available in the CSR papers.

The Company states in their response to clarifications that the MCID for the 10 metre run/walk test is 0.76 seconds [54] but that estimates for the MCID for the other outcomes could not be identified.

The non-randomised trial (study 004) also found that changes in timed function tests were small and not statistically significant 28 days after treatment with ataluren, (data not presented in the CS).

Table 10 Timed function tests, cITT analysis set (secondary outcome measures)

Endpoint[a]	Placebo (n=57)		Ataluren 40 mg/kg/day (n=57)		Observed	MMRM Model	
Mean (SD)	Baseline	Δ At week 48	Baseline	Δ At week 48	Difference[a] between groups	Difference between groups, mean (95% CI)	% Difference, mean[b]
Climb four stairs Time, s	[redacted]						

Descend four stairs Time, s	[redacted]						
Run/walk 10 metres Time, s	[redacted]						
Supine to stand Time, s	[redacted]						

Reproduced from CS Table C9.17, p. 99 (also reported in CS Table C9.15, p91) Δ: change from baseline; MMRM: Mixed Model Repeated Measures; cITT: corrected intention to treat (post hoc analysis).

[a] For timed function tests, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

[b] % Difference, mean calculation = ataluren Week 48 Δ - placebo Week 48 Δ / placebo Week 48 Δ

[c] Corrected figure: please note this is the observed difference based on the cITT population. A calculation error resulted in the 1.4 second difference reported in the publication (Bushby, 2014) and the Translarna SPC

Table 11 Timed function tests, ITT analysis set

Endpoint	Placebo (n=57)		Ataluren 40 mg/kg/day (n=57)		Observed Difference[a]	MMRM Model		
	Baseline, mean		Baseline, mean			(95% CI)		p-value
Climb four stairs Time, s	6.04		6.94		-2.55	(-4.8, -0.29)		0.027
Descend four stairs Time, s	5.52		6.08		-1.71	(-4.17, 0.75)		0.172
Run/walk 10 metres Time, s	6.86		7.45		-1.32	(-3.45, 0.81)		0.222
Supine to stand Time, s	11.5		10.8		-0.01	(-2.34, 2.23)		0.962

Reproduced from clarification response A5.2.

4.2.6.2. Frequency of accidental falls

The change in frequency of accidental falls per day between baseline and week 48, measured by diary record, was lower in the ataluren group (Table 12).

[redacted] The relative risk of accidental falls at week 48 was 0.38 (95% CI 0.16 to 0.94, nominal [redacted], ITT analysis) for ataluren

versus placebo.

[redacted] and the difference between ataluren and placebo change values with confidence limits is not presented. The baseline ataluren rate is half that of the placebo, and 24 patients had missing baseline data (CSR). The Company stated in their clarification request that [redacted] but no further details were provided.

Table 12 Changes in falls per day by treatment group

Treatment arm	Falls / Day (SD)		
	Baseline	Week 48	Change from baseline to week 48
Placebo	[redacted]	[redacted]	[redacted]
Ataluren, 40 mg/kg/day	[redacted]	[redacted]	[redacted]

Reproduced from CS Table C9.18, p. 101.

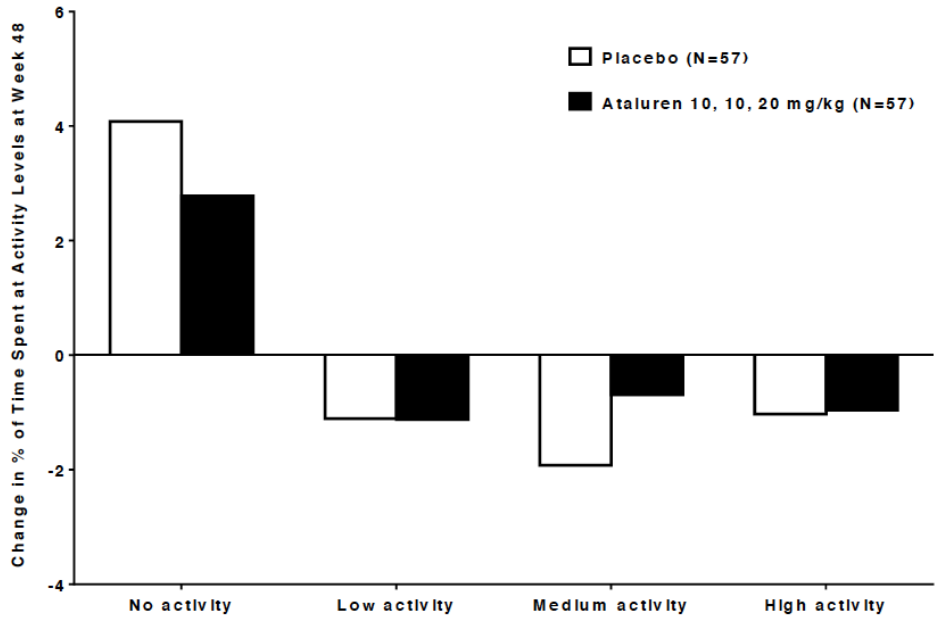
4.2.6.3. Upper and lower extremity myometry tests

The CS reports less decline in muscle strength with ataluren versus placebo, although the differences were not statistically different. Data were not presented.

The non-randomised trial (study 004) also found that changes in myometry scores were small and not statistically significant 28 days after treatment with ataluren, data not reported in the CS.

4.2.6.4. Step activity monitoring

The CS reports a 'trend' favouring ataluren versus placebo, but data and statistical analysis were not presented. In response to a request for clarification the Company reported a difference in mean steps of -649.9 (SD 1717.6) for ataluren 40 mg/kg/day compared with - 901.7 (SD 2000.5) for placebo at week 48. The proportions of time during which the patient is moving at 0 (no activity), 1 to 15 (low activity), 16 to 30 (medium activity), or >30 (high activity) steps per minute were also assessed. The mean changes at Week 48 for both ataluren 40 mg/kg/day and placebo showed trends that favoured the ataluren group compared to placebo with regards to time spent at no activity (0 steps/minute) and at medium activity (16 to 30 steps/minute) although differences were not statistically significant (Figure 2).



No activity = 0 steps/minute; low activity = ≤15 steps/minute; medium activity = 16-30 steps/minute; high activity = >30 steps/minute

For no activity, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients. For medium and high activity, positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

Figure 2 Change from Baseline to Week 48 in Proportion of Time Spent at No, Low, Medium, and High Activity (ITT)

Reproduced from clarification response, A3.1

4.2.6.5. Patient reported wheelchair use

The CS reports a 'trend' favouring ataluren versus placebo, but this is not statistically significant. The mean percentage of days of wheelchair use increased by 4.0% (95% CI -2.77 to 10.68) versus 11.5% (95% CI 4.36 to 18.354), respectively, a difference of 7.5%. At baseline the mean percentage of days of wheelchair use was 13.2% for each group.

4.2.6.6. Health-related quality of life

The CS reports a 'trend' favouring ataluren versus placebo for the physical functioning scale of PedsQL, however the difference in mean change (3.4, 95% CI -5.5 to 12.2) is below the MCID [41] not statistically significant (

Table 13). The Company does not provide details of what is considered to be the MCID in their clarification response. The CS does not discuss the outcomes from the emotional, social or school scales in the narrative. The ERG notes that on observation of the data, the results suggest poorer outcomes with ataluren versus placebo (not statistically significant) on the emotional and social scales. The positive difference seen on the school scale is suggestive of better outcome for those treated with ataluren (again not statistically significant).

Table 13 Patient-reported Health-Related Quality of Life, assessed by the PedsQL, ITT analysis set

Endpoint, score	Placebo (N=57)		Ataluren 40 mg/kg/day total (N=57)		
	Baseline, mean	Δ at week 48, mean	Baseline, mean	Δ at week 48, mean	Difference[a], mean (95% CI)
Physical	61.9	-1	59.3	2.4	3.4 (-5.5, 12.2)
Emotional	70.1	4.3	73.7	-1.8	-6.1 (-14.3, 2.1)
Social	63.4	7.8	65.1	3.9	-3.9 (-11.7, 4.0)
School	64.7	4.1	64.6	6.1	2.1 (-6.0, 10.1)

[a] Positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients

Reproduced from CS Table C9.19 p. 103.

4.2.6.7. Treatment satisfaction

The CS states that treatment satisfaction (assessed by the Treatment Satisfaction Questionnaire for Medication) was similar between groups and no statistically significant differences were observed. Data were not presented in the CS.

4.2.7. Other outcomes

The CS described the following outcomes as similar across groups and differences not statistically significant. Data were not provided in the CS:

- Digit span
- Heart rate

Results are also presented for study 004 on pages 96 and 108-109, for two outcomes not in scope

- Muscle dystrophin expression
- Serum creatinine kinase expression

Again differences were not statistically significant.

4.2.8. Subgroup analyses

The CS also reports planned and post hoc subgroup analyses. None of the analyses reported statistical tests of interaction. Due to limitations inherent with subgroup analyses, these results should be viewed with caution.

4.2.8.1. Mean change in 6MWD: decline phase and <350 m subgroups

Post hoc analysis (cITT set) of the subgroup of patients classed as being in the decline phase (aged 7

years to 16 years, baseline %-predicted 6MWD ≤80%, baseline of 6MWD ≥150 metres and on a stable dose of corticosteroids) found the reduction in 6MWD was 49.9 m less with ataluren compared with placebo (nominal p=0.0096) (Table 14). Data for the subgroup of patients not in the decline phase are not reported or discussed in the CS or the CSR

Pre-specified analysis (cITT set) of the subgroup of patients with baseline 6MWD < 350m the reduction in 6MWD was 68.2 m less with ataluren compared with placebo at 48 weeks (nominal p=0.0053) (Table 14). Data for the subgroup of patients with baseline 6MWD > 350m are not reported or discussed in the CS or the CSR.

Table 14 Subgroup analyses for mean change in 6MWD (cITT analysis)

	Observed, mean (SD)					MMRM Model
Analysis Sub-group	Placebo Baseline	Placebo Δ At week 48	Ataluren 40 mg/kg/day Baseline	Ataluren 40 mg/kg/day Δ At week 48	Difference between groups	Difference between groups (95% CI)
Decline phase Placebo n=31, ataluren n=32	341.9 m (85.0)	-62.2 m (84.9)	341.0 m (84.8)	-12.3 m (69.4)	49.9 m	45.6 m (11.4, 79.9) p=0.0096
Baseline 6MWD <350 m Placebo n=22, ataluren n=25	272.6 m (54.1)	-107.4 m (104.0)	262.5 m (71.9)	-39.2 m (84.3)	68.2 m	59.8 m (18.0, 101.6) p=0.0053

Reproduced from CS Table C9.14 p90. Δ: change from baseline; MMRM: Mixed Model Repeated Measures; cITT: corrected intention to treat (post hoc analysis). The decline-phase subgroup is defined as those aged 7 years to 16 years with a baseline %-predicted 6MWD ≤80% and a baseline of 6MWD ≥150 metres and on a stable dose of corticosteroids.

4.2.8.2. Change in 6MWD: according to percentage predicted 6MWD

Post hoc analysis categorised patients according to their percentage predicted 6MWD at baseline (relative to a healthy boy of the same age and height), as greater than 70%, 50% to 70%, and less than

50% (CS Figure 9.10 p. 96). The CS reports that all categories of patients showed a favourable effect of ataluren compared with placebo over 48 weeks (Difference between ataluren and placebo: 20m, 47m and 41m for categories >70%, 50-70% and <50%, respectively). However, measures of variance are not given and statistical analyses were not provided. In addition, the cut-off values for the categories are not justified.

4.2.8.3. Timed function tests: decline phase and <350 m subgroups

Subgroup analyses for three of the four timed function tests for the decline phase subgroup and the baseline 6MWD < 350 m subgroups were presented in a figure only (Figure 3). The CS states that mean differences between ataluren and placebo were greater for these subgroups than for the overall population, however measures of variance and statistical analyses were not reported. Subgroup analyses for the supine to stand test were not presented.

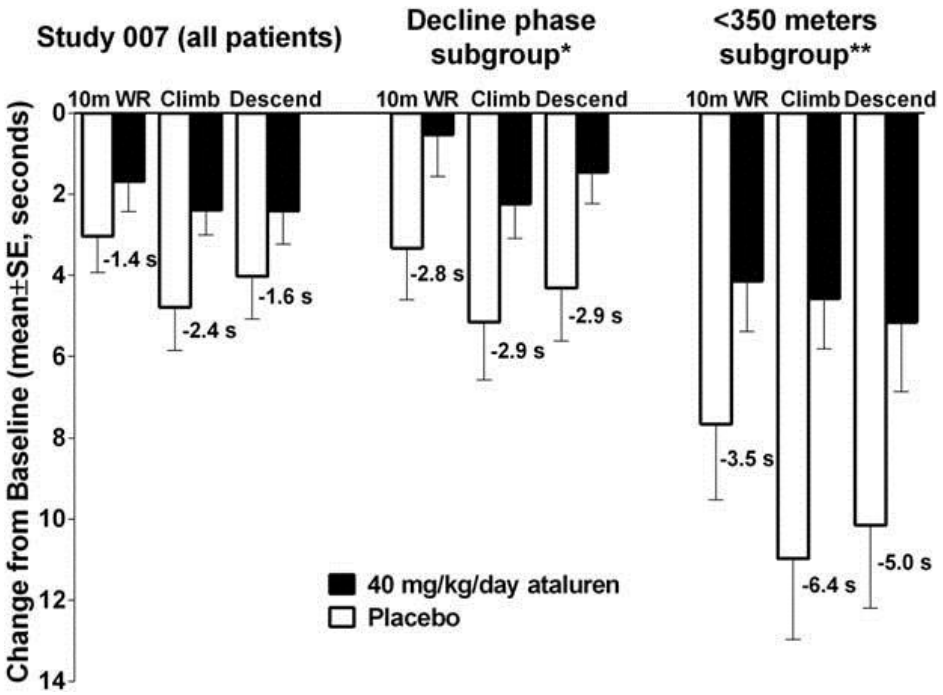


Figure 3 Timed function tests change from baseline to week 48 in Study 007 overall population versus decline-phase subgroup. Reproduced from CS Figure C9.12, p. 100

4.2.8.4. Myometry tests: patients aged 5 to 6 years

Post hoc subgroup analysis of myometry in patients age 5 to 6 only was presented in a figure (Figure 4). The minimum clinically important difference, measures of variance and statistical analysis were not reported. The CS states that in children aged 5 to 6 years who are treated with ataluren 40mg/kg/day there is a stabilisation of their muscle function.

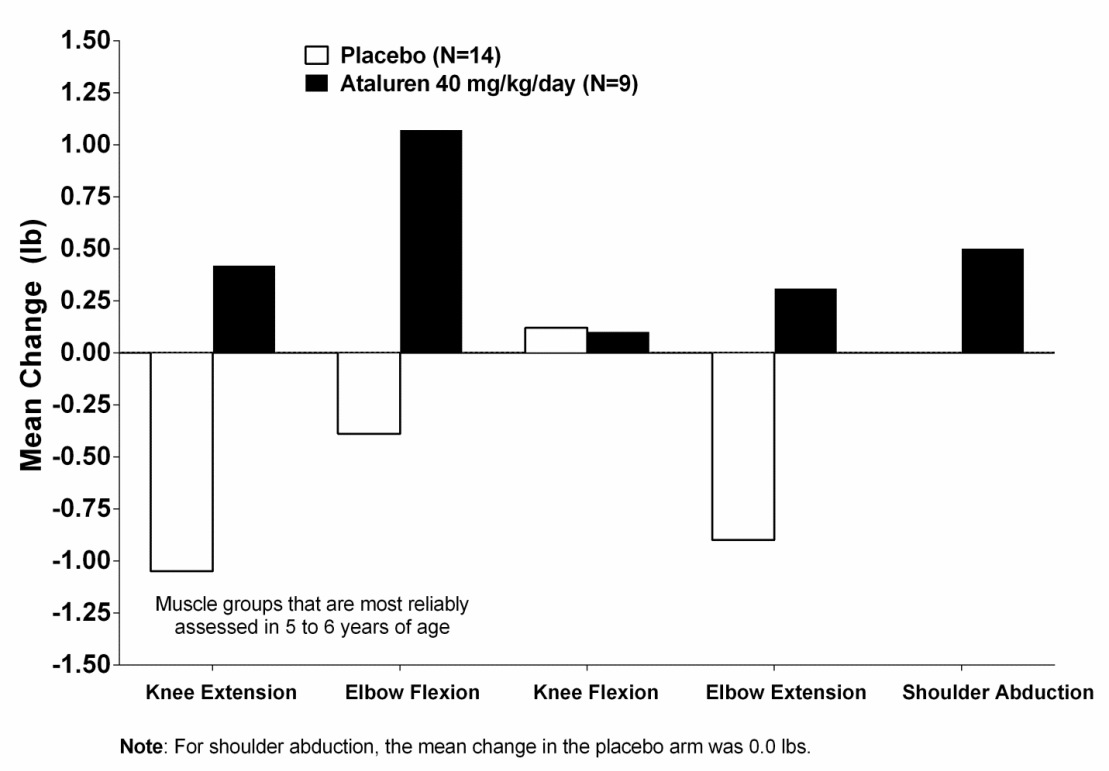


Figure 4 Change from Baseline to Week 48 in Myometry, Measured by Force Exerted, in the Study 007 Patients Aged 5 to 6 Years (post-hoc analysis)

Reproduced from CS Figure 9.14, p. 102

4.2.8.5. Health-related quality of life

The CS states that the difference seen on the physical functioning score of the PedsQL scale was more pronounced in the ambulatory decline phase subgroup (different of 6.1 between ataluren and placebo) at week 48 favouring ataluren. The ERG has been unable to verify these data in the CSR. In response to a clarification question about these data and data for the other scales the Company have responded that these analyses are not available.

4.2.8.6. Pre-specified stratification factors

The ERG requested data for the pre-specified stratification factors of age, corticosteroid use, and baseline 6MWD as the CS notes (on p. 86) that these were likely to have prognostic significance. The Company response states that these should not be considered as subgroups as such, which the ERG agrees with. The data appear to confirm, however, that these factors do have prognostic significance, with those using corticosteroids at baseline, those under 9 years at baseline and those with a baseline 6MWD of less than 350 metres showing significant treatment effects (Table 15). Caution is recommended in the interpretation of these data.

Table 15 Pre-specified stratification factors

Mean change in 6MWD from baseline to week 48 (cITT)						
	ITT analysis			**cITT analysis**		
		MMRM Model			**MMRM Model**	
Analysis Sub-group	number	Difference (95% CI)	p-value	number	Difference (95% CI)	p-value
Corticosteroid use	(placebo n=40, ataluren, n=41)			(placebo n=40, ataluren, n=41)		
No corticosteroid use	(placebo n=17, ataluren, n=16)			(placebo n=17, ataluren, n=16)		
< 9 years	(placebo n=32, ataluren, n=32)			(placebo n=32, ataluren, n=32)		
≥ 9 years	(placebo n=25, ataluren, n=25)			(placebo n=25, ataluren, n=25)		
Baseline 6MWD <350 m sub-group	(placebo n=23*, ataluren, n=25)			(placebo n=22, ataluren, n=25)		
Baseline 6MWD ≥350 m	(placebo n=34, ataluren, n=32)	15m (-23, 52)	0.439	(placebo n=35, ataluren, n=32)		

*One patient randomised to placebo, suffered a knee injury 1 day prior to his baseline visit that affected his walking ability. His baseline 6MWD (309 meters) was incorrectly deemed valid by the clinical evaluator, and he was stratified into the <350 m group. For the cITT analyses, his baseline 6MWD was replaced with his screening 6MWD (395 m), and he was re-stratified into the ≥ 350 m group.

Reproduced from clarification response A5.1.

4.2.9. Adverse events

Adverse events occurring in study 007 are summarised in Table 16 and 17. There were no discontinuations due to adverse events and no deaths were reported. On observation of the data, gastrointestinal disorders, vomiting, falls, investigations, weight decrease, metabolism and nutrition disorders, decreased appetite, musculoskeletal and connective disorders, back pain, nervous system disorders and headache appeared to occur more frequently in the ataluren group, whilst infections and infestations were slightly more common in the placebo group.

The CS presented cumulative summary tabulations of serious adverse events and subject exposure reported in four ongoing and five completed company-sponsored clinical trials of various doses of ataluren (CS Table 9.24, p.113 and CS Table 9.25, p.115). The ERG requested data for the 40mg/kg/day group only, with modified presentation of data to include the total number treated (and percent of cases) and rate per person months of follow-up. The Company provided the data for the 40mg/kg/day group (Table 18) in their clarification response. However the Company did not provide the rate per person months of follow-up, stating that this has not been calculated and that given the time the patients were on each therapy, there are limitations in assessing causality based on these data.

The Company also did not present the total number treated (and percent of cases) in this table as requested by the ERG. Instead the Company provided data we have reproduced in Table 19, which presents the cumulative subject exposure for ataluren and placebo from completed and ongoing clinical trials by estimated duration of exposure in Phase 2 and 3 studies. The Company states that "more patients were treated with ataluren than placebo; approximately 379 patients were treated with ataluren compared with approximately 172 patients treated with placebo as of 31 Jan 2015 (totals include patients who have received blinded study drug as of 31 January 2015 in the ongoing nmDMD Study 020). Also, based on study designs (open-label extension studies only included ataluren treatment), ataluren treatment duration was longer than placebo treatment duration" (Clarification response A8.5). The ERG notes that these numbers include all doses of ataluren (16 mg/kg/day, 40 mg/kg/day and 80 mg/kg/day). Comparison of serious adverse events between the 40 mg/kg/day dose and placebo is therefore limited. However, on observation of the count of cases in Table 18, it appears that 'cardiac disorders', 'infections and infestations', 'injury poisoning and procedural complication' (femur fractures) and total number of serious adverse events are more common among the ataluren group. It is not clear from the information provided whether the difference is due to longer exposure in the ataluren group, and without knowing more detail about exact person time at risk it is almost impossible to gauge relative rates of adverse events in ataluren and placebo groups. Also of note is that a total of 72 cases of serious adverse events occurred with all doses of ataluren (CS Table 9.25 p. 115); the majority, 58 (Table 18), of these occurred with the licensed dose.

Table 16 Overview of treatment emergent adverse events in the as-treated population

Parameter, n (%)	Placebo (N=57)	Ataluren 40 mg/kg/day (N=57)
Patients with ≥1 adverse event	56 (98.2)	55 (96.5)
Adverse events by severity		
Grade 1 (mild)	21 (36.8)	16 (28.1)
Grade 2 (moderate)	26 (45.6)	31 (54.4)
Grade 3 (severe)	9 (15.8)	8 (14.0)
Grade 4 (life-threatening)	0	0
Adverse events by relatedness		
Unrelated	14 (24.6)	8 (14.0)
Unlikely	16 (28.1)	17 (29.8)
Possible	20 (35.1)	25 (43.9)
Probable	6 (10.5)	5 (8.8)
Discontinuations due to adverse events	0	0
Serious adverse events	3 (5.3)	2 (3.5)
Deaths	0	0

Reproduced from CS Table C9.20, p.108 (excluding 80 mg/kg/day arm)

Table 17 Treatment-emergent adverse events with a patient frequency of ≥5%, Study 007

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm	
	Placebo	Ataluren 40 mg/kg/day
	N=57	N=57
	n (%)	n (%)
Gastrointestinal disorders	37 (64.9)	42 (73.7)
Vomiting	22 (38.6)	32 (56.1)
Diarrhoea	14 (24.6)	11 (19.3)
Abdominal pain upper	9 (15.8)	9 (15.8)
Nausea	7 (12.3)	8 (14.0)
Abdominal pain	4 (7.0)	7 (12.3)
Flatulence	4 (7.0)	5 (8.8)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm	
	Placebo	Ataluren 40 mg/kg/day
	N=57	N=57
	n (%)	n (%)
Stomach discomfort	0	4 (7.0)
General disorders	21 (36.8)	23 (40.4)
Pyrexia	12 (21.1)	14 (24.6)
Disease progression	6 (10.5)	4 (7.0)
Asthenia	2 (3.5)	3 (5.3)
Infections and infestations	43 (75.4)	38 (66.7)
Nasopharyngitis	13 (22.8)	13 (22.8)
Upper respiratory tract infection	10 (17.5)	9 (15.8)
Influenza	8 (14.0)	6 (10.5)
Gastroenteritis	4 (7.0)	9 (15.8)
Rhinitis	2 (3.5)	6 (10.5)
Ear infection	3 (5.3)	3 (5.3)
Gastroenteritis viral	3 (5.3)	4 (7.0)
Injury, poisoning and procedural complications	26 (45.6)	28 (49.1)
Fall	7 (12.3)	11 (19.3)
Procedural pain	7 (12.3)	6 (10.5)
Contusion	3 (5.3)	6 (10.5)
Joint sprain	1 (1.8)	4 (7.0)
Investigations	4 (7.0)	10 (17.5)
Weight decreased	1 (1.8)	5 (8.8)
Metabolism and nutrition disorders	3 (5.3)	7 (12.3)
Decreased appetite	2 (3.5)	5 (8.8)
Musculoskeletal and connective tissue disorders	19 (33.3)	25 (43.9)
Pain in extremity	6 (10.5)	7 (12.3)
Back pain	5 (8.8)	9 (15.8)
Muscle spasms	5 (8.8)	3 (5.3)
Muscular weakness	1 (1.8)	3 (5.3)
Nervous system disorders	17 (29.8)	25 (43.9)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm	
	Placebo	Ataluren 40 mg/kg/day
	N=57	N=57
	n (%)	n (%)
Headache	14 (24.6)	22 (38.6)
Dizziness	4 (7.0)	3 (5.3)
Respiratory, thoracic and mediastinal disorders	18 (31.6)	20 (35.1)
Cough	11 (19.3)	9 (15.8)
Nasal congestion	4 (7.0)	5 (8.8)
Oropharyngeal pain	4 (7.0)	6 (10.5)
Rhinorrhoea	6 (10.5)	4 (7.0)
Skin and subcutaneous tissue disorders	18 (31.6)	19 (33.3)
Rash	5 (8.8)	4 (7.0)
Scar	3 (5.3)	4 (7.0)

Abbreviations: MedDRA= medical Dictionary for Regulatory Activities

a Adverse events with a frequency of ≥5% across all three treatment arms are displayed alphabetically by MedDRA System Organ Class and from highest to lowest incidence across all three treatment arms within each System Organ Class. Patients who has the same adverse event more than once are counted only once for that adverse event

Adverse events with a frequency of ≤5% across all 3 treatment arms are not shown.

Reproduced from CS Table 9.21, p. 109 (excluding 80 mg/kg/day arm)

Table 18 Cumulative Summary Tabulation of nmDMD Total SAEs as of 31 Jan 2015: ataluren 40 mg/kg/day and placebo

System Organ Class (SOC)	Preferred Term	Count of Cases - ataluren	Count of Cases - Placebo
Cardiac disorders	Cardiac arrest	2	0
	Cardiac failure	2	0
	Cardio-respiratory arrest	1	0
	Myocardial infarction	1	0
	Tachycardia	3	0
	Ventricular arrhythmia	1	0
	Subtotal	10	0

Gastrointestinal disorders	Abdominal pain	1	1
	Intestinal obstruction	1	0
	Volvulus	1	0
	Subtotal	3	1
General disorders and administration site conditions	Death	1	0
	Lethargy	1	0
	Subtotal	2	0
Infections and infestations	Appendicitis	1	0
	Cellulitis	1	0
	Chicken pox	0	1
	Enterovirus	1	0
	Gastroenteritis	1	0
	Influenza	0	1
	Pneumonia	1	0
	Postoperative wound infection	3	0
	Subtotal	8	2
Injury, poisoning and procedural complications	Back Injury	1	0
	Compression fracture	1	0
	Femur facture	18	1
	Spinal compression fracture	1	0
	Tibia fracture	1	0
	Subtotal	22	1
Metabolism and nutrition disorders	Dehydration	2	1
	Subtotal	2	1
Nervous system disorders	Grand mal convulsion	0	1
	Intracranial pressure increased	1	0
	Loss of consciousness	1	0
	Migraine	1	0
	Subtotal	3	1
Psychiatric disorders	Mental status changes	2	0
	Subtotal	2	0
Renal and urinary disorders	Proteinuria	1	0
	Subtotal	1	0
	Hypoxia	1	0

	Pneumonia aspiration	1	0
	Pulmonary haemorrhage	1	0
	Pulmonary oedema	1	0
	Respiratory failure	1	0
	Subtotal	5	0
		Ataluren	Placebo
	Total	58	6

Reproduced from clarification response A8.5. This is an amended version of CS Table C9.25 p. 115.

Table 19 [redacted]

Reproduced from clarification response A8.5

4.2.10. Unpublished studies and ongoing trials

All relevant unpublished and ongoing trials were reported in the CS. An independent check for ataluren trials by the ERG did not identify any additional unpublished or ongoing trials. The relevant ongoing and unpublished studies were summarised as follows by the Company (page 71):

"*Available data from seven unpublished studies (four of which are on-going) are included in the pooled safety analysis (Table C9.5, and Section 9.7). This includes the original extension studies for Study 007 and Study 004, a Phase 2a open-label study (Study 008) in which patients received ataluren 80 mg/kg/day before the trials were prematurely discontinued due to lack of efficacy of the 80 mg/kg/day dose in Study 007. In addition, data from four on-going studies are included in the safety analysis: two open-label studies assessing the safety of the 40 mg/kg/day dose in patients who originally participated in Studies 007, 007e, 004, 004e or 008 (Study 016 and Study 019), the Phase 3 study (Study 020) and the open label extension of Study 020 (Study 020e).*"

Table C9.5 was reproduced as Table 20 below with some additional comments from the ERG. According to clinical trials.gov, all ataluren 80mg/kg/day trials have been terminated.

In addition to these seven trials one further ongoing trial was mentioned in the CS that did not inform the CS (page 39):

"*A registry study (PTC124-GD-025o-DMD) is being performed as a post-approval safety study, per the Pharmacovigilance Risk Assessment Committee of the EMA, to gather data on ataluren safety, effectiveness, and prescription patterns in routine clinical practice. This study has just started recruiting patients and no data will be available to inform this submission*."

Table 20 Seven unpublished studies (four on-going) included in the pooled safety analysis

Study Name /Data source	Study design	Population	Intervention/ comparator	ERG comment
PTC124-GD-004e-DMD (clinicaltrials.gov)/ Periodic Benefit Risk Evaluation Report, April 2015	Phase 2a, multicentre, open-label safety and efficacy study (complete)	36 patients that participated in Study 004	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for up to 96 weeks	included in the pooled safety analysis terminated according to clinicaltrials.gov
PTC124-GD-007e-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 2b, open-label, safety and efficacy extension study (complete)	173 patients that participated in Study 007	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for up to 96 weeks	included in the pooled safety analysis terminated according to clinicaltrials.gov
PTC124-GD-008-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 2a, open-label, safety and efficacy study (complete)	6 patients ≥7 years of age with nonsense mutation DMD/BMD who have been non-ambulatory for at least one year	Ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) for 2 to 7 weeks	included in the pooled safety analysis terminated according to clinicaltrials.gov
PTC124-GD-016-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Open-label Phase 3 safety trial (ongoing)	Ambulatory and non-ambulatory patients who originally participated in Studies 007, 007e, 004, 004e or 008 (USA). Estimated n=110	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration	included in the pooled safety analysis

PTC124-GD-019-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Open-label Phase 3 safety trial (ongoing)	Ambulatory and non-ambulatory patients who originally participated in Studies 007 and 007e (Europe, Israel, Australia, or Canada). Estimated n=96	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for an open duration	included in the pooled safety analysis
PTC124-GD-020-DMD/ Study 020 (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 3, multicentre, randomised, double-blind, placebo-controlled study (ongoing)	Male patients 7 to 16 years of age with nonsense-mutation dystrophinopathy. Estimated n=220	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) for 48 weeks Placebo	included in the pooled safety analysis
PTC124-GD-020e-DMD (clinicaltrials.gov) / Periodic Benefit Risk Evaluation Report, April 2015	Phase 3, open label extension study (ongoing)	The study will enrol ~ 220 boys with nonsense mutation dystrophinopathy who participated in Study 020	Ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg)for approximately 96 weeks	included in the pooled safety analysis

4.2.11. Details of relevant studies not included in the submission

The ERG did not identify any additional relevant studies that were not included in the submission.

4.3. Summary and critique of Company's Submission

This section critiques the Company's Submission and the decision to only present the outcomes for the 40mg/kg/day ataluren dose.

4.3.1. Overall quality

The ERG's quality assessment of the CS is summarised in Table 21. Overall, the quality of the

Company's systematic review is reasonable. Although the selection process was poorly reported in the CS, the Company provided clarification regarding discrepancies between the PRISMA flowchart and text, and a list of studies with reasons for exclusion, in response to clarification questions.

Two independent reviewers screened titles and abstracts (CS Appendix 17.1 p. 239), however it is not clear whether the same process was used for screening full texts. The processes for data extraction and quality assessment were not described.

The statistical methods used in trial 007 were considered to be appropriate, however a number of post-hoc adjustments as well as post-hoc and sub group analyses were undertaken. Many of these reported findings in favour of ataluren. The adjustments seem to be methodologically appropriate, but reporting these analyses as sensitivity analyses might have been more appropriate. Limited data are presented for some of the secondary outcome measures, and there is some evidence of selective reporting bias.

Despite these limitations, the submitted evidence generally reflects the decision problem, and the chance of systematic error is likely to be low based on the methods employed.

Table 21 Quality assessment of CS review

CRD Quality Item	**Score Yes/No/Uncertain with comments**
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes (CS Table C9.2, p. 66) See ERG report section 4.1.2 for critique
2. Is there evidence of a substantial effort to search for all relevant research?	Yes (CS p.65, CS Appendix 17.1 p234) See ERG report section 4.1.1 for critique
3. Is the validity of included studies adequately assessed?	Yes (CS p.87-89), however a narrative summary is not provided
4. Is sufficient detail of the individual studies presented?	Yes (for trial 007) Fewer baseline characteristics are reported for study 004, however this study makes little contribution to the submission, other than for safety.
5. Are the primary studies summarised appropriately?	Yes Results of trial 007 are presented in narrative

	form with accompanying tables and figures. These are appropriate for the primary outcome. However, limited data are presented for some of the secondary outcome measures. There is some evidence of selective reporting bias. Concerns regarding post hoc adjustments, including the use of cITT, analysis are discussed in section 4.2.3.

4.3.2. Justification for reporting outcomes only for lower ataluren dose

The CS restricted the reporting of effects of ataluren treatment to the lower ataluren dose (40mg/kg/day) as the higher dose (80mg/kg/day) did not result in an observable benefit on the 6MWD in the 007 trial. This was explained with the idea of a bell-shaped dose response curve. Clarification received from the Company for a justification of this explanation is supplemented here with further details from Peltz et al. (2013).[55]

Ribosomes, known as protein builders, move along the mRNA during the process of assembling amino acids, the building blocks of proteins, according to the coding in the mRNA sequence. A stop codon in the mRNA results in the dissociation of the ribosome – RNA complex which terminates protein synthesis. It is believed that ataluren (similarly to aminoglycoside) can bind to the ribosome which enables the read through of a nonsense stop codon. In explaining dose response in ataluren it has been suggested that at low doses ataluren binds to high affinity binding sites on the ribosome and triggers a positive effect, while at high concentrations ataluren binds to low affinity sites and cancels the effect. It should be noted however, that the target of ataluren has not been identified yet.[55]

Animal models have been used to study dose response. In addition study 007 undertook an analysis of 6MWD and timed function tests by ataluren C2h (plasma concentration 2 hours post morning dose)[41] which "showed that ataluren 80 mg/kg/day patients with lower concentrations (i.e., those in the range observed with the 40 mg/kg/day dose) experienced better outcomes than those patients with higher concentrations" (page 124).

In summary, the evidence seems to point towards feasibility of a bell-shaped dose response curve, however evidence on the mechanism of ataluren is still missing and the possibility of a type I error (false positive) related to lack of dose response cannot be excluded.

4.4. Summary and critique of results

In this section the evidence of the clinical effectiveness is summarised in terms of efficacy, safety, adverse events and deaths.

4.4.1. Efficacy

Primary Outcome

One RCT assessed efficacy of ataluren compared with placebo at 48 weeks on the outcomes of 6MWD, timed function tests, accidental falls, myometry tests, step activity monitoring, wheelchair use, HRQoL and treatment satisfaction, digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase. A non-randomised study assessed dystrophin expression, myometry and timed function tests after 4 weeks.

An ITT analysis of the primary outcome measure of a change in 6MWD from baseline to 48 weeks found no statistically significant difference between ataluren and placebo (difference 26.4m; p=0.09).

A cITT analysis (post-hoc corrected ITT analysis) was undertaken of the RCT and gave a statistically and clinically significant difference in 6MWD (difference 31.7m; p=0.02). Analysis of time to persistent 10% 6MWD worsening found a statistically and clinically significant difference that favoured ataluren on both ITT (HR 0.51; p=0.003) and cITT (HR 0.52; p=0.04) analyses.
In addition to the differences between the results of the ITT and the cITT analyses, the ERG noted some discrepancies in reporting of p-values for observed differences between the CS and the CSR.

[redacted]

Secondary outcomes

A number of secondary outcomes were investigated. Of those associated with timed function tests, only time to climb 4 stairs showed a statistically significant difference which favoured ataluren compared to placebo on cITT analyses in the RCT (2.4 seconds vs. 4.8 seconds; p=0.02).

Other outcomes e.g. descending 4 stairs, running or walking 10 metres and moving from supine to standing position found no statistically significant differences on cITT analyses in the RCT.

The frequency of accidental falls was significantly lower for those receiving ataluren than placebo at 48 weeks (RR 0.38; 95% CI 0.16, 0.94; p=[redacted]).

No statistically significant differences between ataluren and placebo were reported for the other

outcomes investigated of muscle strength, step activity, patient reported wheel chair use, HRQoL, treatment satisfaction, digit span, heart rate, muscle dystrophin expression and serum creatine kinase expression, in either study.

Sub-group analyses, which should be interpreted with caution included investigation of two groups of patients who were either in the decline phase (post hoc analysis) or who had a baseline of <350m 6MWD (i.e. more severe condition). Significant differences were found between those receiving ataluren compared to placebo on mean change in 6MWD. Patients in the decline phase subgroup had a reduction in the mean change in 6MWD of 45.6m (p=0.0096) less for ataluren than placebo, while those in the baseline <350m on 6MWD subgroup had experienced a reduction of 59.8m (p=0.0053) less for ataluren than placebo. On measures of change in 6MWD, with patients categorised according to their percentage predicted 6MWD at baseline, timed function tests, myometry and HRQoL, benefits were suggested for ataluren, though no statistical tests were presented.

Outcomes reported in the EMA report

The EMA report also summarises the results of the available evidence which appear to be the same as in the CS.[1] However, some p-values are discrepant between both documents with lower p-values being reported in the CS.

4.4.2. Safety and tolerability

No data were presented.

4.4.3. Adverse events

Adverse events were considered to 'probably be' related to the intervention for 10.5% of placebo and 8.8% of ataluren patients in trial 007. Severe adverse events (grade 3) were reported by 15.8% and 14.0% of placebo and ataluren patients, respectively. Some 5.3% of placebo and 3.5% of ataluren patients reported severe adverse events. Differences were evident in the adverse events reported by people receiving ataluren and placebo. Gastrointestinal disorders, vomiting, falls, investigations, weight decreases, metabolism and nutrition disorders, decreased appetite, musculoskeletal and connective disorders, back pain, headaches and nervous system disorders were more numerous in those receiving ataluren. In contrast, people receiving placebo incurred higher numbers of infections and infestations. A greater number of cases of serious cardiac disorders, infections and infestations, injury poisoning and procedural complications (femur fractures) and total cases of serious adverse events were apparent from a cumulative summary of serious adverse events from four ongoing and five completed Company-sponsored clinical trials. However it is not clear from the information provided whether this is due to longer exposure in the ataluren group. Most of the serious adverse events occurred in children who were receiving the licensed dose of ataluren.

4.4.4. Deaths

No deaths were reported in either study.

4.5. Summary of evidence presented in other submissions

Additional written submissions were received from NHS England, Muscular Dystrophy UK, Action Duchenne and parents/carers of a child with DMD who is participating in the double blind RCT. In addition, two video submissions were received from parents/carers and two expert submissions were received.

4.5.1. NHS England

The NHS England submission states that current treatment for DMD and nmDMD is supportive only. Geographical differences in median survival of patients with DMD have been reduced by widespread adoption of protocols for spinal surgery and for ventilation.

Ataluren is currently only used by trial and ex-trial patients, therefore current variation in use across England arises from the nature of trial recruitment. It is currently provided free of charge to trial and ex-trial patients so there is currently no direct impact on NHS resources. Initiation and monitoring of treatment should take place within expert centres but administration of the drug can take place at home.

The current budget for specialised and highly specialised services is £14bn per annum. Information on the scale of the NHS investment in areas of medicine comparable to nmDMD is not available.
NHS England estimates the budget impact of treating all eligible (i.e. within the licensed indication) patients will be about £15m to £20m per annum, depending on various assumptions about uptake (not defined). The main resource implication is the opportunity cost of high spend on the drug. The specialised services budget is said to be over committed. There may also be some cost from genotyping patients whose mutation is currently unknown, and extra staff costs for clinic time in monitoring the effect of treatment (particularly if loss of ambulation is a stopping criterion).
Guidance will permit the development of uniform clinical policy for patients of the NHS in England.
NHS England consider there to be no Equality or other issues.

4.5.2. Patient organisations

Muscular Dystrophy UK describes the delays in diagnosis that can be experienced by families, and the subsequent delay in receiving appropriate care and appropriate support at school. This is said to have an impact on cognitive and behavioural development. The submission summarises the impact of the condition, including significant time spent at hospital appointments, costs of care that increase as

the child becomes older (such as wheelchair costs, spinal rods, ventilator support), difficulties at school due to learning difficulties and coping with the disability, and the heavy financial and emotional burden on families.

The submission reports that DMD 'costs the …. £71,000 every year per patient' (a missing word makes the sentence unclear), with a 'total nationally of about £120m'. A recent study by Landfeldt et al. (2014) [34] is cited, and it appears these figures refer to the total burden of illness [total annual cost of illness plus intangible costs (a monetary value of the loss in patient and caregiver quality of life)] and the total economic burden of illness (using DMD prevalence estimates published in 2013), respectively. This study also found that in the UK 49% of caregivers reduced their working hours or stopped working completely due to their relative's DMD. The authors of the study acknowledge limitations of the study related to possible selection bias and the cross-sectional study design.

The submission also reproduces part of the parents' submission on the emotional and financial burden of the disease.

The emotional and psychosocial importance of delaying loss of ambulation to children with DMD and their families is emphasised, and quotes from four parents are presented to support this. A reduction in costs of care in the short term, by delaying loss of ambulation is also suggested, but details are not provided.

The submission states that early loss of ambulation is associated with a faster overall progression of the disease and that ataluren offers the prospect of delaying the later decline in physical, cardiac and respiratory function that occurs during the late teens and early adulthood. However the ERG notes that there is currently no evidence on the effects of ataluren beyond 48 weeks.

Muscular Dystrophy UK states that it is not aware of any disadvantages related to taking ataluren and that there is no indication that it would have adverse effects on other aspects of the condition.
The submission states that the current standard course of treatment for ambulant boys is steroid treatment. Severe side effects, including mood swings, weight gain and thinning bones can occur, which result in some families opting out of this treatment course. Steroids only address the symptoms of the condition, rather than address the underlying genetic cause. It is noted that ataluren would be taken alongside steroids, and that specialist physiotherapy and cardiac and respiratory monitoring would be continued.

Muscular Dystrophy UK comment that data show a clinically significant reduction in the decline in walking ability of boys taking ataluren, and that patients would therefore derive benefit from a longer

time spent ambulant and enjoy associated benefits in health and overall quality of life.

They key differences ataluren would make to patients and their families are listed as:

- a slower decline in physical function
- a reduction in some of the burden the disease places on families
- a spreading out of costs of care
- improved quality of life, through a longer period spent ambulant
- a potential lessening of emotional and behavioural difficulties amongst children experiencing rapid loss of ambulation

No Equality issues or other issues were identified.

Action Duchenne estimate around 2500 people have DMD in the UK (reference not provided), which seems slightly higher than the estimates provided by the CS (2200 people) and Muscular Dystrophy UK (2300 people), however the latter two figures are for England only.

The submission states that although treatments such as steroids may slow the progression of DMD, there is no cure. DMD causes the greatest number of deaths among genetic diseases in children and young adults.

Action Duchenne describes the advantages of ataluren to slow the progression of the disease, enabling those living with the condition to walk and be self-reliant for longer. The submission also states ataluren will decelerate muscle wasting around the heart and lungs and will subsequently improve life expectancy, however the ERG are not aware of any evidence for this. Action Duchenne state the improvements will serve to decrease the burden on families and the NHS to meet the support and care requirements associated with the conditions' degeneration. Psychosocial benefits are described as huge, with positive results on a walk test or stair climb and a stabilising of the degenerative impacts of the condition being crucial in giving families and patients more freedom, autonomy and stability in their lives.

Action Duchenne notes that only ambulant patients are eligible for treatment, but that ataluren would 'provide undoubted benefit to those non-ambulant patients whose Duchenne is engendered by a nonsense mutation'. However, the ERG notes there is an absence of evidence for the effects of ataluren in non-ambulant patients.

4.5.3. Parent/carer submissions

A mother and father of a boy with nmDMD each provided a written submission. Their son has been participating in the double blind trial of ataluren, and they are unaware of the allocation to either ataluren or placebo. The submissions describe the life-changing effects of living with DMD and the emotional and financial burden experienced by the family.

The submission outlines the monthly costs that they as a family incur and a list of other 'one off' costs. These include having to move to a house that can be adapted for a disabled child, changing car for easier accessibility, and having to give up work or reduce hours to provide care. Other additional costs include travel expenses, heating, shoes and clothing, counselling for the parents, physiotherapy and private swimming lessons.
The emotional impact of the condition is described, affecting siblings, parent relationships, the wider family and friends.

4.5.4. Video submissions

The first video submission (7 minutes 25 seconds) describes the experience of a 13 year old boy named Ross who has received ataluren. Ross participated in the RCT where he received placebo, and then received ataluren through the extension study for 6 months. Ross was then off the drug for approximately 3 years, and in February 2013 he re-started ataluren again through an open label study. The video appears to have been recorded in October 2013.

In the video Ross talks about his ambitions, the things he likes to do and the benefits of taking part in the trial. He describes how it helps him walk, go up a few stairs and get into the car. His muscles 'feel good' and he doesn't feel pain. He can do more things than he could before, he feels stronger and he has better balance.

Ross's parents describe his involvement in the trial. Towards the end of the 48 week double blind study, during which time he was on placebo, they saw deterioration in his condition. Ross then received ataluren for 6 months during the open label extension study. His parents saw an effect after just two weeks of receiving the drug. They describe how he had completely changed; the first thing they noticed was he could run down the stairs. He could play football, get up from the floor without using the Gower manoeuvre, and walk for two hours up and down hills in a city centre.

Once the drug was stopped his parents noticed a gradual decline, and four months after stopping the drug Ross lost the mobility they had seen when he was on treatment.

Within 2 or 3 months of starting ataluren again (almost 3 years off-drug) Ross was able to get into the car by himself again, and was still able to do so at the time of the video recording (about 8 months

after re-starting ataluren). His balance improved, he was able to stand in the shower, bend down and get up from the couch. He could play football in his bedroom and kick with his right foot instead of using it for balance. His parents conveyed how much it means to Ross's mental state to be able to do things on his own.

The second video submission (3 minutes 28 seconds) shows 11½ year old Isaac and his parents. The video was supported by PTC Therapeutics Ltd, June 2015.

Isaacs's parents describe how they know that the degenerative condition means that in the absence of effective treatment the trajectory is to lose the ability to walk and to suffer heart and lung failure at an early age. Isaac's parents describe his personality and his diagnosis. They say the prospect of new treatment options means hope, and means he can go on doing the things he loves and have real quality of life.

Isaac's parents say that for anyone with a progressive condition, especially one as severe as Duchennes, it is crucial that new drugs are made available as soon as possible: 'our boys don't have time to wait'. They believe that the sooner the children get the treatment, the more mobility (walking or upper body mobility) is preserved and more quality of life is given and that this will allow a 'positive future'.

4.5.5. Expert submissions

Three expert submissions were received by NICE of which two responded to questions listed. Table 22 and Table 23 present all the information reported in the expert submissions and the following section aims to summarise these.

The experts reported the number of boys with DMD in England and the UK (one reported incidence: "100 boys are born every year with DMD in England" and the other reported prevalence: "2200 DMD patients in the UK"). It is noted that around 10-13% might be expected to benefit from ataluren during the time they are above 5 years old and before they lose ambulation. It was reported that around 66 people with DMD would be eligible for ataluren. The people with DMD who are likely to benefit from the drug are those with nonsense mutations. These people are not known to be different in any way from the general group of people with DMD. The DMD population who are eligible to receive ataluren and who might benefit from it due to the specific mutation type is an even rarer subgroup. Small numbers of children who develop early cardiomyopathy have a poorer prognosis. DMD is a uniformly progressive disease and leads to premature death.

The experts reported similar comments regarding the support for DMD. It appears to be mainly

managed by doctors at centres involved in the funded clinical network - North Star (MDUK – see section 2.5). DMD standards of care which have been published in Lancet Neurology[8] An update is being undertaken by Centers for Disease Prevention and Control in Atlanta. There are some variations in practice and different aspects of the service are not met in various areas. Currently, consultants in three specialist neuromuscular centres in the UK are experienced in prescribing and monitoring ataluren (Professor Bushby, Newcastle. Professor Muntoni Great Ormond Street Hospital, Dr Quinlivan, Great Ormond Street Hospital and the National Hospital Queen Square). The expert submissions state that ataluren is not likely to impact on the current level of patient care or services in the UK. It could be provided within the current clinical structure for managing DMD without further need for support.

DMD is currently treated with corticosteroids but there are regional variations concerning the steroid regimen in the UK. The optimal benefit of steroid treatment is being investigated in the 'forDMD' trial. Other management strategies include physiotherapy, cardiomyopathy treatment and spinal surgery for scoliosis, home ventilation, and cough assistance. It is hoped that the side effect profile for ataluren might be favourable to steroids long term but this would need to be confirmed.

The experts agree there is no other intervention currently licensed for this condition and that it is important to fully recognise the benefits of slowing disease progression. Steroid use to slow disease progression in the short term has a long term benefit on disease milestones (e.g. independent ambulation, self-feeding, need for overnight ventilation and development of scoliosis). Ataluren might have a similar long term effect in terms of slowing disease progression. Ataluren has been well tolerated and doesn't appear to have major side effects in the trials available to date. There are no data on the effects on quality of life.

Table 22 Expected place of ataluren in current practice

Name and Organisation and Role	Information on the number of patients in England with the condition and current treatment in the NHS	Subgroups of patients with the condition who have a different prognosis from the typical patient	Impact of the technology on the delivery of the specialised service	Variation in how it is being used in the NHS	Relevant clinical guidelines
Professor Kate Bushby Newcastle University and NUTH A specialist in the treatment of people with the condition for which NICE is considering this technology A specialist in the clinical evidence base that is to support the technology	About 100 boys are born every year with DMD in England. Around 10-13% of them might be expected to benefit from the drug during the time they are above 5 years old and before they lose ambulation (as per label). DMD is managed mainly by doctors and MDTs at centres who participate in a charity funded clinical network	The subset of DMD patients likely to benefit from the drug are those with nonsense mutations. They are not known to be different in any way from the general group of DMD patients	No	N/A	The Lancet Neurology published care considerations for DMD in 2010 in two parts (Bushby et al). these have been NICE process accredited. An update is currently underway led by the CDC in Atlanta and supported by international patient organisations.

	the North Star (MDUK). These centres are mainly trying to be compliant with the DMD standards of care which have been published in Lancet Neurology and which are the basis of the Neurology specialised service annex for neuromuscular diseases. However there are some variations in practice where different aspects of the service are not met in various areas.				
Dr Ros Quinlivan National Hospital for Neurology, UCLH, London A specialist in the	Approximately 2200 DMD patients in the UK, 66 of whom will be eligible for the new treatment.	A small number of children who develop early cardiomyopathy have a poorer prognosis and die at an earlier	The new technology is not likely to impact on the current level of patient care or services	The drug is currently available to some patients in the UK enrolled in a phase three study. It is	There is a NICE accredited guideline for the management of DMD, also published in the Lancet. It is an

treatment of people with the condition for which NICE is considering this technology A specialist in the clinical evidence base that is to support the technology Has acted as a medical expert for PTC bio	The condition is treated with corticosteroids, either daily of 10 days on 10 days off, there is some regional variation for steroid regimen. However, the evidence for which regimen provides optimal benefit is not available. The 'forDMD' trial is currently underway to answer this question. Other management strategies include physiotherapy, cardiomyopathy treatment (ace inhibitors and beta blockers) and spinal surgery for scoliosis, home ventilation -	age.		available in other European countries for prescription	international consensus document which used a DELPHI approach.

	BIPAP, cough assist.				
Dr Adnan Manzur Consultant Paediatric Neurologist, Dubowitz Neuromuscular Centre, GOSH Involved in the treatment of people with Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene and have specialist expertise in this area Work principally for the NHS Published papers on topics in Duchenne muscular dystrophy	No comments received	No comments received	No comments received	No comments received	No comments received

Table 23 The advantages and disadvantages of the technology, relevant evidence, implementation and equality issues

Name	Views on how the technology, when it becomes available, will compare with current alternatives used in the UK.	What is the relative significance of any side effects or adverse reactions?	Relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence	Implementation issues	Equality issues
Professor Kate Bushby	There are no currently licensed drugs for DMD. Current treatment includes corticosteroids. It is hoped that the side effect profile for ataluren might be favourable to steroids long term but this would need to be confirmed by long term studies. The label suggests terminating the drug at loss of ambulation. I am not sure this completely makes sense as it is possible the drug could also benefit non ambulant	As the drug is only newly available there are no new data on side effects, but the drug did not appear to have major side effects in the trials available to date.	The drug has not been available for long enough to be able to generate these data	It could be provided within the current clinical structure for managing DMD without further need for support.	The DMD population is an example of a rare disease group. The population who are eligible to receive ataluren and who might benefit from it due to the specific mutation type is an even rarer subgroup. No other interventions are currently licensed for this disease and it is uniformly progressive and leads to premature death. It is really important not to discriminate against this patient group by not taking full notice of the

	boys but it reflects lack of trials in the non-ambulant population. There were quite a lot of UK children enrolled in the clinical trials and their overall conduct reflects our practice generally.				benefits of slowing disease progression. We have seen with steroid use that slowing disease progression in short term studies has a long term benefit on highly patient relevant disease milestones such as independent ambulation, self-feeding, need for overnight ventilation and development of scoliosis. It could be extrapolated for ataluren that the slowing in disease progression seen in the trials might have a similar long term effect. The current population of DMD patients in England will be discriminated against compared to patients in other EU countries if they are not allowed access to the drug

					at the current level of risk/ benefit which was enough for the regulators to come to a positive opinion. Once skills are lost in DMD they are gone and in the context of a lifespan of maybe 30 years, a couple of years is a significant chunk to await a decision on the use of a drug which might have a beneficial effect. However there is not additional evidence beyond watching how the drug behaves in practice to be able to answer these imponderables- the only way is by approving the drug and watching how it performs with strict guidance on withdrawal if efficacy in the longer term cannot be established.

					It is to me discriminatory that for drugs for rare diseases the high cost of drugs means that inevitably they have a very high threshold to reach. That is not these patients' fault and we have to find a way to square this difficult balance without the patients losing out.
Dr Ros Quinlivan	I was involved in the phase 2b study of this drug and now the phase 3 study.	It is well tolerated by patients with few significant side effects. At this stage, I cannot comment on quality of life because data are not yet available from the phase 3 studies, however, there was a trend for improvement in the phase 2b study. No new side effects have been reported by my patients in the	Results of a Phase 2b, dose-ranging study of ataluren (PTC124®) in nonsense mutation Duchenne/Becker muscular dystrophy (nmDBMD) Finkel et al. (2010)[56] Bushby et al. (2014)[41] Finkel et al. (2011)[57] Haas et al. (2014)[2]	Currently, consultants in 3 specialist neuromuscular centres in the UK are experienced in prescribing and monitoring Ataluren (Professor Bushby, Newcastle. Professor Muntoni Great Ormond Street Hospital, Dr Quinlivan, Great Ormond Street Hospital and The National Hospital Queen Square). These clinicians	If funding of this drug is CCG based it is highly likely that there will be variations in prescribing across the UK because of its cost. Centralised funding should not pose a problem with equality of access

		phase 3 trial. The drug has been used with steroids and cardiac medications in both trials without any interactions.		could either be responsible to prescribing and monitoring treatment within their teams and/or they can disseminate knowledge through the North Star Network of Neuromuscular centres. No additional facilities or equipment are required	
Dr Adnan Manzur	No comments received	No comments received	No comments received	No comments received	No comments received

4.6. Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook additional work required relating to the clinical effectiveness evidence submitted in the CS. The ERG checked the searches, spot checked excluded studies and undertook searches for ongoing trials, the ERG undertook a thematic analysis of the qualitative evidence presented in other submissions and sought advice from a statistician on the trial statistical methods and from the specialised commissioning team at NHS England for a HST commissioning perspective. The outcome from these have fed into the relevant sections of this review.

4.6.1. Thematic analysis of patient submissions

A novel piece of synthesis was undertaken by the ERG. The ERG undertook a crude thematic analysis of the patient submissions from two perspectives, the impact of DMD and the potential for treatment with ataluren. The two patient videos were transcribed and the ERG used an approach based on qualitative principles to code and generate themes from the six patient submissions. Two patient submissions were from one family, providing each parent's perspective of the condition.

4.6.1.1. Impact of DMD on families

Five key themes emerged from the submissions. These were named 'emotional + social', 'practical + financial', 'caring + coping', 'progressive disease' and 'life expectancy'. Table 24 provides details of the number of references made for each of these themes, and the total number of sources that made these references. Example narrative from the submissions is also provided. The emphasis of the impact appeared to be on the emotional and social impacts of DMD.

Table 24 References in patient submissions about the impact DMD has on their lives

Impact Themes	**Number of references / number of sources**	**Examples**
Emotional + social	36 references / 3 sources	"…felt our lives just crumble beneath us" "Over the next couple of years we became very reclusive" "…they see their friends able to do more and more… they are able to do less and less. This can result in severe emotional difficulties"
Practical + financial	10 references / 2 sources	"..impacting on all areas of family life, including in many cases parents' earning capacity".

		"had to move house because our last house was not suitable for a disabled child" "gave up working…and cut down… hours"
Caring and coping	2 caring references / 2 sources 10 coping references / 2 sources	"…loving and caring brother" "continue with normal family life, which is so important to us as a family" "…carries on and always has a smile on his face"
Progressive disease	13 references / 5 sources	"Loss of ambulation is also associated with a faster progression of the disease". "progressive loss of strength" "it was just the power that he seemed to lack, the power at walking".
Life expectancy	8 references / 4 sources	"causes the greatest number of deaths amongst genetic diseases in children and young adults" "conscious of the clock ticking". "we had to tell…live until they're about 30, on average, in the UK".

4.6.1.2. Potential for treatment with ataluren

Three key themes emerged from the submissions. These were named 'self-reliance –reduced burden'; 'hope' and 'effects'. Table 25 provides details of the number of references made for each of these themes, and the total number of sources that made these references. Example narrative from the submissions is also provided. It appears that self-reliance and reduced burden are important to carers.

Table 25 References in patient submissions about potential for treatment with ataluren

Impact Themes	**Number of references / number of sources**	**Examples**
Self-reliance + reduced burden	15 references / 5 sources	"a longer period of ambulation as allowing…to just be one of the boys".

		"enabling those living with the condition to walk and be self-reliant for longer". "It's good to participate in the trial, it helps me walk and go up a few stairs and get into the car and stuff".
Hope	10 references / 6 sources	"Translarna is the first drug that has given us and the whole of the Duchenne community real hope". "there are possible treatments that may come on stream in the future is given and that the picture is one of hope and hopefully a positive future for people with Duchenne". "Our expectation of the drug was to hopefully stabilise…".
Effects / anticipated effects	15 references / 5 sources	"ataluren offers the prospect of delaying the later devastating decline in physical, cardiac and respiratory function that occurs during the late teens and early adulthood". "The sooner they get the treatment, the more mobility, both walking or upper body mobility, the more of that…is preserved and therefore the more quality of life you are giving people". "It will crucially decelerate muscle wasting around the heart and lungs and will subsequently improve life expectancy".

4.6.1.3. Other observations

The ERG notes that there are no references to any negative consequences of treatment with ataluren in the submissions. One submission refers to the questions asked about disadvantages and adverse events, stating that there are no known disadvantages to the treatment or any differences in opinion on the usefulness of the treatment, and that there are no reported side effects.

The submissions testify to a reduction in emotional and psychological burden of the condition with treatment. No submissions report whether there is a reduction in the practical burden, for example, if carers are able to return to work as a result of the greater independence of the child owing to treatment.

There is little discussion of the longer-term effects of treatment with ataluren. One submission discusses the impact that stopping treatment between trials had on the child, where there was a reverse of many of the positive benefits that had been seen.

The ERG notes that there are no details on how generalisable these views are to the wider UK nmDMD community. It is expected that there is a positive response bias to these submissions.

4.6.2. Summary of main conclusions from the EMA

Another additional piece of work undertaken by the ERG was an evaluation of the conclusions drawn from The European Medicines Agency report (2015).[1] This report identified a need for input from a specialist Scientific Advisory Group (SAG) Neurology on three specific questions which are pertinent to this HST. Since our clinical experts advising the ERG on this HST have declared conflicts (e.g. reimbursement from PTC, advisor to PTC,) the ERG decided to summarise these points made by the SAG to gain a broader consideration of the evidence base.

An application was made to the EMA for the following indication:

- Ataluren is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in patients aged 5 years and older.
- Presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.
- Recommended dose of ataluren is 40 mg/kg/day, divided in 3 doses (10 mg/kg in morning, 10 mg/kg at midday and 20 mg/kg in evening) within 30 minutes of a meal.

The EMA report stated that in terms of the chemical, pharmaceutical and biological aspects the quality of ataluren was considered to be acceptable when used in accordance with the conditions defined in the summary of product characteristics (SmPC). The EMA report (page 13) noted that:

"Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way".

In referring to the available evidence presented by the Company, the ERG support this conclusion.

Overall, the Committee for Medicinal Products for Human Use (CHMP) concluded that:

"despite the identified weaknesses of the pharmacology data (on mechanism of action and bell-shaped dose-response hypothesis), the limitations within the nonclinical package could be considered acceptable, if sufficiently compensated by compelling clinical evidence" (Page 23 of EMA).

The ERG are in agreement with these comments, in particular those related to the limited evidence currently available.

4.6.2.1. Dose

The CHMP considered *"that the data on dose- and time linearity/non-linearity were inconclusive, but the clinical trial data suggesting that the steady state is maintained from week 6 through more than two years of treatment were re-assuring."* (page 29 of EMA). Further consideration of dosing are addressed in this section and in Section 8.2 of the ERG report and in clarification question responses by the Company.

No dose response studies were performed. It is noted that CHMP emphasised *"The disabling and life-threatening nature of DBMD [Duchenne/Becker muscular dystrophy], the lack of approved therapies to treat the underlying cause of this disease and the serious consequences of chronic corticosteroid administration in boys with DBMD mandated that the highest tolerable dose be explored in order to maximize the potential for benefit."* (page 30 of EMA).

It was noted by CHMP that *"age-adjusted dosing would not be required and that the data available on patients of other than Caucasian population were limited to allow any conclusions regarding use in different ethnic groups"* (page 29 of EMA). CHMP also noted that there were no specific studies in patients with renal or hepatic impairment. As ataluren is extensively metabolized in liver and renal excretion accounts for 50% of the drug elimination, the ERG noted that the CHMP advised that close monitoring would be required in clinical practice, should patients with hepatic and renal impairment be treated.

The overall pharmacological profile of ataluren in human studies was considered to be not adequately documented. CHMP concluded that *"there was a lack of relevant data on the pharmacodynamics effects of ataluren in humans reinforcing the uncertainties raised on its mechanism of action and the dose-response relationship"* (page 30 of EMA).

4.6.2.2. Clinical efficacy

The EMA confirm available evidence reported by the ERG related to the phase 2b efficacy and safety study of PTC124 in subjects with non-sense-mutation-mediated Duchenne and Becker muscular dystrophy. The CHMP concluded that

"While the effects observed in the pivotal study were considered generally encouraging, the CHMP considered that the clinical efficacy data submitted were not adequate and did not provide sufficient evidence to support the indication of ataluren for the treatment of patients with Duchenne muscular dystrophy." (page 51 of EMA).

The ERG evaluate the evidence and consider these conclusions further in Section 4.5.

4.6.2.3. Additional expert consultation

In the EMA report, CHMP identified a need for input from a specialist Scientific Advisory Group (SAG) Neurology on three specific questions which are pertinent to this HST. The ERG felt it was important to provide a range of clinical opinion on the clinical effectiveness evidence outside of those experts advising the ERG. The following section provides the responses to three key questions:

a) Question 1: Does the SAG consider that the evidence for the mechanism of action of ataluren (nonsense mutation read-through) is convincing, and the results on dystrophin production could be seen as supportive of the pharmacodynamics of ataluren?

"The SAG considered that mechanism of action seemed plausible, but the experts felt that the provided data were still not convincing enough, and that they would need more information in order to be certain. The same was true for the data provided on dystrophin production in this case, that at least the data from the available biopsies, limited as they may be, should be provided. Thus the SAG considered that presently the available data on dystrophin production cannot be used as supportive of the pharmacodynamics of ataluren." (*page 49-50 of EMA).*

In agreement with the evaluation made by the SAG, the ERG noted that there was limited data available, even when considering the more recent available evidence published since the EMA report.

b) Question 2: Does the SAG agree that the presented pre-clinical and clinical evidence supports the bell shaped dose-response curve and hence, the absence of efficacy at the higher dose studied?

"The SAG considered that the proposed hypothesis for the bell shaped dose response curve seemed likely, but once again the experts felt that additional information was needed. More specifically, it was noted that while evidence on the bell-shape dose-response curve was available in several pre-clinical models, no data were generated in the mdx mouse model, relating the production of dystrophin to the levels of ataluren in the muscle fibres. Such evidence would be considered of relevance, as the available data describe only the relationship between plasmatic levels of ataluren and dystrophin production.

Overall, the SAG was of the view that no clear-cut conclusions could be derived on the bell-shaped dose-response hypothesis and the absence of efficacy in the higher dose studied in the Ph II trial." (*page 50 of EMA).*

c) Question 3: Does the SAG consider, based on the data presented by the Applicant, that the observed effects are sufficiently robust and clinically meaningful taking into account the results on the primary and secondary endpoints?

"The SAG considered that although the results were not sufficiently robust, the demonstrated effects were encouraging. The robustness of the results was challenged because of the observed variability in the primary efficacy data, the fact that many of the important conclusions supporting the efficacy of the drug were derived from the performed post hoc analyses, and the fact that there was little supportive evidence of effect from the data on the secondary endpoints. At the same time it was recognized that at the time the study was designed the knowledge of the natural history of the disease was different from what we now know. It was agreed that the applicant has performed the post hoc analyses in line with the most current knowledge about the natural history of the disease, and in this respect the definition of the sub-groups in these analyses is clinically and scientifically justified. The SAG experts considered that the results derived from these may be considered clinically relevant, especially in the sub-group of patients with more advanced disease. Additionally it was considered that the lack of effect on the secondary endpoints could be explained by the expected mechanism of action of the drug i.e. partial restoration of dystrophin production. Most of the secondary endpoints are of such nature that any effect will have to be driven by an increase in strength, rather than an improvement of function. The experts were presented with the latest available data, showing that minimal increase in dystrophin production could lead to functional improvement, but not to improvement of strength, and for the latter to occur, levels of dystrophin close to the ones in normal muscular fibres must be achieved. The SAG experts agreed that this could be a valid explanation of the lack of concordance between the primary and secondary endpoints' efficacy data. It was also the position of the group that despite the fact that efficacy was most prominently shown in the subgroup of patients with more advanced disease, there were trends of efficacy in all the sub-groups by severity,

although of a different magnitude. This effect is to be expected, as according to the data presented by the experts, the decline in function of Duchenne patients is not linear, but rather the speed of functional decline increases with the duration of the disease. In that respect, it would be very difficult to show a significant functional improvement in milder patients in the frame of a controlled clinical trial with duration of 1 or 2 years. On the contrary, in the most severe patients even a small effect on function would be detectable and clinically meaningful. The patients and representatives in the room, in their statements, defended the position that at that late stage of the disease even small effects providing longer independent use of arms and hands, or preserving the ability to feed and drink from a cup on their own, would represent a significant and important effect. Taking all of the above in consideration, the SAG experts felt that there should be no scientific reason for the drug not to be given to milder patients if efficacy is established in more severe ones. The long term benefit on this population could be documented by a follow-up of data collected in specific registries.

Overall, considering the totality of the evidence available to date, the SAG was of the view that while ataluren can be considered as a potentially efficacious drug, the data from the confirmatory phase III trial are necessary before final conclusions on efficacy can be made.

This conclusion was shared by the CHMP."

In summarising the SAG comments, the ERG highlight the following points for consideration:

- Robustness of the results was challenged because of the observed variability in the primary efficacy data
- Many important conclusions supporting the efficacy of ataluren were derived from post-hoc analyses
- There was little supportive evidence of effect from the data on the secondary endpoints.
- Effect of most secondary endpoints are driven by an increase in strength, rather than an improvement of function
- Minimal increase in dystrophin production could lead to functional improvement, but not to improvement of strength
- Efficacy was most prominently shown in the subgroup of patients with more advanced disease
- Trends of efficacy were visible in all the sub-groups by severity, although in different magnitudes.
- Difficult to show a significant functional improvement in milder patients in the frame of a controlled clinical trial with duration of 1 or 2 years.
- In severe patients even a small effect on function would be detectable and clinically

meaningful

- At late stage of the disease even small effects providing longer independent use of arms and hands, or preserving the ability to feed and drink from a cup on their own, would represent a significant and important effect.

4.7. Summary and conclusions of the clinical effectiveness section

4.7.1. Completeness of the CS clinical effectiveness section

- The ERG considered that searches undertaken to identify evidence were generally appropriate and no studies meeting the selection criteria should have been missed. Limitations in the searches included limited search terms for best supportive care, restriction to English language studies, changes in search strategy between main and update searches.
- Identified studies were assessed against broad selection criteria however the methods for this were not completely transparent and the assessments were not well reported. Some inconsistencies were evident in the reporting of the process, particularly in terms of applying the criteria at different stages and in reporting outcomes through PRISMA.
- Clarification from the Company and checks undertaken by the ERG however indicated that it was highly unlikely that any key studies were missed.
- Eligible studies for the systematic review of clinical effectiveness included one RCT - Study 007 (Bushby et al., 2014[41] and [25, 43-49]) and one cohort study (study 004,Finkel et al 2013)[42]
- Some uncertainty was identified around completeness of reporting of outcome measures and estimates and statistics. Limited data or no data were presented for outcomes that were not statistically significant, for example: step activity monitoring, treatment satisfaction, cognitive ability, heart rate monitoring, serum creatinine kinase expression and dystrophin expression. In addition, a number of post-hoc adjustments and post-hoc analyses were undertaken.

4.7.2. Interpretation of treatment effects: CS clinical effectiveness section

- The CS reported the efficacy of ataluren (40mg/kg/day) compared to placebo (or best supportive care) on the outcomes of 6MWD, timed function tests, accidental falls, myometry tests, step activity monitoring, wheelchair use, HRQoL and treatment satisfaction digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase. The populations assessed were boys aged ≥5years with a diagnosis of DMD and an ability to walk at least >75 metres

unaided.

- The clinical and statistical significance of results varied, depending upon the outcome and statistical approach taken (i.e. type of ITT analysis). The RCT did not show a statistically significant benefit in the primary outcome - change in 6MWD from baseline to 48 weeks. A benefit of ataluren compared to placebo only became statistically and clinically significant in the primary outcome when a post-hoc corrected (cITT) approach was taken (ITT: difference 26.4m (p=0.09); cITT: difference 31.7m (p=0.02)). Ataluren had a beneficial effect in extending the time to persistent 10% 6MTW worsening that was both statistically and clinically significant on ITT and cITT analyses (ITT: HR 0.51 (p=0.003); cITT: HR 0.52 (p=0.04)) analyses. [redacted]
- The cITT analysis varied from the ITT analysis by changing the process of analysis and inclusion for two children (adopting screening rather than baseline data with one patient in the placebo group and one patient in the 80mg/kg/day group).
- Post-hoc sub-group analyses focusing on patients with a more severe condition (i.e. decline phase of DMD or a baseline of <350m 6MWD) identified that ataluren conferred a statistically significant benefit in limiting the reduction in the mean change in 6MWD compared to placebo. (Difference in reduction - decline phase: 45.6m (p=0.0096); baseline <350m 6MWD: 59.8m (p=0.0053)).
- These findings indicate that ataluren appears to have some effect on the ability of boys aged ≥ 5 years who could walk unaided >75 metres at baseline in maintaining their ability to ambulate, however whether there is a clear statistical or clinical benefit remains uncertain. It is evident that patients identified as having a more severe condition (i.e. decline phase or baseline <350m 6MWD) appeared to benefit more with ataluren compared to placebo. However, the effects on patients with less severe disease were not reported and, as a consequence, the findings should be viewed with caution.
- On secondary outcomes the evidence was more equivocal. Only time to climb 4 stairs (2.4 seconds vs. 4.8 seconds; p=0.02) and frequency of accidental falls (RR 0.38; 95%CI 0.16, 0.94; p=[redacted]) appeared to benefit significantly from ataluren compared with placebo. For other outcomes, (specifically descending 4 stairs, running or walking 10 metres or moving from supine to standing position, muscle strength, step activity, patient reported wheelchair use, HRQoL, treatment satisfaction, digit span, heart rate, muscle dystrophin expression and serum creatine kinase expression), no statistically significant differences were reported

between ataluren and placebo in either study. On sub-groups defined by condition severity, it was reported that results favoured ataluren over placebo though no statistical tests were reported.

- Similar rates of severe adverse events were experienced by patients receiving ataluren and placebo but there were difference in types of event. Gastrointestinal disorders, vomiting, falls, investigations, weight decreases, metabolism and nutrition disorders, decreased appetite, musculoskeletal and connective disorders, back pain, headaches and nervous system disorders were more likely to occur with ataluren. In contrast, patients receiving placebo had higher rates of infections and infestations. Higher numbers of femur fractures were reported in groups taking ataluren.
- Data were not reported on safety and tolerability of the treatments and no deaths were reported from either study.
- The Company presented a cumulative summary of serious adverse events from four ongoing and five completed Company-sponsored clinical trials. This appeared to suggest that serious cardiac disorders, infections and infestations, injury poisoning and procedural complications and total number of serious adverse events are more common with ataluren than placebo, however it is not clear from the information provided whether this is due to longer exposure in the ataluren group.

4.7.3. ERG assessment of uncertainties in clinical effectiveness

- A key criterion for the appraisal, and for the evaluation undertaken in the RCT and the CS was the definition of loss of ambulation. The NICE scope does not provide a clear definition. The RCT states that for inclusion in the study a loss of ambulation relates to the ability of the patient to walk ≥75 metres. The criteria used in the RCT are adopted by the company in the CS for the systematic review of clinical effectiveness. However, the CS economic model adopted a different definition of loss of ambulation (i.e. inability to walk >0 metres). Inevitably the different definitions may influence the outcomes of the assessment.
- The comparator adopted in the RCT was best supportive care. Given that it was a multinational trial, it was felt that there may be heterogeneity in the comparator that may affect the outcome and influence its external validity.
- The selection of evidence through the search strategy and the selection process had the potential to affect the evidence reviewed in the systematic review of clinical effectiveness. Discrepancies in the search strategy used in the original and update

searches had the potential to affect the results, however the breadth of the searches meant this should not be significant. Although selection processes were not clearly identified in the CS, clarifications from the Company indicated that appropriate steps were taken.

- Similarly, the methods used in the systematic review were not clearly described, providing the opportunity for error and bias.
- The analysis and presentation of outcomes lacked transparency and may have been affected by bias. Post hoc-adjustments and analyses were undertaken which, despite being appropriately conducted, all appeared to favour ataluren compared to placebo. When the primary outcome of 6MWD was analysed using an ITT approach, it found a non-statistically significant benefit for ataluren compared to placebo. This benefit became statistically and clinically significant only when a corrected ITT (adopting screening rather than baseline data for 2 patients) was applied. The analysis also focused on post hoc sub group analyses of the importance of condition severity, presenting results for patients in the decline phase and those <350 metres at baseline on the 6MWD. These groups benefitted significantly on measures of the 6MWD when receiving ataluren compared to placebo. However, similar outcomes were not presented for the non-severe groups to provide an appropriate comparison.
- It was felt that due to concerns around the underestimation of the standard deviation of the primary outcome measure of the 6MWD scores, the trial was underpowered and that this may have affected the statistical significance of the estimates.
- Some outcomes that were assessed in the RCT were not reported in the [redacted]) and for some measures there was no evidence (e.g. carers QoL, lung function, mortality).
- The RCT had a follow-up limited to 48 weeks and the cohort to 28 days. It is possible that neither provided sufficient time for some outcomes to be assessed (e.g. mortality).
- Concerns were raised about possible heterogeneity in the patient population in the RCT, with two patients having Becker's MD. Although the Company indicated that these patients and those with DMD are on the same spectrum and should have similar outcomes, some uncertainty remains.
- Some concerns were raised about the translation of some of the effects into outcomes for patients, specifically in terms of strength and functionality.
- Submissions from patients, clinicians and patient support organisations provide a

valuable source of evidence concerning other considerations that should be taken account of in the appraisal. Key themes from the submissions include the emotional and social impacts of DMD, the anticipated effects of treatment, and the importance to carers of self-reliance and reduced burden. Inevitably, these need to be balanced with the other forms of evidence and appropriate weight given.

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1. Introduction

This chapter reports a critical assessment of whether ataluren for treatment of nonsense mutation Duchenne muscular dystrophy represents value for money for the NHS in England. We draw on the CS which comprises a systematic review of the health economic literature, a de novo health economic model, key model inputs (e.g. clinical and costs), methods and findings. In this chapter we review and critique the Company's systematic review of existing economic analyses (Section 5.2) and give an exposition of the methods and results of the Company's model (Sections 5.3 and 5.4). This is followed by a critique (Section 5.5) of the Company's model.

5.2. Review of existing economic analyses

The Company has undertaken a systematic review of the economic evidence to identify all economic studies for DMD in order to inform the model design/structure and to provide key input parameters for the model. The Company undertook a broad search of relevant electronic databases. The original searches were undertaken in July 2014 and updated on 8th June 2015. The ERG believes that the search strategy and lines appear to have been combined appropriately, but note that there are relevant terms in the original search that are not included in the update and vice versa. Additionally, different interfaces were used in the update. Both these factors may have affected retrieval. The initial search identified 748 studies and the subsequent update identified 72 studies. Further information was provided by the Company at clarification question stage. The Company confirmed that the original search was undertaken on 21st July and that "*the totals given in Appendix 3 were for a preliminary search that was run 3 weeks earlier*". Flow diagrams are provided (see figs D11.1 and D11.2 of the CS). The Company provided lists of excluded studies in response to a clarification question, but state that "*the reason for exclusion from the original economic/HRQoL search was not available*".

Two economic studies met the inclusion criteria and brief synopses of these studies were provided. The Company provided information on patient population, methods and results. However, the ERG believes it would have been useful for the Company to provide more information/results in Table D11.3 of the Company submission, on the health-related quality of life (HRQoL) collected in patients and caregivers in the Landfeldt et al. (2014)[34] study, as HRQoL is one of the outcomes measures of interest in the current study. Also, the ERG thought it would have been useful to have information on the prevalence of DMD (if stated) and the cost year.

Given the search strategy and the inclusion and exclusion criteria, it is unlikely that any key published economic studies will have been missed. However, the ERG would have found it useful if the Company had submitted a list of excluded studies and the reasons for exclusion.

5.2.1. Health-related quality of life

The Company further conducted a systematic review of the literature to identify studies that evaluated HRQoL for people with DMD and their carers, which could be used to derive health state utilities for use in the economic analysis. The search identified one relevant study that evaluated HRQoL for people with DMD using a generic preference based measure. The ERG conducted an independent search for HRQoL data for people with DMD and their carers, but found no other relevant studies.

5.3. Description of the Company's model

5.3.1. Economic evaluation scope

The Company used a semi-Markov model to assess the cost-consequences of using ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy in ambulatory children 8.5 years and older, meaning transitions between health states are derived directly from parametric extrapolations to relevant Kaplan-Meier data. The model simulates a hypothetical cohort of children with nmDMD, with costs and benefits accrued until no patients remain in the ambulatory health state (or 35 years, in a scenario analysis). The model starts with children in an ambulatory health state, who may later progress to a non-ambulatory health state. As severity of nmDMD increases, children may have scoliosis, require ventilation or both have scoliosis and require ventilation. In the model transitions to the death state can occur from all other health states. The Company presented an illustrative semi-Markov structure to depict the transitions that could occur between health states (Figure 5).

5.3.2. Model structure

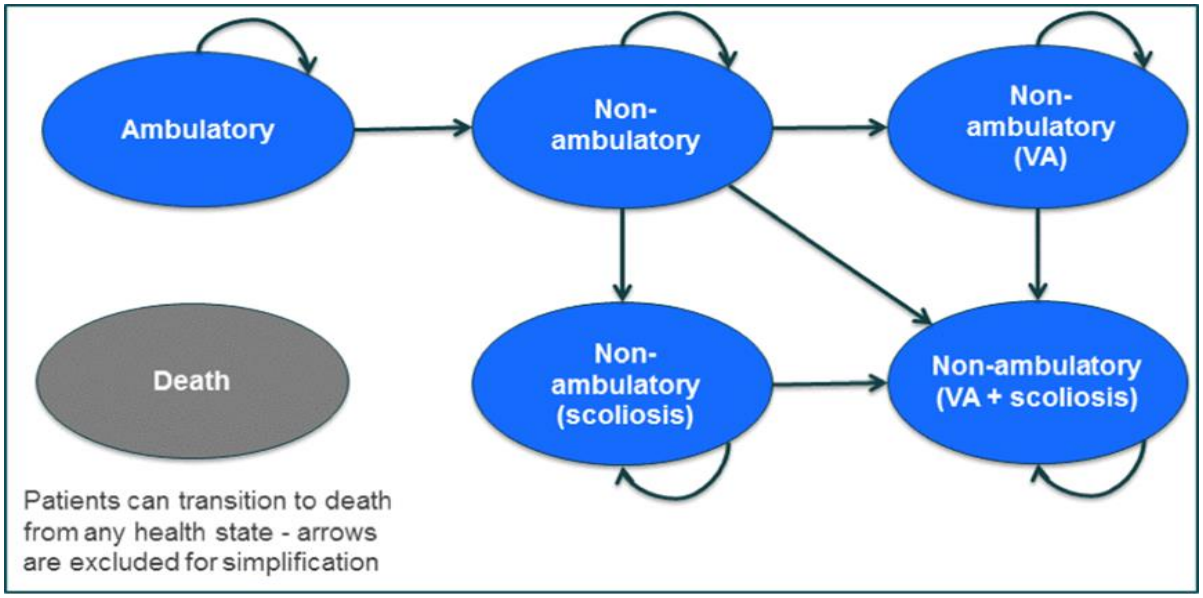


Figure 5 Illustrative Markov model structure

The Company used a semi-Markov structure to estimate the costs and benefits of ataluren and best

supportive care compared with best supportive care alone in children with nmDMD (see Figure 5).

The model simulates the pathway/experience of children in terms of the progression of nmDMD, and the costs, life-years gained (LYG) and QALYs accrued over the duration of the model. The model contains five health states (ambulatory, non-ambulatory, non-ambulatory with ventilation assistance, non-ambulatory with scoliosis and non-ambulatory with ventilation assistance and scoliosis) defined by the severity of nmDMD, and death. These health states have been defined, to some extent, in the glossary but could have been elaborated on in the model structure section. The model starts with a hypothetical cohort of children aged 8.5 years and weighing 28.3kg in the ambulatory health state. The model has a cycle length of three months. Children transition to more severe health states based on time-dependent transition probabilities derived from Study 007 and secondary sources. Costs and benefits are accrued depending on the numbers of people in each health state, in each cycle. Costs represent those associated with treatment and disease management, and benefits are measured in terms of QALYs.

Costs and disutilities for treatment-related severe adverse events were not included in the economic model as it was assumed that differences in adverse events between the ataluren and best supportive care arms would not have a significant impact on the cost of care or the quality of life of the individual. Additionally, monitoring costs were not included because the Company were advised that these costs were negligible as these tests are routinely performed in practice. The health states and pathways for the intervention and comparator arms were identical, but differ in the transition probabilities used for progression from the ambulatory to non-ambulatory health state. This results in different Markov traces between the ataluren and best supportive care arms, thereby enabling a comparison in terms of costs and benefits to be made. Though not explicitly stated, the model appears to assume that individuals were not allowed to jump/skip health states. For example, if children are in an ambulatory health state in a cycle; in the subsequent cycle, they may only progress to the non-ambulatory health state and not progress to the ambulatory and ventilation assisted health state.

The economic model developed appears to have included the appropriate health states and adequately represents the natural disease progression of nmDMD.

5.3.3. Evidence used to inform the Company's model parameters

Table 26 provides a summary of the evidence used to populate the economic model. In this section we provide a summary of the key parameters and uncertainties around these sources. The ways in which the information has been derived will be outlined/discussed in the subsequent section.

Table 26 Summary of key model input parameters and sources as reported in the Company's submission

Model inputs	Source(s)
Time to loss of ambulation: intervention	Derived based on information reported by Bushby et al. (2014)[41]
Time to loss of ambulation: best supportive care	Derived based on information reported by Ricotti et al. (2013)[5]
Non-ambulation to non-ambulation VA	Derived based on information reported by Humbertclaude et al. (2012)[58]
Non-ambulation to non-ambulation and scoliosis	
Non-ambulation to non-ambulation and scoliosis and VA	
Other cause mortality	ONS 2014
Death from nmDMD	Derived based on information reported in Norwood et al. (2009)[29]
Health state costs	Landfelt et al., 2014;[34] ONS 2015; OECD 2015[59]
Health state utility values	Landfeldt et al., 2014[34]
nmDMD, nonsense mutation Duchenne dystrophy; VA, ventilation assisted; ONS, Office of national statistics	

Information required to populate the model was obtained from Study 007 and published sources. Transition probabilities required for the transition to loss of ambulation health state were derived from Study 007. Transitions from the non-ambulant state to more severe health states were derived from Humbertclaude et al. (2012).[58] Information on costs was obtained from secondary sources and converted to UK pounds using UK 2012 purchasing power parity and inflated to 2014 costs using the consumer price index for health. In the ataluren group, treatment was dependent on the bodyweight of children until they reached 19 years old after which a constant weight of 70kg was assumed. Children in the intervention group received treatment until they progressed to the non-ambulatory stage. It was stated that children would continue to receive ataluren treatment for six months after loss of ambulation, but costs for this treatment were not included in the model. In the best supportive care group, children continued to receive the same treatment after loss of ambulation. Adverse events were not considered in the model.

In the model the primary measure of effectiveness was quality-adjusted life-years (QALYs), gained

over the duration of the model. (The time horizon was set at 'until the last patient loses ambulation'). All costs and benefits were discounted at 3.5% per annum. The base care analysis was conducted from an NHS and PSS perspective (with a scenario analysis from a wider societal perspective), and results were presented in terms of disaggregated costs, life-years gained (LYG) and QALYs. In the submission, one-way sensitivity analyses were undertaken by varying direct costs of health states, and patient and caregiver utility values by ± 20%. Also, a number of scenario analyses were undertaken: increasing caregivers' disutilities; increasing costs and disutilities for people requiring ventilatory assistance; inclusion of direct and indirect non-medical costs; and increasing the time horizon of the model.

5.3.3.1. Relative treatment effects of ataluren versus standard care

The model uses clinical effectiveness estimates for ataluren and best supportive care versus best supportive care alone Study 007 (Bushby et al. (2014)[41]) and from other published sources. It is important to note that this approach assumes that the populations from the different studies are comparable. Information on the delay in reductions in ambulatory ability (measured using the 6MWD) with ataluren were obtained from Study 007, and information about loss of ambulation with best supportive care were obtained from Ricotti et al. (2013).[5] Transition probabilities from loss of ambulation to more severe health states were obtained from a study of the natural history of DMD (Humbertclaude et al., 2012).[58] Additional information on background all-cause mortality was obtained from the Office of National Statistics (2014).

5.3.3.2. Transition probabilities for standard care

Improvements in ambulation with ataluren, compared to best supportive care, were estimated based on a least squares regression of changes in 6MWD from week 24 to week 48 of Study 007. The regression analysis was undertaken on the data from Week 24 to Week 48 because it was deemed to be more representative of the long-term treatment effect of ataluren (Company submission: expert opinion). The authors suggested that this is a conservative assumption because ataluren has a greater benefit compared to best supportive care in improving 6MWD in the first 24 weeks of the study.

Results from the regression analysis based on information from Week 24 to 48 showed that there was a decrease in the 6MWD of 59.0m in the best supportive care arm compared to a decrease of 25.2m in the ataluren arm. (33.8m between treatment groups). These declines in 6MWD were linearly extrapolated (from a mean baseline 6MWD of 355.7m) to estimate mean time to loss of ambulation, defined as 6MWD = 0m. As a result of this linear extrapolation, loss of ambulation was assumed to occur in the best supportive care and ataluren arms at week 313 (6 years) and week 733 (14.1 years), respectively. This equated to a difference of 420 weeks/8.1 years. (Please see Section 5.5 of this report for a critique of this approach).

Information on loss of ambulation with best supportive care was obtained from Ricotti et al. (2013).[5] It was suggested in the CS, that this was consistent with the information from the placebo arm of the trial (Study 007). Digitized Kaplan-Meier estimates of time to loss of ambulation for people taking daily corticosteroids were derived using the Ricotti data in order to obtain time-dependent probabilities for transition to the non-ambulatory from the ambulatory health state, in the BSC arm. The Company suggested that a Weibull parametric curve was the best fit to the digitized Kaplan-Meier data.

5.3.3.3. Transition probabilities for ataluren

Information on the loss of ambulation in the ataluren arm was obtained from Study 007 and also from Ricotti et al. (2013).[5] To estimate transition probabilities for loss of ambulation in the ataluren arm, *'the placebo curve was shifted to the right until the difference in median time to LoA between ataluren and placebo was the same as predicted by linearly extrapolating Study 007 data (i.e. 8.1 years) (CS, page 163).'* (Figure 6). A Weibull model was fitted to these curves, and transition probabilities were derived.

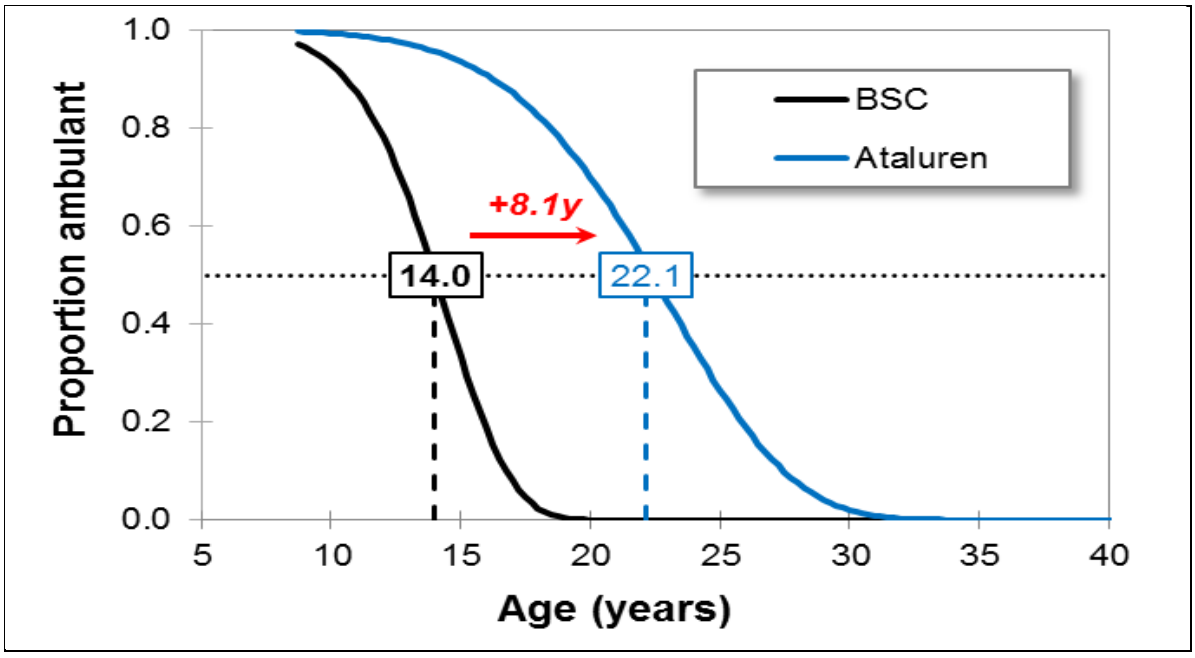


Figure 6 Curve for time to loss of ambulation fit to Kaplan Meier data (as presented in the CS, page 163)

The ERG believes that there may be some inaccuracies in the methodology in terms of shifting the best supportive care curve to the right to obtain a survival curve for the ataluren and best supportive care arm to reflect the linearly extrapolated difference. Please see Section 5.5 for a critique of this approach.

5.3.3.4. Transitions from loss of ambulation to ventilation assistance/scoliosis

People who progressed to loss of ambulation could further progress to more severe health states: with scoliosis, where surgery is required; requiring ventilation assistance; or both. Information required for these transitions was obtained from the Humbertclaude et al. (2012) study. In this study, Kaplan-Meier curves were presented for people who were non-ambulatory and who further progressed to being non-ambulatory with scoliosis, non-ambulatory requiring ventilation assistance, and non-ambulatory with both scoliosis and ventilations assistance. Transition probabilities were estimated based on a Weibull model. Please see Section 5.5 for a critique of this approach.

The ERG believes that the digitized Kaplan-Meier curves presented in the CS do not fully reflect the original curves. As a result, the model fits and derived transition probabilities may be either over- or underestimated. The ERG undertook further pre-model analyses to reconstruct the Kaplan-Meier curve (time to non-ambulation with ventilation assistance) as presented in Humbertclaude et al. (2012).[58]

5.3.4. Model evaluation

5.3.4.1. Health-related quality of life

Data on health-related quality life for children were collected using the Pediatric Quality of Life Inventory (PedsQL) in Study 007. Briefly, the PedsQL instrument consists of four main scales, physical, emotional, social and school functioning, and can be used to measure generic non-preference based HRQoL in children and adolescents. Information on the PedsQL was collected at screening, baseline, and every six weeks until Week 48. The submission stated that it is not possible to estimate health state utilities from this instrument. However these utilities were subsequently provided after clarifications requested by the ERG, using an algorithm from a study conducted by Khan et al. (2014)[60], which mapped non-preference based data from the PedsQL to a generic preference based measure (EQ-5D).. The Company suggested that since the mapping exercise undertaken by Khan was in a healthy population this might not be applicable in the population of interest, however the ERG consider that this approach is acceptable.

The Company further conducted a systematic review of the literature to identify studies which evaluated HRQoL for people with DMD, and their carers, in order to derive health state utilities for use in the economic analysis. The search identified one relevant study by Landfeldt et al. (2014),[34] which evaluated HRQoL for people with DMD using a generic preference based measure (the Health Utilities Index version 3). From this study, patients' and carers' utility values were derived for the analysis. Tables 27 and 28 provide the derived health state utility values for children with DMD and disutility values for carers, respectively.

Table 27 Health state utility values used in the model

Health state	Utility value	Source
Ambulatory	0.66	Landfeldt et al., 2014[34]
Non-ambulatory	0.12	Landfeldt et al., 2014[34]
Non-ambulatory and ventilation assisted	0.12	Landfeldt et al., 2014[34]
Non-ambulatory and scoliosis	0.02	Landfeldt et al., 2014[34] and assumption
Non-ambulatory and ventilation assisted and scoliosis	0.02	Landfeldt et al., 2014[34] and assumption

In the economic analysis, the utility value for children in an ambulatory health state was 0.66, based on the early ambulatory health state data from the Landfeldt et al. [34] study. A utility value of 0.12 was used for the non-ambulatory health state with or without assisted ventilation, also taken from the Landfeldt [34] study.

Table 28 Carers' disutility values used in the model

Health state	Disutility value	Source
Ambulatory	-	Landfeldt et al., 2014[34]
Non-ambulatory	0.11	Landfeldt et al., 2014[34]
Non-ambulatory and ventilation assisted		Landfeldt et al., 2014[34]
Non-ambulatory and scoliosis		Landfeldt et al., 2014[34] and assumption
Non-ambulatory and ventilation assisted and scoliosis		Landfeldt et al., 2014[34] and assumption

The Company used a caregiver disutility value of 0.11 from the Landfeldt [34] study for all states except

the ambulatory health state.

HRQoL information for people who experienced adverse events was not included in the model. In both arms of Study 007, the frequency of adverse events was similar (as discussed in section 4) and the Company suggested that adverse events may not have an impact on HRQoL.

5.3.4.2. Resource use and costs included in the model

Costs included in the model were costs of ataluren treatment, health state costs, surgery costs and surgery follow-up costs, all from the perspective of the NHS and PSS. Costs related to adverse events and costs of ventilation were not included in the analysis.

The recommended dose of ataluren is 40mg/kg daily, administered orally (mixed with liquid or semi-solid food) three times per day (morning 10mg/kg bodyweight, lunchtime 10mg/kg bodyweight and evening 20mg/kg bodyweight). The cost of ataluren was calculated based on a list price of £2,532 per box of 30 x 125mg sachets. The Company highlighted that ataluren is available at £5,064 per box of 30 x 250mg sachets and £20,256 per box of 30 x 1000mg sachets. The cost per patient used in the economic analysis is based on the Royal College of Paediatrics and Child Health growth reference curves,[61] used to estimate the annual increase in weight for a starting cohort with an age of 8.5 years. The median growth reference curves for children aged 5-9 and 9-18 were digitized and the Company assumed that adults 19 years and older would have an average weight of 70kg. The required dose was applied to the cost per treatment and further converted to a cost per three month cycle. For an eight year old child weighing 26kg, ataluren treatment costs £675.20 per day and £246,448 per year. In the CS, administration costs, training costs and monitoring costs were considered negligible.

Other costs required in the model were those related to occupying the various health states. In the submission, health state costs were primarily obtained from the Landfeldt et al. (2014)[34] study. In this study, costs were reported in US dollars and were converted to UK£ using UK 2012 purchasing power parity (PPP) (OECD, 2015).[59] They were then inflated using the consumer price index for health (ONS, 2015). Table 29 below shows the direct costs per cycle for occupying each health state (adapted from Table D12.11 from the Company's submission on page 181). For people in an ambulatory health state, the direct costs were £1,633 per cycle. For people in a non-ambulatory health state with/without ventilation assistance, the direct costs were £4,012 per cycle. For people in a non-ambulatory health state with scoliosis and with or without ventilation assistance the direct costs were also £4,012 per cycle. The cost of £20,986 for the scoliosis related surgical procedure and £1,458 for surgery follow-up were obtained from NHS reference costs 2013/14.

Table 29 Health states and associated direct costs used in the model (per cycle)

Health state	Value (UK£, 2014 prices) (per cycle)
Ambulatory	£1,633
Non-ambulatory	£4,012
Non-ambulatory and ventilation assisted	£4,012
Non-ambulatory with scoliosis Surgery costs Surgery follow-up costs	£4,012 £20,986 £1,458
Non-ambulatory and ventilation assisted with scoliosis Surgery costs Surgery follow-up costs	£4,012 £20,986 £1,458

Costs for adverse events were not included in the analysis. The Company suggested that results from Study 007 showed that there were no significant differences in the incidence of adverse events between the ataluren and placebo arms and that any adverse events would not impact on the differential cost of care between patients in the ataluren and BSC arms.

In a scenario analysis, costs of non-medical community services, aids, devices, home adaptations, informal care and productivity losses were included in the indirect costs. Table 30 below shows the health states and their associated indirect costs (adapted from Table D12.12 in CS on page 181).

Table 30 Health states and associated indirect costs used in the model (per cycle)

Health state	Value (UK£, 2014 prices) (per cycle)
Ambulatory	£7,972
Non-ambulatory	£19,588
Non-ambulatory and ventilation assisted	
Non-ambulatory with scoliosis	
Non-ambulatory and ventilation assisted with scoliosis	

5.4. Results reported in the Company submission

Table 31 shows a summary of the model results compared to the clinical data measured at Week 48 of Study 007. At the Week 48 time point, results in the best supportive care arm showed that the model predicts 5% of boys would have lost ambulation, compared to 11% of boys in the clinical trial

Table 31 Summary of results (model and clinical trial) measured at Week 48

Outcome	Clinical trial	Model
Loss of ambulation at Week 48 (Best supportive care only)	11% (n = 6)	5%
Loss of ambulation at Week 48 (Ataluren and best supportive care)	7% (n = 4)	0.5%

At the same time point, the model predicted that 0.5% of boys would lose ambulation in the ataluren arm compared to 7% of boys in the trial. These results suggest that the model is underestimating the number of events (loss of ambulation) at Week 48. It is possible, therefore, that if this underestimation continued, QALYs would be over-predicted for both arms of the study, with a potentially larger over-prediction in the ataluren arm. The most likely reason for this underestimation is the treatment of the population as a homogeneous cohort, without consideration of inter-patient variability.

Table 32 shows discounted LYG at the model time horizon, for both best supportive care and ataluren, for each health state.

Table 32 Results based on life years gained

Health state	Life years gained	
	Ataluren	**Best supportive care**
Ambulatory	9.857	4.555
Non-ambulatory	0.609	2.160
Non-ambulatory and ventilation assisted	0.032	0.032
Non-ambulatory and scoliosis	1.331	3.812
Non-ambulatory and ventilation assisted and scoliosis	2.667	3.329
Total	**14.497**	**13.888**

The results show that the mean LYG in the ataluren arm were greater than in the best supportive care arm, with LYG of 14.497 and 13.888, respectively. As expected, the LYG in the ambulatory health state were greater (twofold) in the ataluren as compared to the best supportive care arm. The LYG in the non-ambulatory health state were less in the ataluren arm, than those in the best supportive care arm, a result of a larger number of boys losing ambulation earlier in the best supportive care arm. The life years gained in the non-ambulatory and ventilation assisted health states were identical. The mean life years gained in the non-ambulatory with scoliosis with or without ventilation health states were

also greater in the best supportive care as compared to the ataluren arm.

Table 33 shows the mean discounted costs accrued in the ataluren and best supportive care arms, for each health state.

Table 33 Results based on discounted mean costs by health state

Health state	**Costs (£)**	
	Ataluren	**Best supportive care**
Ambulatory	4,984,263	29,752
Non-ambulatory	9,774	34,657
Non-ambulatory and ventilation assisted	521	520
Non-ambulatory and scoliosis	37,961	96,964
Non-ambulatory and ventilation assisted and scoliosis	60,021	73,314
Total	**5,092,540**	**235,207**

The results show that the discounted mean costs were £5,092,540 and £235,207 in the ataluren and best supportive care arms, respectively. In the non-ambulatory health state, mean costs were nearly four times greater in the best supportive care arm compared to the ataluren arm. This is because children in the BSC arm are expected to progress to the non-ambulatory state more rapidly than those in the ataluren arm.

Table 34 shows the mean discounted QALYs associated with the ataluren and best supportive care arms for each health state. The results show that at the model time horizon, ataluren produces 6.152 QALYs compared to best supportive care which produces mean QALYs of 2.385. As expected from the inputs, more boys remain in the ambulatory health state in the ataluren arm for a longer duration compared to the best supportive care arm, hence the greater number of QALYs generated in this health state. In the non-ambulatory and scoliosis with/without ventilation assistance health states, the QALYs gained, though negative, are marginally better in the ataluren arm compared to best supportive care. These negative QALYs are associated with the carer's disutility that was applied.

Table 34 Results based on discounted mean QALYs by health state

Health state	**Quality-adjusted life-years gained**	
	Ataluren	**Best supportive care**
Ambulatory	6.506	3.006
Non-ambulatory	0.006	0.022
Non-ambulatory and ventilation assisted	0.000	0.000

Non-ambulatory and scoliosis	-0.120	-0.343
Non-ambulatory and ventilation assisted and scoliosis	-0.240	-0.300
Total	**6.152**	**2.385**

5.4.1. Sensitivity and scenario analyses

The company conducted a number of sensitivity and scenario analyses. The parameters the model was most sensitive to in terms of costs and consequences (in addition to the cost of ataluren) were the choice of discount rates, followed by the utility for the ambulatory health state. The four scenario analyses undertaken involved increasing the disutilities for caregivers; increasing the costs and disutilities for the ventilation-assisted state; changing to a societal perspective for costs; and using a lifetime (35 year) time horizon. The result of these scenario analyses are given in Table 35.

Table 35 Results of multi-way scenario sensitivity analysis

Parameter	Incremental QALYs	% difference in QALYs	Incremental costs (£)	% difference in costs
Base case	3.767	-	4,857,333	-
Scenario 1 – increased caregiver disutilities	3.959	5%	-	-
Scenario 2 – increased costs and disutilities for ventilation-assisted state	3.893	3%	4,844,091	0%
Scenario 3 – inclusion of wider societal costs	-	-	4,658,698	-4%
Scenario 4 – Lifelong time horizon	3.728	-1%	4,866,868	0%

5.5. Appraisal of the Company's model

In this section we present a critical appraisal of the economic model and the key model input parameters used in the analysis. The economic model which the Company developed appears to have included the appropriate health states and transitions, and adequately represents the natural course of DMD. Hence, our critique focuses primarily on the pre-model analyses conducted, and the input parameters used in the model. Below we outline some of the concerns which relate to the economic analysis:

- Deviation from the NICE scope
- Natural history of nmDMD
- Treatment effect of ataluren
- Methods used to reconstruct IPD from the published sources
- Health state utility values used to derive QALYs

- Resource use and costs excluded from the analysis
    - Costs of ventilation
    - Cost of ataluren treatment six months post losing ambulation

5.5.1. Concerns regarding the scope of the Company's economic analysis

In general, the scope of the economic analysis is similar to that outlined in the NICE scoping document except for the starting age of the population. Whilst the NICE scope indicates that the population of interest is people with nmDMD aged ≥ 5 years in an ambulatory health state, the economic analysis deviates by starting the model with a hypothetical cohort of children aged 8.5 years.. As a result, there will be uncertainty in terms of the costs and benefits of ataluren for children between the ages of 5 and 8.5 years since they were not included in the analysis. The overall costs of treatment may potentially be underestimated and benefits may be overestimated if children begin treatment at a younger age than that included in the model. In addition, the mortality rate (background and disease-related) may be different for children younger than 8.5 years.

5.5.2. Natural history data

In Study 007, ataluren (40mg and 80mg/kg) was compared to best supportive care. In the economic analysis, instead of using data on time to loss of ambulation from the best supportive care arm in Study 007, data were obtained from the study by Ricotti et al. (2013). The rationale for this was that the median time to loss of ambulation was considered similar to the mean time to loss of ambulation in Study 007. The ERG was uncertain, and hence queried which measure of central tendency was used for the comparison. The Company further clarified that for the natural history data from Ricotti et al. (2013), the mean time of loss of ambulation in the placebo group was comparable to the mean time to loss of ambulation in the best supportive care arm in Study 007. It should be noted that median time of loss of ambulation is mentioned on pages 158, 161 and 163. However, no data on comparative measures of central tendency were presented in the CS.

Additionally, the use of this study raised some concerns. Briefly, Ricotti and colleagues conducted an observational study to assess the benefits and adverse effects of intermittent versus daily glucocorticoids in boys with DMD. Three hundred and sixty boys aged 3-15 years who were being treated for DMD in the UK were followed up for seven years. Boys were treated with daily or intermittent (10 days on/10 days off) prednisolone (0.75 mg/kg/day) over a mean period of four years. Baseline information collected included genetic mutation, date of diagnosis and features of muscle biopsy. Both medical (e.g. date of starting glucocorticoids and adverse behavioural changes) and outcome measures (e.g. ambulation status, use of mobility aids and timed 10m run) were taken at various time points during follow-up. Results from the study showed that the median ages at loss of ambulation in the daily group and intermittent group were 14.5 years and 12 years, respectively.

First, we understand from our clinical advisors that in the Ricotti et al. (2013) study not all the cohort were diagnosed with nmDMD. Second, in Study 007, the six minute walking distance (6MWD) was used as the primary outcome measure. However, one of the outcome measures used in the Ricotti study was the 10 metre running time (10mRT), i.e. the time taken to run 10m. The ERG was unclear whether these two measures are interchangeable, and if the choice of the different test was related to the baseline status of the participants. The Company further clarified that the definitions of loss of ambulation from these different tests (6MWD and 10mRT) were interchangeable, and that the choice of test does not relate to the baseline status of the patient.

Finally, in the original company submission, only a Weibull model was fitted to extrapolate data from the Ricotti study, with no justification given for the choice of this particular functional form. In response to a clarification request from the ERG, the Company has now refitted the data with a number of different models to look for the best fitting extrapolation, and the ERG has also undertaken additional model fitting analyses. The impact on the cost-consequence results of additional analyses undertaken by both the Company and the ERG are presented in Section 6.

5.5.3. Treatment effect with ataluren

To obtain a model for loss of ambulation in the intervention arm the Company used an estimated mean time to loss of ambulation for each arm in the 48 week trial conducted by Bushby et al., 2014. To get this estimate the Company performed a least squares linear regression on changes in 6 minute walking distance observed in the trial. These regressions were linearly extrapolated to zero walking distance so as to obtain an average time to complete loss of ambulation. These times were 6 and 14.1 years for the placebo and ataluren arms respectively; adding 8.5 years as the average age of trial participants at baseline yielded the ages of 14.5 years and 22.6 years for the two arms and a difference between arms of 8.1 years. The Company observed that the average age for placebo patients (14.5 years) was close to the median in the Kaplan-Meier plot for age at loss of ambulation in Ricotti et al. Assuming an equivalence of median and mean times to loss of ambulation, the Company shifted the placebo Weibull curve by 8.1 years to obtain the time to loss of ambulation for the ataluren arm.

There are a number of assumptions inherent in the form of analysis undertaken. First, it assumes that the treatment benefits of ataluren are permanent, continuing for as long as people are treated, and that the relative benefit of ataluren over best supportive care remains the same over time. Secondly, it assumes that there is a 100% adherence rate for ataluren, and that no patients discontinue treatment for any reason other than loss of ambulation. Finally, the linear extrapolation of mean differences in 6MWD assumes a homogeneous cohort of patients, all of whom follow identical progression trajectories. Any inter-patient variability in progression trajectory will lead to such a linear extrapolation giving biased results for time to loss of ambulation, and will almost certainly

overestimate the treatment benefit with ataluren.

5.5.4. Methods used to reconstruct IPD from published sources

In order to derive transition probabilities for the economic model, the Company reconstructed time to event data from a number of figures obtained from published sources. Although the methods used were not described in detail it appears that data points were extracted from graphs and this data then used to make Weibull parametric fits using the least squares method. On visual inspection, the ERG noted that the reconstructed curves did not always reflect the original Kaplan-Meier curves from the published sources. In fitting the Weibull models the ERG noted that the submission truncated the published Kaplan Meier plots by omitting data from long flat tails of the published plots when these were present. This was done without explanation or justification. In a later clarification the company provided additional model fits (gamma, log-normal, log-logistic, and Gompertz).

Although truncation of data may be reasonable where uncertainty becomes great or where the plot infers prolonged survival without events which is clinically counterintuitive, a rationale for the procedure would usually be provided. (The company addressed this issue in Excel sheets submitted late in clarification). The least squares method may be acceptable, but we consider that the Guyot et al. (2012) method for reconstruction of IPD offers potentially greater accuracy and utility since parametric fits can be implemented in statistical software using maximum likelihood methods designed for investigation of time to event outcomes. At the clarification stage, the Company indicated that only Weibull models were fitted to the data due to lack of time. However in subsequent clarifications the company provided other data fitting models.

In view of these potential limitations, the ERG has undertaken further pre-model analyses to reconstruct IPD and Kaplan-Meier curves using the method proposed by Guyot et al. (2012), so as to assess appropriate parametric model fits for the economic model. Below we present reconstructed Kaplan-Meier estimates based on those published in the Ricotti et al. (2013), Humbertclaude et al. (2012) and Rall and Grimm (2012) studies. Appendix 2 presents the range of parametric fits explored by the ERG.

In their later clarification, the company provided reasons for selection of parametric models. The company justified rejection of some well-fitting models because of clinical implausibility in extrapolation mainly due to the long flat tails in some of the original published Kaplan Meier plots. The ERG accepts that these considerations are important by our clinical advisor. The ERG also consider that the published analyses of time to loss of ambulation and to deterioration of FVC to < 30% may have benefitted from competing risk analysis in which death was considered as the competing risk. In the absence of patient level information on multiple variables it is not possible to

pursue this issue however beyond commenting on it.

5.5.4.1. Time to loss of ambulation

The company modelled the Ricotti data from 8.5 years onwards. The ERG explored various models (Appendix 2) using reconstructed IPD from Ricotti using the method of Guyot and found the following median times to loss of ambulation.

Table 36 Median time to loss of ambulation predicted by different model fits

Measure	Parametric model					
	Weibull	lognormal	loglogistic	Gompertz	Gamma	Flexible parametric
Median	15.7	15.4	15.2	15.8	15.3	14.8

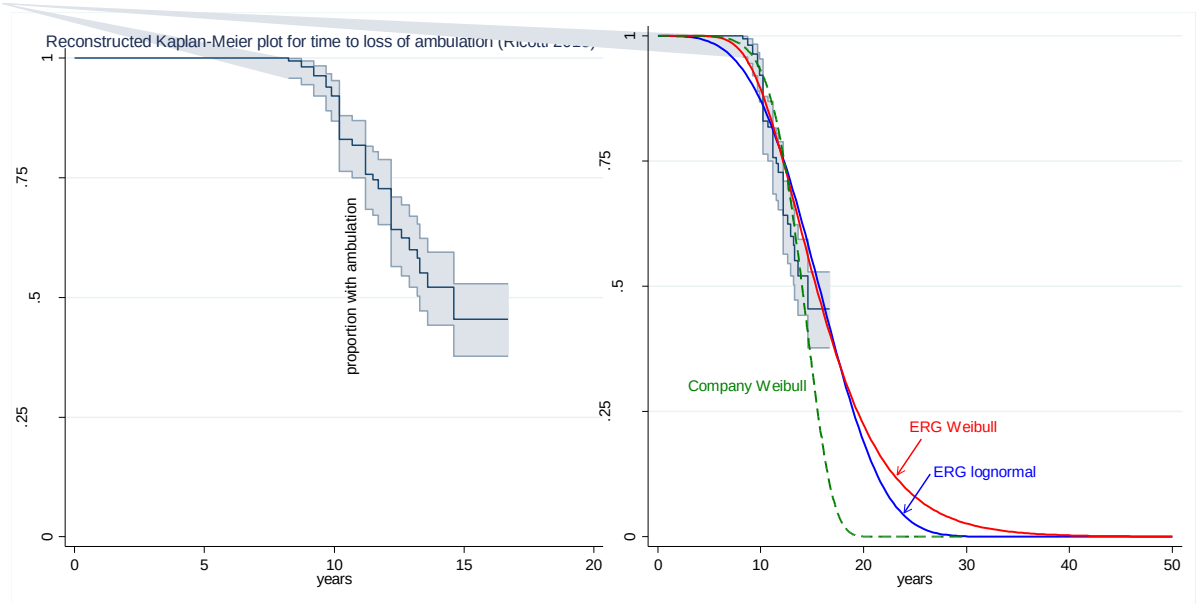


Figure 7 Reconstructed Kaplan-Meier plots and parametric models for time to loss of ambulation for DMD patients on daily corticosteroids

The Company's Weibull parameters were provided and the ERG tested the assumption of equivalence between mean and median times, finding negligible difference (Table 37).

Table 37 Comparison of medians and means

Measure	Placebo	Ataluren
median (years)	14.02	22.15
mean (years)	13.82	21.85

The ERG explored various parametric fits to the reconstructed Ricotti IPD. The best fits were

provided by flexible parametric and Gamma models (Appendix 2). However, because of flattening in the tail of the Ricotti KM plots these models generated significant proportions of patients who retain ambulation beyond 50 years of age. The ERG agree with the company's late clarification comment that these fits are clinically implausible. The remaining models (log-normal, log-logistic, Weibull, and Gompertz) provided similar survival curves (Appendix 2) but the log-normal model provided the lowest AIC and BIC values.

Figure 7 shows the ERG's reconstructed KM data with Weibull and lognormal models and also the company Weibull model. The difference between company and ERG Weibull models may be due to: the company modelling the Ricotti data from 8.5 years onward (ignoring earlier observed data) rather from year 0; the use of least squares methods rather than maximum likelihood; and differences between extracted KM plots due to different methods of data extract and use (Figure 8).

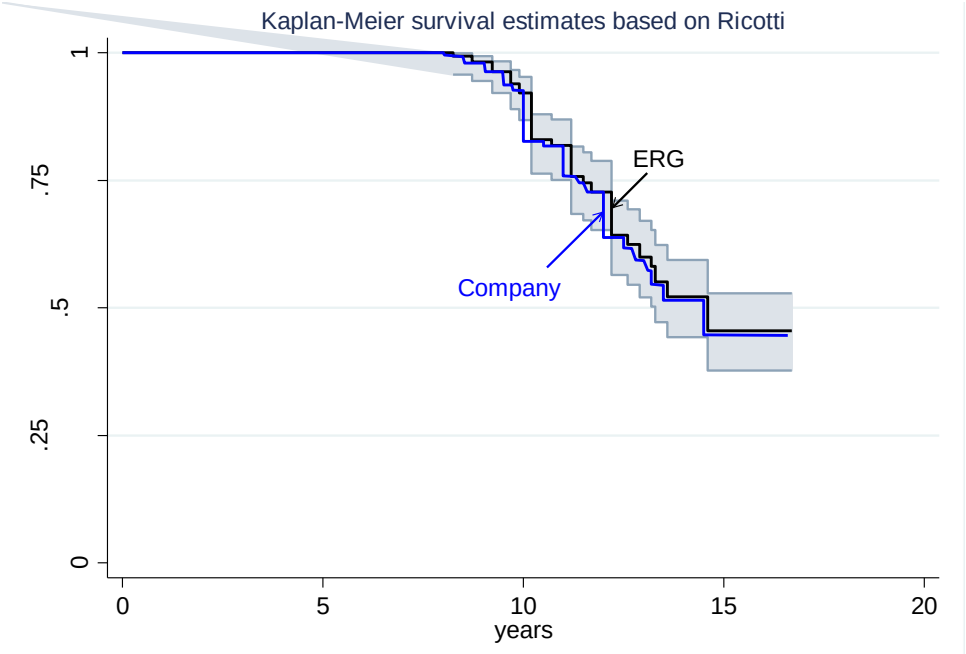


Figure 8 Reconstructed Kaplan-Meier plots and flexible parametric fits for time to loss of ambulation for DMD patients on daily corticosteroids

The ERG has derived time to loss of ambulation in the ataluren arm using the estimate of the difference in mean times of 8.1 years. For this the ERG BSC arm scale parameters for Weibull and lognormal fits were changed sufficiently to deliver a difference in mean time for loss of ambulation of 8.1 years. The resulting plots are shown in Figure 9

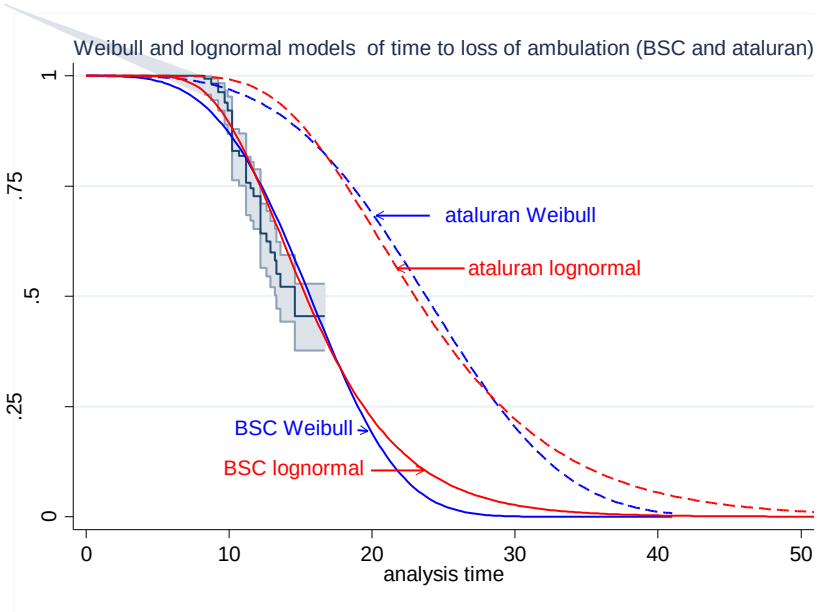


Figure 9 Reconstructed Kaplan-Meier plots and parametric models for time to loss of ambulation for DMD patients on daily corticosteroids

5.5.4.2. Time to scoliosis

The Company used data extracted from Humbertclaude et al. (2012) for model development of scoliosis for the three patients subgroups reported. Weibull models were fitted to this data but other models were not explored. It appears that the Weibull model was fitted to data from about 8.5 years onward (time zero was taken as 8.5 years in the published plots as illustrated in the submission Figure 10 shown below) and data in the flat tails of the KM may have not been included.

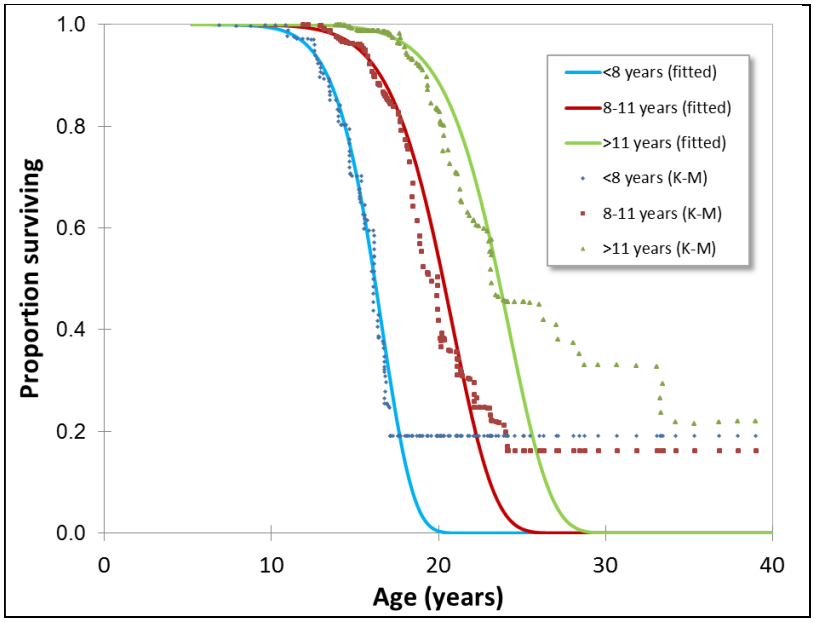


Figure 10 Company's figure D 12.8

The ERG reconstructed KM plots are shown in Figure 11, together with flexible parametric models (other models are shown in Appendix 2).

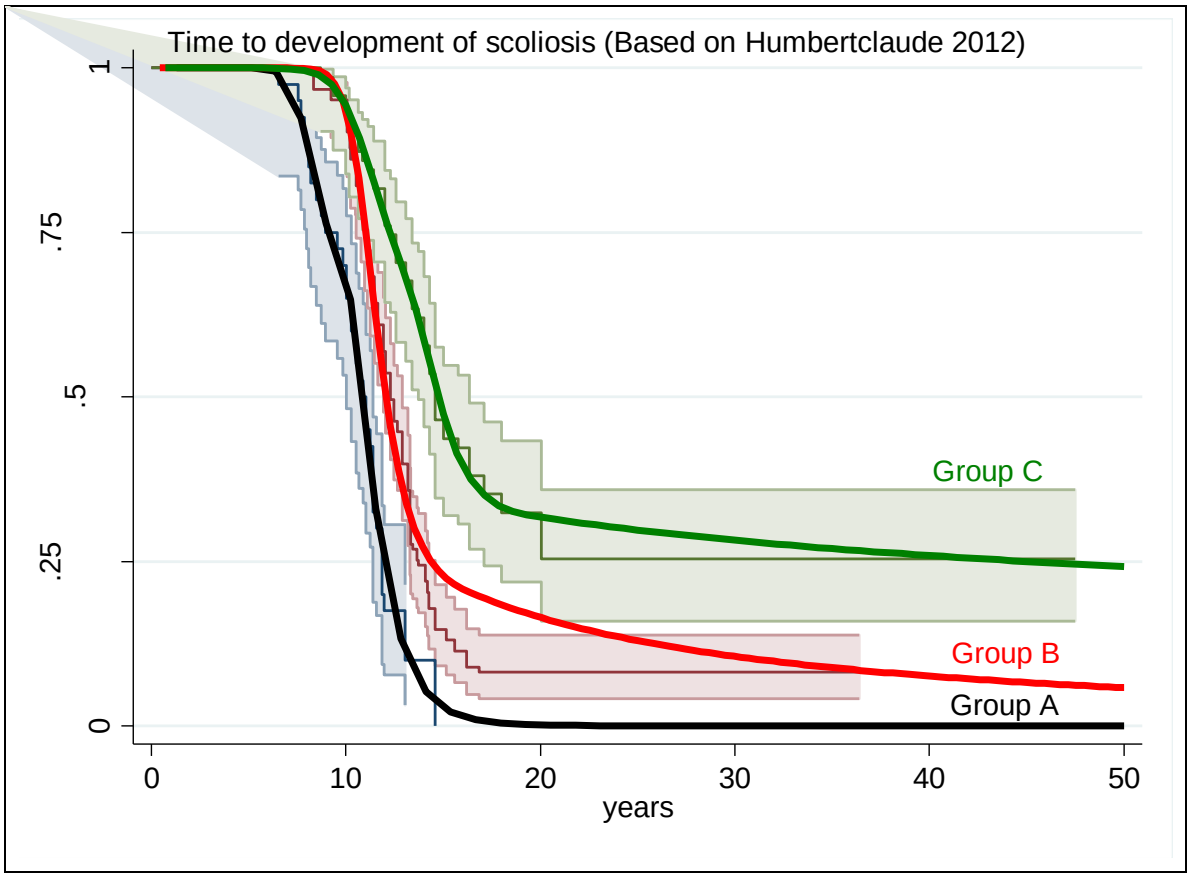


Figure 11 Reconstructed Kaplan-Meier plots and flexible parametric models for three groups of patients according to age at scoliosis diagnosis

5.5.4.3. Time to loss of >30% FVC

The Company again used data extracted Humbertclaude et al. (2012) for model development of <30% FVC for the three patients subgroups reported by Humbertclaude et al., 2012. Weibull models were fitted to this data but other models were not explored. It appears that the Weibull models were again fitted to data from about 8.5 years onward (time zero was taken as 8.5 years in the published plots as shown in the submission figure D 12.9) and data in the flat tails of the KM may have not been included.

The ERG reconstructed KM plots are shown in Figure 12 together with flexible parametric models (other models are shown in Appendix 2).

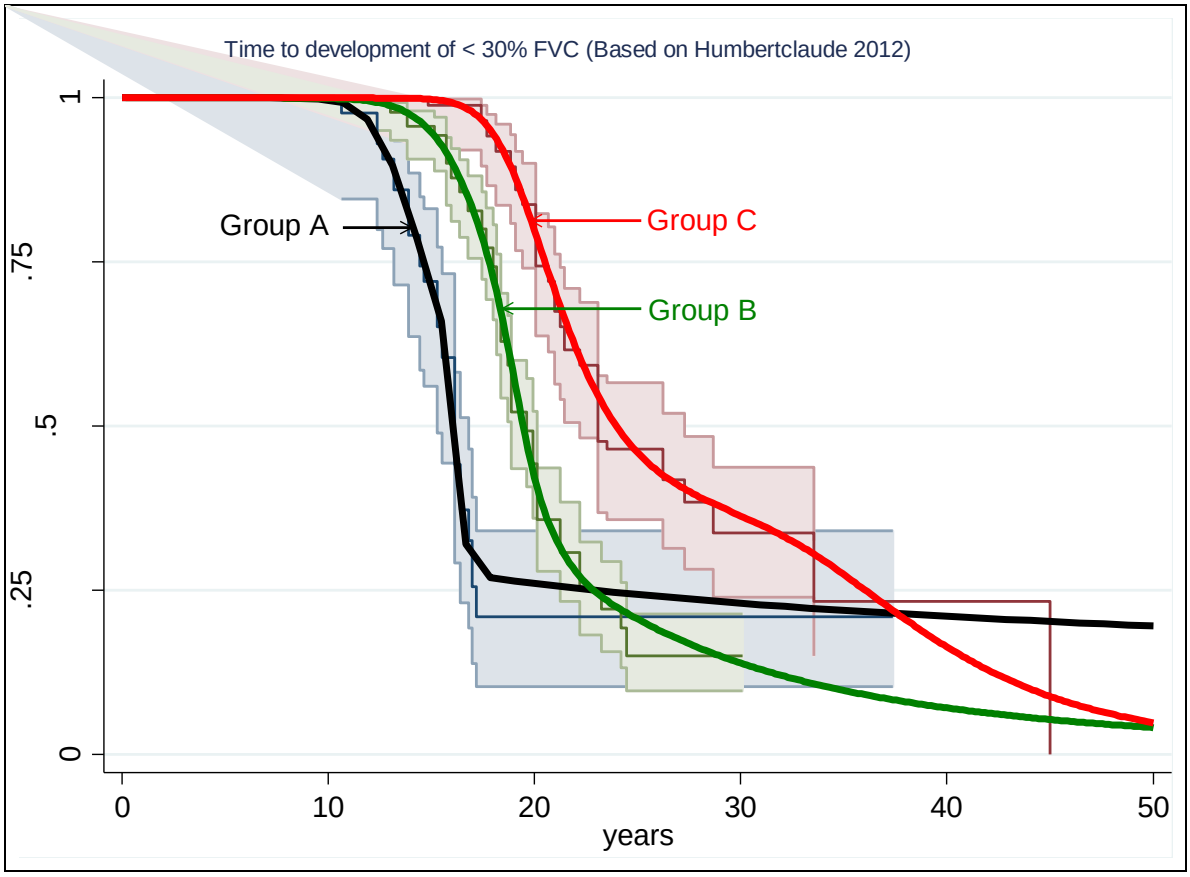
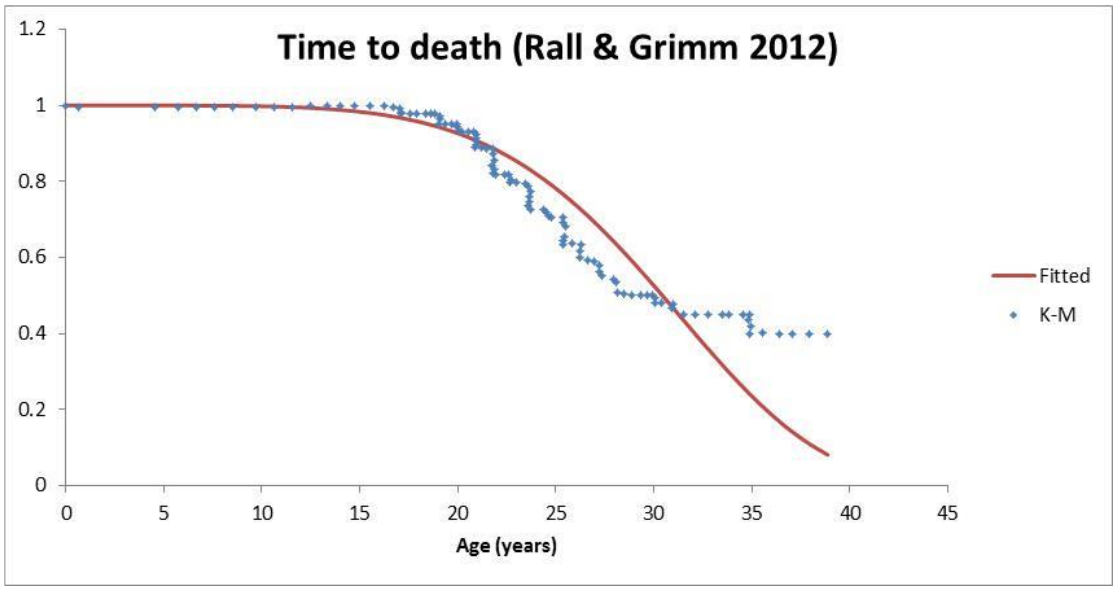


Figure 12 Reconstructed Kaplan-Meier plots and flexible parametric models for the three groups of patients defined according to the age at loss of ambulation

5.5.4.4. Time to death

For time to death as a result of DMD, the Company fitted a Weibull distribution to data extracted from the study of Rall and Grimm 2012 (Figure D 12.11 from the submission is shown below). This fit is somewhat different to the ERG Weibull fit to the same published KM plot, for which the ERG reconstructed IPD using the method of Guyot. These differences are shown in Figure 13.



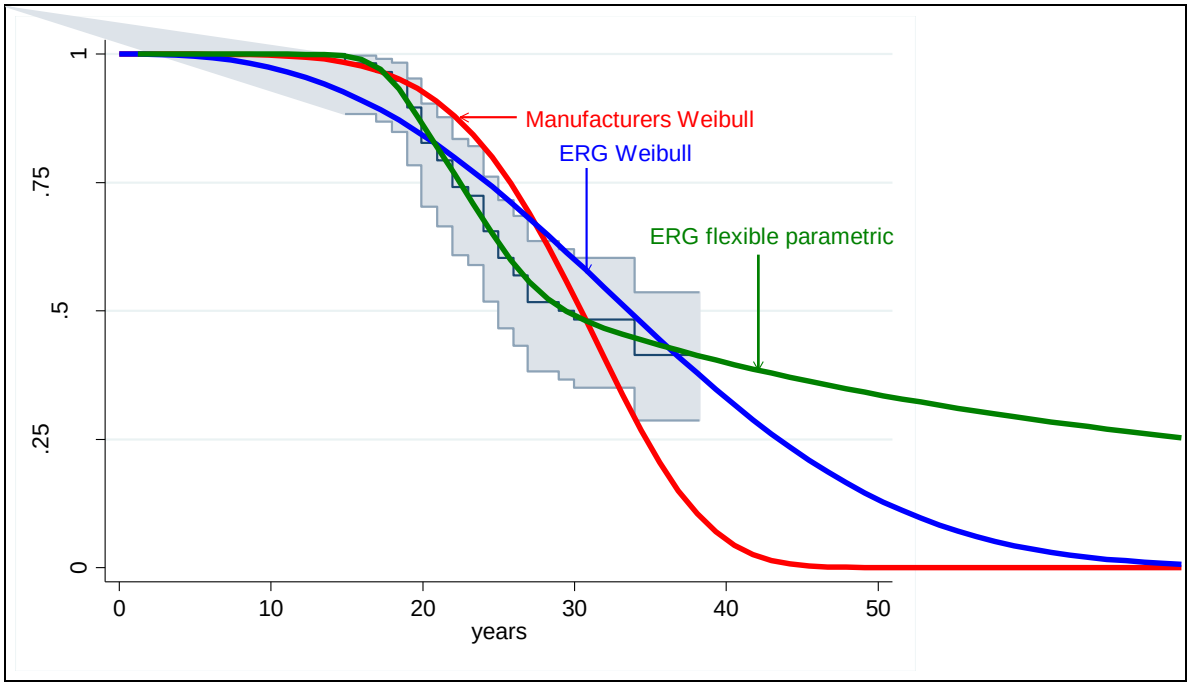


Figure 13 Reconstructed Kaplan-Meier plot and Weibull and flexible parametric models for time to death

The models are variously influenced by the flattening tail of the published KM plot and it is debateable whether the models are informative in extrapolation.

Following a clarification request from the ERG, the company also undertook additional analyses to reconstruct IPD data, including re-digitisation of published curves and using the Guyot method, described above. The impact on the cost-consequence results of the additional analyses undertaken by

both the ERG and the Company are presented in Section 6.

5.5.4.5. Summary: data for transition probabilities between health states

There appears to be a paucity of evidence available on the long term follow-up of people with nmDMD. In the CS, three studies were used to provide useful information on time to loss of ambulation (Ricotti), time to non-ambulation and ventilation assistance, time to scoliosis diagnosis (Humbertclaude), and time to death (Rall and Grimm). The reconstructed Kaplan-Meier curves did not accurately reflect the curves in the published literature, and the transition probabilities derived may have been either over or underestimated based on the model fits to the data. Given the paucity of the evidence and limitations of the plots, the ERG has reconstructed these plots and derived three-monthly transition probabilities which were used in the ERG's exploratory analyses.

5.5.5. Health state utility values used to derive QALYs

As noted above, PedsQL data were collected in Study 007, but were not used as part of the analysis submitted. The ERG, as part of a clarification, requested access to PedsQL data from the trial, in order to see if this could be incorporated into the analysis, to provide robust, trial-based estimates of HRQoL when being treated with either ataluren or best supportive care. Unfortunately, despite a request for individual patient data (so appropriate adjustments could be made for baseline utilities, censoring etc.) data were only supplied at the aggregate level (mean utilities for each treatment, at each time point) and hence it was not possible to make use of these data in any additional analyses. The ERG still believes, however, that in principle these data should be preferred to those from the literature as a source of utility values.

5.5.6. Resource use and costs excluded from the analysis

The resource use and costs included in the submission match the viewpoint of the analysis, that is, costs directly related to the NHS and PSS (as well as wider societal costs in a scenario analysis). The ERG noted that the direct costs for the non-ambulatory with/without ventilation assisted health states were the same, and this may have the impact of underestimating the cost of this health state.

In response to the clarification questions, the Company suggested that ventilation assistance may have high costs, but that these could not be sourced from the literature. Additionally, the Company suggested that 18% of the UK population in the Landfeldt et al. (2014) study required ventilation assistance. Since these costs were obtained from this study the Company suggested that the derived costs included an appropriate proportion of ventilation assistance. The Company noted that in further analyses which included costs for ventilation assistance, there was no impact on incremental costs. The ERG has undertaken a search of the NHS reference costs and obtained costs of £394 and £1,306 for people age 19 years and older and 18 years and under, respectively, undergoing non-invasive

ventilation support assessment. In addition clinical advisors to the ERG consider that ongoing costs for maintenance on ventilation therapy may not be negligible since rates of complications such as chest infections may be increased.

The submission stated that people would be likely to continue ataluren treatment for six months after losing ambulation. These treatment costs were not included in the model, which may lead to an underestimation of costs in the non-ambulatory health state of the ataluren arm.

As a response to a clarification request, the Company indicated that people would be eligible to receive treatment for up to six months, although not everyone is expected to receive this treatment. The Company further clarified that these costs were not included in the model, and further suggested that the mean costs derived are a reasonable reflection of what would occur in clinical practice.

5.6. Discussion of available evidence relating to value of money for the NHS and PSS

This section focuses on the economic analysis on the costs and benefits of ataluren submitted by the Company. The decision analytical model simulated a pathway for a hypothetical cohort of children with nmDMD being treated with ataluren and/or best supportive care, and the costs and benefits were estimated over a time horizon defined in relation to the last person in an ambulatory health state. The results are presented in terms of mean costs and mean benefits as measured in QALYs. The intermediary results showed that ataluren compared to best supportive care delayed the progression to non-ambulation by approximately 8.1 years. Results showed that the mean number of QALYs accrued in the ataluren arm was 6.152 compared to 2.385 QALYs in the best supportive care arm. Mean costs in the ataluren arm were approximately £5,092,500 compared to £235,200 in the best supportive care arm. Sensitivity analysis results were robust to changes except for the utility value for the ambulatory health state and changes made to the discount rates. The Company highlighted that the main drivers of the economic model were treatment costs.

In section 5.5 we provided a critique of the economic model and budget impact model submitted by the Company. They were some concerns noted in the model related to the methods used to extrapolate the treatment effect of ataluren, transition probabilities derived from the published studies and costs and utility data excluded from the analysis.

There are many sources of uncertainty. Some of these are a function of a lack of data in the area. Table 38 below gives a summary of these sources of uncertainty, together with the impact that alternative assumptions might make on the cost-consequence results derived.

Table 38 Sources of uncertainty in cost-consequence results (not related simply to shortages of data)

Parameter/model feature	Current assumption	Likely impact of varying assumption
Patient cohort	Patients are assumed to form a homogeneous cohort, with no inter-patient variability in disease trajectory.	If inter-patient variability is considered to be an important factor, then a linear extrapolation from mean difference in 6MWD from the trial is unlikely to be appropriate.
Age of cohort	The modelled cohort starts at an age of 8.5 years, as opposed to the 5 years given in the scope.	The use of an older starting age will underestimate the total costs of ataluren treatment, and may potentially underestimate the incremental benefits as well.
Definition of loss of ambulation	6MWD = 0m	The extrapolation undertaken assumes the 6MWD has a linear scale (i.e. a change from 350m-300m is equivalent to a change from 50m-0m). If these are not believed to be equivalent, the linear extrapolation model used will not be an appropriate one.
Ataluren treatment benefit	Differences from 24 weeks to 48 weeks in Study 007 are linearly extrapolate forward over time to obtain differences in loss of ambulation. This assumes the treatment benefit of ataluren over BSC remains constant for as long as people remain on treatment.	If the benefits of ataluren were believed to reduce over time, this would mean the current model is overestimating the incremental QALYs obtained from ataluren.
Parametric fits used to extrapolate data	In original submission, all based on Weibull extrapolations.	Additional analyses have been undertaken by the Company and ERG, looking at different model fits (Section 6).
Adverse events	No costs or disutilities for treatment related adverse events	If costs and disutilities were included, this would likely have the

	were included in the model.	impact over increasing incremental costs and decreasing incremental QALYs for ataluren.
Additional costs associated with ataluren treatment	There are no additional costs of administration, training or monitoring associated with the use of ataluren	If there are costs associated with any of these items, this will lead to an increase in the overall cost of ataluren treatment.
Adherence/discontinuation	Ataluren is assumed to have a 100% adherence rate, with no patients discontinuing for reasons other than loss of ambulation.	Adherence rate less than 100%, or additional discontinuations would result in lower incremental QALYs for ataluren.
Treatment post loss of ambulation	Ataluren treatment is stopped at the point of loss of ambulation.	Including the costs of 6 months of ataluren treatment post loss of ambulation would increase the incremental costs for ataluren.
Utility values for individuals with nmDMD	Values from the literature are currently used, as opposed to the prospective data on utilities collected in Study 007.	Unclear, but the use of relevant trial data would normally be recommended as the appropriate source for health state utilities.

6. ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES

6.1. Introduction

This chapter reports on the additional exploratory economic analysis undertaken by both the Company and the ERG, after the initial submission. The objective is to provide a more accurate analysis using the Company's model, but with improved model inputs. It should be noted that the ERG considered the economic model presented in the submission to have a feasible structure for assessment of the cost consequence analysis for comparison of ataluren and best supportive care versus best supportive care alone, and therefore changes to the model structure were not considered.

6.2. Additional analyses undertaken by the company

Following clarification requests, the Company submitted a new version of their model, with the same based structure and cost/utility inputs. The new model was based on re-digitised data, and included full parametric curve fitting and model selection, as comparted to the use of Weibull distributions for all fits as used in the original submission. New fits selected for each of the Kaplan-Meier extrapolations are described below:

Time to loss of ambulation – the best fit was the generalised gamma, but this was rejected as implausible as it was asserted this many people would not be ambulant at higher ages on steroids. Consequently, the 2nd best fit (the log-normal) was chosen instead.

Time to scoliosis (LoA<8y) – log-logistic was selected by the company (2nd best statistical fit). The best statistical fit was provided by the log-normal

Time to scoliosis (8y<LoA<11y) – log-logistic function selected (best fit to data)

Time to scoliosis (LoA>11y) - log-logistic was selected by the company (3rd best statistical fit). The best statistical fit was provided by the generalised gamma

Time to ventilation-assistance (LoA<8y) - log-logistic function selected (best fit to data)

Time to ventilation-assistance (8y<LoA<11y) - log-logistic was selected by the company (2nd best statistical fit). The best statistical fit was provided by the generalised gamma

Time to ventilation-assistance (LoA>11y) - log-logistic was selected by the company (3rd best statistical fit). The best statistical fit was provided by the generalised gamma

Time to death - log-normal was selected by the company (2nd best statistical fit). The best statistical fit was provided by the generalised gamma

Time to death (alternative scenario) – Gompertz model was selected by the company (5th best statistical fit). The best statistical fit was provided by the generalised gamma

Table 39 shows the models chosen for the new analysis undertaken by the Company, together with the best statistically fitting model (as chosen by AIC/BIC) for each set of Kaplan-Meier data.

Table 39 New parametric fits to Kaplan-Meier data, both those selected by the Company, and those viewed as best by looking at statistical criteria (AIC/BIC) alone

Parameter	Company model selection	Statistical model selection
Time to LoA	Log-normal	Generalised gamma
Time to scoliosis (LoA<8y)	Log-logistic	Log-normal
Time to scoliosis (8y<LoA<11y)	Log-logistic	Log-logistic
Time to scoliosis (LoA>11y)	Log-logistic	Generalised gamma
Time to ventilation-assistance (LoA<8y)	Log-logistic	Log-logistic
Time to ventilation-assistance (8y<LoA<11y)	Log-logistic	Generalised gamma
Time to ventilation-assistance (LoA>11y)	Log-logistic	Generalised gamma
Time to death	Log-normal	Generalised gamma
Time to death (alternative scenario)	Gompertz	Generalised gamma

6.2.1. Results of new Company model

A new set of results, equivalent to those from the initial submission, can be extracted from this new model, using the Company's new choices of extrapolation distributions, given above.

Table 40 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Loss of ambulation at 48 weeks / 1 year: best supportive care	11% (n=6)	5%
Loss of ambulation at 48 weeks / 1 year: ataluren	7% (n=4)	0.1%

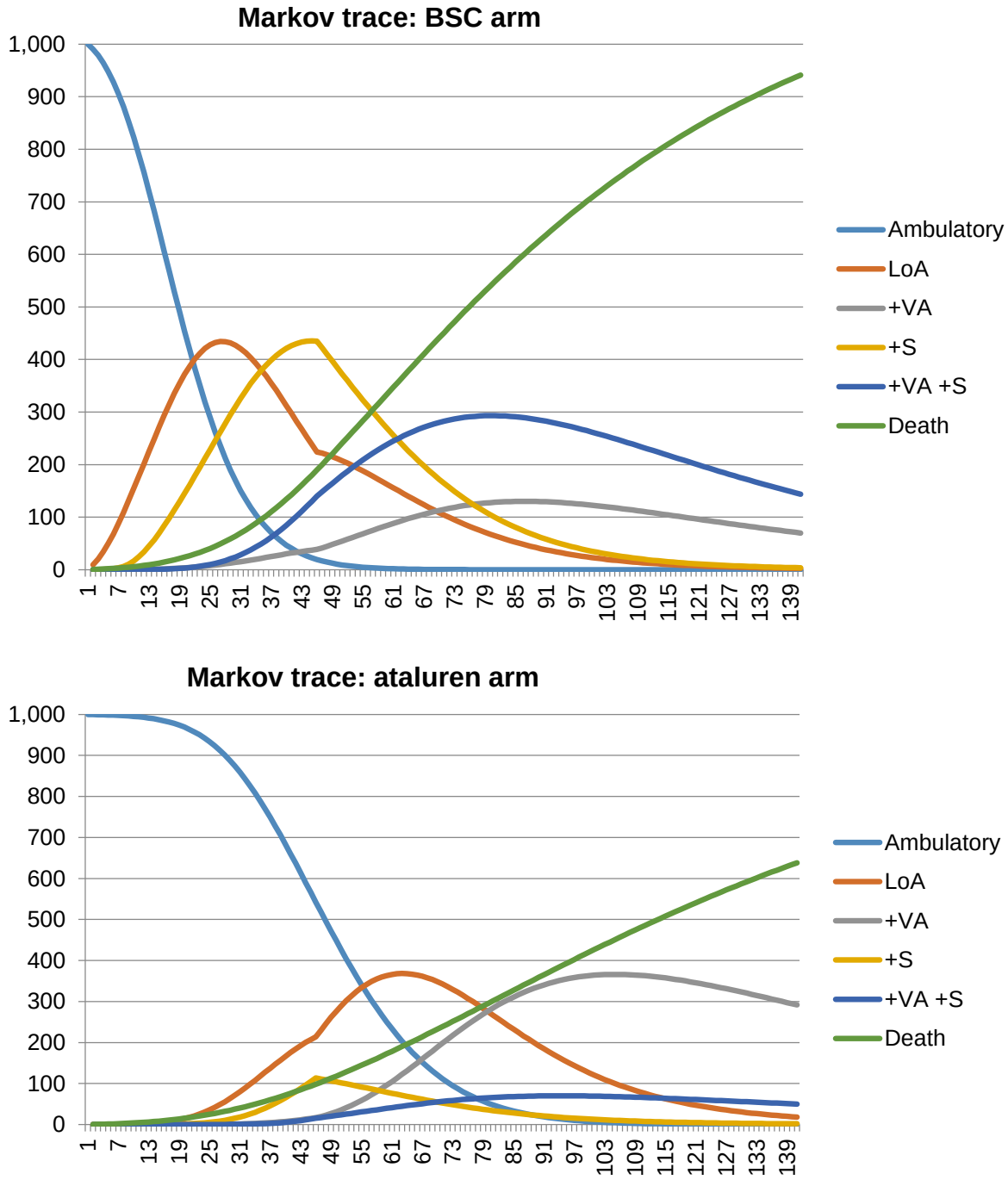


Figure 14 Markov traces - New company model

Table 41 Cost-consequence results from Company's resubmitted model

	BSC	**Ataluren**	**Incremental**
Life years	14.444	15.578	1.134
QALYs	2.254	6.178	3.924
Costs	£236,627	£4,784,895	£4,548,269

6.2.1.Results of new Company model (corrected)

During analysis of the new results submitted by the Company, an error was found in the model which was submitted. Specifically, the new model, despite beginning with a cohort of 1000 people in the BSC arm ended up with over 1,160 people towards the end of the model. This was due to errors in the way that independently estimated extrapolation data were combined. The net effect of this error was to overestimate costs and underestimate QALYs in the BSC arm of the model, thereby overestimating the treatment benefit of ataluren. Since this model was supplied to the ERG so late in the process, it was not possible to reconstruct it from scratch. The ERG therefore applied a correction factor, essentially scaling the results at each time point to give the correct overall number of patients in the model. All of the exploratory analyses undertaken by the ERG also include this correction factor, as applied to the base model provided by the Company. The results of this corrected version of the Company's resubmitted model are given in Table 42.

Table 42 Results from Company's resubmitted model (corrected)

	BSC	**Ataluren**	**Incremental**
Life years	14.080	15.578	1.498
QALYs	2.269	6.178	3.909
Costs	£229,396	£4,784,895	£4,555,499

6.3. Development of the exploratory ERG model

The ERG produced 4 additional sets of analyses, based on the Company's model, but using different input parameters and distributions, to look at the impact these changes would have on the cost-consequence results. These models are all based on the resubmitted Company model, which is statistically more valid than the original model submitted by the Company. Changes made to the Company's model, together with the impact on the cost-consequence results, are presented below for each of the ERG's 4 different analyses.

6.3.1. ERG model 1

The first new model produced by the ERG uses the same survival analysis distributions for extrapolating Kaplan-Meier data as the Company's resubmitted model, but makes the following changes to other parameters:

- The Company's model uses a time horizon of when the last person in the model loses ambulation. In the opinion of the ERG, a lifetime horizon is more appropriate, as we are interested in all potential cost and benefits accrued as a result of treatment, including those that occur post treatment discontinuation. The time horizon was therefore changed to a lifetime horizon.
- Ataluren treatment post loss of ambulation. It seems to be likely that many patients would

continue to be treated for a period post loss of ambulation, and hence the ERG included costs of 6 months of ataluren treatment post loss of ambulation.

The results given by this altered model are shown below.

Table 43 Cost-consequence results from ERG's 1st model

	BSC	**Ataluren**	**Incremental**
QALYs	2.269	6.177	3.908
Costs	£229,396	£4,982,976	£4,753,580

6.3.2. ERG model 2

The second new model produced by the ERG includes the same changes from the Company model as ERG model 1, but now additionally makes use of the best fitting survival curves for various parameters, rather than those chosen by the company. In this analysis, the log-normal survival curve used by the Company for the transition to loss of ambulation was kept, but the following changes were made to other parametric choices:

- Time to scoliosis (LoA<8y): Changed from log-logistic to log-normal.
- Time to scoliosis (LoA>11y): Changed from log-logistic to generalised gamma.
- Time to ventilation-assistance (8y<LoA<11y): Changed from log-logistic to generalised gamma.
- Time to ventilation-assistance (LoA>11y): Changed from log-logistic to generalised gamma.
- Time to death: Changed from log-normal to generalised gamma

This analysis is still based on the re-digitised Kaplan-Meier data supplied by the Company, but now the best statistical fitting distributions are used for all parameters other than loss of ambulation.

The results given by this altered model are shown below:

Table 44 Cost-consequence results from ERG's 2nd model

	BSC	**Ataluren**	**Incremental**
QALYs	2.334	6.214	3.880
Costs	£225,583	£4,980,189	£4,754,606

6.3.3. ERG model 3

The third model produced by the ERG includes all the same changes made in models 1 and 2, but now

also changes the distribution for time to loss of ambulation from a log-normal to a generalised gamma. Unfortunately, despite this being the best fitting distributions (by statistical criteria), this was not used in any iteration of the Company model. Unlike in previous examples where shifting either the median or mean by 8.1 years (to adjust for delays in loss of ambulation with ataluren) made little difference to the results, here the differences based on mean or median shifts were more substantial. The ERG believe shifting the mean to be the more appropriate approach, and we therefore used this method to obtain the ataluren curve. Again, this analysis is still based on the re-digitised Kaplan-Meier data supplied by the Company. The results given by this altered model are shown below:

Table 45 Cost-consequence results from ERG's 3rd model

	BSC	**Ataluren**	**Incremental**
QALYs	3.641	5.363	1.722
Costs	£203,128	£4,498,592	£4,295,464

It should be noted that this model was originally rejected by the Company as predicting too many people stay in an ambulatory state with BSC (30% remain ambulatory at age 18, 17% at age 25), and therefore consideration should be given to the clinical plausibility of these results.

6.3.4. ERG model 4

The final model produced by the ERG makes use of the digitisations and reconstruction of IPD undertaken by the ERG, as well as the model fitting undertaken on that data. Hence, whilst it makes use of the same data sources as the Company submission, it is based on a whole new set of calculated transition probabilities, based on those derived in Section 5.5.4. In brief, flexible parametric models are used for all transitions other than from the ambulatory to non-ambulatory state. For these transitions, a flexible parametric model again gave the best statistical fit, but as with model 3 above, it predicted proportions of people ambulant in the long-term on BSC which may not be clinically plausible. Hence, to deal with this problem, a log-normal model was used for transitions to the loss of ambulation state.

The results given by this final model are shown below:

Table 46 Cost-consequence results from ERG's 4th model

	BSC	**Ataluren**	**Incremental**
QALYs	3.804	6.853	3.049
Costs	£199,194	£5,744,175	£5,544,981

6.4. Cost-consequence results produced using the Company and ERG models

In summary, there are now a total of six models that have been produced, all based on the same underlying data sources but making different assumptions about costs, time horizons and extrapolation. A brief summary of these six different models is given below.

Model 1: The Company's original submission, were all extrapolations are based on Weibull distributions.
Model 2: The Company's new submission, where full model fitting has been conducted, but the best fitting curves have not always been selected for use in the model.
Model 3: The same as model 3, but with corrections made for coding errors in the model submitted by the Company.
Model 4: The same as model 2, but with a lifetime horizon and with the costs of ataluren treatment included post loss of ambulation.
Model 5: The same as model 3, but with all extrapolation curves (except that for loss of ambulation) changed to the best statistical fitting model supplied by the Company.
Model 6: The same a model 4, but with the extrapolation curve for loss of ambulation replaced by the best fitting one supplied by the Company.
Model 7: Based on re-digitisation, IPD reconstruction and model fitting undertaken by the ERG, using a log-normal distribution for loss of ambulation, and flexible parametric distributions for all other transitions.

A summary of the cost and QALY results generated by each of these models is given below:

Table 47 Results from all models produced

Model	Incremental costs	Incremental QALYs
1	£4,857,333	3.767
2*	£4,548,269	3.924
3	£4,555,499	3.909
4	£4,753,580	3.908
5	£4,754,606	3.880
6	£4,295,464	1.722
7**	£5,544,981	3.049

*Company's preferred model

**ERG's preferred model

6.5. Discussion

The first four models all give relatively similar results, but the 5th and 6th are very different, due principally to the change in distribution used to extrapolate loss of ambulation in the best supportive care arm. The 5th model uses the distributions with the best statistical fit, but it is also important to consider whether the results it produces are deemed clinically plausible. Model 6 is based on re-digitisations of data undertaken by the ERG, together with the best statistically fitting models, adjusted for clinically plausibility (specifically time before loss of ambulation in the BSC model). Model 2 is the most recent analysis undertaken by the company, whilst model 6 is the ERG's "most plausible" scenario.

In addition to the elements of uncertainty which the ERG has been able to address quantitatively, there are a number of other areas of uncertainty it is important to consider. Some of these are related directly to a lack of underlying data, but others are as a result of choices made in the modelling process which have not been quantitatively considered in the Company submission. These include:

- The use of a cohort with a starting age of 8.5, rather than 5 years as specified in the scope.
- The assumption that the treatment benefit with ataluren is permanent, with the advantage over best supportive care found between weeks 24 and 48 of Study 007 continuing until people lose ambulation.
- The use of a linear extrapolation of mean difference in 6MWD which relies on the assumption of a homogeneous population following the same trajectory of progression. Such an approach is not valid if this assumption is not met.
- No additional treatment related adverse events with ataluren which engender costs or reductions in quality of life.
- Treatment adherence to ataluren is 100%, and no-one will discontinue treatment for any reason other than loss of ambulation.
- There are no additional costs for administration, training or monitoring related to ataluren treatment.

All these assumptions appear to be optimistic ones and it therefore seems appropriate to regard the results produced by the model as an optimistic upper bound on the possible benefits of ataluren treatment.

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1. Summary of submitted evidence relating to the costs to the NHS and PSS

The Company's submission includes a budget impact model which was used to estimate the total costs to the NHS over a five-year duration. This model was presented alongside the cost-consequence analysis. The budget impact model considered only the ataluren arm of the cost-consequence model, and results were presented in terms of the absolute costs of ataluren treatment to the NHS.

The CS clearly outlined the objective of the model, the eligible population for treatment, the time horizon and the perspective of the analysis, and provided a description of the analytical framework with information on the inputs and their sources. In terms of the inputs, data required included prevalence of nmDMD, proportion of people with nmDMD, incidence of nmDMD, and mortality rate. Prevalence of nmDMD was derived using the population of England, and the number of males in the population. A DMD prevalence of 8.29 per 100,000 males was obtained from Norwood et al. (2009).[29] The proportion of people (10%) with nmDMD was obtained from the TREAT-NMD DMD Global database. Information required on the proportion of those with DMD ≥ 5 years and older with nmDMD ([redacted] was obtained from the Cooperative International Neuromuscular Research Group (CINRG) DMD Natural History Study (DMD-NHS). The incidence of 19 per 100,000 for DMD was obtained from Moat et al. (2013). An annual mortality rate of [redacted] and a [redacted] rate of loss of ambulation were used and the CS indicated that these were derived from the cost-consequence model, assuming constant event rates over time.

In the CS it was anticipated that no additional costs would be required for additional genetic testing to identify people eligible for treatment. In addition, no extra costs would be required for infrastructure or initiation of treatment. Minimal monitoring of patients was considered to be required. In terms of resource savings associated with ataluren, the Company anticipated that fewer surgical procedures, and surgical follow-up costs would be required along with a reduced or delayed requirement for respiratory and palliative support. The Company acknowledged that these costs were not included in the budget impact model.

The Company suggested that people would remain in an ambulatory health state over a longer duration, and hence would be older and stronger, and might be able to maintain upper body strength and to continue to use self-propelled wheelchairs, thus allowing for savings in the costs of electric wheelchairs

The model estimated the total number of people who are likely to be treated with ataluren. The estimate for Year one is based on 66 people with nmDMD, seven people being diagnosed with

nmDMD, [redacted] people losing ambulation and [redacted] deaths. The model predicted [redacted] people who are eligible to receive ataluren treatment. Based on the level of identification of ([redacted]) of known people who are in the ambulatory state ([redacted]), and a market uptake of ([redacted]), the model predicted that 35 people are likely to receive ataluren treatment. The annual cost was estimated to be approximately £8.6 million in the first year rising to £16 million in the fifth year at an average of £12.2 million per year. The total budget required over the five year period was estimated to be approximately £73.3 million.

Table 48 below shows the main results of the budget impact analysis by the Company.

Table 48 Summary of budget required over a five-year period (adapted from Table D13.5 CS p209) and additional ERG scenario analyses

	Year					Average
	1	2	3	4	5	
Prevalence	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	7	7	7	7	7	7
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential (theoretical) available patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Level of patient identification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Known patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	35	42	49	57	65	50
Total annual costs	£8,625,680	£10,350,816	£12,075,952	£14,047,536	£16,019,120	£12,223,821
ERG Additional Scenario analyses						
Scenario 1 -39kg	£13,456,065	£16,147,278	£18,838,491	£21,914,163	£24,989,835	£19,069,166
Scenario 1 -53kg	£18,286,450	£21,943,740	£25,601,030	£29,780,790	£33,960,550	£25,914,512

7.2. ERG critique of the Company's budget impact analysis

The budget impact analysis provides an estimate of the changes/impact to the NHS budget should ataluren treatment be adopted. The model provided an estimate of the total number of people eligible for ataluren treatment, annual costs of ataluren, uptake of treatment to derive the cost of illness over the five year time horizon. Information required on the epidemiology of DMD and nmDMD, and on

loss of ambulation was derived from secondary sources and on the cost-consequence model. The choice of sources for data inputs was described and justified, and was considered appropriate. As a result of the limitations outlined in chapter 5, the inputs derived from the cost-consequence model may have been either under- or over estimated. Below we present some other considerations related to the budget impact analysis:

- The budget impact analysis assumes a median weight between 24-26kg for people being treated with ataluren, the weight from the bottom of the eligible treatment age range. Since treatment is gauged on a per kilogram basis, patient weight is an important factor in the estimates. The budget impact model does not include an average weight across all eligible patients, and across affected patients across all affected age ranges. The inclusion of people weighing ≥25kg would increase budget impact estimates. At the clarification stage, the company suggested that the median weight in the placebo and ataluren (40mg/kg) arms in Study 007 was 25.6kg and 27.0kg, respectively. Using the RCPCH growth reference curves, an eight year old boy will weigh 25.5kg at the 50th percentile, and this weight was used in the budget impact calculations. However, these were the weights of people at baseline in the trial, which does not necessarily represent the average weight of people who would be initiated on treatment or who might continue to receive treatment.
- The analysis does not include cost estimates for people who continue to have treatment six months after loss of ambulation as recommended by the Company in the CS. Including this cost would increase the budget impact estimates
- The analysis does not include any additional monitoring costs that may be needed for people receiving ataluren treatment
- The analysis does not include additional training of staff. The ERG consulted with an expert who suggested that health care staff may require special training when diagnosing complete loss of ambulation in order to make decision on treatment continuation plans
- Sensitivity/scenario analyses were not undertaken

7.3. ERG exploratory scenario analyses of budget impact analysis

We have conducted one-way scenario analyses to explore the impact on the annual budget requirement. These analyses were based on the Company's model estimates for rates of annual background mortality and loss of ambulation and are presented in Table 48 (above) for comparative purposes:

- Scenario 1: changing the average weight for people being treated with ataluren
    - Average weight (39kg) derived from the best supportive care group
    - Average weight (53kg) derived from the ataluren group

  These weighted average weights were derived based on the number of people remaining in

the ambulatory health state per cycle.

- Scenario 2: changing the average weight for people being treated with ataluren and using an annual background mortality rate of [redacted] with a [redacted] rate of loss of ambulation based on the ERG's model.
    - Weighted average weight (39kg) derived from the ataluren group
    - Weighted average weight derived (53kg) from the best supportive care group

  The results for Scenario 1 are presented at the end of Table 48 (see above). Results for Scenario 2 are not substantively different to those for Scenario 1 are not shown here.

7.4. ERG budget impact analysis summary

In summary the ERG believes that using an average weight of 39kg provides the most appropriate estimates of budget impact, as this is the average weight of people from the best supportive care arm (corresponding most closely to current practice and to the population eligible for treatment were ataluren to be adopted. This leads to an average annual budget impact of £19,069,166, as opposed to the £12,223,821 reported in the initial Company submission. We also consider that this figure may be an underestimate of the total budgetary impact, as it does not include costs associated with administration, training or monitoring.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1. Summary of cost savings estimated within the Company Submission

8.1.1. Nature of estimates presented

The majority of the costs savings estimated for ataluren treatment are with respect to costs borne outside an NHS and PSS perspective. Estimates of impact of ataluren are on non-medical community services (e.g. home help, personal assistants and transportation), informal care, indirect costs (loss of productivity), out-of-pocket payments, intangible costs and the costs of loss of leisure time. These estimates are predominantly based on the study by Landfeldt et al. (2014).[34] Briefly, the aim of this study was to estimate the total cost of illness and economic burden of people with DMD. People with DMD and their carers from four countries (Germany, USA, Italy and the UK) were invited to complete a questionnaire on resource use, health-related quality of life, work status, informal care and household expenses in order to estimate costs associated with DMD from a societal perspective. Costs collected in this study were presented in US dollars, were converted using purchasing power parity (PPP) calculations and were inflated using the 2014 Consumer Price Index. In the next sections we include the costs estimates presented by the Company and a critique of these estimates.

8.1.2. Societal costs

Due to the nature of nmDMD, the majority of people are unable to work. From the Landfeldt study, a small proportion of people from the UK were reported to be in employment. In addition substantial losses of productivity were recorded for people who were caregivers. In the submission, total annual costs of DMD were estimated to be approximately £53,300 with 46% of these costs relating to the costs of informal care and loss of productivity. Table 50 below shows a summary of the societal cost estimates as presented in the CS.

Table 49 Summary of costs estimates on annual cost of DMD in the UK

Component	Percentage of cost of illness	Per-patient cost (US dollars, 2012)	Per-patient cost (GBP 2014)[e]
Hospital visits[a]	3%	2,300 (1,500–3,720)	1,683
Visits to physicians and other health care practitioners	11%	8,230 (6,360–13,150)	6,023
Tests and assessments	2%	1,580 (1,450–1,750)	1,156
Medications	1%	930 (820–1,070)	681
Non-medical community services[b]	27%	19,250 (13,240–28,670)	14,087
Aids, devices and investments[c]	10%	7,520 (5,690–9,790)	5,503

Informal care	20%	14,340 (13,030–15,990)	10,494
Indirect costs (production losses)	26%	18,700 (16,280–21,150)	13,684
Total annual cost of illness	-	72,870 (64,350–84,150)	53,325
Intangible costs[d]	-	46,080 (42,360–50,050)	33,720
Total burden of illness	-	118,950 (108,280–132,710)	87,045

Data presented as mean (95% confidence interval), rounded to nearest 10 US Dollars.

a Including emergency and respite care.

b Home help, personal assistants, nannies, and transportation services.

c Include investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).

d cost (costs due to pain, anxiety, social handicap, etc.) was estimated by assigning a monetary value to the loss in quality of life for patients and caregivers in relation to the age- and sex-specific mean quality of life in the general population.

e Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

The costs estimates provided above are related to societal costs, and all appear to be relevant. The majority of the quoted costs were drawn from the Landfeldt publication. The CS noted that these costs are based on a cross-sectional study, whereby resource use and costs are gathered from a questionnaire administered at one time-point, so in some cases resource use data were extrapolated to obtain annual estimates. This method is likely to produce some inaccuracies in extrapolating costs, as DMD is a progressive disease and the circumstances of the patient and their caregivers are likely to change over time. The ERG also noted that there was a 42% response rate across all countries in the Landfeldt study[34]. This is low so that the cross sectional resource use estimates may suffer from bias and may be either under- or overestimated. Further it would also have been useful to know the response rate by country – specifically among the UK population, as it is not clear whether these estimates can be considered representative of the DMD population in England, since expectations for example of the needs for, nature and extent of household adaptation may differ between countries.

8.1.3. Costs borne by patients

The CS estimates costs borne by patients were considered to include out-of-pocket payments, insurance premiums, co-payments for medical services, medicines and community services, loss of leisure time, intangible costs and per patient income loss. Table 51 below shows the estimated costs presented in the CS. All costs were obtained from the Landfeldt study and were converted to UK pounds and inflated to current prices. Estimates of costs are based on per-patient annual household burden of DMD.

Table 50 Summary of cost estimates on per-patient annual household burden of DMD in the UK as presented in CS

	Cost (in 2012 US dollars)	**Per-patient cost (GBP 2014)[b]**
No. (%) living with caregiver	188 (98)	138
Total out-of-pocket payments	3,490 (2,220–5,570)	2,554
Insurance premiums	10 (0–30)	7
Co-payments for medical services	60 (30–140)	44
Co-payments for medications	100 (60–140)	73
Co-payments for community services	140 (60–290)	102
Out-of-pocket payments for investments[a]	3,180 (2,020–5,710)	2,327
Income loss	750 (440–1,200)	549
Loss of leisure time	13,590 (12,410–14,980)	9,945
Intangible costs	45,770 (42,070–49,670)	33,493
Total per-patient annual household burden	63,600 (58,790–68,370)	46,541

a Include non-reimbursed payments for medical and nonmedical aids and devices, as well as investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).
b Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

Co-payments costs were estimated to include expenses for medical services, medication and community services. Loss of leisure time for the caregiver was estimated at approximately £9,990 per patient. This cost was estimated based on the inability to perform regular daily activities, based on a weekly loss of 44 hours of leisure time (Landfeldt et al., 2014).

Intangible costs were estimated at £33,500 including costs due to pain, anxiety, and social handicap. This cost was estimated by assigning a monetary value to loss in quality of life for people with DMD and their caregivers in relation to age- and sex-specific mean quality of life from the general population. Landfeldt et al. (2014) stated that the willingness-to-pay (WTP) for one year in full health varies by method of assessment and setting. In the US, the WTP is thought to be between US$50,000 and US$100,000 per QALY. In this analysis, the WTP was US$75,000 per QALY. The ERG note that this WTP threshold is higher than that generally used in the UK, hence this estimate of intangible costs may be overestimated.

The costs estimates provided above are related to costs borne by people with DMD and their care givers. The cost estimates provided appear to be relevant. However it was not clear whether the Landfeldt publication, from which the majority of these costs were drawn, included people who had been diagnosed with scoliosis. In addition, the mean age of the children included in the cost analysis was 12 years with a range from 8-17 years old. Uncertainty for the age range 5-8 years old may still exist as these cost estimates were not included for this age group. Costs estimates for out-of-pocket payments which include non-reimbursed payments for medical and non-medical aids and devices, as well as investments for reconstruction of the home (e.g. adaptations for wheelchair use) were included, but it was unclear if costs included wheelchairs for children with nmDMD.

Landfeldt and colleagues indicated that the costs for loss of production were estimated for one caregiver, and that these costs may therefore represent a conservative estimate. In addition they do not include costs associated with end of life care. Paid informal care was valued using the human capital approach, which is entirely acceptable but which may result in higher estimates of costs than using alternative approaches such as the friction approach where labour availability is taken in to account.

8.1.4. Cost savings to government bodies

In the CS, it is anticipated that treatment with ataluren could potentially lead to savings to the educational, local government and welfare budgets. However, cost estimates for these savings were not presented in the CS. Also, it would have been useful for the Company to include scenario analyses based on the uptake of ataluren treatment on these costs savings.

8.1.5. Summary of wider societal costs and costs savings

The CS, presented appropriate wider societal costs and some potential savings. The ERG consider that whilst the categories of costs and saving were appropriate, the heavy reliance on the Landfeldt study which was a) undertaken in 2012, b) broadly based across a number of countries and c) had a low response rate, may mean that these costs might be either under- or overestimated. Also, because the data were cross-sectional, whilst it gave information on the cost burden of DMD, it was not possible to assess quantitatively which, if any, of these costs would be alleviated by the use of ataluren.

8.2. Impact of the technology on the delivery of the specialised service

In the following section we cover potential impacts on service delivery, although most of the issues related to service delivery are already included in the cost-consequence analysis and are discussed in previous sections. The main issues relate to diagnosis and eligibility for treatment and to monitoring and criteria for starting, continuing and stopping treatment. As far as diagnosis and eligibility are concerned the CS and our clinical advisors both considered that there should be no additional impact on the service as all necessary tests would already be in place anyway for children with nmDMD.

8.2.1. Treatment continuation and stopping rules

On page 23 of the CS a stopping rule for ataluren is described:

"If a patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician should consider stopping ataluren treatment.

Treatment should not be stopped while the patient has any degree of ambulatory ability as it has been shown with other treatments (corticosteroids) that withdrawal of medication at this time can have negative consequences. Patients should not stop treatment ***until at least 6 months*** *after becoming fully non-ambulant."*

Trial 007 was a 48 week trial in which patients in the treatment arm received ataluren for 48 weeks and no subjects discontinued treatment during the trial. There is therefore no evidence on the effectiveness and safety of stopping ataluren and no evidence available concerning the rationale for continuing treatment for 6 months after patients become fully non-ambulant.

Clarification received from the Company elaborated on the issue confirming that none of the clinical trials included stopping criteria and that the longest individual continuous exposure to ataluren (lower dose) is [redacted]. A stopping criterion was requested during the development of the NHS commissioning policy and the '6 months post LoA' stopping rule was devised based on clinical expert opinion and experience with corticosteroids. Information submitted during clarification suggests that Dr Quinlivan advised on stopping criteria. This stopping criterion was adopted for NICE. "*The decision to stop treatment no later than 6 months after becoming fully non-ambulant will be captured within follow-up clinic appointments which occur at least 6 monthly*" (page 143) and would therefore not involve additional monitoring.

As mentioned in section 3.3.1, there is uncertainty around the threshold of LoA. While NHS England states that patients should receive treatment six months beyond not being able to walk 75m without assistance (E. Jessop personal communication), the Company used a threshold of >0m. This uncertainty renders the stopping rule impractical. Further we consider that when a definitive rule is agreed, clinicians might require some training on how to implement such a rule in clinical practice. As currently no 6MWD test is undertaken in clinical practice in the assessment of nmDMD patients due to time constraints and lack of resources in the clinic setting (Dr Rosaline Quinlivan personal communication) introduction of a standardised measure to assess LoA may prove resource intense.

8.2.2.Eligibility criteria for ataluren treatment

Ataluren is licenced for nmDMD patients aged 5 years who are ambulatory. The 5 year cut-off was a pragmatic cut-off in study 007 as children are usually diagnosed at around this age. In clinical practice it is believed that ataluren will be given to children who are four and half years old (E. Jessop personal communication). This seems to imply uncertainty as to whether treatment should be given to children diagnosed at a younger age.

The uncertainty around the definition of ambulation for the stopping rule also applies to the assessment of eligibility to initiate treatment. Before implementation of ataluren into clinical practice is feasible agreement on a definition of ambulation and of how it can be measured reliably are required.

8.2.3.Monitoring

The CS states that minimal monitoring of ataluren will be required in clinical practice. The following recommendations were made (page 62):

- *"Total cholesterol, LDL, HDL, and triglycerides are monitored on an annual basis in nmDMD patients receiving ataluren".*
- *"Resting systolic and diastolic blood pressure are monitored every 6 months in nmDMD patients receiving ataluren concomitantly with corticosteroids"*
- *"Serum creatinine, BUN (blood urea nitrogen), and cystatin C are monitored every 6 to 12 months in nmDMD patients receiving ataluren"*

Blood pressure monitoring and blood tests are currently carried out on an annual basis for all patients with DMD. Cystatin C tests should be used to measure renal function in DMD patients in order to monitor the efficacy and safety of ataluren. Clarification received from the Company confirmed that this consists of the only test that is required in addition to standard clinical monitoring. The CS reported that two experts were consulted who stated "*that most of the above tests are performed routinely and are associated with a negligible cost*." (Page 179) Monitoring costs for ataluren were not included in the cost-consequence analysis.

Dose adjustment was not mentioned as part of monitoring in the CS. During clarification the Company confirmed that no patients on ataluren received dose adjustments in either of the two trials 004 and 007. No dose adjustments are needed for patients that have lost ambulation. However, as dosing occurs per kg some adjustment of dose to adjust for body weight will need to be considered. Furthermore, the CS states that "*patients with renal or hepatic impairment should be monitored*

closely" (page 37) while on ataluren, however, no patients with renal or hepatic impairment were included in the ataluren trials and it is unclear what this 'close monitoring' might entail for this patient group.

8.2.4. Summary of impact on services

In summary the likely impact of ataluren on the delivery of the specialised services for DMD and for nmDMD in particular is not yet clear in a number of respects, the most important being the need for clinical input in additional monitoring and in making decisions on initiation, continuation and stopping the treatment for patients.

9. DISCUSSION

9.1. Statement of principal findings – clinical effectiveness

- The CS identified one RCT (study 007 reported in Bushby et al., 2014[41], 8 additional publications [25, 43-49]) and one cohort study (study 004 by Finkel et al 2013)[42] that assessed the effectiveness of ataluren compared with placebo in boys aged ≥5 years of age with an ability to walk at least >75 metres unaided. The studies were considered to be of reasonable methodological quality when assessed on recognised criteria. The CS reported the efficacy of ataluren (40mg/kg/day) compared to placebo (or best supportive care) on the outcomes of 6MWD, timed function tests, accidental falls, myometry tests, step activity monitoring, wheelchair use, HRQoL and treatment satisfaction, digit span, heart rate monitoring, muscle dystrophin expression and serum creatine kinase.

- When assessed on the primary outcome measure of change in 6MWD from baseline to 48 weeks, the benefit conferred by ataluren compared to placebo only became statistically and clinically significant through a post-hoc analysis using a corrected (cITT) approach (ITT: difference 26.4m (p=0.09); cITT: difference 31.7m (p=0.02)). Time to persistent 10% 6MWD worsening was both clinically and statistically significant on both ITT and cITT analyses (ITT: HR 0.51 (p=0.003); cITT: HR 0.52 (p=0.04)) analyses.

- A post-hoc analysis assessing the effects of ataluren on patient sub-groups defined by measures of the severity of the condition (i.e. decline phase of DMD or a baseline of <350m 6MWD) identified that ataluren conferred a statistically significant benefit in limiting the reduction in the mean change in 6MWD compared to placebo (Difference in reduction - decline phase: 49.9m (p=0.0096); baseline <350m 6MWD: 68.2m (p=0.0053)). Outcomes for the non-severe groups were not presented and, as such, the sub-group analysis should be viewed with caution.

- The relative effects of ataluren compared to placebo on secondary outcome measures were less certain. Ataluren led to statistically significant benefit on the outcomes of time to climb 4 stairs (2.4 seconds vs. 4.8 seconds; p=0.02) and frequency of accidental falls (RR 0.38; 95%CI 0.16, 0.94; p=[redacted]). There were no statistically significant differences between ataluren and placebo in descending 4 stairs, running or walking 10 metres or in moving from supine to standing position or in any of the other outcomes measured including muscle strength, step activity, patient reported wheel chair use, HRQoL, treatment satisfaction, digit span, heart rate, muscle dystrophin expression and serum creatine kinase expression. On sub-groups defined by condition severity, it was reported that results favoured ataluren over placebo though no statistical tests are reported.

- The extent of adverse events differed little between ataluren and placebo in trial 007, though some differences were evident in the types of events. Ataluren was associated with gastrointestinal disorders, vomiting, falls, investigations, weight decreases, metabolism and nutrition disorders, decreased appetite, musculoskeletal and connective disorders, back pain, headaches and nervous system disorders. Patients receiving placebo had higher rates of infections and infestations and of hip fracture. No deaths were reported by the included studies.

- From a cumulative summary of serious adverse events in four ongoing and five completed company-sponsored clinical trials of various doses of ataluren, 'cardiac disorders', 'infections and infestations', 'injury poisoning and procedural complication' (femur fractures) and total number of serious adverse events appeared to be more common among the ataluren group. Without knowing more detail about exact person-time at risk it is almost impossible to gauge relative rates of adverse events in ataluren and placebo groups. The ERG requested clarification from the Company but the required information was not provided.

- Patients, the public and consultees in general were very strong in their support of the potential introduction of ataluren and its perceived benefits.

9.2. Cost-consequence analysis

The Company undertook a review of existing literature to investigate the costs and consequences of ataluren treatment. Given the search strategy, and the inclusion and exclusion criteria it is unlikely that any key published economic studies may have been missed. However, the ERG would have found it useful if the Company had submitted a list of excluded studies and the reasons for exclusion.

The Company built a semi Markov model to investigate the costs and consequence of ataluren in addition to best supportive care versus best supportive care. The base case model was built from an NHS and PSS costing perspective, included disutilities for carers of individuals with nmDMD, used discount rate of 3.5% for costs and outcomes, with the time horizon of the model being the point where the last individual left the ambulant health state. The base-case comparison of ataluren with best supportive care alone was based LYG, costs and QALYs.

The list price for ataluren was taken as £2,532 per box of 30 x 125mg sachets, with a recommended dose of 40mg/kg/day. In the CS, the cost for an 8 year old was estimated as £675 per day, £246,448 per year. The Company estimated direct and indirect costs for the different health states. Direct and indirect costs for the ambulatory state were estimated as £1,633 and £7,972, respectively, and for the non-ambulatory state were £4,012 and £19,588, respectively.

Mean LYG in the ataluren arm in the original Company model submitted were greater than in the best supportive care arm (14.497 versus 13.888). Total mean discounted costs were estimated as £5,092,540 for ataluren and £235,207 for BSC. The results from the model showed that at the treatment time horizon, ataluren produced 6.152 QALYs compared to best supportive care which produced a mean of 2.385 QALYs.

Whilst the economic model developed by the Company appears to have included the appropriate health states, and transitions and represents the natural disease progression of nmDMD, the ERG has concerns regarding deviation from the scope in the age of children entering the model and the derivation of transition probabilities used for time to loss of ambulation, time to scoliosis, requirements for ventilation and time to death. The ERG is also concerned about the derivation of health state utilities and of resources use assumptions particularly in relation to use of ventilatory assistance**.**

After the initial submission, additional analyses were undertaken by both the Company and the ERG. In additional analyses the Company re-digitised Kaplan-Meier data and reconstructed IPD. They used this to undertake model selection in order to find better fitting survival curves than the Weibull models used in the initial submission. After adjustments made by the ERG for errors in the model submitted by the company (where an initial cohort of 1,000 people in the BSC arm increased to 1,160 by the end of the model), this improved model estimated costs and QALYs of £4,784,895 and 6.178 for ataluren, and £229,396 and 2.269 for best supportive care, with incremental costs and QALYs of £4,555,499 and 3.909.

The ERG performed a number of additional analyses. The ERG's preferred model incorporated the following changes from the revised model submitted.

- A lifetime horizon rather than until the last individual losses ambulation.
- The inclusion of the costs of 6 months of ataluren treatment post loss of ambulation, in line with clinical advice.
- The ERG refitted survival curves to the various sets of Kaplan-Meier data, using a log-normal distribution for time to loss of ambulation, and flexible parametric distributions for other transitions.
- Correction to errors in the model code (as described above).

The revised estimates of costs and QALYs from this model were £5,744,175 and 6.853 for ataluren, and £199,194 and 3.804 for best supportive care, with incremental costs and QALYs of £5,544,981

and 3.049.

There are a number of sources of uncertainty remaining in the model which the ERG were not able to assess quantitatively. Some of these are directly related to the shortage of evidence in a rare clinical area, but others come from assumptions made by the Company in the modelling process. These assumptions include:

- The use of a cohort with a starting age of 8.5, rather than 5 years as specified in the scope.
- The assumption that the treatment benefit with ataluren is permanent, with the advantage over best supportive care found between weeks 24 and 48 of Study 007 continuing until people lose ambulation.
- The use of a linear extrapolation of mean difference in 6MWD relies on the assumption of a homogeneous population following the same trajectory of progression. Such an approach is not valid if this assumption is not met.
- There are no additional treatment related adverse events with ataluren which either cost money or lead to reductions in quality of life.
- Treatment adherence to ataluren is 100%, and no-one will discontinue treatment for any reason other than loss of ambulation.
- There are no additional costs for administration, training or monitoring related to ataluren treatment.

9.3. NHS budget impact and societal analysis

The ERG had a number of concerns in relation to the budget impact analysis:

- The budget impact analysis assumes a median weight between 24-26kg for people being treated with ataluren, the weight from the bottom of the eligible treatment age range. The inclusion of people weighing ≥25kg would increase budget impact estimates.
- The analysis does not include cost estimates for people who continue to have treatment six months after loss of ambulation as recommended by the Company in the CS. Including this cost would increase the budget impact estimates
- The analysis does not include any additional monitoring costs that may be needed for people receiving ataluren treatment
- The analysis does not include additional training of staff. The ERG consulted with an expert who suggested that health care staff may require special training when diagnosing complete loss of ambulation in order to make decision on treatment continuation plans
- Sensitivity/scenario analyses were not undertaken.

The Company's assessment of the estimated annual budget impact, over the first five after treatment

implementation, was £12,223,821. The ERG conducted a modified analysis, using the average weight of treatment eligible individuals from the best supportive care arm of the cost-consequence model (39kg). This gave an estimated annual budget impact of £19,069,166.

The majority of the costs savings estimated by ataluren treatment are with respect to costs borne outside of the NHS and PSS perspective. The estimates of impact of ataluren are on non-medical community services (e.g. home help, personal assistants and transportation), informal care, indirect costs (loss of productivity), out-of-pocket payments, intangible costs and loss of leisure time. These estimates in the CS were predominantly based on the study by Landfeldt et al. (2014).[34] The CS, presented appropriate wider societal costs and some potential savings. The ERG consider that whilst the categories of costs and saving were appropriate, the heavy reliance on the Landfeldt study which was a) undertaken in 2012, b) broadly based across a number of countries and c) had a low response rate may mean that these costs might be either under- or over estimated. In summary the likely impact of ataluren on the delivery of the specialised services for DMD and for nmDMD in particular is not yet clear in a number of respects, the most important being the need for clinical input in additional monitoring and in making decision on continuation and stopping o the treatment for patients.

Additionally, whilst the Company submitted evidence showing the costs and burden associated with nmDMD across a number of areas, what reduction (if any) that there might be expected in these costs due to the introduction of ataluren was not clear. In particular, there was no clear link between reductions in the rate at which people's ambulation levels reduce, and reductions in costs to the individual and other services.

10. CONCLUSIONS

10.1. Overarching conclusions

The ERG consider that, given the immature evidence and the small size of the population, the Company submission presents a good report of available evidence and of the relevant trial. Patients, the public and consultees in general were very strong in their support of the introduction of ataluren and its perceived benefits. An appropriate model was provided by the Company and this (after corrections for errors in the model) suggested that total mean discounted costs were £4,784,895 for ataluren with best supportive care and £229,396 for best supportive care alone. At the treatment time horizon, ataluren produced 6.178 QALYs compared to best supportive care which produced a mean of 2.269 QALYs, giving incremental costs and QALYs of £4,555,499 and 3.909.

The ERG's preferred scenario model revision estimates resulted in total mean discounted costs of £5,744,175 for ataluren and £199,194 for best supportive care, and total mean discounted QALYs of 6.853 and 3.804. Mean incremental costs where therefore £5,544,981, and mean incremental QALYs 3.049.

10.2. Continuing uncertainties

The ERG consider that the likely impact of ataluren on the delivery of the specialised services for DMD and for nmDMD in particular is not yet clear in a number of respects. The most important remaining uncertainties centre around:

i. The likely benefits of ataluren in practice given that the ITT analysis in the trial showed no significant benefit.
ii. With the assumption that the cITT analysis is appropriate, the actual most likely estimates of LY and QALYs gained for the ataluren arm compared to the best supportive care arm.
iii. The estimates of service impact e.g. the need for clinical input in additional monitoring, and in making decisions on initiation, continuation and stopping of the treatment for patients.
iv. Extrapolation from 6MWD to LoA through to mortality.
v. The impact on independence of patients and allowing carers to remain in work for longer.
vi. The safety profile of ataluren, in particular in relation to serious adverse events.
vii. Issues related to dose response and mechanism of action.
viii. Relevance of secondary outcome measures.

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12. APPENDICES

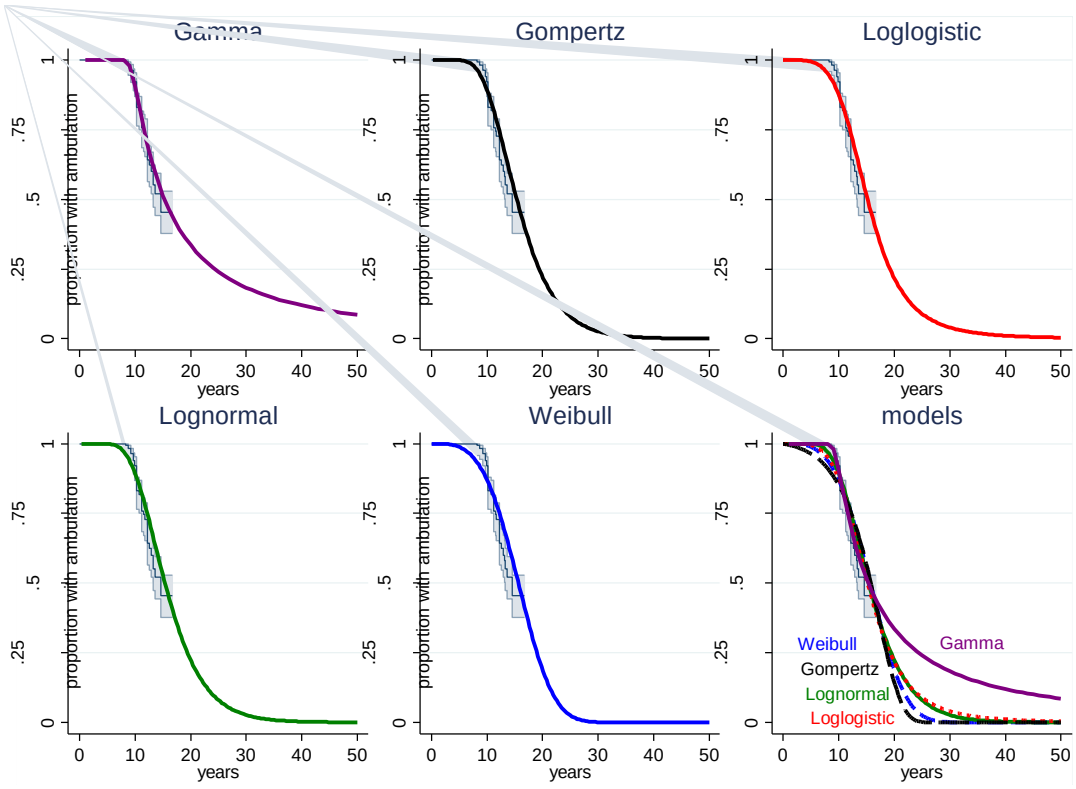
Appendix 1 List of centres that specialise in the management of DMD in England and Wales

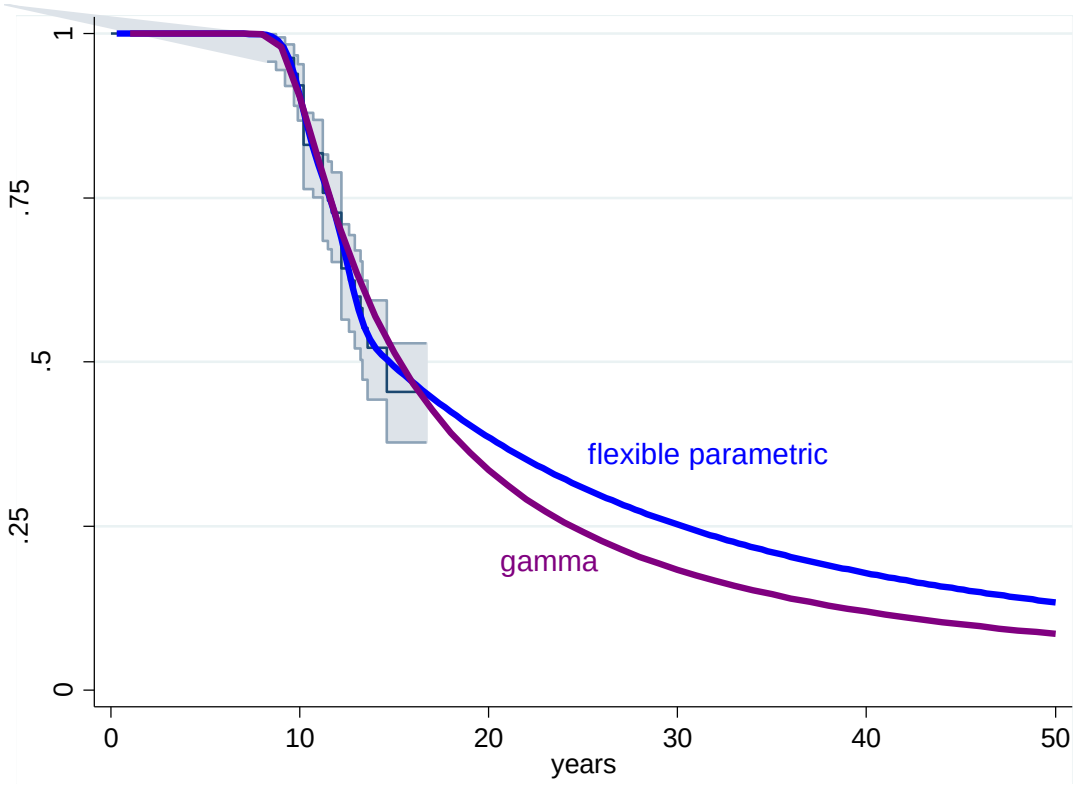
- Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne
- Leeds General Infirmary
- Sheffield Children's Hospital NHS Trust
- Alder Hey, Liverpool
- Manchester Children's Hospital
- Preston Royal
- Nottingham University Hospital
- Heartlands Hospital, Birmingham
- John Radcliffe Hospitals, Oxford
- Southmead Hospital, Bristol
- Southampton General
- Addenbrookes, Cambridge
- The Robert & Agnes Hunt Orthopaedic Hospital, Oswestry
- London (Great Ormond Street Hospital)
- London (National Hospital for neurology & Neurosurgery)
- London (St Thomas's)
- University Hospital Wales, Cardiff
- Morriston Hospital, Swansea

Appendix 2 ERG exploration of parametric models

Ricotti et al. 2013

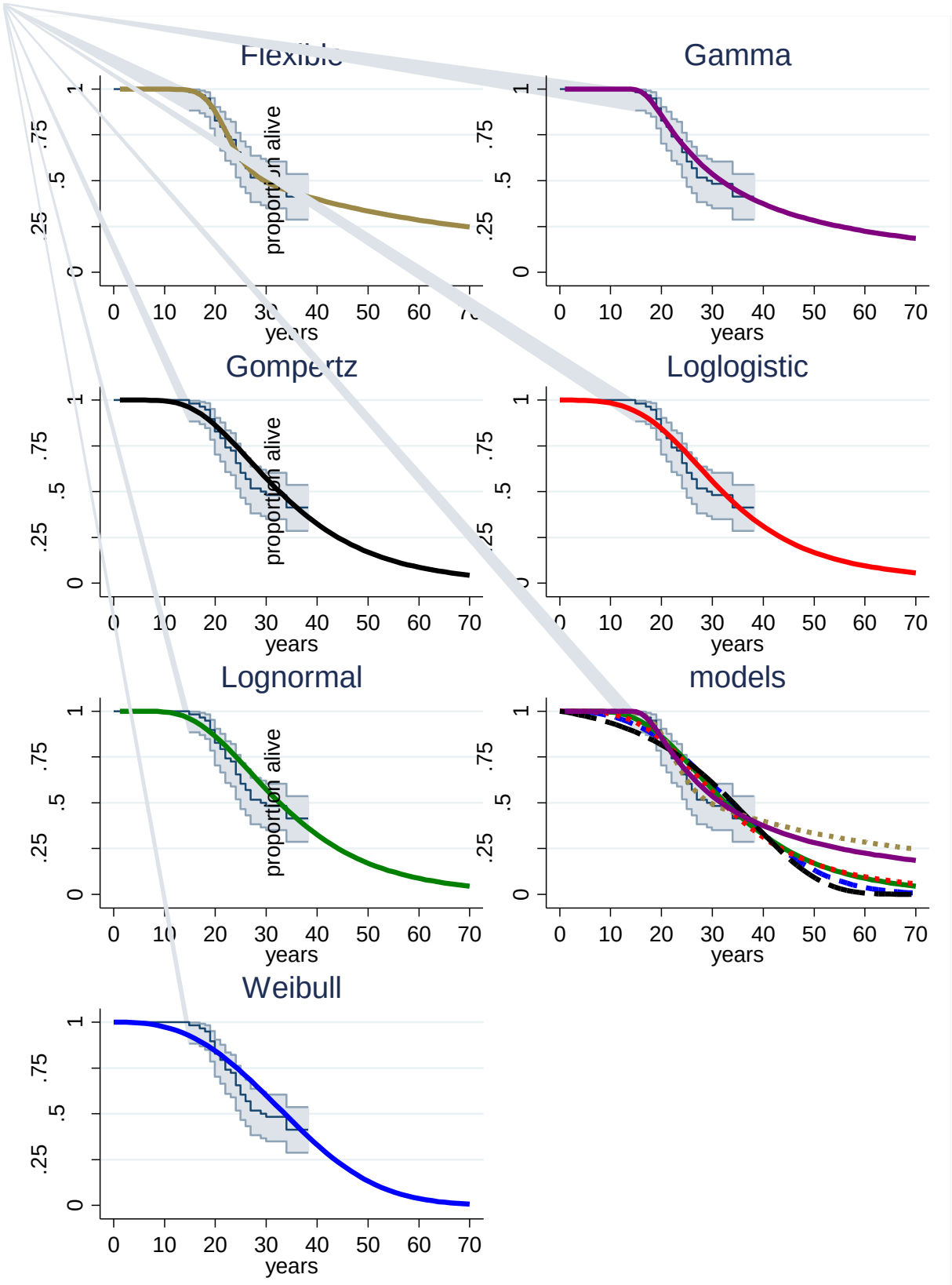
Model	Obs	ll(model)	df	AIC	BIC
gamma	165	-73.2959	3	152.5918	161.9097
exponential	165	-161.075	1	324.1505	327.2565
Weibull	165	-103.105	2	210.2104	216.4223
gompertz	165	-114.639	2	233.278	239.4899
lognormal	165	-91.229	2	186.4579	192.6698
loglogistic	165	-95.5587	2	195.1173	201.3292
flexible parametric	165	-72.6758	4	153.3515	165.7753
flexible parametric	165	-68.1392	5	146.2784	161.8082
flexible parametric	165	-67.8728	6	147.7456	166.3813





Flexible parametric extrapolation is strongly influenced by the later part of observed data where the uncertainty is at its maximum. For this reason the gamma fit may arguably be preferable.

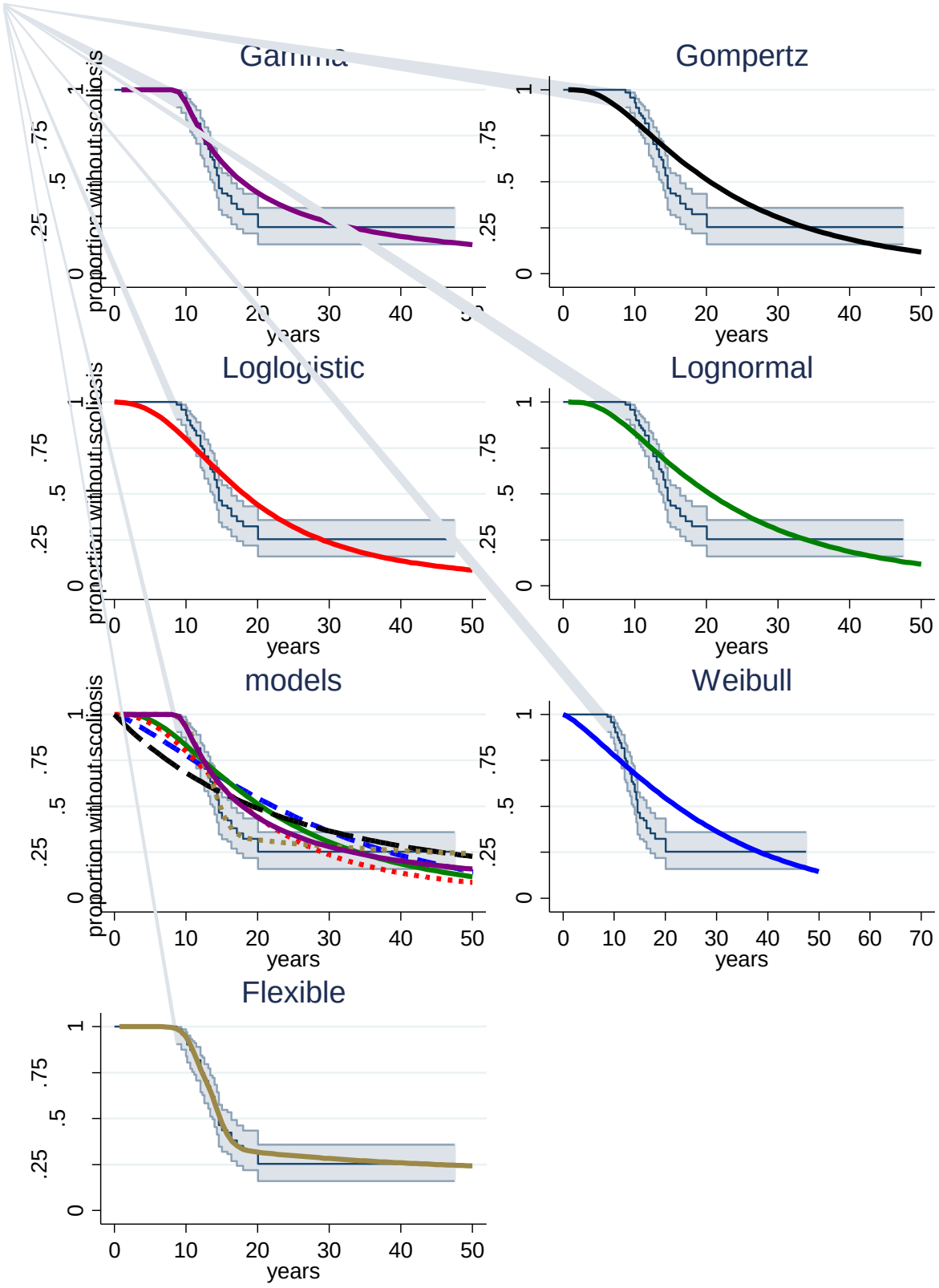
Rall SI, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myol:2012;31(2):117-20.



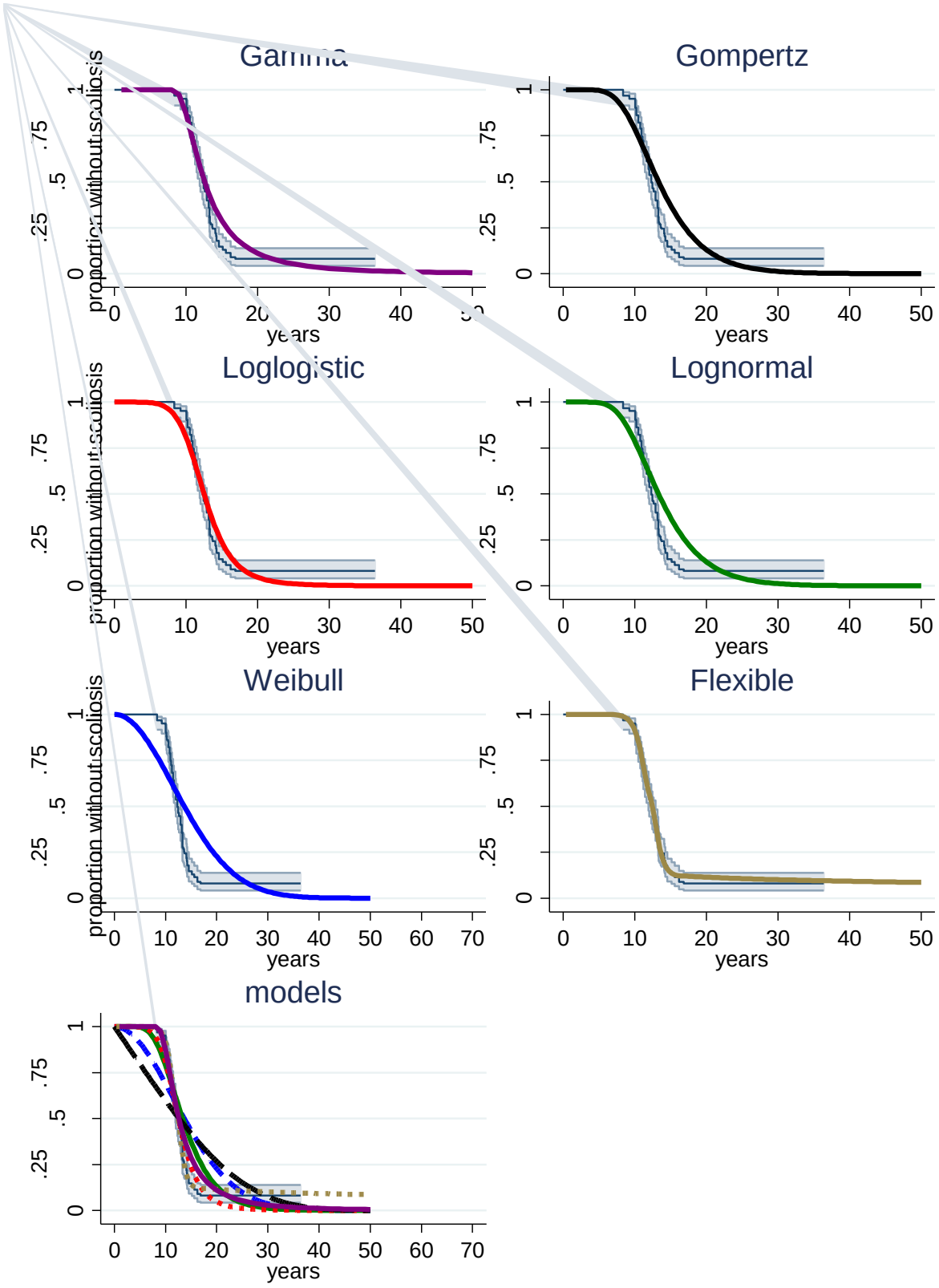
Model	Obs	ll(model)	df	AIC	BIC
gamma	58	-34.6902	3	75.38031	81.56164
exponential	58	-60.3379	1	122.6759	124.7363
weibull	58	-45.559	2	95.11806	99.23895
gompertz	58	-50.333	2	104.666	108.7869
lognormal	58	-40.998	2	85.99596	90.11685
loglogistic	58	-42.5272	2	89.05439	93.17528
flexible parametric	58	-42.5272	2	89.05439	93.17527
flexible parametric	58	-33.0169	3	72.03387	78.2152
flexible parametric	58	-32.9303	4	73.86061	82.10238
flexible parametric	58	-32.6169	5	75.23382	85.53604
flexible parametric	58	-32.6626	6	77.32513	89.68779

Gamma and Flexible parametric extrapolations are strongly influenced by the later part of observed data where the uncertainty is at its maximum leading to counterintuitive survival times for some individuals. For this reason other fits may arguably be preferable.

Time to scoliosis group C



Time to scoliosis group B



National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene [ID 428]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Thursday 3 September 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Please note: The page numbering on the ERG report varies when printing / viewing the report on different operating systems. We have tried to ensure the page numbers included in this pro-forma response are accurate, but some of the quoted page numbers may be the page before of after the document viewed on your system.

Key: Academic-in-confidence data and Commercial-in-confidence data

Issue 1 Report incorrectly states clinical data were not presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1.3, page 16 "However, the effects on patients with less severe disease were not reported and, as a consequence, the findings should be viewed with caution."	Please delete this sentence.	Figure C9.10 of the submission shows results across the disease spectrum based on percent-predicted 6MWD. Further information was also provided in clarification questions.	Not a factual inaccuracy, no change required. The paragraph refers to subgroup analyses of patients not in the decline phase (as defined by the CS) or with baseline 6MWD >650. These subgroups are not presented in Figure C9.10.
Table 7, page 49 The answer to the question "Are the main findings of the study clearly described?" was "No".	Please change the answer to "Yes".	The primary endpoint of the study was the 6MWD for which results are clearly presented and discussed. Myometry was a secondary outcome and cannot, therefore, be considered a "main finding".	Not a factual inaccuracy, no change required. Table 7 refers to the non-RCT (004). 6MWD was not an outcome in study 004.The question refers to main outcomes, not primary or secondary. Muscle strength is considered a main outcome as is specified in the NICE scope.
Table 7, page 49 The answer to the question "Were the main outcome measures used accurate (valid and reliable)?" was	Please change the answer to "Yes".	The primary endpoint of the study was the 6MWD which is a validated and reliable outcome in this population. This is clearly presented and discussed in the submission. Myometry was a secondary outcome and cannot, therefore, be considered a "main outcome	Not a factual inaccuracy, no change required. Table 7 refers to the non-RCT (004). 6MWD was not an outcome in study

"Unclear".		measure".	004
1.3, page 16; 4.2.2, page 46 and Table 5, page 47 "Limited data or no data were presented for outcomes that were not statistically significant, for example: step activity monitoring, treatment satisfaction, cognitive ability, heart rate monitoring, serum creatinine kinase expression and dystrophin expression."	Please delete this sentence.	There is a difference between "limited data" and "no data". On pages 102-104 of the submission, we state that step activity, treatment satisfaction, cognitive ability (as measured with the digit span task), heart-rate monitoring and serum creatinine kinase expression showed similar results across treatment groups and differences were not statistically significant. We also state it was not possible to obtain reliable data from the muscle biopsy samples on dystrophin expression. NICE asks for succinct report and full disclosure of all data was provided in the CSR. In addition, where further information was requested by the ERG, we provided any data via the response to the clarification questions.	Not a factual inaccuracy, no change required.
1.2, page 15 "Limited assessment was made of some other outcomes, such as ability to undertake activities of daily living, cardiac function, and time to wheelchair use."	Please delete this sentence.	There is no validated tool in the DMD literature to measure 'Activities of daily living'. Results of timed function tests (climbing 4 stairs, descending 4 stairs, running/walking 10 metres) that were presented in the submission are representative of activities of daily living. Patient reported wheelchair use was presented on page 102 of the submission.	Not a factual inaccuracy, no change required. For example, activities of daily living that are important to patients such as washing and self-feeding were not assessed. Time to wheelchair use (rather than number of days a wheelchair was used or not) was not reported

1.3, page 17; 4.7.2, page 106 "Data were not reported on safety and tolerability of the treatments"	Please delete this sentence.	It is not clear what this sentence is intending to convey as safety and tolerability data were clearly reported in section 9.7 of the submission.	Sentence deleted on p 17 and p 106
3.3.4, page 40 "There appears to be potential evidence of selective reporting of outcomes." 4.4.2, page 46 "This suggests the possibility of selective reporting which may introduce bias in the CS." 4.2.3 g, page 52 "…the ERG considers that the reporting of outcomes was selective." 4.2.4.1, page 53 "This indicates selective reporting of results." 4.3.1, page 77 "… there is some evidence of selective reporting bias" Table 21, page 78 "There is some evidence of	Please remove all suggestions of selective reporting of outcomes.	This is a subjective statement. NICE asks for succinct report and full disclosure of all data was provided in the CSR. In addition, where further information was requested by the ERG, we provided any data via the response to the clarification questions. [redacted]	Not a factual inaccuracy, no change required. The ERG stands by this statement.

selective reporting bias."			
Table 5, page 47 The ERG answer to the question "Is there any evidence to suggest that the authors measured more outcomes than they reported?" was "Yes".	Please change the answer to "No".	This is a subjective statement with no evidence provided by the ERG to support it. NICE asks for succinct report and full disclosure of all data was provided in the CSR. In addition, where further information was requested by the ERG, we provided any data via the response to the clarification questions.	Not a factual inaccuracy, no change required. The ERG stands by this statement.

Issue 2 Clarification on p-value

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.2.3g, page 52 "Notably, the p-values reported for the cITT MMRM analysis (the corrected analysis reporting a 31.7m (95% CI 5.1, 58.3) treatment effect of ataluren) in the CS (nominal p=0.0197, adjusted p=0.0367) do not match the values reported in the EMA report (nominal p=0.0281, adjusted p=0.0561)."	Please delete this sentence.	Please refer to the EMA report Table 4 (Haas, 2015). The figures are identical. The figures the ERG referred to (nominal p=0.0281, adjusted p=0.0561) are for the permutation test, not the MMRM model.	The analysis sources of the p-values are unclear in the CS. Sentence on p.52 changed to: The p-values for the cITT MMRM analysis (the corrected analysis reporting 31.7m (95% CI 5.1-58.3) treatment effect of ataluren in the CS (nominal p=0.0197, adjusted p=0.0367) appear to include the only adjusted p-value reported in the CS. The analysis sources of the p-values are unclear in the CS. Please refer to section 4.2.5 for further detail. Change also to section 4.2.5 p58:

			The ERG was unclear why the reported p-values for the modelled difference (MMRM column) in the CS are different to the p-value for the main outcome reported in the EMA report (p= 0.0281) for the nominal (unadjusted) p value.

Issue 3 Misunderstanding of the definition of loss of ambulation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.7.3, page 106 and 1.7, page 19 "The RCT states that for inclusion in the study a loss of ambulation relates to the ability of the patient to walk ≥75 metres" 3.3.1, page 36 "In the CS there is inconsistency between the clinical (at least 75 metres unassisted) and cost consequence (walk some distance) assessments concerning the definition of 'ability to walk'." 3.4, page 40 "Bias may have been introduced in the CS assessment due to different thresholds of ambulation in the clinical and cost-	Remove all statements suggesting that loss of ambulation was defined as 6MWD ≤75m. Remove all statements suggesting there is a difference in the definition of ambulation or loss of ambulation between the clinical and economic sections of the submission.	This is misleading. The RCT is not defining loss of ambulation by 6MWD ≤75m; it is an inclusion criterion for the study. As stated in the draft NHS commissioning policy for ataluren, loss of ambulation is defined as complete wheelchair dependency. Study 007 included ambulatory boys who, at baseline, could walk at least 75m in the 6MWT but this cut-off was not the definition of non-ambulatory. During the study, patients who lost the ability to complete the 6MWT due to disease progression were considered to have lost ambulation. For analysis purposes, the protocol specified that such patients should be assigned a	4.7.3, page 106 and 1.7, page 19 Sentences changed as follows: A key criterion for the appraisal, and for the evaluation undertaken in the RCT and the CS was the definition of ambulatory. The NICE scope does not provide a clear definition. The RCT states that for inclusion in the studypatients had to be able to walk ≥75 metres. The criteria used in the RCT are adopted by the company in the CS for the systematic review of clinical effectiveness. However, the CS economic model adopted a definition of loss of ambulation

effectiveness assessments”		6MWD of 0 for all visits at which they were unable to perform the 6MWT due to loss of ambulation. There is, therefore, consistency between loss of ambulation within the trial and the economic model (6MWD=0m).	(i.e. inability to walk >0 metres). Inevitably the different definitions may influence the outcomes of the assessment. 3.3.1, page 36 Not a factual inaccuracy, no change required. 3.4, page 40 Not a factual inaccuracy, no change required.

Issue 4 Incorrect reporting of differences in adverse events between ataluren and placebo

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1.3, page 17; 4.2.9, page 69; 4.4.3, page 81; 4.7.2, page 105; 9.1, page 155 “It is not clear from the information provided whether the difference is due to longer exposure in the ataluren group.”	Please remove statements of uncertainty about length of exposure and replace with: “…although the pooled analysis includes a greater number of patients at-risk in the ataluren group (379 versus 172).”	We have stated that the exposure is significantly greater in the ataluren group than in the placebo group as evidenced in the ERG report: “The Company states that more patients were treated with ataluren than placebo; approximately 379 patients were treated with ataluren compared with approximately 172 patients treated with placebo as of 31 Jan 2015” (4.2.9, page 71 and Table 19, page 76). In all studies there are more SAEs in the ataluren patients due to longer	Not a factual inaccuracy, no change required. Data on rate per person months of follow-up were requested by the ERG at the clarification stage but were not provided by the Company. The longer exposure may or may not be the reason for the difference in count of adverse events. The numbers treated included all doses of ataluren, not just

		length of exposure. However, the data have already been assessed by the EMA (the EU competent authority for pharmacovigilance) in our Periodic Benefit Risk Evaluation Reports and the benefit/ risk remains positive for ataluren.	the licensed dose.
4.7.2, page 106 "Higher numbers of femur fractures were reported in groups taking ataluren."	Move this statement to the last bullet with 4.7.2.	Previous statements in this bullet were in relation to Study 007 but this statement on femur fractures is referring to the pooled safety analysis, which includes a much greater number of patients at risk in the ataluren arm.	P 106 Sentence deleted and final bullet point amended as follows: This appeared to suggest that serious cardiac disorders, infections and infestations, injury poisoning and procedural complications (specifically, femur fractures) and total number of serious adverse events are more common with ataluren than placebo

Issue 5 Suggested deviation from scope in age of patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1.5, page 18; Table 2, page 34; 5.5.1, page 122; Table 38, page 133; 9.2, page 156 "Whilst the NICE scope indicates that the population of interest is people with nmDMD aged ≥ 5 years in an ambulatory health state, the economic analysis	Remove any suggestion that the cost-consequence model is not in line with the NICE scope because it starts at a mean baseline age of 8.5 years.	The scope indicates the population of interest is nmDMD patients aged 5 years **and over**.	The model presented only represents a subset of the scope population, and hence deviates from the full population mentioned in the scope. There will, for example, be uncertainty in resource use

deviates by starting the model with a hypothetical cohort of children aged 8.5 years."			and costs for children between 5 years and 8.5 years.

Issue 6 Inclusion of two patients with BMD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1.2, page 15; 3.3.1, page 38; 3.4, page 40, 4.7.3, page 107 "Bias may have been caused from inclusion of patients with Becker's muscular dystrophy (BMD)."	Please remove the suggestion that bias was caused by including these two patients.	Both of these patients met in the inclusion criteria for the study and therefore there is no suggestion of any bias.	Not a factual inaccuracy, no change required. Whilst these patients met the inclusion criteria for the study they did not meet the inclusion criteria for the scope for this NICE HST. Other studies and our clinical advisors confirmed that these patients have a different disease trajectory.

Issue 7 Statistical significance of treatment effect of ataluren

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
3.3.1, page 37 "Submission relies heavily on post-hoc sub-group analysis of the latter [decline phase] group for the argument of a statistically significant treatment effect of ataluren."	Please delete this sentence.	The statement implies that a statistically significant treatment effect was only observed in a post-hoc subgroup of patients. In fact, a statistically significant treatment effect on the primary endpoint was observed in the full (cITT) population (page 94 of submission). The statistical methods used to analyse	Not a factual inaccuracy, no change required. The ERG stand by their statement that the submission relies on post hoc analysis. This also includes the cITT analysis itself.

		this patient group and outcome was deemed methodologically appropriate by the ERG (4.2.3, page 52). An analysis that subjects the MMRM cITT analysis to a randomization test was conducted for the EMA to check for the effect of possible deviations from assumptions such as normality, homogeneity of variance and dynamic randomization. In this test, 10,000 re-randomizations of the 6MWD data were created and analysed by MMRM. The p-value was computed by calculating how many of the 10,000 MMRMs had a good or better result than obtained with the original randomization. This test provides results (p=0.0281, p=0.561) that are most statistically justifiable. This type of extensive computing confirmation of the MMRM results is seldom done but we decided to conduct it to address potential concerns about deviations from necessary assumptions in the 6MWD.	

Issue 8 Assumed bias in favour of ataluren

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.5.3, page 123-4 “Any inter-patient variability in	Delete this sentence or provide justification for why bias would favour ataluren.	This statement suggests we have biased the results by linearly	The justification provided by the company for amending the

progression trajectory will lead to such a linear extrapolation giving biased results for time to loss of ambulation, and will almost certainly overestimate the treatment benefit with ataluren.”		extrapolating 6MWD data observed in Study 007. If there is inter-patient variability, there is no evidence to suggest that this would be different for ataluren over placebo and therefore no reason why the extrapolation would be biased in favour of ataluren. The mean decline observed in Study 007 was in patients with a range of baseline 6MWD and a range of ages so the mean value captures the decline at various points in disease progression. Consequently, it is valid to assume that the observed mean can be extrapolated until 6MWD=0m. The slope at each patient level would follow a distribution with mean equal to the slope fitted at the group level. Guided by the law of large numbers, the results of the 5,000 simulations will be literally the same regardless of slope fitting at patient level or group level.	ERG statement is not accurate. As a demonstration, consider two (purely illustrative) examples: 1) A population starting with a 6MWD of 100m, where everyone declines at 10m per year, giving a mean loss of ambulation at 10 years. 2) A population beginning at 100m, where half decline at 5m per year and half at 15m per year (hence the same mean decline). Half the patients thus lose ambulation at 20 years, and half at 6.67 years, with a mean loss of ambulation at 13.33 years. Thus, including inter-patient variability leads to a delay in mean loss of ambulation. Whilst it is true this would apply in both arms, delays in LoA in both will lead (due to discounting), to reduced QALY benefits for ataluren versus placebo.

Issue 9 Blinding in study design

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.2.4, page 53	Please delete this statement.	It is clearly stated in the CS (Table	P 53 Statement deleted.

"…it is not clear in the CS whether the assessor was blinded. In response to a clarification question the Company confirmed that the clinical evaluator was blinded to allocation"		C9.6) that study personnel were blinded. It is important for transparency that the ERG and committee know that we provided this information in the first instance as well as is response to the clarification questions.	sentence changed to: The 6MWD test is known to be at risk of inter-operator bias through encouragement,[51] however the Company confirmed that the clinical evaluator was blinded to allocation

Issue 10 Validity of myometry

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.2.4.3, page 54 "The CS also justifies the inclusion of post hoc subgroup analysis in patients aged 5 to 6 by stating that "myometry can only be adequately evaluated in younger patients" (CS p. 102). The validity of myometry in the trial population is therefore uncertain."	Please delete the last sentence.	The ERG has misinterpreted information provided in the CS. The validity of myometry is not in question; it is the applicability across the full age range of patients with nmDMD that is under question. It is likely to be most applicable to younger patients who are still in their maturational phase. Nevertheless, and as stated in the CS, most of the myometry parameters showed less mean decline over 48 weeks for ataluren-treated patients versus placebo.	P 54 Last sentence of parapgraph changed to: The applicability of myometry in the whole trial population is therefore uncertain.

Issue 11 Rationale for using published data on time to loss of ambulation for cost-consequence model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.5.2, page 122	"Study 007 was not powered to show a	It is important that the ERG	The company's justification is

"In the economic analysis, instead of using data on time to loss of ambulation from the best supportive care arm in Study 007, data were obtained from the study by Ricotti et al. (2013)."	difference in loss of ambulation over a 48 week period. Therefore, in the economic analysis, data for the best supportive care arm were obtained from Ricotti et al. (2013) which included 3.9 years of follow-up."	provides our justification for using published data rather than using clinical trial data for this model parameter. It would have been inappropriate to use the clinical trial data on loss of ambulation in the cost-consequence model.	clearly stated in their submission, and hence it is not necessary to restate the same issues once again.

Issue 12 Mapped trial quality of life would not be preferred to published utility data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.5.5, page 131 "The ERG still believes, however, that in principle these data should be preferred to those from the literature as a source of utility values." Table 38, page 134 "the use of relevant trial data would normally be recommended as the appropriate source for health state utilities"	Please amend or delete these sentences.	According to NICE guidelines, utilities sourced from the literature are preferable to mapped trial data (NICE Guide to the Methods of Technology Appraisal, 2013). Henricson et al have determined that the PedsQL is not a sensitive outcome measure of DMD disease progression (Henricson, 2013). Furthermore, the mapping of EQ-5D utility scores from PedsQL showed higher prediction errors for children in poorer health states (Khan, 2014). Consequently, mapping PedsQL data measured in Study 007 patients to the EQ-5D would be subject to confounding error and would not be robust. Therefore, data from Landfeldt et al (2014) is the optimal source of utilities in this appraisal where EQ-5D was not collected directly in the	The NICE Guide to the Methods of Technology Appraisal (2013) states that utility values based on the EQ-5D are preferable. The guide further states that if EQ-5D values were not collected from a clinical trial, they can be sourced from the literature. In the Landfeldt et al (2014) study health related quality of life for people with DMD was measured using the Health Utility Index Mark III instrument. The appraisal guide further states that where EQ-5D values are not available, data could be estimated from undertaking a mapping exercise from other health related quality of life measures, onto the EQ-5D.

		trial.	

Issue 13 Description of ERG's preferred model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 47, page 141 states the ERG's preferred model is Model 7 but 6.5, page 142 says Model 6 is the ERG's preferred model.	Amend 6.5, page 142 to "…whilst model 7 is the ERG's preferred "most plausible" scenario.	Clarification on which is the ERG's preferred scenario is required.	Amended on page 142 to clarify model 7 is the ERG's preferred model.

Issue 14 ERG model scenario is clinically unrealistic

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
6.3.3, page 140 "The third model produced by the ERG … changes the distribution for time to loss of ambulation from a log-normal to a generalised gamma … It should be noted that this model was originally rejected by the Company as predicting too many people stay in an ambulatory state with BSC (30% remain ambulatory at age 18, 17% at age 25), and therefore consideration should be given to the clinical plausibility of these results."	Please remove this scenario.	In this scenario conducted by the ERG, 17% of best supportive care patients are ambulatory at the age of 25 years, which is clinically unrealistic, based on published evidence and clinical opinion (Ricotti, 2013). It is not appropriate to present a scenario that is clinically unjustifiable simply because it is the best fitting distribution in statistical terms. It is misleading to present a scenario to the Evaluation Committee that is clinically inappropriate when we have made every effort to ensure the cost-consequence model is clinically valid.	We have clearly stated the company's belief that this scenarios is not plausible, and hence the committee is able to choose to ignore this data if they agree with this assumption. The scenario is still included for completeness.

6.3.4, page 140 "flexible parametric models are used for all transitions other than from the ambulatory to non-ambulatory state" and "a log-normal model was used for transitions to the loss of ambulation state." Figure 7 shows that 15-20% of patients remain ambulant at the age of 20 when receiving best supportive care. Figure 13 shows that in the ERG flexible parametric model, 25% of DMD patients are alive at the age of 70 years.	Please amend this scenario to use a more clinically realistic parametric model for loss of ambulation and survival.	In this scenario conducted by the ERG, 15-20% of best supportive care patients are ambulatory at the age of 20 years and 25% are alive at the age of 70 years, which is clinically unrealistic. It is not appropriate to present a scenario that is clinically unjustifiable simply because it is the best fitting distribution in statistical terms. It is misleading to present a scenario to the Evaluation Committee that is clinically inappropriate when we have made every effort to ensure the cost-consequence model is clinically valid.	The company's arguments around clinical plausibility are presented in the ERG report, and the committee is able to make its own assessment as to which scenarios it considers plausible.

Issue 15 Description of ERG model scenarios

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
6.4, page 141 "Model 2: The Company's new submission, where full model fitting has been conducted, but the best fitting curves have not always been selected for use in the model."	"Model 2: The Company's new submission, where full model fitting has been conducted and best fitting curves were selected on statistical fit and clinical plausibility."	The revised submitted model was populated with best fitting parametric models according to clinical feasibility and statistical fit. The statistically best fitting models were often not clinically plausible (particularly the generalised gamma) thus the most clinically realistic scenarios were presented. We made every effort to ensure the cost-consequence model is	It is indeed reasonable in certain cases to reject the best fitting statistical curves as not clinically plausible, but the statement that the best fitting curves were not selected remains accurate.

		clinically valid.	

Issue 16 Use of DMD and nmDMD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
2.5, page 31 "It is unclear whether at times the terms DMD and nmDMD were being used interchangeably due to limited evidence on nmDMD"	Please remove this statement.	The terms DMD and nmDMD were used appropriately in the submission.	Change sentence to: The information provided directly related to nmDMD was limited and it is unclear to what extent the information on DMD is applicable to nmDMD.

Issue 17 Additional evidence from the EMA reviewed by the ERG is selective

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.6.2, page 100-105 In the reporting of EPAR, only the first session is referenced, no information about the re-examination of the data is presented and thus section 4.6.2 is biased as it does not consider the totally of evidence.	Please amend this section to account for the re-examination of evidence that was conducted by the EMA or remove this section.	Whilst accurately reflecting the comments of the SAG, the ERG selectively omit to mention that there is a re-examination of the data by the CHMP leading to a conclusion that *"The effects observed in the pivotal study were considered generally encouraging, as also supported by the previous input from the SAG, and in the context of a revised position on the mechanism of action and on the issue of dose-response relationship, the CHMP was of the view that the observed results could reflect a true effect and thus*	The aim of section 4.6.2 was to summarise points made by the Scientific Advisory Group on three specific questions. The ERG felt that given the conflicts of interest declared by the clinical experts advising the ERG, this summary would provide the Committee with a broader consideration of the evidence base. The SAG's comments were presented in context of the EPAR's initial conclusions. However, in order to avoid bias the initial conclusions have been

		constitute evidence of efficacy." *… "Overall, the CHMP was of the view that the risks of the product could be considered acceptable and that the data provided sufficient level of evidence that ataluren may be beneficial in delaying disease progression in nmDMD. Therefore, the CHMP concluded that a favourable benefit-risk balance could be established at this point."* *…"Considering that the beneficial effects were most prominent in a sub-population of ambulatory patients in the decline phase of their walking ability (effect size of approximately 50 metres on the 6MWD), the CHMP discussed whether this finding would imply the need for restricting the indication to a population defined accordingly, i.e. patients in ambulatory decline phase. In line with the previous position of the SAG, the CHMP agreed that scientifically there should be no reason for the drug not to be given to milder patients if efficacy had been established in more severe ones. Furthermore, the CHMP considered that while less prominent, a clinically meaningful effect was seen also in the overall population studied. Thus, the CHMP concluded that ataluren can be*	removed. P99-102 amended (section reduced therefore p102 is now blank)

		authorised in the indication"	

Issue 18 Discussion of unlicensed dose

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Whole of section 4.3.2, page 79	Please remove this section.	The discussion around the 80mg/kg dose is irrelevant because it is not a licensed dose and therefore not included in the NICE scope.	Whilst the 80mg dose is not included in the scope, it can still provide valuable contextual information.

Issue 19 Evidence on monitoring requirements and training needs from clinical experts is ignored

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
3.3.5, page 40 "The training of staff that will be required for assessing patients on ataluren was not fully covered in the CS. As noted by the specialised commissioning expert, training will form an important part of the implementation of ataluren in order to measure 6MWD accurately, reliably and consistently across centres if it is going to be used as a stop criterion (E. Jessop personal communication)." 8.2.1, page 151 "While NHS England states that patients should receive treatment six months beyond not being able to walk 75m without assistance (E. Jessop personal communication), the Company used a threshold of >0m. This uncertainty renders the stopping rule impractical. Further we consider that when a definitive rule is agreed, clinicians might require some training on how to implement such a rule in clinical practice. As currently no 6MWD test is undertaken in clinical practice in the assessment of	Please delete these statements.	As discussed in issue 3, the proposed stopping criterion is based on clinical observation of complete wheelchair dependency and therefore does not require special training or instruments. The ERG reports states "Consultants in three specialist neuromuscular centres in the UK are experienced in prescribing and monitoring ataluren. The expert submissions state that ataluren is not likely to impact on the current level of patient care or services in the UK. It could be provided within the current clinical structure for managing DMD without further need for support." (4.5.5, page 86 of ERG report).	Our report is structured on presenting a detailed summary of the report submitted by the company then a critique from the ERG. The statement presented here is based on what was reported in the company's submission. While appraising the submission we contacted a specialised commission expert and he provided his views on administration, training and monitoring should ataluren treatment be provided nationally. We valued his input, hence we have included it into the report.

nmDMD patients due to time constraints and lack of resources in the clinic setting (Dr Rosaline Quinlivan personal communication) introduction of a standardised measure to assess LoA may prove resource intense."			

Issue 20 Clarification on difference in scope in submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
3.2, page 33 Format of table reporting scope different in NICE HST template. "The CS states in its statement of the decision problem (Table A1.1, pages 31-32) that the submission does not deviate from the NICE scope in any of its factors. Table 2 presents a summary of the decision problem as set out in the NICE scope and some comments from the ERG considering the CS. It should be noted that the table presented within the CS differs slightly from the factors included in the final NICE scope. Factors added included "subgroups to be considered". 'Impact of the new technology' was omitted from the CS table and 'other considerations' were rephrased to 'special considerations including	This statement needs to be removed or replaced with: The CS follows the format as instructed in the HST template for *Table A1 Statement of the decision problem.*	The NICE HST template has a different table to the final scope table. We recognise that the HST process is evolving and that there are differences in the HST template compared to the Single Technology Appraisal template. We believe the ERG may have not appreciated the differences in the format of the Decision Problem Table for a HST and STA submission or that different versions of the NICE STA and HST template are updated on the NICE website from to time but that NICE do not appear to routinely notify companies (or ERGs) of these changes, so older versions of templates can end up being used by mistake. It is also possible that the format of the table used in the Scoping Document is not aligned	We agree that there are no issues with the format of the table as presented by the Company; however, the statement by the ERG remains factually accurate.

issues related to equality'." "		with that in the HST template and therefore this needs to be addressed by NICE in future to avoid confusion. In this case we used the latest version of the HST template on the NICE website.	

Issue 21 Consistency in source of evidence for proportion of DMD patients with a nonsense mutation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1.1, page 14 "Nonsense mutation Duchenne muscular dystrophy (nmDMD) is a specific sub type of DMD and represents approximately 13% of the whole DMD patient population (286 children in England)."	nmDMD represents approximately 10% of the whole DMD patient population (220 children in England).	The estimation of patient numbers should be based on evidence that 10% of DMD patients have a nonsense mutation as this is the most recent source of evidence and is based on the TREAT-NMD DMD global database, which contains over 7,000 mutations (Bladen,	We note that different estimates exist in the background literature. No change required.

2.2.2, page 23-24 "Patients with nmDMD represent between 10 and 13% of the whole DMD patient population; which equates to around 2400 patients with nmDMD in the EU and approximately 286 patients in England."		2015). The quoted 13% is based on a study in 2005 of 84 patients with Duchenne or Becker muscular dystrophy, representing 68 index cases and is therefore less robust (Dent, 2005).	

Issue 22 Source of data for DMD mortality in cost-consequence model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 26, page 113 "Death from nmDMD derived based on information reported in Norwood et al. (2009)[29]"	Table 26, page 113 Death from nmDMD was derived based on information reported in Rall et al. (2012)	The reference for DMD mortality was: Rall S, Grimm T. (2012) Survival in Duchenne muscular dystrophy. Acta Myol. 31(2): 117-120.	Text amended as suggested

Issue 23 Starting weight in cost-consequence model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.3.2, page 112 "The model starts with a hypothetical cohort of children aged 8.5 years and weighing 28.3kg in the ambulatory health state"	"The model starts with a hypothetical cohort of children aged 8.5 years and weighing 27.5kg in the ambulatory health state"	The weight of 28.3kg was the first cycle of the model; the weight at baseline was 27.5kg.	Text amended as suggested

Issue 24 Overestimated weight of patients applied in budget impact model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
7.3, page 145 "Scenario 1: changing the average weight for people being treated with ataluren • Average weight (39kg) derived from the best supportive care group • Average weight (53kg) derived from the ataluren group These weighted average weights were derived based on the number of people remaining in the ambulatory health state per cycle."	Please amend this scenario to use the same weight as applied in our submitted model (24-26kg). If you wish to present sensitivity analysis with higher weights, please also present a clear explanation of what analysis has been conducted to derive the average weights and why different weights (39kg and 53kg) are applied to the ataluren and best supportive care arms, despite the budget impact analysis only looking at the ataluren arm.	The ERG has overestimated the weight of patients likely to receive ataluren. The justification for the median weight used was provided in response to clarification question B8.	The weight used in the budget impact model assumes that all patients beginning treatment are at the lower end of the eligible age range. Since it might be expected that all ambulant patients would initially be started on treatment (regardless of age), using the mean age of ambulant patients from the BSC arm of the model (representing the current distribution) seems the most reasonable assumption to make.

Issue 25 Overestimation of ERG proposed budget impact

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
7.4, page 146 "We also consider that this figure may be an underestimate of the total budgetary impact, as it does not include costs associated with administration, training or monitoring."	Please delete this statement or add that savings will be made as discussed in section 7.1 (fewer surgical procedures, fewer surgical follow-up costs, reduced or delayed respiratory and palliative support, use self-propelled wheelchairs rather than electric wheelchairs).	It cannot be assumed that the budget impact is an overestimation when we have not factored in significant additional cost savings as discussed in section 7.1 (fewer surgical procedures, fewer surgical follow-up costs, reduced or delayed respiratory and palliative support, use self-propelled wheelchairs rather than electric wheelchairs). As discussed in Issue 19, the ERG has ignored statements from clinical experts currently using ataluren that state that no additional monitoring or training is required above what is done is current practice. Given that ataluren is an oral treatment, there will not be any administration costs. Therefore, including costs associated with administration, training or monitoring will not increase the budget impact and thus by not incorporating the savings described above, the budget impact analysis is likely to be an overestimate, not an underestimate.	Our report is structured on presenting a detailed summary of the report submitted by the company then a critique from the ERG. The statement presented here is based on what was reported in the company's submission. While appraising the submission we contacted a specialised commission expert and he provided his views on administration, training and monitoring should ataluren treatment be provided nationally. We valued the experts input, hence we have included it into the report.

Issue 26 Use of outdated reference for 6MWD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
4.2.4.1, page 51 "However, the 6MWD test is known to be at risk of inter-operator bias through encouragement"	Please delete sentence or provide a more contemporary reference for this statement	The 6MWD is a validated, reliable outcome measure in this and other populations. There are many recent publications that support this and it therefore seems selective to choose a reference from 1984.	Not a factual inaccuracy, no change required. Two other references (2011 and 2013) are already cited in this paragraph.

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

ERRATUM

Replacement pages following the factual accuracy check

10th September 2015

Produced by ERG: Warwick Evidence

Similar rates of adverse events were experienced by patients receiving ataluren and placebo. No deaths were reported from either study. A cumulative summary of serious adverse events from four ongoing and five completed company-sponsored clinical trials appeared to suggest that serious cardiac disorders, infections and infestations, injury poisoning and procedural complications and total number of serious adverse events are more common with ataluren than placebo, however it is not clear from the information provided whether this is due to longer exposure in the ataluren group.

Outcomes from the six patient submissions and the patient organisations Muscular Dystrophy UK and Action Duchenne were highly positive in nature and no known disadvantages to the treatment were reported. However, a reverse of benefits after stopping treatment was observed in one case. Key themes identified by the ERG included the emotional and social impacts of DMD, the anticipated effects of treatment, and the importance to carers of self-reliance and reduced burden No details on how generalisable these views are to the wider UK nmDMD community were reported.

Summary of evidence submitted on value for money

The Company's submission included a decision analytical semi-Markov model to compare the costs and benefits of ataluren with best supportive care versus best supportive care for people with nonsense mutation Duchenne Muscular Dystrophy. The model starts with a hypothetical cohort of children age 8.5 years and weighing approximately 25kg and simulates the clinical pathway for people with nmDMD. In each three-monthly cycle people incur costs and benefits depending on their health state and the cost consequences are assessed. The model time horizon was set at the time at which the last individual leaves the ambulant health state. The discount rate was 3.5% per annum. Results are presented in terms of mean costs and mean benefits, measured in QALYs. Information required to populate the model was obtained from various sources, with data on the treatment benefit of ataluren versus best supportive care mainly drawn from Study 007. One-way sensitivity analyses and scenario analyses were undertaken to determine the impact of changes in parameter values and assumptions on the base case results.

The initial model submitted by the Company estimated mean costs for ataluren and best supportive care of £5,092,540 and £235,207, with equivalent mean QALYs of 6.152 and 2.385, giving incremental costs and QALYs of £4,857,333 and 3.767. A revised model was subsequently submitted by the Company, which included improvements in the distributions used to extrapolate data forward over time. This model was found to have an error, but after

- The inclusions of the costs of 6 months of ataluren treatment post loss of ambulation, in line with clinical advice.
- Refitting of survival curves to the various sets of Kaplan-Meier data, using a log-normal distribution for time to loss of ambulation, and flexible parametric distributions for other transitions.

The ERG ran a number of different models, using different assumptions for the distributions used to extrapolate trial results over time. These generated incremental cost estimates ranging from £4,295,464 to £5,544,981 with a range of associated QALY estimates of 1.722-3.924. The ERG's best estimate of cost and QALYs, which uses a log-normal distribution for loss of ambulation, and the statistically best fitting models for all other events, includes treatment with ataluren for 6 months post loss of ambulation and a life time horizon, giving incremental mean costs of £5,544,981 and associated QALYs of 3.049. The ERG undertook additional analyses of budget impact taking account of the expected weight of patients with nmDMD likely to be eligible for ataluren use leading to estimates of an average annual budget impact of £19,069,166, as compared to the £12,223,821 reported in the initial Company submission.

1.7. Effects of technology beyond direct health benefits and on provision of specialised services

The ERG considered that the company presented appropriate wider societal costs and some potential savings for ataluren. However the ERG were concerned about the heavy reliance on the Landfeldt study for this and were concerned that these wider societal costs might be either under- or overestimated. Because of the uncertainty it was not possible to assess quantitatively which, if any, of these costs would be alleviated by the use of ataluren. The likely impact of ataluren on the delivery of the specialised services for DMD and for nmDMD in particular is not yet clear in a number of respects. The most important potential impact is the likely need for clinical input for additional monitoring and decisions on continuation and stopping of treatment.

A key criterion for the appraisal, and for the evaluation undertaken in the RCT and the CS was the definition ambulatory. The NICE scope does not provide a clear definition. The RCT states that for inclusion in the study, patients had to be able to walk ≥75 metres. However, the Company's economic model adopted a definition of loss of ambulation (i.e. inability to walk >0 metres). Inevitably the different definitions may influence the outcomes of the assessment and it remains unclear which definition should be used in clinical practice. This is of importance as the suggested stopping rule for ataluren is based on the

using the technology over and above usual clinical practice. In summary no additional tests are believed to be required to identify patients eligible for treatment with ataluren.

Monitoring of ataluren treated patients is considered in section 8.2.3.

Currently NHS England[32] has a policy statement which suggests that since ataluren is being considered by NICE as a Highly Specialised Technology Evaluation to test the benefits and costs, it will not be commissioned until the outcome is known. NHS England also state that '*Where an individual's clinician believes that there may be exceptional clinical circumstances that might warrant consideration of funding outside of this policy, an application can be made under NHS England's Individual Funding Request (IFR) procedure'.*

2.5. Critique of background information provided in the CS

The ERG consider the background information provided by the Company to be fair, comprehensive and appropriate, and the ERG clinical advisors agree that this is an accurate overview of the condition relevant to the decision problem.

The Company provide a detailed coverage of the underlying nature of DMD, the prevalence as well as the epidemiology of DMD and a concise coverage of the underlying aetiology of DMD.

The information provided directly related to nmDMD was limited and it is unclear to what extent the information on DMD is applicable to nmDMD.

The CS did not discuss diagnosis of DMD in the background but touches on the benefits of early diagnosis to maximise the treatment effect of novel treatments, i.e. ataluren if approved.

The CS provided some relevant information about the impact of the DMD on the carers' QoL. The specific impact on carers' quality of life in nmDMD specifically remains unclear. No QoL data for carers was presented.

A concise overview of the impact of DMD on the health related quality of life (HRQoL) in boys was provided. However, it is unclear whether the impact of DMD on the QoL in girls, which make up a more diverse group with a variable degree of disability, is the same to that reported in boys with this condition and whether this can be extended to patients with nmDMD.

Finally, the Company could have referred to the North Star Clinical Network which was set up in 2003 to help improve services and set national standards of care for children living with DMD.[39] The

supplement appendix of the Bushby paper 2014, [41] states that: *"For these reasons the permutation test provides a more accurate assessment than the pre-specified rank test of the treatment differences in this study*".

f) Post-hoc analysis

Additional analyses were carried out in a sub-population of subjects in the decline phase (>7 years of age, treated with corticosteroids, 6MWD ≥150 m, <80% predicted 6MWD) as this group of patients was believed to be the most likely to display the greatest measureable effect with ataluren treatment. While this analysis was believed to be clinically and scientifically justified according to the CHMP, the EMA also noted that: "…*the patients in the decline phase of their ambulation constituted of a subset of the study 007 population and the analysis should be seen as exploratory*."

g) Adjustment for multiplicity

"*The p-values of the primary and secondary outcome measures were adjusted for comparison of two dose levels against placebo*"[41] (p. 479). The method for adjustment was not reported. Reported nominal p-values were not adjusted for multiplicity. The ERG noted that the reported nominal p-values were generally lower than the adjusted values and that the values for the MMRM analyses were lower than for the observed data. The outcomes table C9.14 on page 90 in the CS does not report any p values for the observed differences, but reports p-values for the MMRM model which for all comparisons except the ITT analysis suggests that the difference was statistically significant. The analysis does not state whether these are nominal or adjusted p-values, but the text on page 94 clarifies that these are nominal p-values. The p-values for the cITT MMRM analysis (the corrected analysis reporting 31.7m (95% CI 5.1-58.3) treatment effect of ataluren in the CS (nominal p=0.0197, adjusted p=0.0367) appear to include the only adjusted p-value reported in the CS. The analysis sources of the p-values are unclear in the CS. Please refer to section 4.2.5 for further detail.

Summary

The statistical methods used in the 007 trial were appropriate, however, a number of post-hoc adjustments as well as post-hoc analyses were undertaken all of which appeared to favour the intervention (ataluren) arm of the trial. Both trial 007 and the CS were transparent about adjustments and justifications; however, the ERG considers that the reporting of outcomes was selective. The ERG would have expected clear reporting of outcomes separately according to pre-specified analyses using rank-transformed data with post-hoc analyses using permutation. The ERG would have also expected reporting of both adjusted and nominal p-values throughout with p-values for differences of observed data in table C9.14 on page 90 of the CS. While the observed difference between ataluren and placebo might be clinically significant, the statistical significance of some reported outcomes should be viewed with extreme caution as this was derived following several post-hoc adjustments. The

adjustments seem to be methodologically appropriate but reporting as sensitivity analyses might have been more appropriate. This should be considered when assessing the evidence of the reported treatment effect in the primary and secondary outcomes in section 4.2.5.

4.2.4. Summary of selected outcomes measures

The NICE scope listed 11 outcome measures to be considered. Some of these outcomes were not adequately measured or reported by the CS (described below). The relevant results are all from the single eligible RCT (trial 007), other than for adverse effects. The CS refers to outcomes of myometry and timed function tests from study 004 but no data are reported.

4.2.4.1. Ambulation

The primary outcome in the CS is 6MWD, a measure of ambulation, which was also the primary outcome in the 007 trial. The CS states on p. 62 and 125 that prior to this trial there were no established primary or secondary endpoints for studies in DMD patients.

The 6MWD test is a measure of exercise tolerance and functional status where the individual is asked to walk on a flat surface for 6 minutes. It is a reliable measure and shows only small variation at individual level over short periods of time. However a recent systematic review looking at nine chronic paediatric conditions, which included three studies in DMD, found evidence that the measurement properties of the 6MWD test varied between studies.[50] The authors concluded that caution is recommended in the interpretation of changes in 6MWD in children with chronic conditions. The CS states on p.125 that a 30 metre change in 6MWD versus placebo is in the range in which other drugs have been approved in multiple inherited conditions. The 6MWD test is known to be at risk of inter-operator bias through encouragement,[51] however the Company confirmed that the clinical evaluator was blinded to allocation. In addition, de Groot et al (2011)[52] discuss potential variations that can occur in the administration of the 6MWD test, for example differences in the distance between turning points, the choice of circuit layout (e.g. circle, squares or use of a treadmill), and instructions given. They note that guidelines for the standardised administration of the test are available. Standardisation between different centres is therefore important. In response to a clarification question the Company provided details of the standardisation of the 6MWD test across study centres, which appear appropriate.

The CS also reported the proportion of patients who experienced at least 10% worsening in 6MWD compared with baseline. The rational for the 10% cut-off was not provided.

[redacted] This indicates selective reporting of results.

The results of the 6MWD test from trial 007 were used as for the measure of time to loss of ambulation in the CS economic evaluation.

4.2.4.2. Muscle function

Muscle function was measured by four timed function tests, stand from supine, 4-stair ascend, 4-stair descent, 10 metre run/walk. The CS states that timed function tests are established clinical assessments in DMD. The CS does not report details of these tests or how these were standardised between centres. However the ERG consider that standardised administration of the test between different centres is an important consideration. The ERG is not aware of any evidence for the validity of these tests as measures of muscle function. Minimal clinically important differences (MCIDs) have been published for these outcomes, based on trial 007.[53] In response to a clarification question the Company confirmed that a clinical evaluator training group developed standardised procedures for timed function tests and training and a manual were provided to all study sites, including refresher training after approximately one year.

In the North Star group, standard annual assessment of ambulatory patients with DMD includes measurement of 10m walk/run, time to stand from supine and stair climb. These tests have been validated by the North Star group for use in clinical monitoring and their measurements are included in other trials. The ERG requested information on the MCID for the timed function tests. The Company response stated that for the 10 metre walk/run the MCID is 0.76 seconds,[54] but that estimates of the MCID for the other timed function tests could not be identified.

4.2.4.3. Muscle strength

Force exerted during knee flexion and extension, elbow flexion and extension, and shoulder abduction was measured using myometry. The CS states on p. 101 (Results section) that "*myometric evaluation of limb strength is less sensitive to changes in disease status compared to TFTs, and muscle strength, although severely affected in ambulatory patients with DMD, deteriorates at a much slower rate than muscle function.*" The CS also justifies the inclusion of post hoc subgroup analysis in patients aged 5 to 6 by stating that "*myometry can only be adequately evaluated in younger patients*" (CS p. 102). The applicability of myometry in the whole trial population is therefore uncertain.

4.2.4.4. Ability to undertake activities of daily living

'Activities of daily living' were not evaluated by a specific validated tool, however the CSR states that the timed function tests (stand from supine, 4-stair ascend, 4-stair descent, 10 metre run/walk) measure the ability of patients to perform brief activities that are typical of patients' activities of daily living in a home, school, or community setting (CSR p.124, also confirmed in the response to clarifications). The ERG notes that there are other activities of daily living that are not captured in

Analysis	Placebo Baseline	Placebo Δ At week 48	Ataluren 40 mg/kg/day Baseline	Ataluren 40 mg/kg/day Δ At week 48	Difference between groups	Difference between groups (95% CI)
ITT All patients Placebo n=57, ataluren, n=57	359.6 m (87.7)	-42.6 m (90.1)	350.0 m (97.6)	-12.9 m (72.0)	29.7 m	26.4 m (-4.2, 57.1) p=0.0905
cITT All patients Placebo n=57, ataluren, n=57	361.1 m (87.5)	-44.1 m (88.0)	350.0 m (97.6)	-12.9 m (72.0)	31.3 m	31.7 m (5.1, 58.3) p=0.0197

Reproduced from CS Table C9.14 p. 90. Δ: change from baseline; MMRM: Mixed Model Repeated Measures; cITT: corrected intention to treat (post hoc analysis); ITT: Intention to treat.

Statistical significance can only be inferred for the modelled difference using MMRM from Table 8. P-values for the observed difference are not reported in the CS. The ERG was unclear why the reported p-values for the modelled difference (MMRM column) in the CS are different to the p-value for the main outcome reported in the EMA report (p= 0.0281) for the nominal (unadjusted) p value. The EMA also reported the adjusted p-value = 0.0561 which suggests lack of statistical significance of the difference between ataluren and placebo in 6MWD. The CSR was consulted to investigate this discrepancy. The following table (Table 9) was reproduced from Table 28 on page 100 of the CSR with the following outcomes reported for the ataluren 10, 10, 20 mg/kg vs placebo comparison.

Table 9 Post hoc MMRM Analysis of Change in Untransformed 6MWD Based on

Analysis	**Ataluren 10, 10, 20 mg/kg vs Placebo**			
	Difference		**p-value**	
	mean	**95% CI**	**nominal**	**adjusted**
MMRM[a]	31.7	5.1, 58.3	0.0197	0.0367[b]
Permutation test[c]	--	--	0.0281	0.0561[d]

[a] MMRM model: 6MWD = baseline 6MWD (covariate) + arm + visit + visit*arm + baseline 6MWD*visit + age group (<9 vs =9 years) + corticosteroid (yes vs no); unstructured variance/covariance matrix.
[b] Dunnett's test was applied to adjust for the comparison of 2 dose levels vs placebo.
[c] Permutation test of 10,000 re-randomizations. For each re-randomization, patients were dynamically re-randomized in the same order as they originally entered the study (starting seed = 14576).
[d] Based on the proportion of the 10,000 permutations in which the maximum effect size among the 2 comparisons (10, 10, 20 mg/kg vs placebo and 20, 20, 40 mg/kg vs placebo) exceeded the observed maximum

The submissions testify to a reduction in emotional and psychological burden of the condition with treatment. No submissions report whether there is a reduction in the practical burden, for example, if carers are able to return to work as a result of the greater independence of the child owing to treatment.

There is little discussion of the longer-term effects of treatment with ataluren. One submission discusses the impact that stopping treatment between trials had on the child, where there was a reverse of many of the positive benefits that had been seen.

The ERG notes that there are no details on how generalisable these views are to the wider UK nmDMD community. It is expected that there is a positive response bias to these submissions.

4.6.2 Summary of main conclusions from the EMA

Another additional piece of work undertaken by the ERG was consideration of The European Medicines Agency report (2015).[1] This report identified a need for input from a specialist Scientific Advisory Group (SAG) Neurology on three specific questions which are pertinent to this HST. Since our clinical experts advising the ERG on this HST have declared conflicts (e.g. reimbursement from PTC, advisor to PTC,) the ERG decided to summarise these points made by the SAG to gain a broader consideration of the evidence base.

a) Question 1: Does the SAG consider that the evidence for the mechanism of action of ataluren (nonsense mutation read-through) is convincing, and the results on dystrophin production could be seen as supportive of the pharmacodynamics of ataluren?

"The SAG considered that mechanism of action seemed plausible, but the experts felt that the provided data were still not convincing enough, and that they would need more information in order to be certain. The same was true for the data provided on dystrophin production in this case, that at least the data from the available biopsies, limited as they may be, should be provided. Thus the SAG considered that presently the available data on dystrophin production cannot be used as supportive of the pharmacodynamics of ataluren." (*page 49-50 of EMA).*

In agreement with the evaluation made by the SAG, the ERG noted that there was limited data available, even when considering the more recent available evidence published since the EMA report.

b) Question 2: Does the SAG agree that the presented pre-clinical and clinical evidence supports the bell shaped dose-response curve and hence, the absence of efficacy at the higher dose studied?

"The SAG considered that the proposed hypothesis for the bell shaped dose response curve seemed likely, but once again the experts felt that additional information was needed. More specifically, it was noted that while evidence on the bell-shape dose-response curve was available in several pre-clinical models, no data were generated in the mdx mouse model, relating the production of dystrophin to the levels of ataluren in the muscle fibres. Such evidence would be considered of relevance, as the available data describe only the relationship between plasmatic levels of ataluren and dystrophin production.

Overall, the SAG was of the view that no clear-cut conclusions could be derived on the bell-shaped dose-response hypothesis and the absence of efficacy in the higher dose studied in the Ph II trial." (*page 50 of EMA).*

c) Question 3: Does the SAG consider, based on the data presented by the Applicant, that the observed effects are sufficiently robust and clinically meaningful taking into account the results on the primary and secondary endpoints?

"The SAG considered that although the results were not sufficiently robust, the demonstrated effects were encouraging. The robustness of the results was challenged because of the observed variability in the primary efficacy data, the fact that many of the important conclusions supporting the efficacy of the drug were derived from the performed post hoc analyses, and the fact that there was little supportive evidence of effect from the data on the secondary endpoints. At the same time it was recognized that at the time the study was designed the knowledge of the natural history of the disease was different from what we now know. It was agreed that the applicant has performed the post hoc analyses in line with the most current knowledge about the natural history of the disease, and in this respect the definition of the sub-groups in these analyses is clinically and scientifically justified. The SAG experts considered that the results derived from these may be considered clinically relevant, especially in the sub-group of patients with more advanced disease. Additionally it was considered that the lack of effect on the secondary endpoints could be explained by the expected mechanism of action of the drug i.e. partial restoration of dystrophin production. Most of the secondary endpoints are of such nature that any effect will have to be driven by an increase in strength, rather than an improvement of function. The experts were presented with the latest available data, showing that minimal increase in dystrophin production could lead to functional improvement, but not to improvement of strength, and for the latter to occur, levels of dystrophin close to the ones in normal

muscular fibres must be achieved. The SAG experts agreed that this could be a valid explanation of the lack of concordance between the primary and secondary endpoints' efficacy data. It was also the position of the group that despite the fact that efficacy was most prominently shown in the subgroup of patients with more advanced disease, there were trends of efficacy in all the sub-groups by severity,

creatine kinase expression), no statistically significant differences were reported between ataluren and placebo in either study. On sub-groups defined by condition severity, it was reported that results favoured ataluren over placebo though no statistical tests were reported.

- Similar rates of severe adverse events were experienced by patients receiving ataluren and placebo but there were difference in types of event. Gastrointestinal disorders, vomiting, falls, investigations, weight decreases, metabolism and nutrition disorders, decreased appetite, musculoskeletal and connective disorders, back pain, headaches and nervous system disorders were more likely to occur with ataluren. In contrast, patients receiving placebo had higher rates of infections and infestations.
- No deaths were reported from either study.
- The Company presented a cumulative summary of serious adverse events from four ongoing and five completed Company-sponsored clinical trials. This appeared to suggest that serious cardiac disorders, infections and infestations, injury poisoning and procedural complications (specifically femur fractures) and total number of serious adverse events are more common with ataluren than placebo, however it is not clear from the information provided whether this is due to longer exposure in the ataluren group.

4.7.3 ERG assessment of uncertainties in clinical effectiveness

- A key criterion for the appraisal, and for the evaluation undertaken in the RCT and the CS was the definition of ambulatory. The NICE scope does not provide a clear definition. The RCT states that for inclusion in the study patients had to be able to walk ≥75 metres. The criteria used in the RCT are adopted by the company in the CS for the systematic review of clinical effectiveness. However, the CS economic model adopted a definition of loss of ambulation (i.e. inability to walk >0 metres). Inevitably the different definitions may influence the outcomes of the assessment.
- The comparator adopted in the RCT was best supportive care. Given that it was a multinational trial, it was felt that there may be heterogeneity in the comparator that may affect the outcome and influence its external validity.
- The selection of evidence through the search strategy and the selection process had the potential to affect the evidence reviewed in the systematic review of clinical

Table 1 Summary of key model input parameters and sources as reported in the Company's submission

Model inputs	Source(s)
Time to loss of ambulation: intervention	Derived based on information reported by Bushby et al. (2014)[41]
Time to loss of ambulation: best supportive care	Derived based on information reported by Ricotti et al. (2013)[5]
Non-ambulation to non-ambulation VA	Derived based on information reported by Humbertclaude et al. (2012)[58]
Non-ambulation to non-ambulation and scoliosis	
Non-ambulation to non-ambulation and scoliosis and VA	
Other cause mortality	ONS 2014
Death from nmDMD	Derived based on information reported in Norwood et al. (2009)[29]
Health state costs	Landfelt et al., 2014;[34] ONS 2015; OECD 2015[59]
Health state utility values	Landfeldt et al., 2014[34]
nmDMD, nonsense mutation Duchenne dystrophy; VA, ventilation assisted; ONS, Office of national statistics	

Information required to populate the model was obtained from Study 007 and published sources. Transition probabilities required for the transition to loss of ambulation health state were derived from Study 007. Transitions from the non-ambulant state to more severe health states were derived from Humbertclaude et al. (2012).[58] Information on costs was obtained from secondary sources and converted to UK pounds using UK 2012 purchasing power parity and inflated to 2014 costs using the consumer price index for health. In the ataluren group, treatment was dependent on the bodyweight of children until they reached 19 years old after which a constant weight of 70kg was assumed. Children in the intervention group received treatment until they progressed to the non-ambulatory stage. It was stated that children would continue to receive ataluren treatment for six months after loss of ambulation, but costs for this treatment were not included in the model. In the best supportive care group, children continued to receive the same treatment after loss of ambulation. Adverse events were not considered in the model.

In the model the primary measure of effectiveness was quality-adjusted life-years (QALYs), gained

over the duration of the model. (The time horizon was set at 'until the last patient loses ambulation'). All costs and benefits were discounted at 3.5% per annum. The base care analysis was conducted from an NHS and PSS perspective (with a scenario analysis from a wider societal perspective), and results were presented in terms of disaggregated costs, life-years gained (LYG) and QALYs. In the submission, one-way sensitivity analyses were undertaken by varying direct costs of health states, and patient and caregiver utility values by ± 20%. Also, a number of scenario analyses were undertaken: increasing caregivers' disutilities; increasing costs and disutilities for people requiring ventilatory assistance; inclusion of direct and indirect non-medical costs; and increasing the time horizon of the model.

5.3.3.1. Relative treatment effects of ataluren versus standard care

The model uses clinical effectiveness estimates for ataluren and best supportive care versus best supportive care alone Study 007 (Bushby et al. (2014)[41]) and from other published sources. It is important to note that this approach assumes that the populations from the different studies are comparable. Information on the delay in reductions in ambulatory ability (measured using the 6MWD) with ataluren were obtained from Study 007, and information about loss of ambulation with best supportive care were obtained from Ricotti et al. (2013).[5] Transition probabilities from loss of ambulation to more severe health states were obtained from a study of the natural history of DMD (Humbertclaude et al., 2012).[58] Additional information on background all-cause mortality was obtained from the Office of National Statistics (2014).

5.3.3.2. Transition probabilities for standard care

Improvements in ambulation with ataluren, compared to best supportive care, were estimated based on a least squares regression of changes in 6MWD from week 24 to week 48 of Study 007. The regression analysis was undertaken on the data from Week 24 to Week 48 because it was deemed to be more representative of the long-term treatment effect of ataluren (Company submission: expert opinion). The authors suggested that this is a conservative assumption because ataluren has a greater benefit compared to best supportive care in improving 6MWD in the first 24 weeks of the study.

Results from the regression analysis based on information from Week 24 to 48 showed that there was a decrease in the 6MWD of 59.0m in the best supportive care arm compared to a decrease of 25.2m in the ataluren arm. (33.8m between treatment groups). These declines in 6MWD were linearly extrapolated (from a mean baseline 6MWD of 355.7m) to estimate mean time to loss of ambulation, defined as 6MWD = 0m. As a result of this linear extrapolation, loss of ambulation was assumed to occur in the best supportive care and ataluren arms at week 313 (6 years) and week 733 (14.1 years), respectively. This equated to a difference of 420 weeks/8.1 years. (Please see Section 5.5 of this report for a critique of this approach).

6.5 Discussion

The first four models all give relatively similar results, but the 5th and 6th are very different, due principally to the change in distribution used to extrapolate loss of ambulation in the best supportive care arm. The 5th model uses the distributions with the best statistical fit, but it is also important to consider whether the results it produces are deemed clinically plausible. Model 6 is based on re-digitisations of data undertaken by the ERG, together with the best statistically fitting models, adjusted for clinically plausibility (specifically time before loss of ambulation in the BSC model). Model 2 is the most recent analysis undertaken by the company, whilst model 7 is the ERG's "most plausible" scenario.

In addition to the elements of uncertainty which the ERG has been able to address quantitatively, there are a number of other areas of uncertainty it is important to consider. Some of these are related directly to a lack of underlying data, but others are as a result of choices made in the modelling process which have not been quantitatively considered in the Company submission. These include:

- The use of a cohort with a starting age of 8.5, rather than 5 years as specified in the scope.
- The assumption that the treatment benefit with ataluren is permanent, with the advantage over best supportive care found between weeks 24 and 48 of Study 007 continuing until people lose ambulation.
- The use of a linear extrapolation of mean difference in 6MWD which relies on the assumption of a homogeneous population following the same trajectory of progression. Such an approach is not valid if this assumption is not met.
- No additional treatment related adverse events with ataluren which engender costs or reductions in quality of life.
- Treatment adherence to ataluren is 100%, and no-one will discontinue treatment for any reason other than loss of ambulation.
- There are no additional costs for administration, training or monitoring related to ataluren treatment.

All these assumptions appear to be optimistic ones and it therefore seems appropriate to regard the results produced by the model as an optimistic upper bound on the possible benefits of ataluren treatment.

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

ADDENDUM

Additional analyses following Department of Health approval of a patient access scheme for ataluren

14th September 2015

Produced by ERG: Warwick Evidence

VALUE FOR MONEY FOR THE NHS AND PSS

The tables below represent updated versions of the 7 analyses listed in the original ERG report for ataluren (see section 6.4 of the report for full details of each model). In each case, the only change made from the initial models presented is a reduction in the price of ataluren from £84.40 per 125mg to [redacted].

Model 1 – Original model submitted; all extrapolations based on Weibull distributions

	BSC	Ataluren	Incremental
QALYs	2.385	6.152	3.767
Costs	£235,207	[redacted]	[redacted]

Model 2 – Company's second submission (contains coding errors in submitted model)

	BSC	Ataluren	Incremental
QALYs	2.254	6.178	3.924
Costs	£236,627	[redacted]	[redacted]

Model 3 – Company's second submission (coding errors adjusted for by ERG)

	BSC	Ataluren	Incremental
QALYs	2.269	6.178	3.909
Costs	£229,396	[redacted]	[redacted]

Model 4 – ERG model 1

	BSC	Ataluren	Incremental
QALYs	2.269	6.177	3.908
Costs	£229,396	[redacted]	[redacted]

Model 5 – ERG model 2

	BSC	Ataluren	Incremental
QALYs	2.334	6.214	3.880
Costs	£225,583	[redacted]	[redacted]

Model 6 – ERG model 3

	BSC	Ataluren	Incremental
QALYs	3.641	5.363	1.722
Costs	£203,128	[redacted]	[redacted]

Model 7 – ERG model 4

	BSC	**Ataluren**	**Incremental**
QALYs	3.804	6.853	3.049
Costs	£199,194	[redacted]	[redacted]

COST TO THE NHS AND PSS AND OTHER SECTORS

For a summary of the Company's budget impact analysis and ERG's critique please see Chapter 7 of ERG's report. Here we present an estimated total costs to the NHS over a five-year duration using the discounted costs of [redacted] provided by NICE. Additionally, we present results for the ERG exploratory scenario analyses.

Table 1 Summary of budget required over a five-year period (adapted from Table D13.5 CS p209) and additional ERG scenario analyses

	Year					Average
	1	2	3	4	5	
Using a cost of [redacted] for 125mg ataluren						
Total annual costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG additional scenario analyses						
Scenario 1 -39kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 -53kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using a cost of [redacted] for 125mg ataluren						
Total annual costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG additional scenario analyses						
Scenario 1 -39kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 -53kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Impact of patient access scheme

Results from the patient access scheme showed that the annual cost was estimated to be [redacted] in year one rising to [redacted] in year five (as opposed to [redacted] in year five as reported in the PAS evidence submission template) at an average annual cost of [redacted].

ERG budget impact analysis summary

Using the cost of [redacted] for 125mg ataluren in the budget impact model submitted by the Company, the annual cost was estimated to be [redacted] in the first year and rising to [redacted] in year five at an average of [redacted] per year.

Results from our scenario analyses showed that using an average weight of 39kg lead to an estimated

cost of [redacted] in the first year and rising to [redacted] in the fifth year at an average annual cost of [redacted]. Scenario analysis based on an average weight of 53kg lead to an estimated cost of [redacted] in the first year to [redacted] in the fifth year with an average annual cost of [redacted].