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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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.

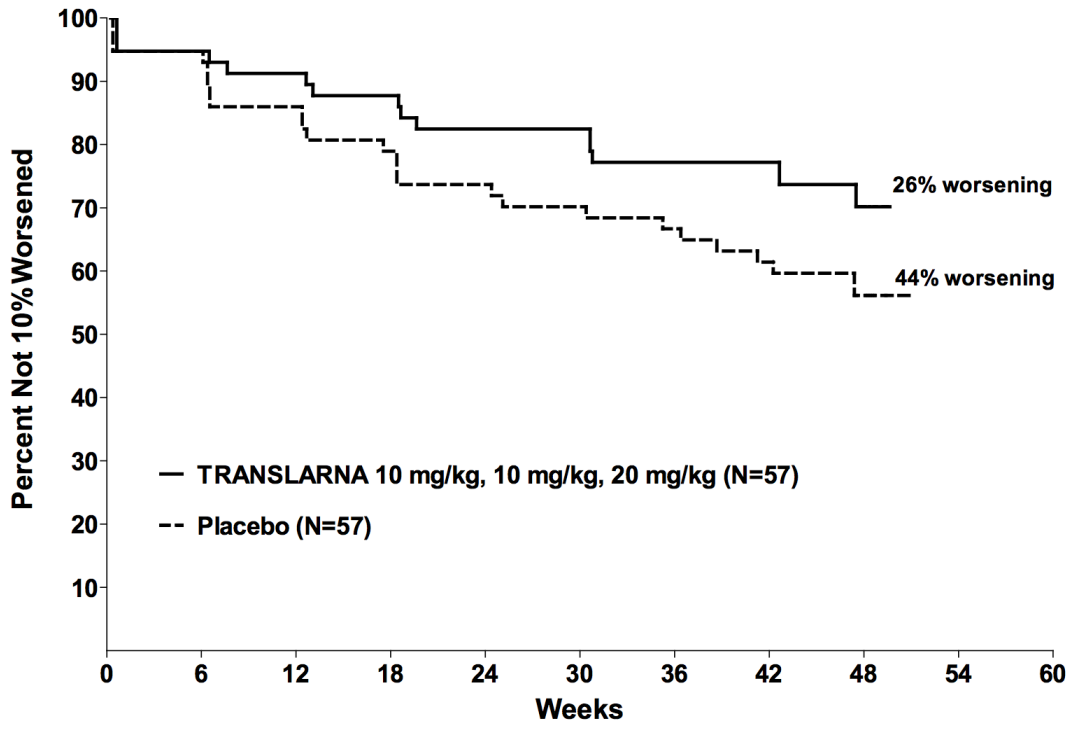


Figure 1 Time to persistent 10% 6MWD worsening, cITT analysis set (pre-specified analyses)
Reproduced from CS Figure 9.11 p. 97

[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.

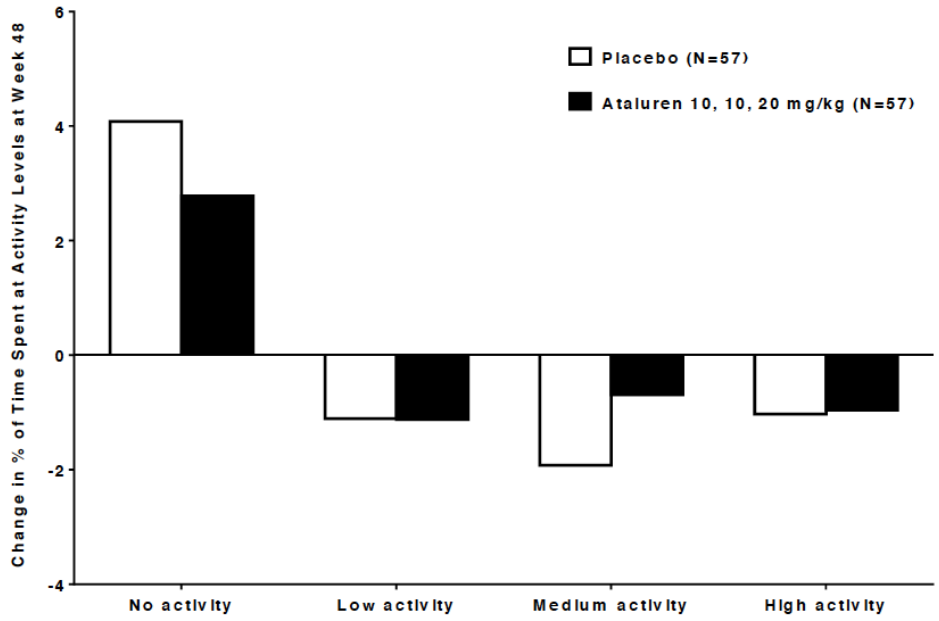
4.2.6.3. Upper and lower extremity myometry tests

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.

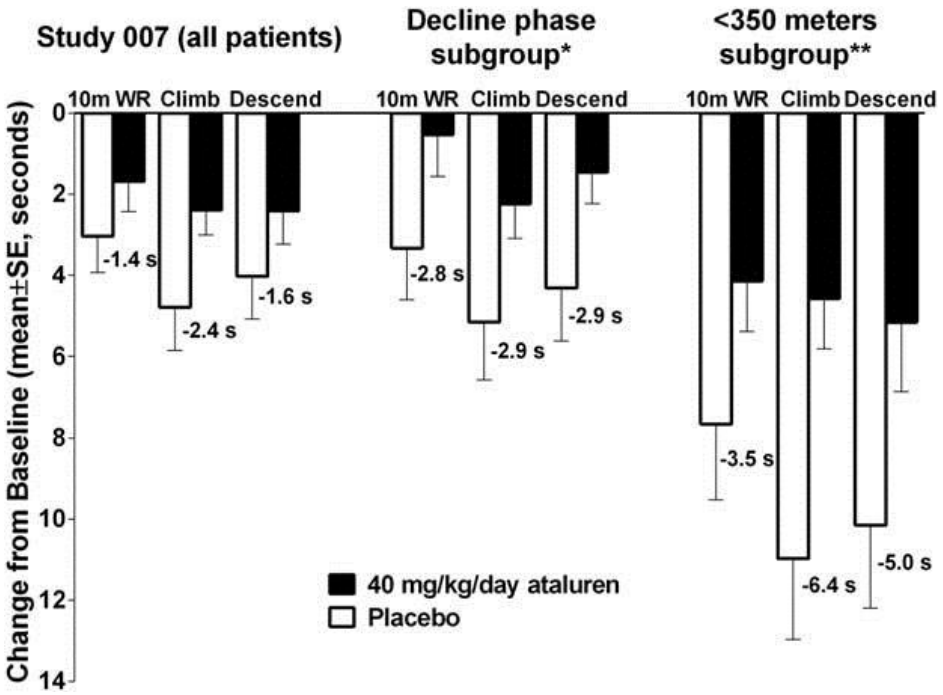


Figure 3 Timed function tests change from baseline to week 48 in Study 007 overall population versus decline-phase subgroup. Reproduced from CS Figure C9.12, p. 100

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.

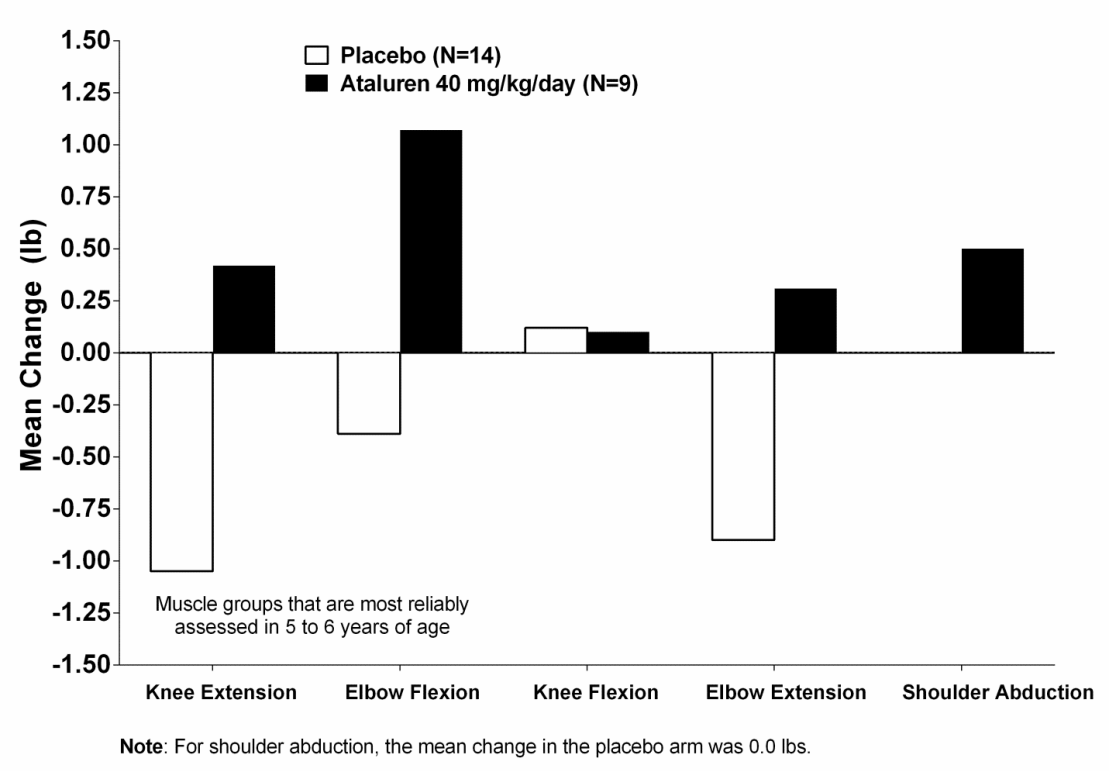


Figure 4 Change from Baseline to Week 48 in Myometry, Measured by Force Exerted, in the Study 007 Patients Aged 5 to 6 Years (post-hoc analysis)

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)	[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)	[redacted]	[redacted]
Baseline 6MWD ≥350 m	(placebo n=34, ataluren, n=32)	15m (-23, 52)	0.439	(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.

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

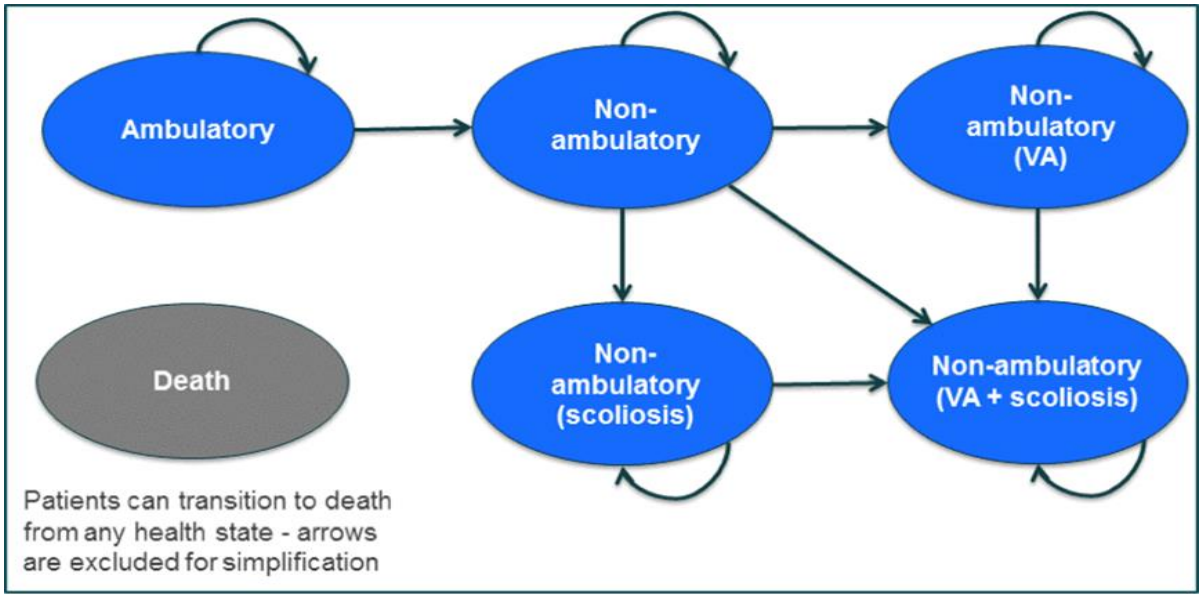


Figure 5 Illustrative Markov model structure

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.

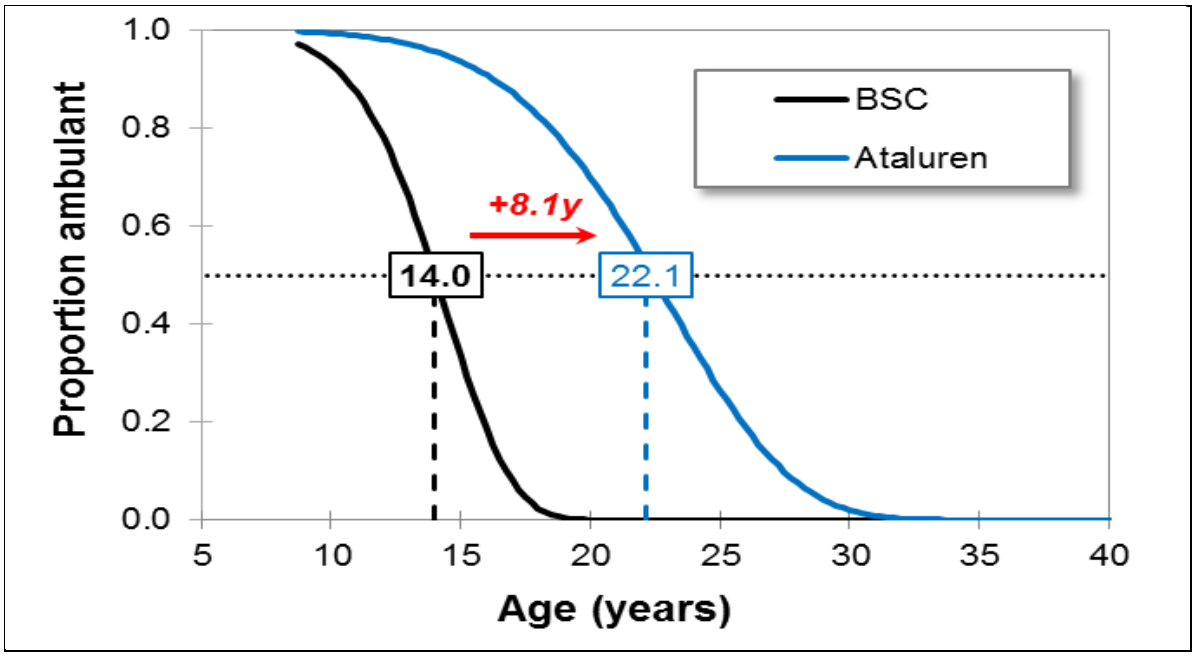


Figure 6 Curve for time to loss of ambulation fit to Kaplan Meier data (as presented in the CS, page 163)

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

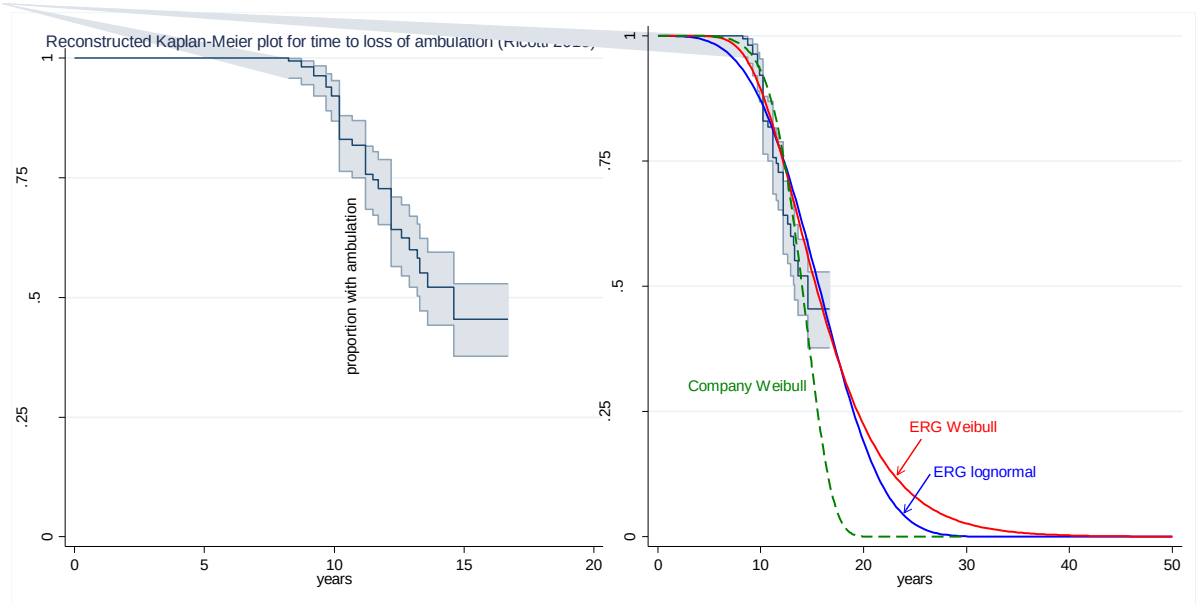


Figure 7 Reconstructed Kaplan-Meier plots and parametric models for time to loss of ambulation for DMD patients on daily corticosteroids

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).

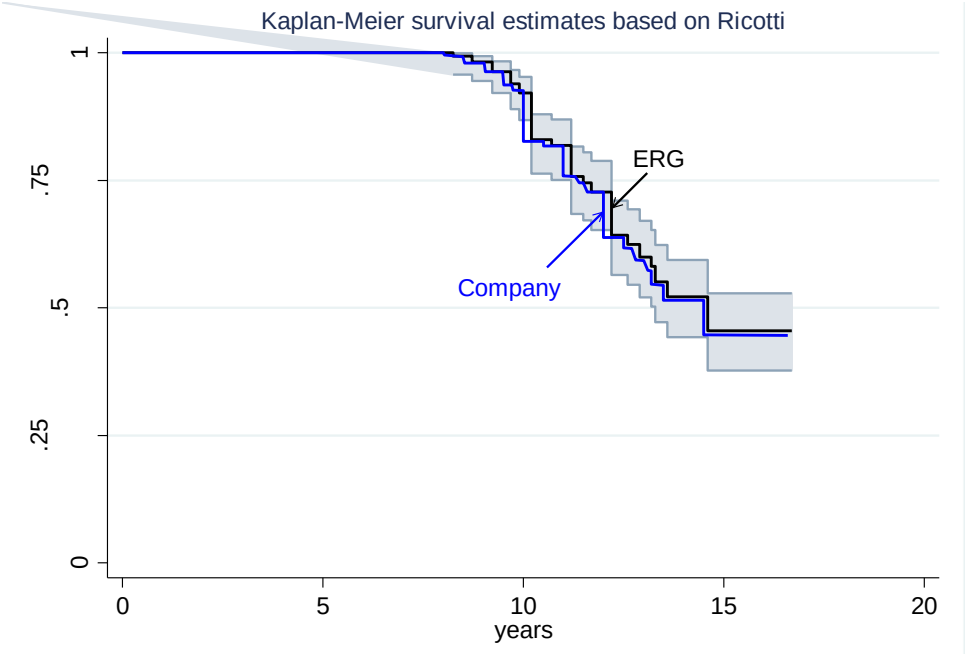


Figure 8 Reconstructed Kaplan-Meier plots and flexible parametric fits for time to loss of ambulation for DMD patients on daily corticosteroids

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

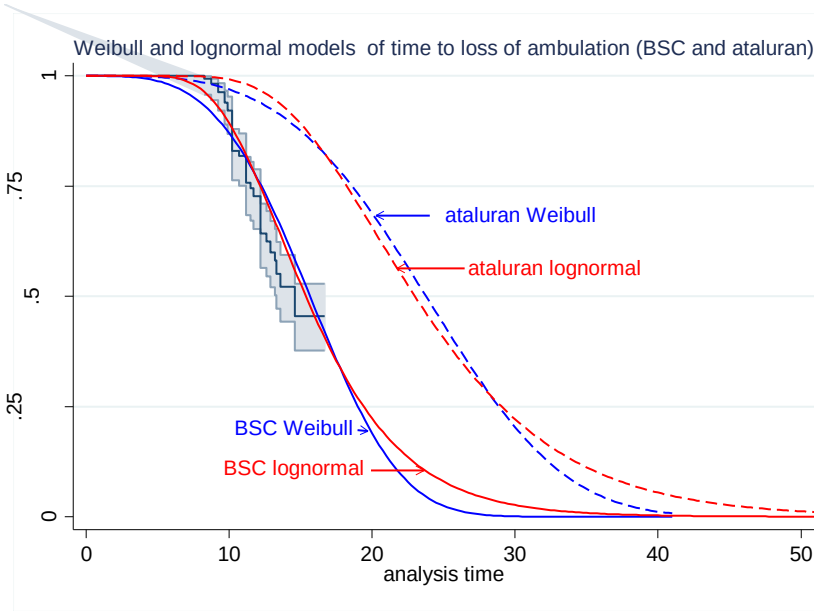


Figure 9 Reconstructed Kaplan-Meier plots and parametric models for time to loss of ambulation for DMD patients on daily corticosteroids

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.

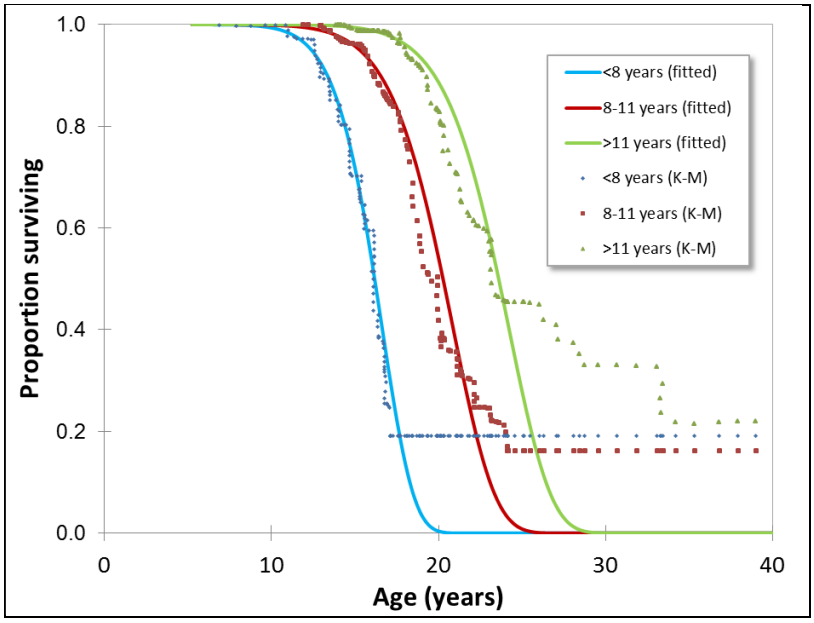


Figure 10 Company's figure D 12.8

The ERG reconstructed KM plots are shown in Figure 11, together with flexible parametric models (other models are shown in Appendix 2).

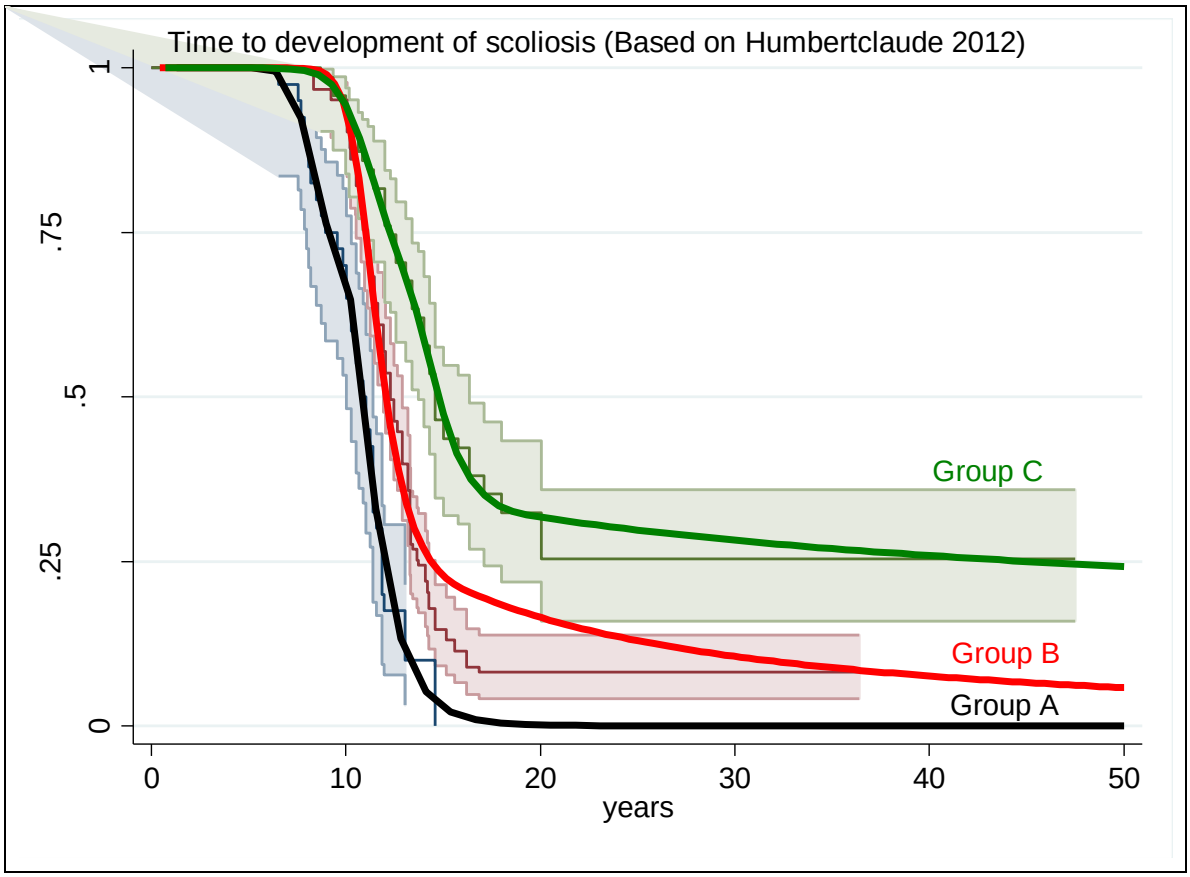


Figure 11 Reconstructed Kaplan-Meier plots and flexible parametric models for three groups of patients according to age at scoliosis diagnosis

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).

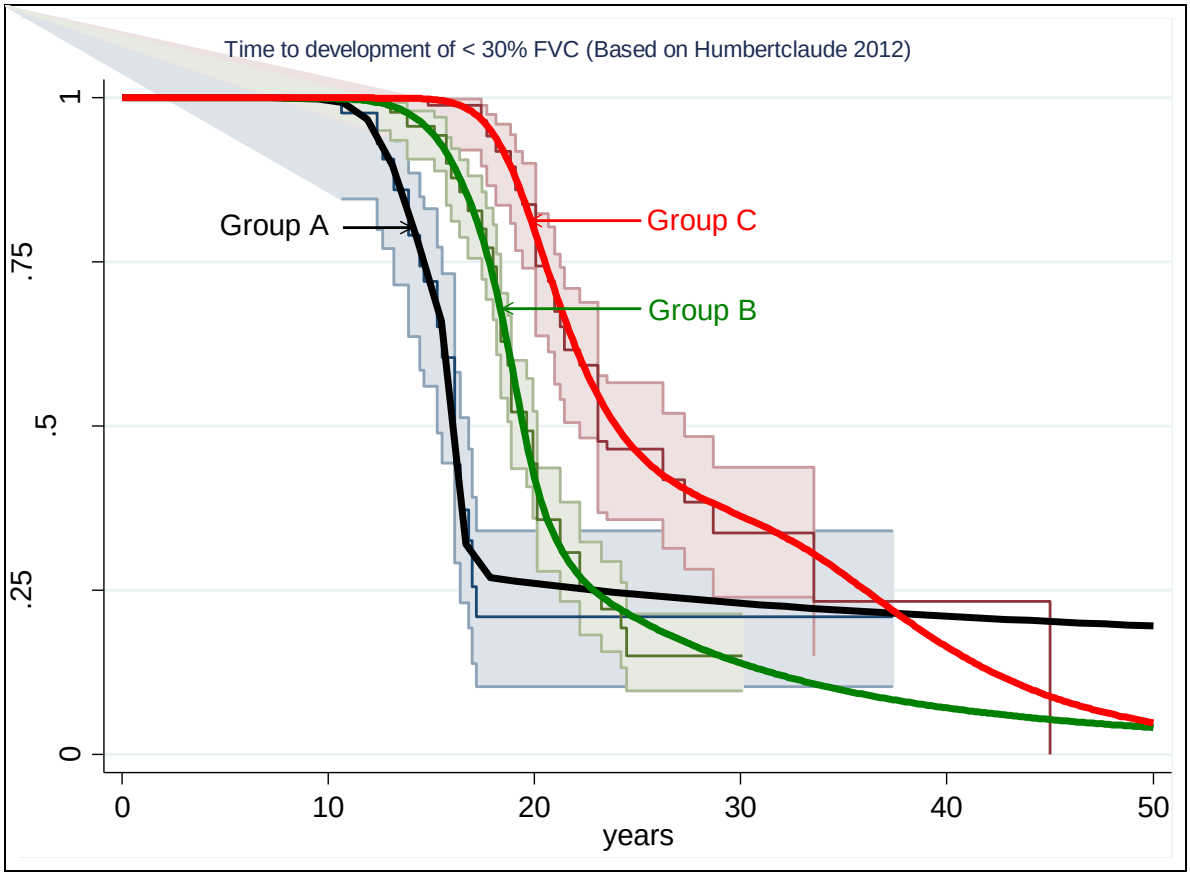
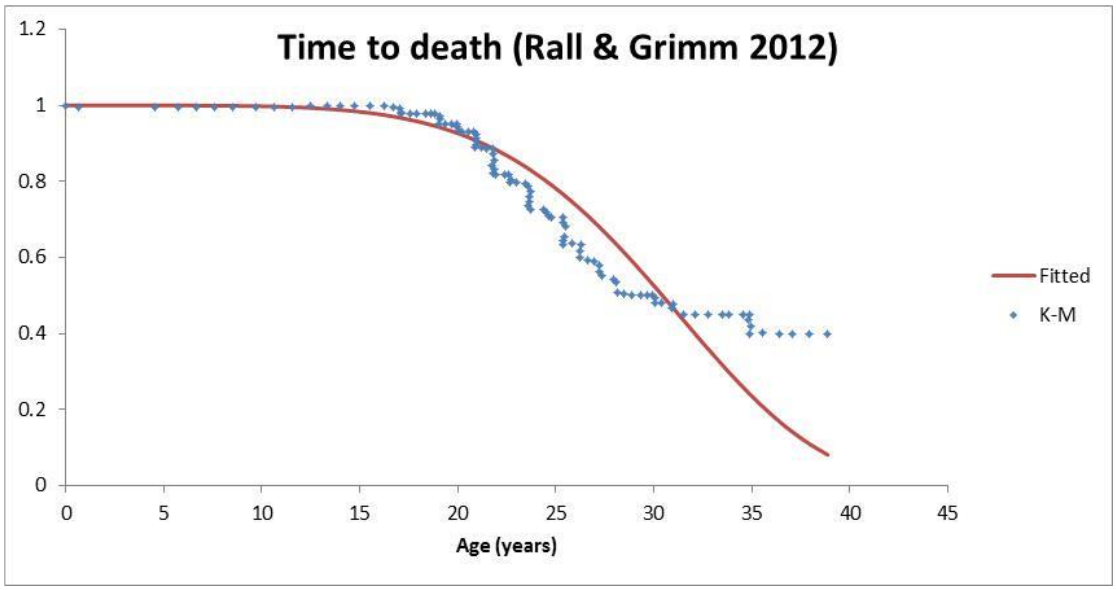


Figure 12 Reconstructed Kaplan-Meier plots and flexible parametric models for the three groups of patients defined according to the age at loss of ambulation

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.



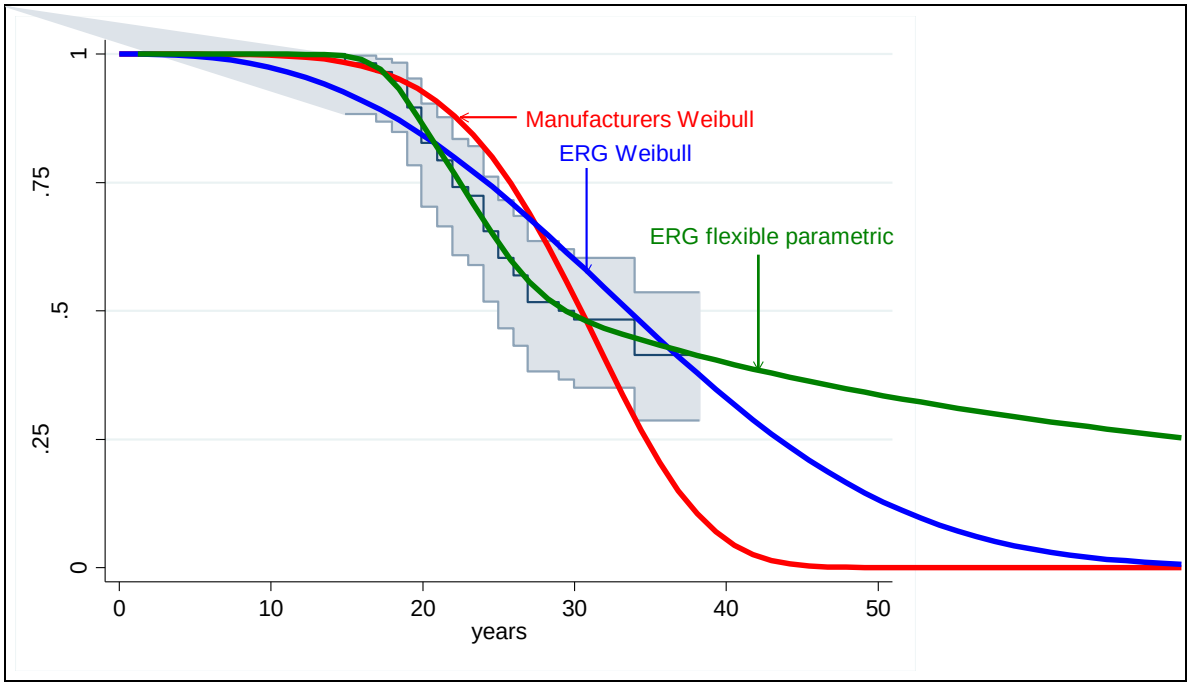


Figure 13 Reconstructed Kaplan-Meier plot and Weibull and flexible parametric models for time to death

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%

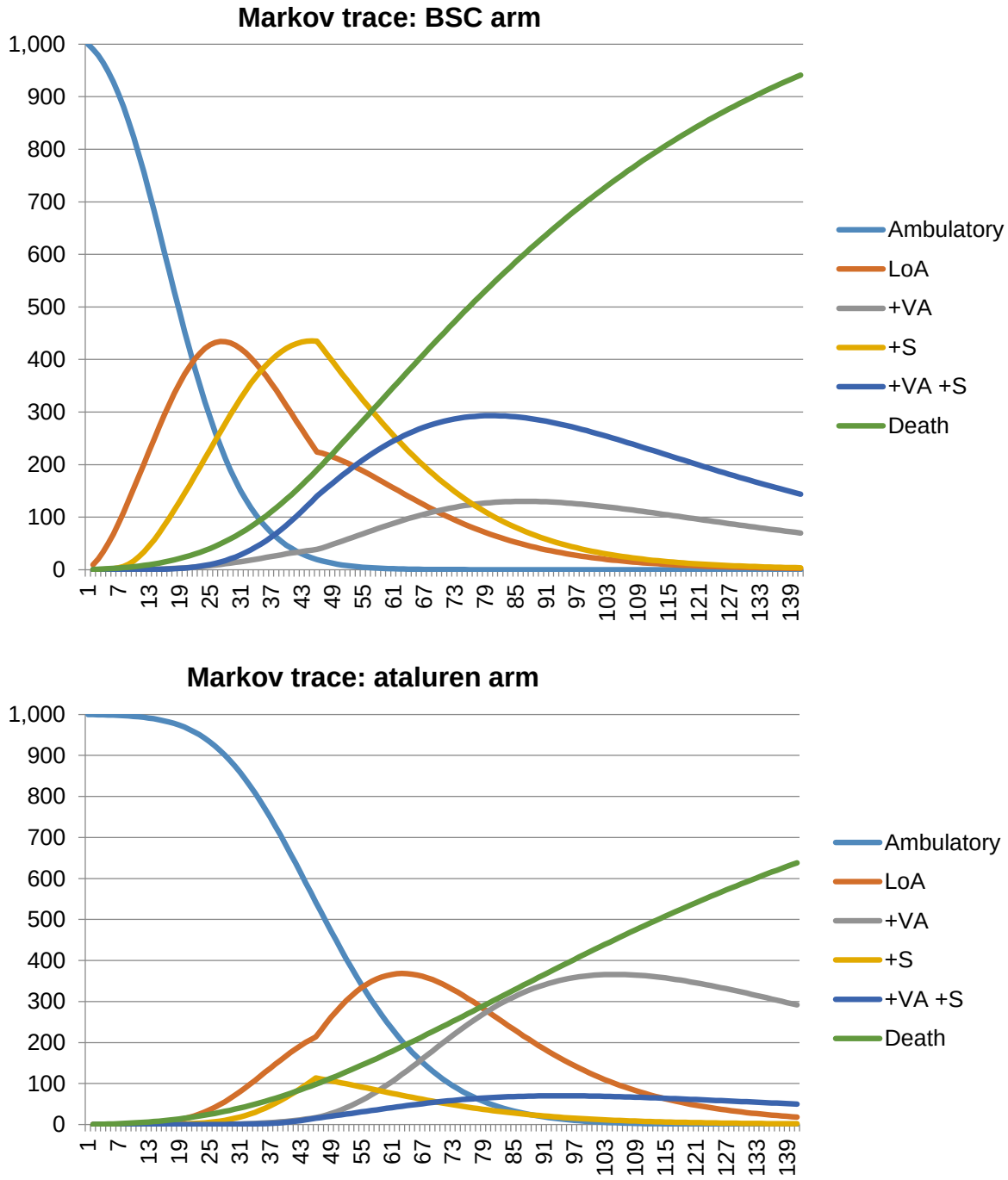


Figure 14 Markov traces - New company model

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

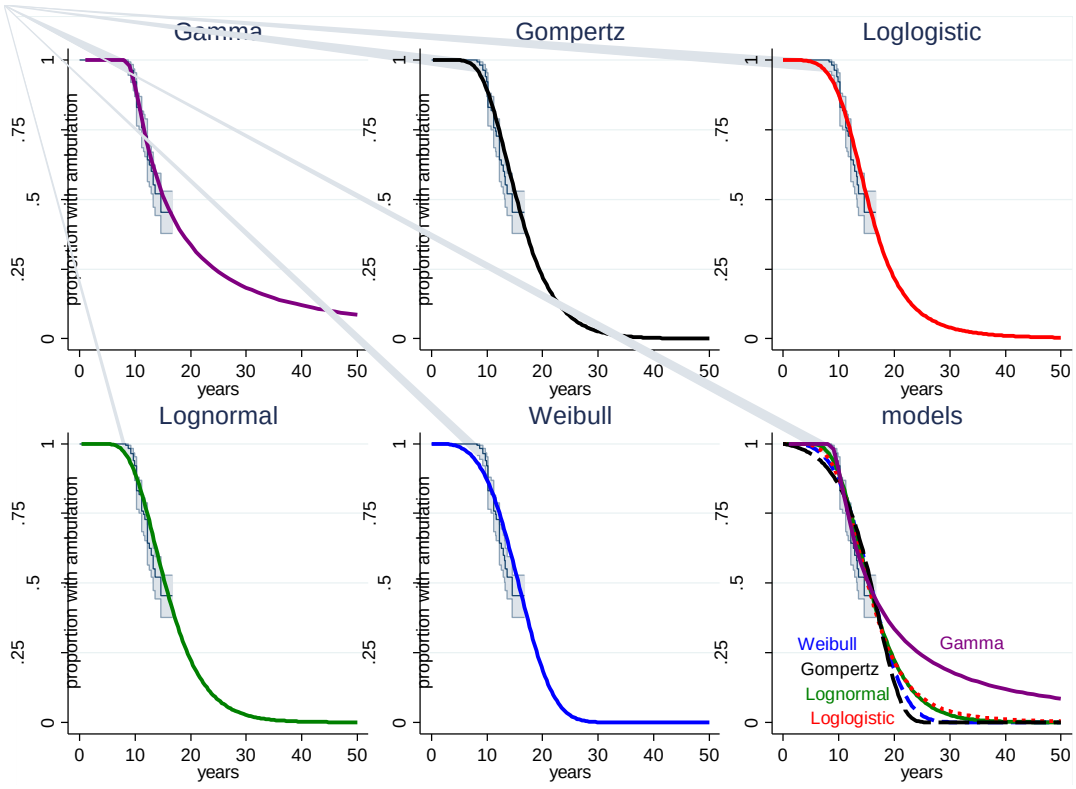
Appendix 1 List of centres that specialise in the management of DMD in England and Wales

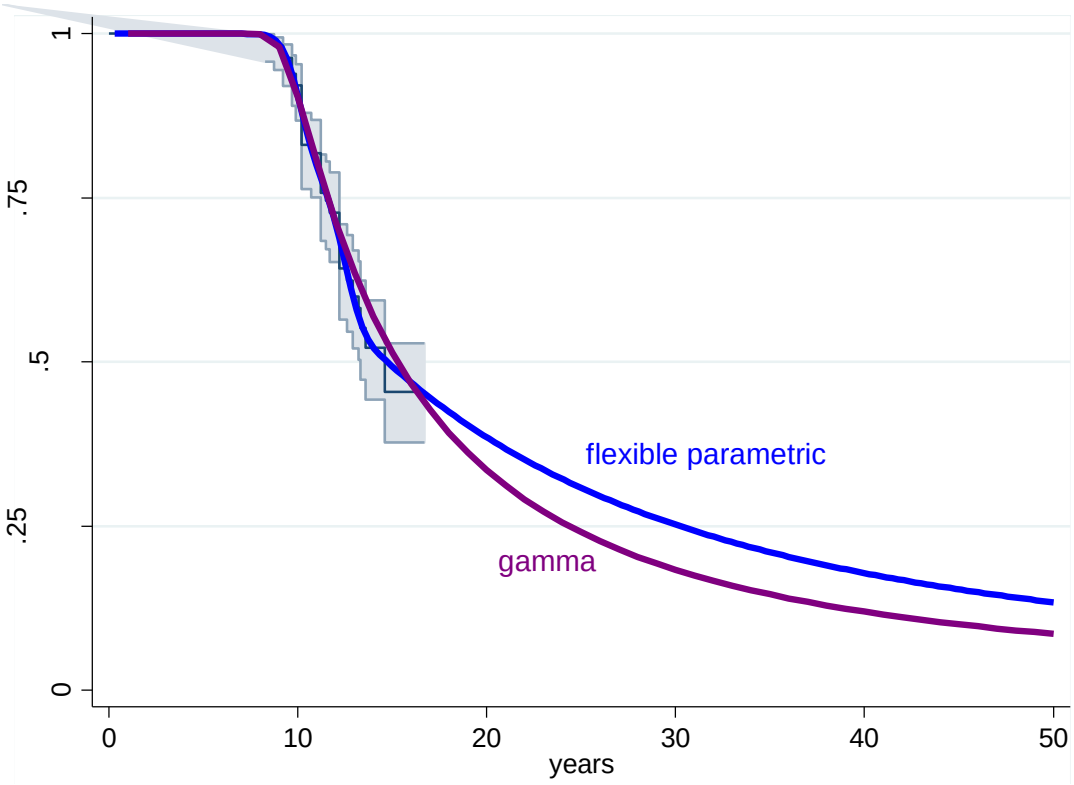
- Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne
- Leeds General Infirmary
- Sheffield Children's Hospital NHS Trust
- Alder Hey, Liverpool
- Manchester Children's Hospital
- Preston Royal
- Nottingham University Hospital
- Heartlands Hospital, Birmingham
- John Radcliffe 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

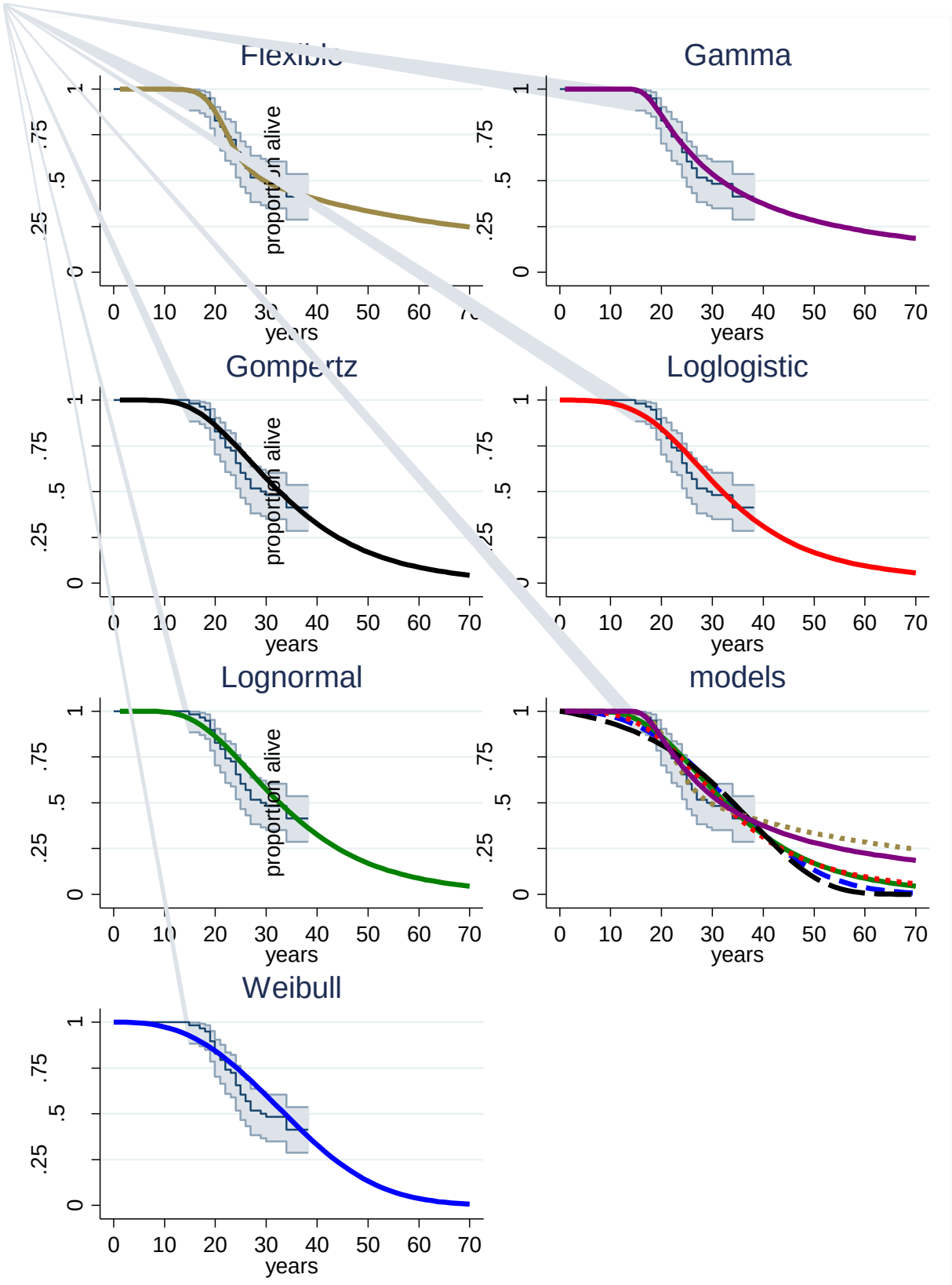
Model	Obs	ll(model)	df	AIC	BIC
gamma	165	-73.2959	3	152.5918	161.9097
exponential	165	-161.075	1	324.1505	327.2565
Weibull	165	-103.105	2	210.2104	216.4223
gompertz	165	-114.639	2	233.278	239.4899
lognormal	165	-91.229	2	186.4579	192.6698
loglogistic	165	-95.5587	2	195.1173	201.3292
flexible parametric	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.

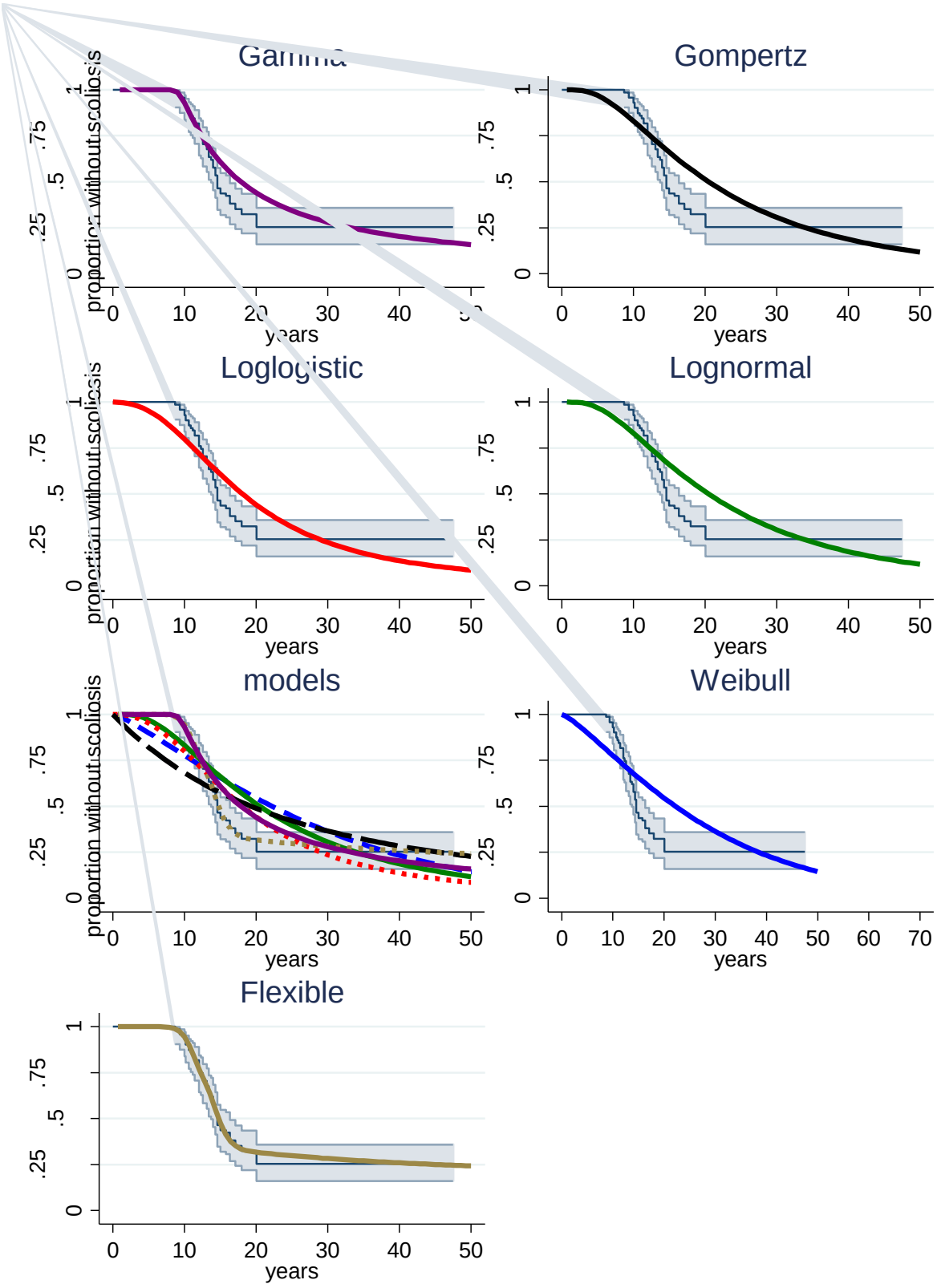
Rall SI, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myol:2012;31(2):117-20.



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