NICE National Institute for Health and Care Excellence

Highly Specialised Technology

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

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

Contents:

The following documents are made available to consultees and commentators:

Access the final scope and final stakeholder list on the NICE website.

Pre-technical engagement documents

1. **Company submission** from PTC Therapeutics

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Joint statement from Muscular Dystrophy UK and Action Duchenne
   b. NHS England

4. **Expert personal perspectives** from:
   a. Katherine Wedell – patient expert, nominated by Action Duchenne
   b. Mark Silverman – patient expert, nominated by Action Duchenne

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company**

8. **Technical engagement responses and statements from experts:**
   a. Anne-Marie Childs, Consultant Paediatric Neurologist – clinical expert, nominated by PTC Therapeutics
   b. Katherine Wedell – patient expert, nominated by Action Duchenne
   c. Mark Silverman – patient expert, nominated by Action Duchenne

9. **Technical engagement responses from consultees and commentators:**
   a. Muscular Dystrophy UK

10. **Evidence Review Group critique of company response to technical engagement** prepared by School of Health and Related Research (ScHARR)

11. Evidence Review Group cost-effectiveness results for exploratory analyses:

a. Including list price for ataluren

b. Including decision modifier weighting

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Review following a period of managed access

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

Specification for company submission of evidence

Date of submission

9 March 2022

Table of contents

List of tables and figures

Glossary of terms

Abbreviation	Full term
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADL	Activities of daily living
AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
BIC	Bayesian information criterion
BMI	Body mass index
BSC	Best supportive care
BURQOL-RD	Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe
CHMP	Committee for Medicinal Products for Human Use
CHU-9D	Child Health Utility Instrument (9 dimensions)
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
cITT	Corrected intention-to-treat
CK	Creatine kinase
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
DT-VAD	Destination ventricular assist device
EAP	Early access program
EC	European Commission
ECL	Electrochemiluminescence
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HDL	High-density lipoprotein
HERCULES	HEalth Research Collaboration United in Leading Evidence Synthesis

Abbreviation	Full term
HR	Hazard ratio
HRQL	Health-related quality of life
HST	Highly Specialised Technology
HTA	Health Technology Assessments
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan-Meier
LDL	Low-density lipoproteins
LoA	Loss of ambulation
LS	Least-squares
MAA	Managed access agreement
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated-measures
mRNA	Messenger ribonucleic acid
NA	Non-ambulatory
NHM	Natural history model
NICE	National Institute for Health and Care Excellence
nmDMD	Nonsense mutation Duchenne muscular dystrophy
NSAA	North Star Ambulatory Assessment
PAS	Patient access scheme
PedsQL™	Paediatric Quality of Life Inventory™
PK	Pharmacokinetics
PODCI	Paediatric Outcomes Data Collection Instrument
PSS	Personal social service
PUL	Performance of Upper Limb
QALY	Quality-adjusted life years
QoL	Quality of life
R/S	Randomisation and stratification

Abbreviation	Full term
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SPC	Summary of Product Characteristics
STRIDE	Strategic Targeting of Registries and International Database of Excellence
TEAE	Treatment-emergent adverse event
TFT	Timed function test
TID	Three times a day
TREAT-NMD	Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases

Executive summary

The technology

Ataluren (Translarna™) is the first and only targeted treatment for patients with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (nmDMD). Ataluren is indicated in ambulatory nmDMD patients aged 2 years and older.[1] The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

A nonsense mutation in the DNA results in a premature stop codon within an mRNA that prevents generation of a full-length protein. Ataluren enables ribosomal readthrough of mRNA containing a premature stop codon, resulting in production of full-length dystrophin proteins.[1]

Ataluren is given orally three times per day with a recommended total daily dose of 40 mg/kg body weight. Ataluren is available as granules for oral suspension, provided in 125 mg, 250 mg or 1000 mg sachets.

Ataluren is a long-term chronic therapy available to patients in England and Wales under the conditions of the Managed Access Agreement (MAA), until patients lose ambulation, and no later than 6 months after becoming fully non-ambulant.[2] Based on input from clinical experts in England, treatment with ataluren should continue beyond loss of ambulation. This is supported by 13 patients in England who have remained on ataluren after loss of ambulation as part of a compassionate care programme.[3]

Nature of the condition

Duchenne muscular dystrophy (DMD) is a severe, progressive, and rare X-linked inherited muscle wasting disease. It is characterised by a relentless decline in physical functioning from early childhood and eventual pulmonary and cardiac failure, leading to death in early adulthood.[4] DMD predominantly, though not exclusively, affects males. Most genetic subtypes of DMD present with a similar course and timescale of disease progression, with nonsense mutations following a typical progression among DMDs.

In children with DMD, absence of functional dystrophin protein leads to long-term irreparable damage of all their muscles, with limited potential to regain function.[5,6] DMD follows a well-defined pattern from early childhood. As DMD is a genetic disease, dystrophin production is first affected *in utero*, with muscle degeneration occurring anytime thereafter and symptoms usually become apparent between 1 and 3 years of age.[7-10]

The most devastating and obvious effect of DMD is on the skeletal musculature, causing progressive muscle weakness, and loss of strength and function. This results in high morbidity, early mortality and reduced quality of life.[11] After the age of 7 years, patients experience a significant decline in their walking ability, and activities such as rising from the floor and ascending stairs become more difficult.[12,13] As their ambulatory ability continues to deteriorate, DMD patients lose the ability to walk independently and become wheelchair dependent at a median age of 12 to 13 years (early non-ambulatory stage).[14,15]

Following loss of ambulation (LoA) and therefore permanent wheelchair reliance, deterioration in the upper extremity, respiratory and cardiac muscles become more apparent. Loss of upper body strength may make activities of daily living (such as bathing, dressing, sitting unsupported and eating) difficult or impossible to perform independently.[10]

By around 16 years of age, key pulmonary parameters (including forced vital capacity [FVC]) fall below 50% of predicted values,[16,17] at which point, patients start to develop signs of moderate pulmonary dysfunction, are likely to require nocturnally-assisted ventilation and are at a higher risk of suffering pulmonary complications. Dependence on permanent ventilation, which may require tracheostomy, usually occurs before 23 years of age.[18,19] Ultimately, absolute FVC declines below 1 litre, a threshold that is strongly predictive of mortality.[20,21]

DMD has a devastating impact on children's lives, as well as on their parents and families. From a young age, children with DMD have a reduced capacity to engage in physical activity, meaning they cannot keep up with their peers, have problems walking, running and climbing stairs, with frequent falls. In addition, children with DMD experience fatigue and cognitive-behavioural difficulties that further impact on social activities and their emotional wellbeing.[22] Quality of life deteriorates as the disease progresses and physical capacity decreases. The most prominent loss of health-related quality of life (HRQL) occurs following LoA.[23] However, in non-ambulatory adolescents and young adults, there is gradual loss of upper limb, trunk and neck functions, so that grooming, toileting, bathing, dressing, sitting unsupported, and eating become impaired or impossible to perform by oneself.[10] The progressive decline in pulmonary function leading to breathing difficulties and ultimately the need for ventilation, further impacts on their quality of life.[10,24]

The burden of care for parents of children with DMD is substantial; as DMD is a long-term degenerative disease, it entails heavy involvement of families in patients' care and caregiving can become very demanding.[25,26] Most DMD patients will remain entirely dependent on others for their continued care in early adulthood. The last few years of their lives are spent non-ambulatory, requiring ventilation support and fully dependent on caregivers. Providing informal care to a patient with DMD has been found to be associated with impaired health and HRQL, poor sleep quality, reduced family function, increased risk of depression, anxiety, elevated levels of stress, sexual dysfunction, and considerable impact on work life and productivity.[27] The mean number of hours of informal care per week has been estimated at 63 hours in the UK.[27] Given that parents provide care throughout their child's lifetime, the burden is substantial.

The key measures of disease progression focus on level of mobility for ambulant patients and extent of pulmonary dysfunction for patients who are non-ambulatory. Project Health Research Collaboration United in Leading Evidence Synthesis (HERCULES) was a pioneering project in which, patients, clinicians, pharmaceutical companies, and regulatory representatives collaborated to develop tools and evidence to support health technology assessments and reimbursement decisions for treatments of DMD. [28] The availability of data, collected during real-world use of ataluren, and consensus formed as part of project HERCULES, were used to inform the clinical effectiveness outcomes which feed into the economic analysis. The primary measures of disease progression are the age to reach the following disease milestones: loss of ambulation, the requirement for night-time ventilation (assumed to equate to a predicted FVC<50%), the requirement for full-time ventilation (assumed to equate to a predicted FVC<30%), and overall survival.

Management of DMD, including nmDMD

DMD is best managed in a multidisciplinary care setting.[29] Current standard of care in the UK includes physiotherapy, orthopaedic intervention, and off-label use of corticosteroids, in addition to ataluren in those with nmDMD. Although corticosteroids can stabilise muscle strength in DMD patients for a period of time, their use is associated with safety issues, especially in the long-term. [30]

Since corticosteroids do not address the underlying cause of the disease, the clinical benefits must be balanced with associated side effect profile that presents significant challenges.[29]

Despite advances in the management of DMD in the past years, patients' clinical outcomes remain poor during their short lifetime. In the last 15 years, survival rates in patients with DMD have improved due to a more comprehensive therapeutic approach that includes pulmonary and cardiac management. However, most patients with DMD still die from heart or lung failure in adolescence or early adulthood, and patients rarely survive beyond their third decade.[4] The mean age for respiratory deaths increased from 17.7 years to 27.9 years in patients who could benefit from mechanical ventilation.[4]

In children with DMD, loss of muscle mass is most likely irreversible and in the absence of disease-modifying treatment, patients are left with an extremely severe disease. DMD specific treatments that address the underlying lack of dystrophin protein are needed to stabilise or slow disease progression as early as possible. Ataluren is the first and only drug to stimulate the production of complete dystrophin protein and contribute to a delay in disease progression, to be conditionally approved by the EMA or MHRA for the treatment of nmDMD, in ambulatory patients aged 2 years and older.[1,31]

Regulatory approval for the use of ataluren in patients aged 2 years and older is an extension to the license since the original submission to NICE (HST3) recommended use in patients aged 5 years and older as per the licence. This licence extension has been granted as the regulators have recognised the potential benefit of beginning treatment earlier in a child's development, impeding the rate of irreversible functional decline during the patient's early life.[1]

Impact of the new technology

In addition to the two placebo-controlled randomised double-blinded studies, (Study 007)[32] and (Study 020),[33] which formed the main evidence base for the original NICE assessment, a number of long-term follow-up studies and real-world evidence investigating the treatment effect of ataluren are available following the original submission, the most prominent of which being the STRIDE registry.

The key clinical evidence supporting the efficacy and safety of ataluren presented in this submission is a global registry following nmDMD patients receiving ataluren plus BSC in clinical practice for at least 5 years (STRIDE) (January 2021 data cut). STRIDE represents the largest nmDMD data cohort for real-world outcomes analysis and enables the evaluation of ambulatory and non-ambulatory milestones in 269 nmDMD patients (evaluable population) aged 2 years and older.[34] As all patients in STRIDE receive ataluren, comparative data with BSC alone was obtained from a DMD natural history registry. As such, data from STRIDE has been propensity score matched to the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) to provide key long-term comparative efficacy data for the cost-effectiveness model. In STRIDE, [redacted] patients were treated in the UK, the majority of which are likely to have received ataluren as part of the MAA.

As the STRIDE registry is the largest cohort of treated ataluren patients, has over 5 years of follow-up, includes the majority of the MAA patients, and records the relevant outcome measures required to evaluate disease progression, the STRIDE/CINRG propensity score matched comparison is the most comprehensive data available to inform the clinical parameters within the economic analysis.

The STRIDE/CINRG analysis showed that ataluren plus BSC delayed LoA for over 5 years, which allowed patients to live their lives more fully as children. Ataluren treatment in STRIDE was

associated with a delay in LoA by 5.4 years compared with CINRG DNHS matched controls (17.9 years of age vs 12.5 years of age, respectively). Ataluren statistically reduced the risk for LoA by 63% relative to BSC alone in CINRG DNHS (p<0.0001, hazard ratio [HR] 0.374).[35] Ataluren-treated patients also retained their ability to stand from supine for longer, with a [redacted] lower risk of reaching a time to rise from supine in more than 10 seconds compared to matched patients in CINRG DNHS ([redacted]).[36]

Across early pulmonary function milestones, patients in STRIDE were older than propensity-matched subjects from the CINRG DNHS database at the time each milestone was reached.[37] The median age at % predicted FVC <60% was 17.6 years for STRIDE subjects and 15.8 years in the CINRG propensity score matched population (p=0.0051; HR 0.544). Similar results were observed for the milestones of % predicted FVC [redacted]. A delay in reduction in pulmonary function was also observed in a propensity score matched Study 019 and CINRG comparison, with a 3-year median delay in decline of predicted FVC to <60% in non-ambulatory patients when compared to a propensity score matched population from CINRG (18.1 years and 15.1 years respectively, p=0.0004).[38] There is also evidence from the Study 019/CINRG analysis that, once a patient loses ambulation, the time before a significant reduction in pulmonary function is also extended when receiving ataluren. Ataluren patients had a median duration of 4.9 years from LoA to pFVC<60% compared with a median duration of 3.6 years for match supportive care patients (p=0.219).

Other clinical evidence to support the safety and effectiveness of ataluren includes the two placebo-controlled randomised double-blinded studies; (Study 007)[39] and (Study 020)[33] which formed the main evidence base for the original NICE assessment. In these studies, ataluren reduced the decline in 6-minute walk distance (6MWD) over 48 weeks compared with BSC alone, and consistently demonstrated benefit across multiple measures of muscle strength and function.[32,33] A clinically meaningful benefit in the decline in 6MWD was observed in Study 007 with a mean difference of 31.3m less average decline for ataluren patients compared to controls.[32,40] Following completion of Study 007, patients with a baseline 6MWD of ≥300 to <400 metres were identified as the optimal group as these patients have a considerable loss of walking ability, but still have enough mobility to be able to show a drug effect on 6MWD over 48 weeks.[33] The treatment effect was evident in the pre-specified subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres in Study 020, with a statistically significant least-squares (LS) mean difference of 42.9 metres between the two groups (p=0.007).[33]

A pre-specified meta-analysis of Study 020 and Study 007 (patients who met Study-020 criteria) was conducted to increase the sample size to 171 patients in both the ataluren and placebo treatment arms, resulting in statistically significant treatment effects of a mean difference in the change in 6MWD of 17.2m compared to placebo.[41] Further meta-analyses that provide additional data also demonstrated improved 6MWD and timed function test (TFT) results that were statistically significant in all patient subgroups.

Following the original submission (HST3), Study 030 (Phase 2) evaluated the safety, pharmacokinetics and efficacy of ataluren in patients with nmDMD aged 2 to less than 5 years.[42] Based on the positive results of this study that included improvements in physical functioning with ataluren, comparable drug exposure with older patients and an acceptable safety and tolerability profile, expansion of the label to include ambulatory children aged 2 to 5 years with nmDMD was approved by the European Commission (EC) on 23 July 2018.[1]

A further open-label extension study (Study 019) conducted after HST3, provides additional evidence for the efficacy of ataluren, including its beneficial effects on loss of ambulation and on pulmonary function in non-ambulatory patients.[43] A propensity score matching exercise using ataluren patients from study 019 and the CINRG natural history registry provides a comparative efficacy analysis between ataluren patients and natural history patients which demonstrates a delay in loss of ambulation of 2.2 years (p=0.0006).

As a condition of the NICE recommendation in 2016, to receive ataluren, eligible patients must sign up to the MAA.[2] In July 2021, a contract variation was agreed, which extended the period of the MAA to allow for additional data collection.[44] The MAA primary efficacy measure is the change in the North Star Ambulatory Assessment (NSAA), over the course of a 3 to 4-year period. In order to assess response to treatment, patients receiving ataluren in the MAA have been compared to a matched control group receiving BSC alone, identified from DMD patients without the nonsense mutation included in the North Star registry. The data indicate that treatment with ataluren [redacted] disease progression compared to BSC alone, with [redacted] ataluren-treated patients losing functions on the NSAA over 36 months. In an analysis of patients who completed 36 months of treatment, the change from baseline over 3 years in linear NSAA (scale from 0 to 100) was a mean (SD) [redacted] points for ataluren and a mean (SD) [redacted] points for BSC alone. The NorthStar registry cohorts were matched using propensity scores, however, a key prognostic variable "age at first symptom" was not recorded within the registry and therefore not included as a matching covariate. The resulting matched cohort of 59 patients for each treatment arm were not well balanced on key covariates and suffered from missing data at later timepoints. In addition, more than [redacted]% of BSC patients were aged <7 years (compared to [redacted]% in ataluren-treated patients), and in these patients' disease history data suggests ambulatory function improves in DMD children until approximately 7 years old. For this reason, many BSC patients NSAA increased during the first stages of follow-up, and then declined at a slower rate than their matched ataluren counterparts. This introduces potential bias into the analysis and limits the ability to form meaningful conclusions from this study.

Ataluren is well tolerated in nmDMD patients as young as 2 years old. In clinical trials and long-term studies, the observed safety and tolerability profile of ataluren is comparable to that of BSC. In the two placebo-controlled studies the most common reported adverse reactions were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients.[1] Safety data from 28 weeks of therapy showed a similar safety profile of ataluren in patients 2–5 years as compared with patients aged 5 years and older.[1] In the long-term observational study of ataluren in nmDMD (STRIDE), interim safety results continue to be consistent with the known safety profile of ataluren.

In a degenerative disease with progressive and irreversible loss of functions, that eventually leads to death, stopping or slowing the progression of the disease is considered meaningful to patients, as this would preserve their abilities and delay subsequent loss of functions. This is illustrated in quotes from caregivers of patients receiving ataluren:[22]

"Yesterday again, for example, he got out of his all-terrain hopper and he walked for I would say a good 20 minutes or more yesterday. Without Translarna, I don't think he would be able to do that"

"It's just good to see that [he] can be stable. Obviously, we know that things will change at some point but it's a much slower decline so it gives you just more time to play with really and it's just positive all round."

The additional analyses of the STRIDE and Study 019 data compared to CINRG following the original submission demonstrate that the dystrophin-restoring mechanism of action of ataluren can be beneficial to patients with nmDMD for all types of skeletal muscles throughout different stages of the disease, regardless of ambulatory status. Ataluren can provide further benefit to that already conferred by corticosteroids (given as part of BSC) and preserve vital functions for longer such as the patients' ability to breathe independently.

Both the clinical evidence and expert clinical opinion support the ability for ataluren to preserve muscle function beyond loss of ambulation. The previous NICE guidance for ataluren stipulates patient should discontinue treatment within 6 months of LoA. Under the current guidance, patients are being deprived of potential treatment benefit and therefore PTC propose that treatment with ataluren should continue beyond loss of ambulation.

The treatment benefit demonstrated with real-world use of ataluren reduces the cumulative impact of DMD on the quality of life of families and caregivers. Availability of ataluren enables carers of children with nmDMD to continue to work for longer before having to reduce their working hours or give up work entirely to look after their child. Changes to caregiver impacts following ataluren treatment, including less anxiety and stress, and the positive impact on work, have been described.[45]

"I go to work now, and I don't worry about what's happening at nursery, is he going to fall over? Am I going to get a phone call from the ambulance saying he's in hospital? … I'm not worrying, I'm able to focus more on my day to day. So I don't feel like I'm worrying about him, because I know how well he's doing."

"I'm able to have more of a social life, I can do more things. He can be left alone for you know hours and hours, I can go out for instance from say 9am until 5pm and [son] will cope perfectly fine at home without me or anyone here, so that's a big change. So, yeah, I can do a lot more, going to work full-time and just doing more or less normal day to day stuff that most other people would do now."

Value for money

A cost-utility analysis of ataluren within its licensed indication, patients aged ≥2 years old with Duchenne muscular dystrophy resulting from nonsense mutation (nmDMD), was conducted from the perspective of the NHS and PSS. The analysis used a partition survival model, consisting of five health states to reflect the progressive and heterogeneous nature of nmDMD, which was based on the HERCULES natural history model. Patients entered the model in the ambulatory health state and progress to non-ambulation (i.e., fully wheelchair bound). Following loss of ambulation, health states were defined by pulmonary status according to predicted FVC greater than 50%, less than 50%, or less than 30%. An absorbing death health state was included in the model, which patients could move to from any health state.

The analysis estimated the lifetime costs, quality-adjusted life years (QALYs) and life years (LY) associated with ataluren plus BSC, and BSC alone. The analysis was conducted over a lifetime horizon of 70 years, with three-month cycle lengths. Costs and health effects were discounted at 3.5%. As proposed in the original submission, a patient access scheme (PAS) with a simple discount is incorporated in the cost-utility analysis with results at both list and PAS discounted prices.

STRIDE registry data was used to inform the economic model. STRIDE patients were propensity score matched to patients in CINRG DNHS and used to inform the clinical inputs of intervention and comparator arms of the model, respectively. Due to the lack of clinical efficacy data for patients aged 2 to 5 years old, the model assumes that patients receiving ataluren at an early age (2 to 5 years)

will benefit from a delay in loss of ambulation, predicted FVC, and death. These early treatment delays have been validated by clinicians as part of an unpublished Delphi panel study. The model also assumes that once patients reach the final non-ambulatory health state (predicted FVC <30%), they die within three years, which was informed by published literature and validated by clinicians.[20,21]

Health effects include patient and caregiver utilities, and bereavement due to loss of a child. Patient utilities were treatment specific, based on outcomes from a Delphi panel study conducted by Landfeldt et al. Caregiver utilities were assumed equal for intervention and comparator, and patients were assumed to have two caregivers based on validation by UK clinicians. The model applied 9% of the loss of life due to nmDMD to account for bereavement, where greater QALY loss was observed for BSC alone due to delayed death with ataluren.

Over a 70-year time horizon, at a 3.5% discount rate, patients receiving ataluren and their caregivers accrued an additional [redacted] discounted QALYs compared to standard of care (SoC), at an additional cost of [redacted] (list) or [redacted] (PAS) per patient. This corresponds to an incremental cost-effectiveness ratio (ICER) of £336,555 based on list price and [redacted] on PAS. Applying weights based on the incremental number of undiscounted QALYs in the HST decision modifier, rescales the ICERs so that they can be compared with the £100,000 per QALY threshold. Applying the weight associated with 23 undiscounted incremental QALYs gives ICERs of £145,514 and [redacted] based on list and PAS discounted prices, respectively.

Deterministic, probabilistic and scenario analyses were performed showing that patient and caregiver utilities, number of caregivers, treatment compliance, and patient weight are key drivers of the cost-effectiveness results. The majority of these analyses produced ICERs based on the PAS discounted price that are below or close to the £100,000 per QALY threshold, indicating that ataluren is cost-effective.

The budget impact model assumes [redacted] prevalent nmDMD patients aged ≥2 years, based on the number of patients in the MAA, and 6 incident patients per year. Assuming an annual mortality rate and rate of patients reaching predicted FVC <50% of [redacted] and [redacted], respectively, each year on average [redacted] patients are eligible to receive ataluren.

Applying a market uptake of 100% and a treatment compliance rate of 95% in Year 1 to 5, the estimated budget impact with ataluren ranges from [redacted] in year 1 to [redacted] year 5, at the list price and [redacted] in year 1 to [redacted] in year 5 with the PAS discount applied.

Impact of the technology beyond direct health benefits

A substantial proportion of the benefits of ataluren treatment are incurred outside of the NHS and personal social services. Due to its early onset and rapid progression, DMD results in severe disability and consequent lack of independent living by the early twenties with death usually occurring before the age of 30. [4] As a result, adults with DMD rarely succeed in participating in a working life. A considerable amount of time, which increases with progression of their son's disease, is spent by family members in providing care. The burden on caregivers results in substantial losses in productivity, with many DMD caregivers terminating their employment or reducing their working hours to find the time needed to care for their sons.

A treatment that changes the course of nmDMD by slowing disease progression enables children with nmDMD to participate in education for longer, remain more self-sufficient and have an increased

chance of employment in adulthood. This would also mean that caring for their children would be less intensive for parents/ caregivers and may allow them to stay in paid work for longer.

Ataluren treatment delays loss of ambulation and delaying progression to the non-ambulatory stage of disease would delay the occurrence of the associated costs, of which a large proportion are made up of costs to households incurred outside of the NHS and personal social services.[24,27]

Conclusion

Ataluren is an innovative, first-in-class drug and is the first specifically approved therapy for nmDMD that addresses the underlying cause of the disease. Since ataluren received conditional regulatory approval by the EMA in 2014, no other treatments for DMD have been approved in Europe, highlighting the current and future need for ataluren as an effective treatment option.

The significant volume of data accumulated during the period since the original submission, including data from STRIDE, provide compelling evidence that long-term treatment with ataluren in nmDMD slows disease progression and, consequently, improves quality of life, reducing the burden on caregivers, and is ultimately expected to prolong survival.

A Decision problem

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

1 Statement of the decision problem

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

Table A-1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk	None	**Note:** Whilst this aligns with the indication wording for ataluren, we would highlight that continued treatment with ataluren beyond loss of ambulation is expected to provide continued benefit by preserving remaining muscle function and vital functions such as pulmonary and cardiac function.
Intervention	Ataluren	None	Not applicable
Comparator(s)	Established clinical management without ataluren	None	Not applicable
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 (for patients and carers).	Data on cardiac outcomes are not presented.	Whilst cardiac assessments are included in the patient registry (STRIDE) these data are immature and effect on cardiac function is unable to be presented in the submission.
Subgroups to be considered	None	None.	**Note:** Subgroup analysis relating to outcomes in patients based on baseline 6-minute walk distance

			(6MWD) will be included in the clinical evidence, however these do not reflect specific populations to be treated in practice and are not presented in the economic 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	None	Not applicable
Cost to the NHS and PSS, and Value for Money	• cost-effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used	None	Not applicable
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation	None	Not applicable

	• the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise		
Special considerations, including issues related to equality	None	None	Not applicable

2 Description of technology under assessment

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

Brand name: Translarna™

Approved name: Ataluren

Therapeutic class: M09AX03

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

A nonsense mutation in DNA results in a premature stop codon within an mRNA. This premature stop codon in the mRNA causes disease by terminating translation before a full-length protein is generated. Ataluren enables ribosomal readthrough of mRNA containing such a premature stop codon, resulting in production of a full-length protein.[1]

2.3 Please complete the table below.

Table A-2. Dosing Information of technology being evaluated

Pharmaceutical formulation	Granules for oral suspension (125 mg, 250 mg, 1000 mg sachets)
Method of administration	Oral
Doses	The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight). Table A-3 below provides information on which sachet strength(s) to use in the preparation of the recommended dose by body weight range.[1]
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	Ataluren is a long-term chronic therapy. Under the conditions of the Managed Access Agreement, treatment may be continued until patients lose ambulation, as follows: If a patient has lost all ambulation (i.e., can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment. In such cases, patients should stop treatment no later than 6 months after becoming fully non-ambulant.[2] Based on input received by PTC from clinical experts in England and the average time on treatment observed in the clinical evidence base, treatment with ataluren should

	continue beyond loss of ambulation, until ventilation support is required (i.e. patients achieve predicted FVC <50%)
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.
Dose adjustments	Dose should be adjusted according to body weight as shown in Table A-3. No other dose adjustments are required.

Table A-3: Translarna dosing

Weight Range (kg)		Number of sachets								
		Morning			Midday			Evening		
		125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets	125 mg sachets	250 mg sachets	1000 mg sachets
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	1	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

Source: Translarna SPC[1]

3 Regulatory information

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

Yes. Ataluren received a conditional marketing authorisation from the EC on 31 July 2014 for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

In July 2018, an expansion of the label to include ambulatory patients as young as 2 years of age was granted by the EC.[46]

In July 2020, the conditional registration was renewed by the EC. At this time, Section 4.1 of the SPC was updated to remove the sentence "efficacy has not been demonstrated in non-ambulatory patients" based on SPC guideline and the 'Guide for Assessors of Centralised Applications' on the wording of the therapeutic indication'.[1,47]

In January 2021 ataluren was authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) for use in the UK based on automatic recognition of the EC approval.

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

Not applicable.

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

Ataluren is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Israel, Republic of Korea, Brazil, Russia and Belarus, and aged 5 years and older in Chile and Ukraine (under special state registration). In Brazil, the indication is restricted to paediatric male patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

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

Since July 2016 ataluren has been available in England under a managed access agreement (see section 6.2).

4 Ongoing studies

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

This should include unpublished and ongoing studies, and studies awaiting publication. Also include post-marketing surveillance and register data.

There are three ongoing studies investigating ataluren for the treatment of nmDMD (Table A-4). Data from Study 016 [redacted]. Data from the randomised phase of Study 041 [redacted] with top line results expected to be announced publicly in Q2 2022. The STRIDE Registry is ongoing, and data are analysed on a biannual basis, with the next data cut planned in January 2023.

Table A-4. List of ongoing studies

Study ID(s)	Description
Study 016 PTC124-GD-016-DMD NCT01247207 **Study Title**: An Open-Label, Safety Study for Previously Treated Ataluren (PTC124) Patients With Nonsense Mutation Dystrophinopathy **Start**: 11/2010 **End:** ongoing, estimated 12/2023	**Study type:** Phase 3 open-label safety study for patients with a history of exposure to ataluren in a prior PTC study or treatment plan in nmDMD and effected siblings of those participants **Total sample size:** 120 (as of 31 July 2020) **Population:** nmDMD **Intervention(s):** 40mg/kg/day; TID **Comparator(s):** None **Outcomes:** Safety (adverse events, laboratory abnormalities, abnormal physical findings)
Study 041 PTC124-GD-041-DMD NCT03179631 **Title**: A Phase 3, Randomised, Double-blind, Placebo-controlled Efficacy and Safety Study of Ataluren in Patients with Nonsense Mutation Duchenne Muscular Dystrophy and Open-Label Extension **Start:** 07/2017 **End:** 09/2022 (double-blind phase)	**Study type:** Phase 3 long-term disease progression study, randomised, double-blind, placebo 72-week study with 72-week open-label extension **Total sample size**: 250 Approximately 340 ([redacted] have been randomised) **Population:** Male, 5 years and older, nmDMD, ambulatory, 6MWD ≥150 metres **Intervention(s):** Ataluren 40 mg/kg/day; TID **Comparator(s)**: Placebo **Outcomes:** Primary: change 6MWD; Secondary: change from baseline in 6MWD, TFTs, NSAA, time to LoA, time to loss stair-climbing, time to loss stair-descending, risk of loss of NSAA, TEAEs.
Study 025o (STRIDE Registry) PTC124-GD-025o-DMD NCT02369731 Title: Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care Start: 04/2015 End: 05/2025 Mercuri et al. 2020[7]; Mercuri et al. 2021[34]; Tulinius et al. 2021[37]	**Study type: Ongoing observational registry** **Study Design: Multicentre, observational, cohort** **Total sample size: 360** (288 enrolled at data cut-off 31 January 2021) **Population: nmDMD** **Intervention(s):** Usual care, commercial ataluren or early access program 40 mg/kg/day; TID **Comparator(s):** None **Outcomes:** Safety; Efficacy evaluations conducted as per usual care: 6MWD, TFTs, LoA, NSAA, pulmonary and cardiac assessments

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ECL, electrochemiluminescence; ADL, activities of daily living; CK, creatinine kinase; LoA, loss of ambulation; nmDMD, nonsense mutation Duchenne muscular dystrophy;

NSAA, North Star Ambulatory Assessment; PedsQL, Paediatric Quality of Life Inventory; PK, pharmacokinetic; Paediatric Outcomes Data Collection Instruction (PODCI), Paediatric Outcomes Data Collection Instrument; PUL, Performance of Upper Limb; QoL, quality of life; TEAE, treatment-emergent adverse event; TID, three times daily; TFT, timed function test

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

In early 2021 ataluren underwent initial assessment by the Scottish Medicines Consortium (SMC) for prescribing within the ultra-orphan pathway. In February 2022 the SMC recommended that ataluren can be prescribed within this pathway while further evidence is collected and reassessed 3 years after this decision. [48]

5 Equality

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

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

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

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

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

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

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Not applicable.

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

Not applicable.

B Nature of the condition

6 Disease morbidity

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

6.1.1 DMD overview

DMD is a severe, progressive, and rare inherited muscle wasting disease. It is characterised by a relentless decline in physical functioning from early childhood and eventual pulmonary and cardiac failure, leading to death in early adulthood (usually before the age of 30).[4] DMD is an X-linked recessive disorder and therefore predominantly, though not exclusively, affects males.

DMD is caused by a mutation in the dystrophin gene that results in the absence of functional dystrophin protein. The role of the dystrophin protein is to act as a shock absorber, bearing the mechanical stresses that occur during muscle contraction, stabilising muscle cell membranes, and protecting muscles from injury.[49] The lack of functional dystrophin leads to long-term irreparable damage of all muscles, including the diaphragm and cardiac muscle, with limited potential to regain function.[5,6]

In DMD, dystrophin gene alterations can be caused by a nonsense mutation (nmDMD), resulting in a premature stop codon in the mRNA sequence that codes for the dystrophin protein.[50,51] This premature stop codon halts the ribosome and stops translation, resulting in a truncated protein that is too short and often too unstable to function properly leading to loss of protein function and consequent disease.[52]

Most subtypes of DMD present with a similar course and timescale of disease progression. While there is some evidence that certain mutation types may have a milder phenotype, patients with nonsense mutations have a disease progression trajectory similar to other DMD subtypes,[14] with potentially no correlation between dystrophin genotype and DMD disease progression.[53]

Given the similar disease course across different types of DMD, data from patients with DMD type other than the nmDMD subtype, in terms of disease progression and prognostics, are considered to be generalisable. More specifically, this submission presents evidence collected on a range of DMD patients, including other cohorts of genetic mutations, and these data are considered to be generalisable or representative of the type of DMD for which ataluren is indicated as comparable evidence.[53]

6.1.2 Disease progression and symptoms

DMD is a severe, progressive muscle wasting disease that follows a well-defined pattern from early childhood. As DMD is a genetic disease, dystrophin production is first affected *in utero*, with muscle degeneration occurring anytime thereafter and symptoms usually become apparent between 1 and 3 years of age.[7-10]

Age of first symptoms is predictive of the age at LoA, with earlier onset predicting earlier age at LoA.[54] Progressive muscle weakness is initially seen in the lower extremity muscles with loss of strength and function. Young children usually have subtle symptoms of delayed walking or delayed speech compared to their peers.

As the disease progresses, earlier signs and symptoms that were mild or subtle worsen and inevitably become more severe, and functional tasks become increasingly difficult. At around 5 years of age, impairment of physical ability becomes increasingly evident (some children may never develop the ability to jump or run properly) and almost all patients must adopt compensatory manoeuvres, such as Gowers' sign and toe walking.[55] Due to natural healthy development, motor skills, including walking ability, improve up to around 7 years of age; however, this improvement occurs at a slower rate than in healthy children and functional performance is already impaired at this age.[10,13,56-58]

After 7 years of age significant decline in walking ability occurs, and activities such as rising from the floor and ascending stairs become more difficult.[12,13] Accidental falls can result in fractures, thereby further incapacitating DMD patients, with fractures to the femurs (40%), lower legs (35%), feet and toes (44%) resulting in an accelerated decline towards permanent LoA.[12,59]

As ambulatory ability continues to deteriorate, DMD patients lose the ability to walk independently and become wheelchair dependent at a median age of 12 to 13 years.[14,15]

LoA is a critical functional milestone in the lives of patients and their families and is associated with substantial decline in quality of life (see Section 7.1). Up to two-thirds of a DMD patient's life occurs after they can no longer walk, and the underlying pathology remains unchanged after this milestone. In addition, LoA does not entail complete loss of meaningful lower-limb function. The ability to stand briefly, to transfer from the wheelchair, and to turn over in bed require functional lower-limb musculature after ambulation has been lost. The age at LoA predicts subsequent disease milestones such as the development of scoliosis (see below) and moderate and severe pulmonary insufficiency.[60]

Due to permanent use of a wheelchair and continuing deterioration of upper limb functions, activities (e.g., personal grooming, toileting, bathing, dressing, sitting unsupported, and eating) become difficult or impossible to perform independently.[10] Eventually, even the ability to operate an electric wheelchair and take part in recreational activities requiring dexterity, such as playing videogames or using mobile phones, is lost. Additionally, further skeletal muscle deterioration may then lead to complications including contractures and skeletal deformities such as scoliosis due to weakening of the back muscles.[61-63] Scoliosis is a musculoskeletal deformity that can restrict lung function and predisposes to respiratory system complications e.g., chest infections, pneumonia with consequential hospitalisation. The need for orthopaedic intervention to correct scoliosis carries its own risk of complications and may not be successful/appropriate without concurrent ability for the patient to rehabilitate their spinal muscles to support the spine post-operatively.

Pulmonary function, as measured by percent predicted FVC, is affected from a young age; however, the decline becomes more apparent following LoA. Natural history data show that percent predicted FVC values are modestly impacted at 7 to 9 years of age remaining above 80%.[16] However, by 10 to 11 years of age, both parameters fall below the 80% predicted threshold, which is generally defined as the lower limit of normal and defines restrictive pulmonary disease or low lung volume. Below this threshold, pulmonary function decline is established.[17,64,65] Crossing the 80% of predicted FVC threshold and subsequent decline generally coincides with the time DMD patients become non-

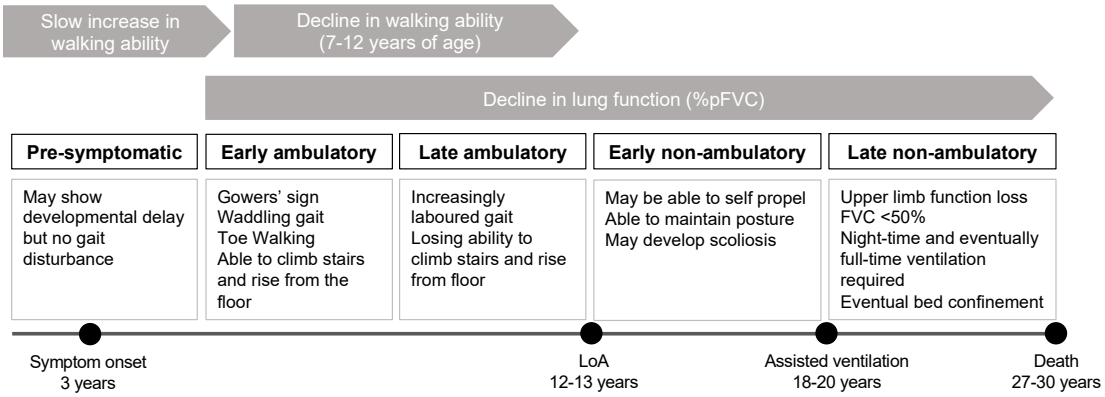
ambulant during their early teenage years.[17] From around 10 years of age, there is a steady decline in pulmonary function as measured by percent predicted FVC and this is paralleled by percent predicted PEF.[17] This decline is reported to continue at a rate of 4% to 9% per year in various studies that included DMD patients being treated with corticosteroids (GCs).[16,60,66-71]

By 16 years of age, key pulmonary parameters (including FVC, PEF, FEV1, MIP, and MEP) are <50% of predicted values of healthy children.[16,17] An FVC less than 50% predicted is considered to be a clinically relevant threshold as patients start to develop signs of moderate pulmonary dysfunction, requiring nocturnally-assisted ventilation and more frequent monitoring as patients are at a higher risk of suffering pulmonary complications (see section 6.1.3.2).[72] Nocturnally-assisted ventilation and other types of non-invasive ventilatory support can cause their own complications in the long-term, e.g., carbon dioxide retention and risk of type II respiratory failure which can cause recurrent and serious complications including hospital admissions and the need for further invasive respiratory support in a higher dependency setting.

Patients with DMD require assisted ventilation at a median age of 18 to 20 years due to pulmonary decline.[72-74] Dependence on permanent ventilation, which may require tracheostomy, usually occurs before 23 years of age.[18,19] Ultimately, absolute FVC declines below 1 litre, a threshold that is strongly predictive of mortality within 3 years and a 4-fold increased risk of death.[20,21]

Although DMD progresses along a continuum, the deterioration in muscle strength and function results in loss of function milestones, such as LoA, that can be used to describe various stages of the condition. As part of Project HERCULES (Duchenne UK 2020[75]), a multinational collaboration set up by Duchenne UK, to develop tools and evidence to support health technology assessments and reimbursement decisions for new treatments for DMD, the University of Leicester is leading a project to build a natural history model (NHM) for DMD. One of its aims is to define health states that represent a change in either HRQL and/or resource use/cost, and to which clinical trial outcomes can be applied. The health states in the HERCULES NHM closely reflect those shown in Figure B.1.

Figure B.1. Milestone and Stages of DMD



%p, percent predicted; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; LoA, loss of ambulation
Note: Milestones are reported as medians. Median age at death is reported for patients receiving assisted ventilation.
Sources:[4,9,10,14,15,18,19,72-74,76,77]

6.1.3 Assessment of disease progression in clinical trials

6.1.3.1 Ambulatory outcome measures

The 6-Minute Walk Test (6MWT)

The 6MWT that measures the distance a patient is able to walk for a total of six minutes on a hard, flat surface, is a validated and global functional measure supported by both the European Medicines Agency (EMA) and Food and Drug Administration (FDA).[78,79] The 6MWT outcome measure also shows a strong positive correlation with other functional endpoints[58] and predicts the age at loss of future clinically meaningful milestones.[10] Natural history data indicate an optimal window for detecting a treatment effect is in patients with a 6MWD between 300 and 400 metres (see section 6.1.3.3).

Timed Function Tests (TFTs)

In addition to the ability to walk, other skills are important for patients and their caregivers as milestones in the progression of the disease, such as being able to get up from a lying position, climb stairs, and eat unassisted.[80] TFTs measure the time needed to carry out certain functional activities as quickly as possible such as the time it takes to get up or down four steps as quickly as possible; to get up from a lying position; or to walk 10 metres. These tests are easy to apply, can be reproduced, are representative for the performance of general daily activities and have a predictive value for the disease progression.

A treatment effect of greater than 1.0 to 1.5 seconds on a TFT translates to differences in physical and social activity in patients with DMD.[81,82] The minimal clinically important difference (MCID) has been estimated to be 1.4 to 2.3 seconds for the run/walk 10-metre test, 2.1 to 2.2 seconds for the climb 4 stairs test, and 3.6 to 3.7 seconds for the supine to stand test.[58] There is a strong linear relationship between the 6MWT and the 10-metre run/walk test: a 6-second performance on the time to run/walk 10 metres corresponds to 358 metres on the 6MWT. In addition, a time of greater than 10 to 12 seconds on the time to run/walk 10 metres is associated with a high risk of Load over 12 months.[58,83] TFTs measure a burst of activity whereas 6MWT measures endurance. Patients not able to perform a 6MWT, may still be able to perform a TFT prior to completely losing ambulation. Hence, TFTs may also be more reliable in patients with 6MWD <300 metres.[13]

North Star Ambulatory Assessment (NSAA)

NSAA is a validated tool that assesses motor function in ambulatory children with DMD. The test is recommended as an endpoint in the EMA guidelines for conducting clinical trials on drugs for the treatment of DMD.[84] The scale was developed and piloted in the UK by the North Star Clinical Network for Paediatric Neuromuscular Disease and is comprised of 17 tasks with the possible values for each item being 0, 1, or 2 (0=unable to perform task, 1=performs with difficulty and 2=able to perform).[85,86]

The NSAA assesses motor abilities that are necessary to remain functionally ambulant and that are important for daily life, especially for children of school age (e.g., ability to rise from the floor, ability to get from lying to sitting, and sitting to standing), and which are known to progressively deteriorate in untreated patients.[87] NSAA scores directly correlate with upper limb muscle function, lung function and risk of developing cardiomyopathy, meaning that a benefit in the NSAA score in an ambulatory

patient could positively impact the patient's disease progression during the non-ambulatory stage.[87,88]

There are two ways to evaluate NSAA results. The first method involves the summing of scores from all 17 measurements to obtain a total score of 0 to 34. A one-point difference in the NSAA total score is clinically meaningful, as a decrease of this magnitude relates directly to either loss of a motor ability (transition from a score of 1 to 0) or need for compensation to perform it independently (transition from a score of 2 to 1). The challenge of the total score is that it is difficult to interpret the meaning of the result, since a one-point change does not mean the same across the breadth of the scale. For this reason, raw 0.lolscores can be transformed to a linearised score.[85] The second approach is to determine the number of functions that were preserved by calculating the odds ratio of patients that lost the ability to perform individual functions (i.e., change from a score of two or one to a score of zero) over the course of the study. It has recently been proposed that this approach is more meaningful in that it allows a comparison of the degree of preservation of function in treated versus placebo.[89]

While the NSAA score is an effective measure of mobility functionality used within an randomised controlled trials (RCT) setting, the potential influence of confounding variables, such as age, makes the interpretation of comparative NSAA scores problematic for real-world evidence when matching has failed to account for imbalances across these variables.[15,53]

Loss of ambulation

Preserving walking ability for longer, thus delaying permanent wheelchair use, is a key goal in DMD as it allows patients to live their lives more fully as children and potentially reach adulthood with a greater degree of independence. Ambulation represents an indicator of disease progression, therefore delaying LoA means that upper limb function and pulmonary function are preserved for longer.[60]

In clinical practice defining a patient as "ambulatory" or "non-ambulatory" is a matter of the individual treating physician's clinical judgement. However, loss of ambulation is generally defined as requiring full-time wheelchair use and the inability to walk 10 metres without assistance or orthoses.

Definitions of ambulatory and non-ambulatory used in ataluren clinical trials are as follows:

- An open-label extension study (Study 019) evaluating the long-term safety of ataluren enrolled both ambulatory and non-ambulatory patients who had previously participated in phase 2 ataluren studies. "Non-ambulatory" was defined as being "unable to run/walk 10 metres in ≤30 seconds".[90]
- The STRIDE Registry, an ongoing observational study evaluating the long-term safety and effectiveness of ataluren in real-world routine clinical practice, enrols patients receiving usual care treatment with ataluren outside of ataluren clinical trials. For the analysis of registry data, "non-ambulatory" has been defined as "full-time wheelchair requirement".[91]

Similarly, in the CINRG study loss of ambulation is defined as continuous wheelchair use, verified by inability to walk 10 metres unassisted.[14,92,93]

6.1.3.2 Pulmonary Function

Delaying the loss of pulmonary function can prolong the time DMD patients are independent as well as extend their lives.[21,72]

FVC is the best global assessment of pulmonary muscles because it requires a full inspiration (function of inspiratory muscles) and full expiration (function of expiratory muscles).[64] Serial measurements of FVC provide a simple, reliable and clinically useful measure of assessing disease progression in DMD and are used especially during the non-ambulatory stage where pulmonary function declines more rapidly.[21]

Patients with DMD then require increasing levels of pulmonary intervention starting at night-time, and ultimately need continuous assisted ventilation. Disease milestones indicative of increasing deterioration in pulmonary function and disease progression are percentage predicted FVC of <60%, <50% and <30%, and absolute FVC of <1 litre.[20,21,60,72,94] Predicted FVC of <60% is indicative of the first need for intervention using lung volume recruitment, when patients require mechanical ventilation (through a manual ventilation bag or an insufflation–exsufflation device) to preserve lung function.[72] Predicted FVC of <50% is indicative of the need for assisted coughing techniques and nocturnal-assisted ventilation; non-invasive ventilation is strongly recommended.[72] Once patients with DMD have declined to a predicted FVC of <30% they are considered to have severe pulmonary insufficiency, for which non-invasive ventilation is necessary.[60,94] Absolute FVC decline to <1 litre is a threshold that is strongly predictive of mortality within 3 years and is associated with a four-fold increased risk of death.[20,21]

Given the clear association between pulmonary function and disease progression, including mortality, FVC is an important assessment, especially for patients in the non-ambulatory stage of the disease.

6.1.3.3 Challenges in DMD clinical trial design

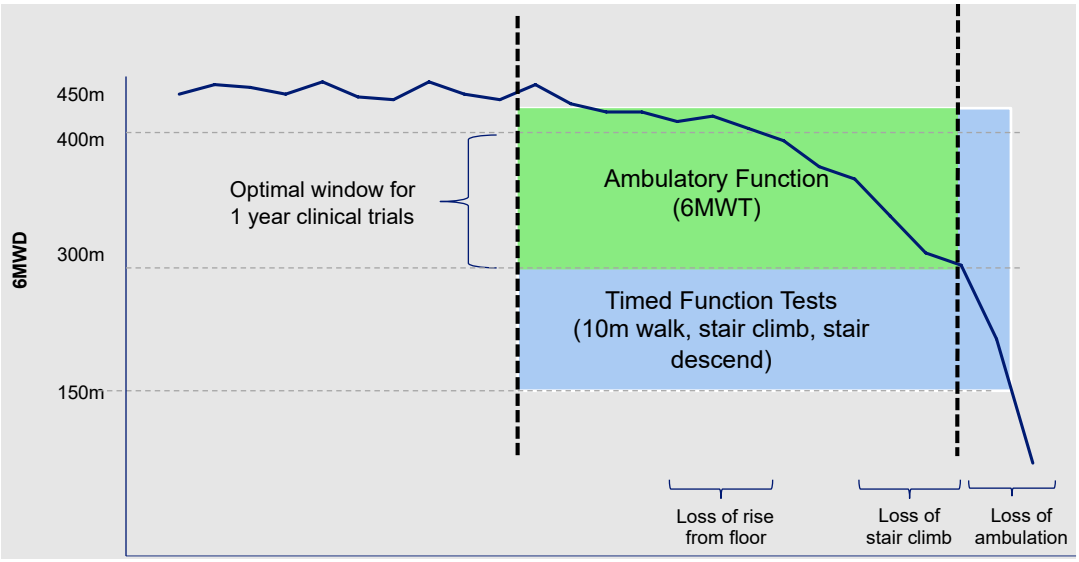
The assessment of treatment effects in DMD clinical trials is intrinsically associated with significant challenges due to the rarity of the disorder, the heterogeneity of the patient population and the variable nature of the decline in endpoints such as 6MWD, TFTs and FVC over a relatively short follow period, i.e. 48 weeks.[95,96] Ambulatory functional decline in DMD occurs progressively over a decade,[80,97] meaning a treatment effect may not be captured over a trial period. Thus, long-term outcome data in the real-world setting are required to truly understand the clinical benefits of a therapy, such as loss of ambulation and decline in pulmonary function. However, given that the course of DMD is irreversible, randomising patients to placebo for years, while they deteriorate and permanently lose meaningful function, is not ethically tenable.[84,98] These challenges are highlighted by the fact that it has taken more than a decade to demonstrate the long-term benefit of corticosteroids in the symptomatic treatment of DMD.[97]

Assessment of outcomes in clinical trials can be challenging due to the rarity of the disorder, the heterogeneity of the patient population and the duration and variable nature of disease progression.[84]

Natural history data indicate that the optimal window for detecting a treatment effect, in clinical trials, is in patients with a 6MWD between 300 and 400 metres, where patients have a demonstrable decline in ambulation but still have sufficient lower-limb muscle mass to detect a drug effect over a 48-week study period (Figure B.2). Patients with baseline 6MWD >400 metres are relatively stable and the 6MWT is not sensitive enough to be able to detect a statistically significant treatment effect

over a 48-week time period in these patients.[32,33] Conversely, patients with a 6MWD <300 metres have severe muscle loss and are at high risk for precipitous declines in ambulation.[58]

Figure B.2. Progressive Loss of Function Highlights the Complexities Associated with Conducting Clinical Studies in DMD



6MWD, 6-minute walk distance; 6MWT, 6-minute walk test

Note: Illustration was created by PTC based on McDonald et al. 2013, McDonald et al. 2017, Pane et al. 2014 and Mazzone et al. 2010[33,58,99,100]

Experience to date has shown that studies of at least 1-year duration may be necessary to capture the treatment effect of an investigational therapy on measures of ability, for example 6MWD. However, maintaining randomisation groups in placebo-controlled studies for much longer than 12 or 18 months, during which they deteriorate and permanently lose meaningful function, is not ethically tenable and would be rightly resisted by patients, parents, investigators, and review boards. Due to the gradual nature of the decline in pulmonary function over time, FVC requires long-term follow-up to adequately assess a treatment effect, precluding its assessment in a randomised placebo-controlled study in ambulatory DMD patients.

Data collection in a post-approval setting (e.g., registry) and evaluation of the safety and efficacy by comparing the collected data with external historic control groups is often required to determine long-term outcomes of treatment.[84,98] As discussed in section 9.4.1.1, an accepted and frequently employed statistical tool for comparing two cohorts is propensity score matching. Propensity score matching requires a sufficiently large pool of DMD patients and availability of established markers of disease severity. Age at first symptom, age at first corticosteroid use, duration of corticosteroid use and, duration of deflazacort use represent key factors that are known to alter the course of the disease (more details are presented in 9.4.1.1). Exclusion of any of these covariates means that patients may not be matched on severity and thus progression of disease.

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

Currently in England there are [redacted] patients being treated with ataluren under the MAA, rising from [redacted] in the first year following introduction. In 2017, [redacted] patients started ataluren treatment, and thereafter [redacted] patients started ataluren treatment each year. In total [redacted] patients have discontinued ataluren treatment under the MAA. [redacted].

Based on the budget impact analysis (see section 13.1), an estimated [redacted] patients will be treated with ataluren on average, over the five years (Table B-1). These figures are based on [redacted] prevalent patients in Year 1 (number of patients in MAA, as at December 2021), and an estimated 6 incident patients per year. The estimated number of incidence patients aligns to the number of incident patients observed in the MAA since 2019.

These estimated number of patients are also based on an annual mortality rate and rate of treatment stopping (i.e., patients reaching predicted FVC <50%) of [redacted] and [redacted], as indicated by median age at survival and median age at predicted FVC <50% in the cost-effectiveness model.

Table B-1. Number of patients receiving ataluren each year

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	6	6	6	6	6	6
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule (predicted FVC <50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Despite advances in the management of DMD in the past years, patients' clinical outcomes remain poor during their short lifetime. In the last 15 years, survival rates in patients with DMD have improved due to a more comprehensive therapeutic approach that includes pulmonary and cardiac management. Despite this, most patients with DMD die from heart or lung failure in adolescence or early adulthood, and patients rarely survive beyond their third decade.[4]

In a UK study that included 100 patients with DMD, median age of death was 30 years old for those who had had spinal surgery and received ventilator support, compared to 17.1 years for those who did not have spinal surgery or receive ventilatory support.[76]

Three European long-term retrospective cohort studies have traced patients over a minimum of 30 years. All three studies (one each from Italy, France, and Germany) reported median survival between 24 and 26 years.[74] In an Italian case review of 835 DMD patients, the overall mean age for cardiac deaths was 19.6 years. The overall mean age for pulmonary deaths was 17.7 years in patients without ventilator support, which increased to 27.9 years in patients benefitting from mechanical ventilation.[4] Similarly, in a study of 119 DMD patients in France, the mean age of death

was 21.8 years for patients without ventilatory support and 28.3 years for ventilated patients.[19] In a study of 67 DMD patients born in Germany between 1970 and 1980, median survival was 24.0 years (95 % CI 21.3–26.7 years). Again, ventilation significantly prolonged survival: median survival of non-ventilated patients was 19.0 years (95% CI 17.7–20.3 years) compared to 27.0 years for those who were ventilated (95% CI 20.2-33.8 years).[77]

Age at loss of ambulation is associated with time to pulmonary failure and age at death in patients with DMD.[60,77,101] Hence any delay in LoA would be expected to translate into a delay in reduced pulmonary function.

7 Impact of the disease on quality of life

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

7.1.1 Patient quality of life

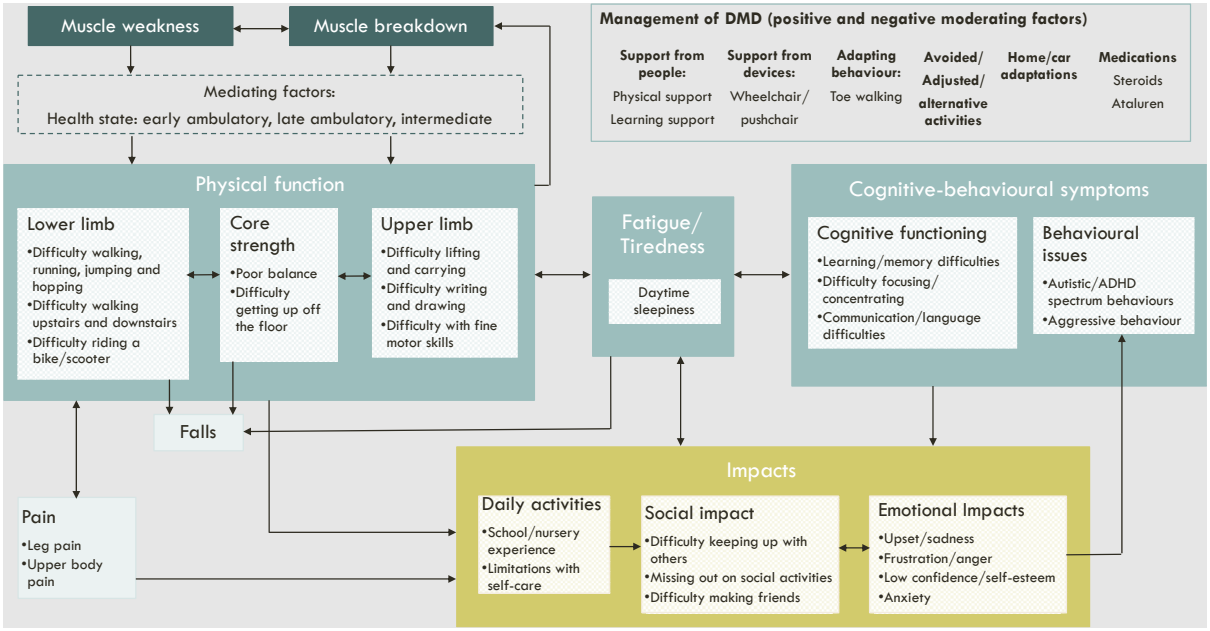
From a young age, children with DMD have a reduced capacity to engage in physical activity. Children with DMD cannot keep up with their peers, have problems walking, hopping, running, and climbing stairs, and fall frequently. Children with DMD rarely have the chance to fully engage in physical activities normal for their age: running around and playing games with friends, playing football, or riding a bike. As disease progresses, they experience increased difficulty in walking, and are eventually only able to walk indoors with occasional wheelchair use, after which time they progress quickly to permanent wheelchair use, and completely lose the ability to walk.[59,102,103]

Children with DMD consistently report significantly lower HRQL than their healthy peers,[16,103,104] as do adults with DMD.[26] Quality of life deteriorates as the disease progresses and physical capacity decreases. Patient (or parent)-reported measures of HRQL, such as the Paediatric Quality of Life Inventory™ (PedsQL™) and PODCI, correlate with clinician-measured outcomes of ambulatory function (the 6MWT and 10-metre run/walk velocity, (see section 7.1.3),[16] demonstrating that HRQL declines with walking ability. The HRQL of adults with DMD was assessed in a cross-sectional study of eight European countries (Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK).[26] The average EQ-5D index score for adults with DMD was 0.24, much lower HRQL than that of the general population (0.77 to 0.99 for those under 45 years of age).[105]

Chronic pain is a common and frequent problem in individuals with DMD and is associated with their physical limitations and aspects of the disease such as vertebral fractures and scoliosis.[106] In a study that included 43 boys with DMD, pain was reported to occur at least once a week, with a mild-moderate range of intensity. Pain occurred most commonly in the lower back, spine, legs, and pelvic region, and was typically described as aching pain.[107] In a study of adults with DMD (n=79), 73.4% experienced pain, most commonly in the legs; 65% had had pain for longer than 3 months; and 25% used pain medication, mostly nonsteroidal anti-inflammatory drugs.[108]

Qualitative research conducted in the UK with caregivers of individuals with nmDMD treated with ataluren has been carried out to understand the symptoms of nmDMD and its impact on HRQL.[22] Ten interviews were conducted with the parents of individuals aged 4 to 19 years. The study highlights the key symptoms of muscle weakness, pain, fatigue and cognitive-behavioural symptoms, and the impact on daily activities (e.g., limitations with self-care), social activities (e.g., difficulty keeping up with others) and emotional wellbeing (e.g., frustration). These concepts and relationships were illustrated in a conceptual model Figure B.3. Increasing severity of DMD was related to decreasing physical function and independency, such as the ability to walk, run/jump, climb stairs and get up off the floor, and increasing fatigue. This impacted the individuals' ability to take part in daily and social activities, and their emotional wellbeing. This declining physical function was reflected in an increased level of care and emotional burden reported by caregivers.[109]

Figure B.3. Conceptual Model of the Impact of nmDMD

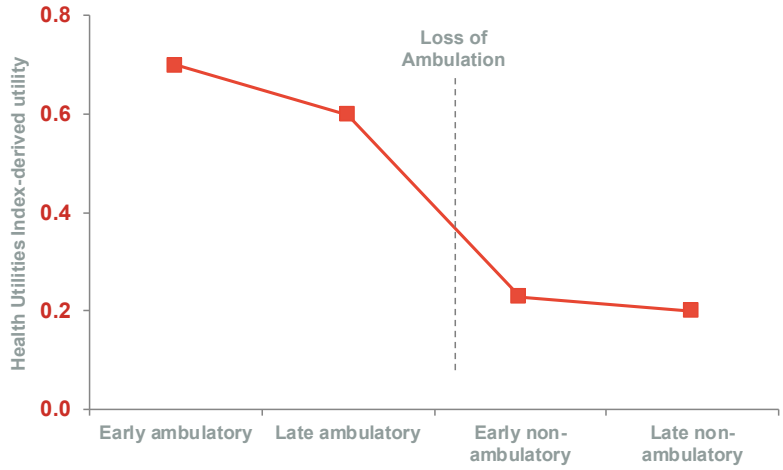


Source: Illustration was created based on Williams et al. 2021[22]

Losing the ability to walk and becoming permanently dependent on the use of a wheelchair is a key milestone in the lives of children, with the most prominent loss of HRQL following loss of ambulation.[23] Losing the ability to walk has an obvious impact on mobility. The inability to carry out daily tasks such as washing, dressing and being able to easily get to a toilet may lead to social isolation.[10,24] In a large study by Landfeldt et al.[24] the health utilities index (HUI)-derived utility decreased through the four stages (early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory) (Figure B.4). In non-ambulatory adolescents and young adults, there is gradual loss of upper limb, trunk and neck functions, so that grooming, toileting, bathing, dressing, sitting unsupported, and eating become impaired or impossible to perform by oneself — severely affecting the quality of life of patients, their caregivers and families.[10]

Due to assisted ventilation, adults with DMD typically live into their late twenties. By that time, they have hardly any muscle function left, except for the facial muscles, which are relatively spared until a late stage of the disease. Muscles needed for chewing and swallowing are also affected, leading to problems with nutrition.

Figure B.4. Patient-Assessed Quality of Life Score (utility) by Ambulatory Status



Note: Health Utilities Index–derived utility: 0 indicating death, 1 perfect health
Source: Illustration was created based on Landfeldt et al. 2014[24]

Moreover, children with DMD suffer from a progressive decline in pulmonary function leading to breathing difficulties and ultimately the need for ventilation, further impacting on their quality of life.[10,24] The last few years of their lives are spent non-ambulatory, requiring ventilation support and fully dependent on caregivers.[10]

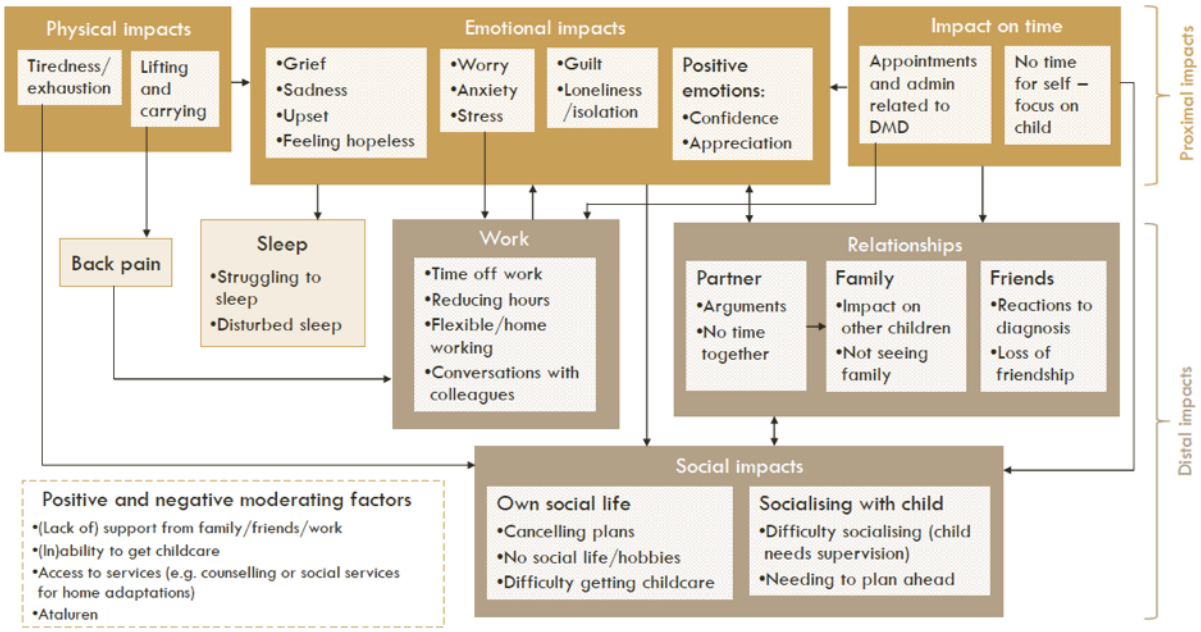
Children with DMD frequently report emotional problems. In one study, anger was the most frequently reported emotional problem reported by boys with DMD (19%) and their parents (15%). Teenage boys also reported frequently worrying about what is going to happen to them, as well as worrying about their family and about being treated differently from their peers.[104] 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%).[104]

In addition to the motor function disabilities and the incident rate of neuropsychiatric disorders, including attention-deficit hyperactivity disorder, autism, and obsessive–compulsive disorder is higher in DMD patients than in the general population.[110] A study with non-ambulatory adult DMD patients has shown that about 20% of adult DMD patients experience depression and about 25% experience anxiety as comorbidities significantly decrease HRQL and that DMD patients recorded a lower mean health utility score than patients with Down syndrome, deafness, and autism.[108,111]

7.1.2 Caregiver burden

The burden of care for parents of children with DMD is substantial; as DMD is a long-term degenerative disease it entails heavy involvement of families in patients' care and caregiving can become very demanding.[25,26] In addition to having to provide physical help with dressing, feeding and lifting, some families struggle with the behavioural issues often seen in DMD patients. It is not unusual for parents of DMD children and adolescents to have to wake up six to ten times per night to adjust their sons' position in bed and help with ventilation and/or coughing.[10] Concerning the provision of informal care, the mean number of hours of informal care per week is estimated at between 44 and 63 hours in the UK.[27] In a qualitative UK survey, direct impacts on caregivers were physical (e.g., lifting their child), emotional (e.g., anxiety/worry/stress) and time-related (e.g., administrative tasks). These were associated with an impact on work (e.g., time off work due to back pain), relationships (e.g., with partner) and social life (Figure B.5).[45]

Figure B.5. Conceptual Model of the Impact of nmDMD



Source: Illustration based on Williams et al. 2021[45]

Providing informal care to a patient with DMD has been found to be associated with impaired health and HRQL, poor sleep quality, reduced family function, increased risk of depression, anxiety, elevated levels of stress, sexual dysfunction, and considerable impact on work life and productivity.[27]

In the qualitative UK survey, most caregivers described a substantial emotional impact of caring for an individual with nmDMD. This included grief and sadness at the individual's condition, feeling hopeless, worry, anxiety, stress and loneliness. Some described how some of these emotional impacts had been particularly profound when the individual's abilities declined.[109]

"*It impacted us all as a family because we were very involved with it all. When [he] goes through a hard time emotionally, then that just has a knock-on effect for me and I think we both found 2018 to 2019-ish quite a hard year emotionally with some of his decline in his abilities*."

An increase in caregiver burden and decrease in caregivers' quality of life (QoL) are positively correlated with increasing DMD patient age,[112] and parents experience the greatest emotional impact of their child's DMD around the time of loss of ambulation.[113] Anxiety and depression are common in caregivers and are associated with the perceived health and mental state of the patient.[114] The subjective burden reported by parents has also been shown to be associated with support received, tracheotomy, active coping by the patient and anxiety in patients and parents.[25]

In the UK, 98% (N=188) of caregivers are a parent and 49% (N=93) of caregivers reduced their working hours or stopped working completely because of their child's or relative's DMD.[24] Similarly, another study estimated that in the UK over 50% of caregivers ('the majority of mothers') stopped working completely to care for a patient with DMD.[27] In a German study, more than half of parents themselves developed medical problems due to the burden of their son's disease, leading to further consumption of medical treatment due to parents' physical or mental problems. Overall, physical and mental problems of parents and caregivers increased with the severity of their son's impairment.[23]

Specifically, concerning estimates of the overall caregiver burden, the mean Zarit Burden Interview (ZBI) score (ranging from 0 [low burden] to 88 [high burden]) has been estimated at 28 in a sample

comprising caregivers from Europe; and 29 in a sample from Germany, Italy, the UK, and the USA.[26,27,112,115] Concerning overall HRQL in caregivers to patients with DMD, the mean EQ-5D-3L utility has been estimated at 0.71 in a sample comprising caregivers from Europe and 0.81 in a sample from Germany, Italy, the UK, and the USA.[25-27,115]

7.1.3 Measuring HRQL in clinical studies

Patient HRQL

Paediatric Quality of Life Inventory™ (PedsQL™)

The PedsQL scale is a widely used generic quality of life instrument in healthy children and those with acute and chronic health conditions covering an age range of 2 to 18 years. The PedsQL questionnaire consists of 23 questions, covering four domains of quality of life: physical, emotional, social and school functioning. The questionnaire is available in child-report (5 to 7, 8 to 12, and 13 to 18 years) and parent proxy-report (2 to 4, 5 to 7, 8 to 12, and 13 to 18) formats.[104,111,116]

The PedsQL components are only weakly correlated with clinical outcome measures that have been validated in DMD, such as the 6MWT and the 10-metre run/walk.[16,117] For these reasons, the PedsQL is less likely to be used by the DMD community in clinical trials.

Paediatric Outcomes Data Collection Instruction (PODCI)

The PODCI is a quality of life instrument, that has several domains measuring functional ability. Each domain is scored from 0 to 100, with 100 representing the highest level of functioning and as little pain as possible. The PODCI domain scores 'transfers/basic mobility' and 'sport/physical functioning' are significantly related to progression of the disease in patients with DMD. The domain 'transfers/basic mobility' assesses the difficulties encountered by the patient in performing routine motor activities in daily life. The domain 'sport/physical functioning' assesses the difficulties encountered in participating in more active recreational activities.[118]

PODCI scores correlate strongly with the 6MWT and the 10-metre run/walk test, and changes in PODCI scores after one year are more strongly correlated with changes in the 6MWT after one year than PedsQL scores.[16] For these reasons, the DMD community has now accepted the PODCI for use in current clinical trials and the PedsQL is no longer being used.

CHU9D

The CHU9D is a paediatric generic preference-based measure of HRQL suitable for 7- to 17-year-olds. It consists of a short questionnaire and a set of preference weights using general population values. The questionnaire has 9 questions with 5 response levels per question and is self-completed by the child (or proxy completed for younger children).[119]

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

Treatment with ataluren allows boys to maintain their ability to walk and carry out everyday tasks such as climbing and descending stairs, thereby improving their independence and their ability to participate in normal activities, attend mainstream school, keep up with their peers, play with friends and keep active. Delaying ambulatory decline provides the direct clinical benefit of affording boys with nmDMD a longer period of self-sufficiency. By slowing ambulatory decline and delaying the point at which more rapid decline occurs, ataluren also delays complete loss of ambulation and wheelchair reliance. As well as allowing greater mobility and independence, this is of further significance since the age at loss of ambulation predicts the age at which subsequent loss of upper limb function occurs.[16] Ataluren also delays pulmonary function decline, and therefore delays the need for ventilation assistance which can have a significant impact on quality of life.

In a degenerative disease with progressive loss of functions, eventually leading to death, stopping or slowing the progression of the disease is considered meaningful to patients as this would preserve their abilities and delay the next loss of function. Treating children early when they have the greatest amount of muscle to preserve is likely to delay muscle wasting and preserve function for longer. The following quote illustrates the urgency felt by parents for an effective treatment:[120]

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

In a study assessing expectations and experiences of investigators and parents involved in the ataluren Phase 2b trial (Study 007), all parents reported some degree of direct benefit for their boys (who were in the ataluren treatment arm), ranging from obvious improvements to subtle changes. These benefits included improved strength, endurance, and cognitive performance. A few parents described being unsure about whether there was benefit until they noted declines following the sudden end of access to the drug:[120]

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

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

The impact of ataluren has more recently been assessed in the UK survey by Williams et al.[22] In addition to improvements in mobility, caregivers reported that their son's energy levels and concentration had improved since they started taking ataluren. Improvements in social interactions and emotional wellbeing were also reported by some caregivers (results are discussed further in section 9.6.1.8). Therefore, ataluren is expected to have a wider impact than just slowing disease

progression and delaying physical deterioration and may help boys to enjoy their childhood with friends and achieve more at school. By delaying the milestones of disease progression that limit boys' independence they may also go onto have more productive and fulfilling working lives.

Furthermore, use of ataluren is expected to enable carers of boys with nmDMD to continue to work for longer before having to reduce their working hours or give up work entirely to look after their child. Changes to caregiver impacts following ataluren treatment have been described in the survey by Williams et al.[45] Positive changes included less anxiety and stress. One caregiver said that they were now able to go to work without worrying about their son and were better able to focus on their own tasks:

"I go to work now, and I don't worry about what's happening at nursery, is he going to fall over? Am I going to get a phone call from the ambulance saying he's in hospital? I'll go to work and it will be, "Oh how's [son] today at nursery? Has he done this, has he done that?" I'm not worrying, I'm able to focus more on my day to day. So I don't feel like I'm worrying about him, because I know how well he's doing"

Similarly, another participant reported that they were able to have more of a social life now because their son could now be left alone for several hours.

"I'm able to have more of a social life, I can do more things. He can be left alone for you know hours and hours, I can go out for instance from say 9am until 5pm and [son] will cope perfectly fine at home without me or anyone here, so that's a big change. So, yeah, I can do a lot more, going to work full-time and just doing more or less normal day to day stuff that most other people would do now."

Two caregivers described an overall positive impact of ataluren on their quality of life because they could see their son improve.

"I think the worry is going to be there no matter what, it's always going to be there because it's a progressive disease. But even though it's a progressive disease, with [ataluren] it's like having a new lease of life, it's like he's been given an extra chance, he's been given a few more years of walking, maybe longer. I'm aware of children on [ataluren] who are 11 or 12 and still walking and showing no signs of getting ready for a wheelchair yet. So I believe with his determination, and the way he carries on, that he'll be one of these children that are still walking about. That's what gets me through each day now, just watching him become this stronger, more determined than he was before, young boy"

8 Extent and nature of current treatment options

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

In 2016 NICE published guidance recommending the use of ataluren for treating nmDMD (see section 8.2). No other treatments have since been approved by NICE for the treatment of DMD.

In 2018, the DMD Care Considerations Working Group published updated care considerations on the diagnosis and management of DMD. These care considerations, published in three parts, provide comprehensive guidelines on the following topics:

- Part 1: diagnosis, neuromuscular management (including physiotherapy and corticosteroids and a description of emerging treatments including ataluren), rehabilitation management, endocrine management, and gastrointestinal management (including nutrition and dysphagia)[29]
- Part 2: respiratory, cardiac, bone health, and orthopaedic management[72]
- Part 3: of primary care, emergency management, psychosocial care, and transitions of care across the lifespan[121]

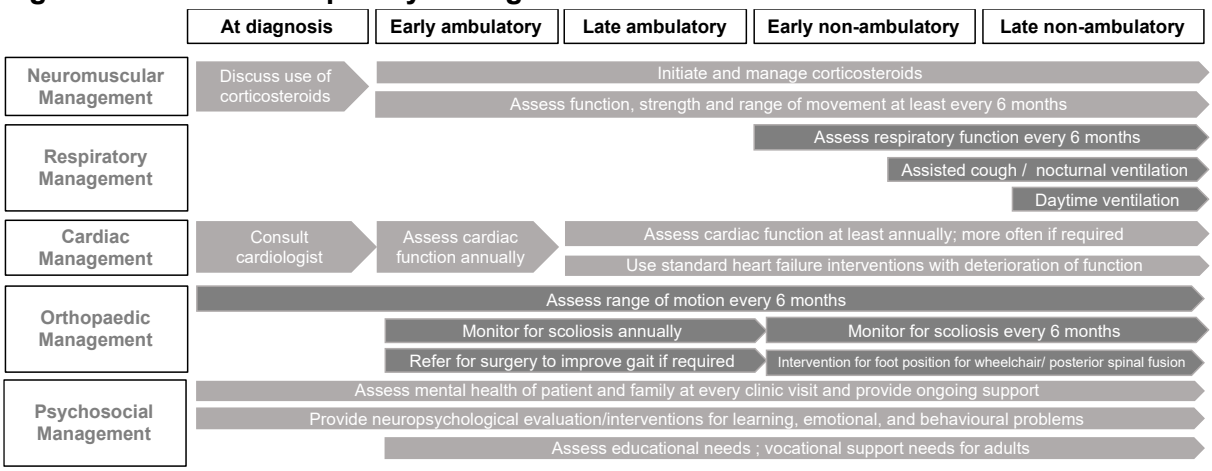
8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Achieving a timely and accurate diagnosis of DMD is a crucial aspect of care. After the suggestive signs and symptoms of DMD are noticed, the patient is referred to a neuromuscular specialist, and the diagnosis is confirmed through testing for serum creatinine kinase (CK) and DNA mutation analysis.[29]

Neuromuscular specialists coordinate their care within a multidisciplinary care setting. Advances in this type of multidisciplinary care have been shown to improve the natural history and survival of DMD. The goal of any therapy is to slow or stabilise DMD progression and prolong patients' ability to manage activities of daily living.[29]

Figure B.6 provides a summary of aspects of multidisciplinary care for patients with DMD. Other aspects of care described in the DMD care considerations published in 2018[29] include rehabilitation management, endocrine, gastrointestinal and nutritional management, and management of bone health.

Figure B.6: Interdisciplinary Management of DMD



DMD, Duchenne muscular dystrophy

Source: Adapted from Birnkrant et al. 2018[29]

As noted in the 2018 DMD Care Considerations, corticosteroids are a standard of care for all patients with DMD.[72] Corticosteroids temporarily slow the decline in muscle strength and function, and their use in patients with DMD as part of improved standards of care has changed the rate of progression

of disease manifestations.[56,122-125] The benefits of steroids include LoA at a later age, preserved upper limb function and pulmonary function, and avoidance of scoliosis surgery.[29]

Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. Following the NICE recommendation in July 2016, ataluren has been available in England under the MAA for the treatment of nmDMD in people aged 5 years and older who can walk.[2] In line with the licence extension in July 2018, the scope of the MAA was expanded to include patients aged between 2 to 5 years with nmDMD (with effect from April 2019).[126] .

Ataluren is added to existing standard treatment, including use of corticosteroids.

The following start and stop criteria, as part of the MAA, are applied for patients receiving ataluren treatment:[2,127]

Start Criteria

- Patients must have a confirmed diagnosis of nonsense mutation DMD (nmDMD), which is the identified presence of an in-frame nonsense mutation in the dystrophin gene as determined by genetic testing (full sequencing).
- Patients must be aged 2 years and older and able to crawl, stand with support or walk.
- Patients should only start once a full set of standard baseline criteria has been obtained and once they have signed the Managed Access Patient Agreement.

Stop Criteria

- The patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14-month period).
- If a patient has lost all ambulation (i.e., can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment.
- In such cases as defined above, patients should stop treatment no later than 6 months after becoming fully non-ambulant.
- Patients who are taken off treatment will continue to be monitored and supported with normal best standard of care. These patients will continue to be assessed to allow gathering of important information regarding natural history of non-ambulatory patients.

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

In DMD loss of muscle mass is most likely irreversible, and therefore disease-modifying treatments are needed to stabilise or slow disease progression as early as possible. Prior to ataluren, there were no approved drug therapies, and otherwise very limited supportive care options for patients with nmDMD.

It is well established that corticosteroids can stabilise muscle strength in DMD patients for a period of time. However, they do not address the underlying cause of the disease. Despite treatment with

steroids children with DMD still lose muscle function, resulting in loss of walking ability and permanent wheelchair dependency at 12 to 13 years of age.[14,15]

It is not established which corticosteroid is most effective and at what dose they are most effective.[29] In addition, the benefits of corticosteroids must be balanced against a side effect profile that presents significant challenges, including excessive weight gain, increased risk of bone fracture, behavioural abnormalities, hypertension, Cushingoid appearance, and excessive hair growth. Due to the side effect profile, not all children are able to tolerate steroids.[97]

Even with multidisciplinary care and with ventilation and cardiac support, patients with DMD have an expected survival of less than 30 years of age.[19,76,77] The last few years of their lives are spent non-ambulatory, requiring ventilation support and fully dependent on caregivers.[10]

Hence, alternative treatment options are needed for DMD that go beyond supportive and symptom management and address the underlying lack of dystrophin protein.

Ataluren targets the underlying cause of nmDMD and is the first and only drug to demonstrate efficacy and be approved by the EMA or MHRA for the treatment of nmDMD, in ambulatory patients aged 2 years and older.

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

Not applicable.

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

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

Since ataluren received regulatory conditional approval by the EMA in 2014, no other treatments for DMD have been approved in the European Union or UK, highlighting the challenges of developing an effective treatment and conducting clinical trials in this condition.

There have been a limited number of large, clinical trials or prospective studies in DMD, and, through the ataluren study programme, PTC Therapeutics are pioneering clinical trial research in this disease area. Despite the challenges of generating clinical evidence in areas of (ultra)-rare slowly progressing diseases, PTC has accumulated data on over 995 patients with nmDMD by conducting the largest clinical program in nmDMD to date[32,33,52] and developing the largest international nmDMD observational cohort for clinical effectiveness and safety (STRIDE Registry)[7,128]. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials.

In the Phase 2 and 3 clinical studies (007 and 020), ataluren reduced the decline in 6MWD over 48 weeks compared with placebo and consistently demonstrated benefit across multiple measures of muscle strength and function.[32,33] During the initial regulatory assessment in 2014, the EMA considered ataluren to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need and this resulted in the early approval of ataluren for the treatment of nmDMD ambulatory patients aged 5 years and older. Based on data from an additional study, in July 2018, an extension was granted to include ambulatory nmDMD patients aged 2 to less than 5 years old.[46]

The STRIDE Registry is the first drug registry for patients with DMD and is the largest real-world study of patients with nmDMD to date (within the evaluable population of STRIDE, n=269, 58 patients were from the UK). STRIDE provides data on patterns of ataluren use and long-term patient outcomes in real-world routine clinical practice. Ataluren treatment in STRIDE was associated with a delay in LoA by 5.4 years compared with propensity score-matched natural history controls, reducing the risk for LoA by 63% relative to BSC alone ($p<0.0001$).[35] Treatment with ataluren also delayed pulmonary function decline compared to BSC alone.[37]

In clinical trials of patients with nmDMD, the observed safety profile of ataluren was overall comparable to that of placebo. Adverse reactions were generally mild or moderate and only one of 232 patients in the two randomised studies discontinued ataluren treatment due to an adverse reaction.[1]

As such ataluren represented a step-change in management of nmDMD and has provided an effective treatment option for children in England with this life-threatening condition.

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

Not applicable as ataluren is already available. The introduction of ataluren did not result in any changes to the way services are delivered.

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

Ataluren is already available. Since all children presenting with suspected DMD in England undergo testing for dystrophin gene mutations, no additional tests are required to identify patients eligible for ataluren.

As part of the MAA, patients are currently required to attend their clinics at least 2 times within a 14-month period for monitoring and dose adjustment.[2]

During ataluren treatment total cholesterol, LDL, HDL, and triglycerides should be monitored on an annual basis, blood pressure should be checked every 6 months and serum creatinine, BUN, and cystatin C should be monitored every 6 to 12 months.[1] In current practice, blood pressure monitoring and blood tests are carried out on an annual basis during routine visits, regardless of ataluren treatment. As such monitoring of ataluren does not increase the burden of care.

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

Not applicable as ataluren is already available.

Ataluren is an oral therapy and administration does not require any particular supervision. In addition, ataluren has no special storage requirements such as refrigerated storage.

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

While data are not available, it is possible that the availability of ataluren has reduced the need for orthopaedic interventions during childhood and adolescence and may delay the requirement for later cardiac and pulmonary interventions such as assisted ventilation.

C Impact of the new technology

9 Published and unpublished clinical evidence

9.1 Identification of studies

Published studies

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

A systematic literature review (SLR) was conducted to identify studies reporting clinical evidence for the efficacy, safety and effectiveness of ataluren with BSC in nmDMD (See appendices, section 17.1). The SLR included RCTs, non-randomised controlled studies and uncontrolled studies.

The original review searches were conducted on the 10 June 2019 in MEDLINE and Embase, and on 11 June 2019 in The Cochrane Library. For the update review, searches were conducted on the 10 September 2021, thus providing up-to-date evidence for the present submission.

Unpublished studies

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

The U.S. National Institutes of Health clinical trials registry and results database (ClinicalTrials.gov) was searched to identify study results that may not have been published.

PTC has provided all relevant unpublished data that supports the indication related to this submission.

9.2 Study selection

Published studies

9.2.1 Complete Table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C-1. Selection criteria used for published studies

	Inclusion	Exclusion
Population	People with nonsense mutation DMD	People without nonsense mutation DMD
Intervention	Ataluren (PTC-124)	Not ataluren
Comparators	No restriction; any comparator	
Outcomes	• All efficacy or effectiveness outcomes e.g., mortality, ambulation, loss of ambulation, time to wheelchair, number of falls, lung function, cardiac function, muscle function, muscle strength, mobility, quality of life, ability to undertake activities of daily living • All safety outcomes e.g., any grade of adverse events, discontinuation rate due to adverse events	Any outcomes other than efficacy, effectiveness or safety
Study design	• Only original papers of in-human studies	• Comment • Letter to editors • Editorial • Notes • Reviews • Animal studies
Geographical location	No restriction; any geographical location	
Language	No restriction; any language	
Publication date	No restriction; any study date	

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

It is recommended that the number of published studies included and excluded at each stage is reported using the PRISMA statement flow diagram (available from www.prisma-statement.org/statement.htm)

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams illustrated in Figure C.1 and Figure C.2, for the original and update reviews respectively, presents how clinical references were reviewed and extracted.

In the original review, of the 293 titles and abstracts screened 206 did not meet the criteria. Hence, full texts of the remaining 87 references were retrieved and reviewed based on the eligibility criteria. Including publications identified in the grey literature search, 59 references were about studies that met the eligibility criteria and were considered for extraction. The 59 references related to 10 individual studies.

In the update review, of the 82 titles and abstracts screened 51 did not meet the criteria. Hence, full texts of the remaining 31 references were retrieved and reviewed based on the eligibility criteria. Including publications identified in the grey literature search, 30 references were about studies that met the eligibility criteria and were considered for extraction. The 30 references related to 5 individual studies (3 of which had already been identified in the original review, giving 12 studies in total).

Figure C.1. PRISMA – original review

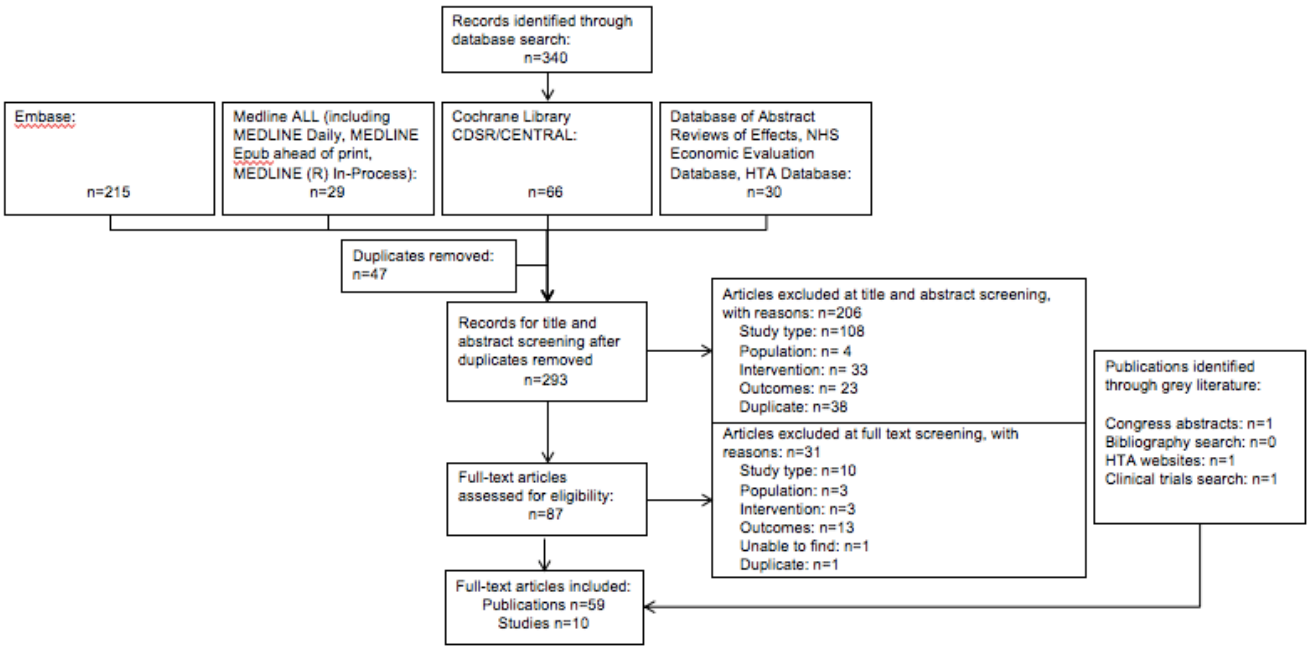
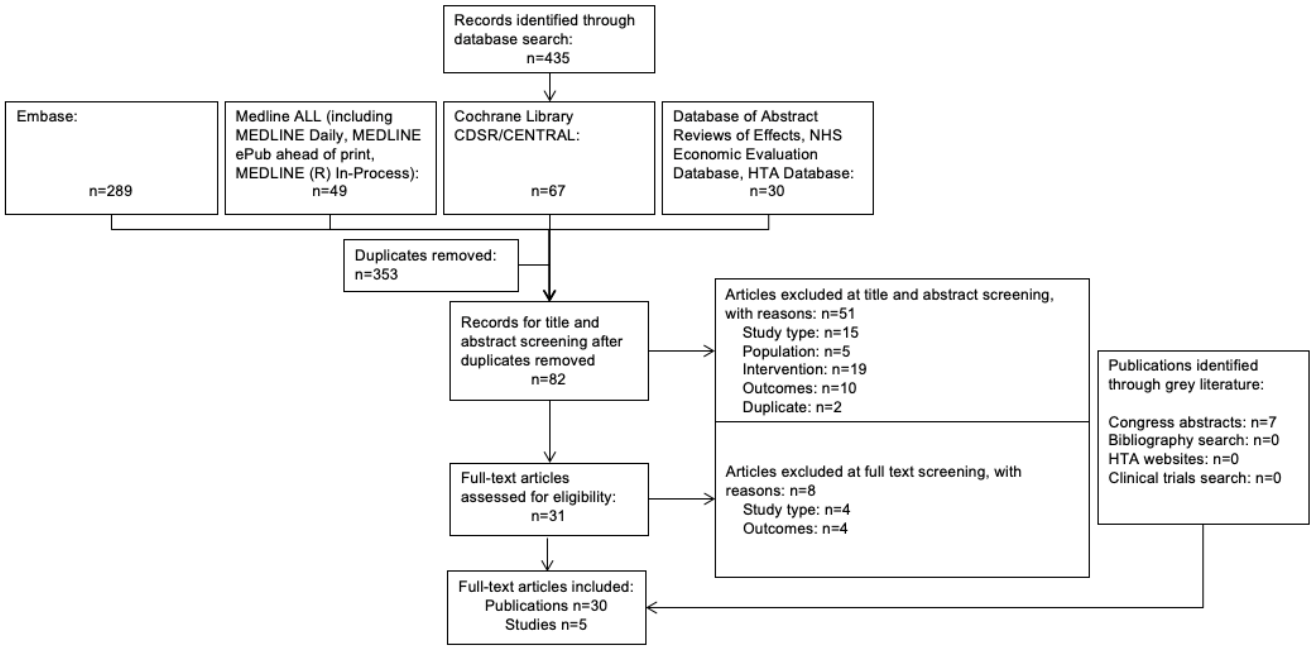


Figure C.2. PRISMA – update review



Unpublished studies

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

Inclusion and exclusion criteria were as per Table C-1.

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

See Figure C.1 and Figure C.2.

9.3 Complete list of relevant studies

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

The literature review identified a total of 12 studies. Seven of these relate to the ataluren clinical studies shown in Table C-2 and Table C-3. Five additional studies were identified (Table C-4). Three were case studies and one was a cohort study (N=55) that included 9 patients that had been treated with ataluren. The remaining study was a qualitative study by Williams et al.[22] that reported on the symptoms and impacts of nmDMD in ambulatory individuals prior to the initiation of ataluren (previously discussed in section 7.1). This study also explored their experience with ataluren.

Since completion of the SLR, one further study by Michael et al.[129] has been published on long-term experience of ataluren treatment in Sweden.

The final evidence relevant to this submission is the data collection and analysis carried out for the MAA.

Table C-2. List of relevant published studies

Study ID(s) /name **Start/end date** Key publication(s)	**Description**	**Results Presented**
Study 004 PTC124-GD-004-DMD NCT00264888 **Title**: A Phase 2 Study of PTC124 as an Oral Treatment for Nonsense Mutation-Mediated Duchenne Muscular Dystrophy **Start:** 12/2005 **End:** 05/2007 Finkel et al. 2013[52]	**Study type:** Phase 2a proof-of-concept, multicentre, open-label, sequential dose-ranging **Total sample size**: 38 **Population:** males, age 5 to 17 years, nmDMD **Intervention(s):** Ataluren 40 mg/kg/day (mid dose); TID (28 days) **Comparator(s):** Ataluren 16 mg/kg/day (low dose) and 80 mg/kg/day (high dose); TID (28 days) **Outcomes:** Primary: change in dystrophin expression on muscle biopsy by immunofluorescence Secondary: changes in serum CK level, muscle strength and function by myometry, safety and PK, Immunofluorescence evidence and western blot evidence of changes in muscle biopsy specimen, TFTs and study drug compliance	Original submission HST3
Study 007 PTC124-GD-007-DMD NCT00592553 **Title**: A Phase 2B Efficacy and Safety Study of PTC124 in Subjects with Nonsense Mutation-Mediated Duchenne and Becker Muscular Dystrophy **Start:** 02/2008 **End:** 12/2009 Bushby et al. 2014[32]	**Study type:** Phase 2b efficacy and safety, international, multicentre, randomised, double-blind, placebo-controlled, dose-ranging **Randomised N**: 174 **Population:** males, age 5 to 20 years, nmDMD, ambulatory **Intervention(s):** Ataluren 40 mg/kg/day or ataluren 80 mg/kg/day; TID **Comparator(s):** placebo; TID **Outcomes:** Primary: change in 6MWD baseline Week 48; Secondary: TFTs, at-home activity, myometry, accidental falls, PedsQL, treatment satisfaction, serum CK, digital span task, heart rate monitoring, muscle dystrophin expression patient daily diaries,	Original submission HST3 and **Company resubmission** Section 9.6.1.2 (Efficacy)
Study 020 (ACT-DMD) PTC124-GD-020-DMD NCT01826487 **Title**: A Phase 3 Efficacy and Safety Study of Ataluren in Patients with Nonsense Mutation Dystrophinopathy **Start:** 03/2013 **End:** 08/2015 McDonald et al. 2017[33]	**Study type:** Phase 3 efficacy and safety study, international, multicentre, randomised, double-blind, placebo-controlled **Randomised N**: 230 **Population:** males, age 7 to 14 years, nmDMD, ambulatory, on corticosteroids, baseline 6MWD ≥150 metres but ≤80% predicted **Intervention(s):** Ataluren 40 mg/kg/day; TID **Comparator(s)**: Placebo; TID **Outcomes:** Primary: change 6MWT Week 48; Secondary: time to 10% worsening 6MWD and TFTs Exploratory endpoints: NSAA, PODCI, ADL.	Original submission HST3 and **Company resubmission** Section 9.6.1.3 (Efficacy)

Study ID(s) /name **Start/end date** Key publication(s)	**Description**	**Results Presented**
Study 019 PTC124-GD-019-DMD NCT01557400 **Title**: An Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy McDonald et al. 2021[130]	**Study type:** Long-term open-label safety and efficacy for patients who participated in one or more prior PTC-sponsored studies of ataluren in nmDMD **Total sample size**: 94 **Population**: nmDMD **Intervention(s):** Ataluren 40 mg/kg/day; TID **Comparator(s)**: None **019 Outcomes:** long-term safety at 48 and 240 weeks	**Company resubmission** Section 9.6.1.4 (Efficacy) Section 9.7.2.3 (Safety)
Study 030 PTC124-GD-030-DMD NCT02819557 **Title**: A Phase 2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Ataluren (PTC124) in Patients Aged ≥2 to <5 Years Old with Nonsense Mutation Dystrophinopathy **Start:** 06/2016 **End:** 02/2018 Tian et al. 2018[131]	**Study type:** Phase 2, safety and pharmacokinetic study, multiple-dose, open-label, evaluation of safety, pharmacokinetics, and pharmacodynamics **Total sample size**: 14 **Population:** males ≥2 to <5 years, nmDMD **Intervention(s):** Ataluren 40 mg/kg/day; TID (4 weeks PK portion and 48 weeks extension) **Comparator(s)**: None **Outcomes:** Primary: safety; Secondary: PK at 4 weeks, TFTs, NSAA and growth parameters	**Company resubmission** Section 9.6.1.5 (Efficacy) Section 9.7.2.4 (Safety)
Study 025o (STRIDE Registry) PTC124-GD-025o-DMD NCT02369731 **Title**: Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care **Start:** 04/2015 **End:** 05/2025 Mercuri et al. 2020[7] Mercuri et al. 2021[34] Tulinius et al. 2021[37]	**Study type:** Ongoing observational registry **Study Design:** Multicentre, observational, cohort **Total sample size**: 360 (288 enrolled at data cut-off 31 January 2020) **Population**: nmDMD **Intervention(s):** Usual care, commercial ataluren or early access program 40 mg/kg/day; TID **Comparator(s)**: None **Outcomes:** Safety; Efficacy evaluations conducted as per usual care: 6MWD, TFTs, LoA, NSAA, pulmonary and cardiac assessments	**Company resubmission** Section 9.6.1.6 (Efficacy) Section 9.7.2.5 (Safety)

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ADL, activities of daily living; CK, creatinine kinase; LoA, loss of ambulation; nmDMD, nonsense mutation Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; PedsQL, Paediatric Quality of Life Inventory; PK, pharmacokinetic; PODCI, Paediatric Outcomes Data Collection Instrument

Table C-3. List of relevant unpublished studies

Study ID(s)	Description	Presented
Study 020e PTC124-GD-020e-DMD NCT02090959 **Title**: A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy **Study type:** Phase 3 efficacy and safety study extension, international multicentre, open-label extension of the 48-week double-blind Study 020 **Start:** 03/2014 **End:** 06/2018	**Total sample size**: 218[a] **Population**: nmDMD **Intervention(s):** Ataluren 40 mg/kg/day; TID for up to 144 weeks **Comparator(s)**: None **Outcomes:** Primary: safety (adverse events, laboratory abnormalities); Secondary: 6MWD, NSAA, TFTs, PUL, PODCI, ADL, QoL, age at LoA, pulmonary function, blood levels	**Company resubmission** Section 9.6.1.3 (Efficacy – limited results) Section 9.7.2.2 (Safety)
NHSE Managed Access Agreement (MAA) **Title:** Managed Access Agreement: Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD) **Study type:** Observational real-world study **Start:** 08/2016 **Finish:** 01/2023	**Total sample size**: 59 (matched analysis) **Population**: nmDMD, ambulatory aged 2 years and above **Intervention(s):** Ataluren 40 mg/kg/day **Comparator(s)**: None **Outcomes:** NSAA, patient quality of life (CHU9D), caregiver quality of life (EQ-5D)	**Company resubmission** Section 9.6.1.7 (Efficacy)

Table C-4. List of additional published studies (case studies, cohort and qualitative studies)

Study	Study citation
Ebrahimi, 2018[132]	Ebrahimi-Fakhari D, et al. Off-Label Use of Ataluren in Four Non-ambulatory Patients With Nonsense Mutation Duchenne Muscular Dystrophy: Effects on Cardiac and Pulmonary Function and Muscle Strength. Frontiers in Paediatrics. 2018;6:316
Ruggiero, 2018[133]	Ruggiero L, et al. One year follow-up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: is earlier better? Therapeutic Advances in Neurological Disorders. 2018:11
Bazancir, 2018[134]	Bazancir Z, et al. Ataluren and physiotherapy in a boy with nonsense mutation Duchenne muscular dystrophy: 2 years' follow-up case report. Acta Myologica. 2018;37(2):180
Blaschek 2020[135]	Blaschek A, et al. Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy? Neuropediatrics. 2020;51(5):342-348.
Williams 2021[22]	Williams K, et al. Symptoms and impacts of ambulatory nonsense mutation Duchenne muscular dystrophy: a qualitative study and the development of a patient-centred conceptual model. Journal of Patient-reported Outcomes. 2021;5(1):75.
Michael 2021[129]	Michael, S et al. Long-term treatment with ataluren-the Swedish experience. BMC Musculoskelet Disord. 2021 Sep 30;22(1):837

9.3.1.1 Ataluren clinical study overview

In addition to data gathered during the MAA, the key clinical evidence supporting this submission is a global registry following patients receiving ataluren plus BSC in clinical practice for at least 5 years (STRIDE) (January 2021 data cut). The study initially enrolled patients aged 5 years or older, expanding to 2 years and older with the Translarna (ataluren) licence extension in Europe granted in 2018. STRIDE represents the largest nmDMD data cohort for real-world outcomes analysis and enables the evaluation of ambulatory and non-ambulatory milestones in 269 nmDMD patients (evaluable population) aged 2 years and older.[34] As such, data from STRIDE in comparison to a natural history study, the CINRG DNHS provide key long-term efficacy data for the cost-effectiveness model.

The submission also presents data from the clinical trial programme in patients with nmDMD aged 5 years and above:

- PTC124-GD-007-DMD (Study 007), a Phase 2b, placebo-controlled study, the results of which were used to support the conditional approval of ataluren by the EMA in 2014 (N=174)[32]
- PTC124-GD-020-DMD (Study 020), a Phase 3, placebo-controlled study (N=230),[33] and its extension (Study 020e)
- A published meta-analysis of studies 007 and 020 (N=342)[41]
- PTC124-GD-019-DMD (Study 019), a long-term open-label safety and efficacy for patients with nmDMD who participated in one or more prior PTC-sponsored studies of ataluren (N=94)[130]

In addition, PTC124-GD-030-DMD (Study 030), a Phase 2, open-label safety and pharmacokinetic study in younger patients aged >2 to <5 years, which supported the indication extension in this population (N=14), is presented.[131]

9.3.1.2 Clinical trials

The safety and efficacy of ataluren with BSC has been demonstrated in two placebo-controlled randomised double-blinded studies; PTC124-GD-007-DMD (Study 007; phase 2b)[32], and PTC124-GD-020-DMD (study 020; phase 3),[33] which formed the main evidence base for the original NICE assessment in 2015/2016 (HST3). These pivotal studies were presented during the previous NICE assessment and are presented again in this submission in addition to data from the Study 020 extension (Study 020e).

Supportive data from a Phase 2a proof-of-concept study (PTC124-GD-004-DMD/ Study 004) were also presented in the previous NICE submission but are not reported again in this submission, as its focus is now on subsequent clinical evidence. Two Phase 2 trials, PTC124-GD-046-DMD (NCT03796637) and PTC124-GD-045-DMD (NCT03648827), were small single-arm studies evaluating the ability of ataluren to increase dystrophin protein levels in patients with nmDMD. These studies were not included as they do not provide outcome data relevant to this submission.

In Study 007 and Study 020 a substantial proportion of patients were not in the ambulatory transition phase. Consequently, a pre-specified meta-analysis of 020 and 007 (patients who met study 020 criteria) was conducted to increase the sample size, resulting in statistically significant treatment effects in the 6MWT.[33] Further meta-analyses that provide additional data with a more conservative

approach, including a larger and more heterogeneous population, also demonstrated improved 6MWT and TFT results that were statistically significant in all patient subgroups.[41]

The 240-week open-label extension Study 019 (Phase 3) was primarily conducted to assess long-term safety and tolerability of ataluren in nmDMD patients who had previously received ataluren during their participation in one or more prior PTC-sponsored studies. Study 019 provides additional evidence for the efficacy of ataluren, including its beneficial effects on pulmonary function in non-ambulatory patients.[43]

In light of the importance of early intervention in patients with DMD, before muscle degeneration and fibrosis occur, Study 030 (Phase 2) evaluated the safety, pharmacokinetics and efficacy of ataluren in patients with nmDMD aged 2 to less than 5 years [42]. Based on the positive results of this study that included improvements in physical functioning with ataluren, comparable drug exposure with older patients and an acceptable safety and tolerability profile, expansion of the label to include ambulatory children aged 2 to 5 years with nmDMD was recommended by the Committee for Medicinal Products for Human Use (CHMP) of the EMA on 31 May 2018 and endorsed by the European Commission on 23 July 2018.

9.3.1.3 Translarna patient registry (PTC124-GD-025o-DMD/ STRIDE)

Patients with nmDMD receiving ataluren have been enrolled into STRIDE, an ongoing, prospective, observational safety and effectiveness study. The study initially enrolled patients aged 5 years or older, expanding to 2 years and older with the licence extension in Europe in 2018. STRIDE is designed to collect information on the long-term safety and effectiveness of ataluren in the real-world setting as part of routine clinical practice. It represents the largest study of patients with nmDMD to date, enabling the evaluation of 360 patients for a period of over five times the length of previous DMD clinical trials. Patients are followed for at least 5 years from the date of enrolment or until withdrawal from the study or death, whichever comes first, thereby addressing the most significant challenges encountered when conducting clinical trials in nmDMD. As mentioned in Section 9.3.1.2, these challenges include small sample population, measurement of disease progression over the long-term, heterogeneity of the patient population and the variable nature of the decline in endpoints such as 6MWD and TFTs over the relatively short period of a clinical trial.

To eliminate bias and enable a more robust comparison between STRIDE and a natural history cohort (CINRG), propensity score matching was used to identify comparable subsets of patients according to established predictors of disease progression (see section 9.4.1.1).

STRIDE provides compelling evidence of the true benefit that ataluren offers to nmDMD patients including delayed LoA and slower pulmonary function decline, compared to propensity-matched controls receiving BSC alone.[7,34,37] Preliminary results from STRIDE in comparison to BSC alone from CINRG were published by Mercuri et al. in 2020.[7] Data cut-off date for inclusion in the published analyses was on 09 July 2018. As STRIDE is ongoing, and data are currently available up to January 2021, analysis of the most recent data set has been presented, in alignment with the data used in the health economic model.

9.3.1.4 Managed access agreement (MAA)

As a condition of the NICE recommendation in 2016, to receive ataluren, eligible patients must sign up to the MAA.[2] Under this agreement, data is collected from all patients when they start ataluren

treatment and at all subsequent clinic visits and entered into the North Star database. In 2019, the scope of the MAA was expanded to include nmDMD patients aged between 2 and 5 years, in line with the extension of the licensed indication.[127]

In July 2021, a contract variation was agreed, which extended the period of the MAA up to either publication of the updated NICE HST guidance or 20 January 2023, whichever occurs earliest.[44]

Patients receiving ataluren in the MAA have been compared to a matched control group receiving BSC alone in order to try and assess response to treatment over the period of the MAA. The matched control group were identified from patients included in the North Star registry.

9.3.1.5 State the rationale behind excluding any of the published studies listed in Tables C3 and C4.

The three case studies and one cohort study shown in Table C-4 (Ebrahimi, 2018[132] Ruggiero, 2018[133] Bazancir, 2018[134] Blaschek 2020[135]) are not included in the submission as they do not provide meaningful data that add to the evidence base for ataluren.

9.4 Summary of methodology of relevant studies

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

9.4.1.1 Comparison of data to natural history control using propensity score matching

An accepted and frequently employed statistical tool for comparing two cohorts is propensity score matching which attempts to estimate treatment effect by accounting for the independent variables that predict the receipt of treatment. The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17 supports the use of propensity score matching to replicate randomisation to identify comparable cohorts when comparing real-world evidence. [136] This analysis compensates for the lack of important design features in the historical control group. This statistical analysis allows the matching of the historical control group with the treatment group across important baseline and prognostic variables and thereby addresses the absence of randomisation.

The long-term benefit of ataluren beyond the duration afforded by the randomised placebo-controlled studies and the preservation of pulmonary function, were analysed in propensity score matched comparisons of ataluren-treated patients in Study 019 and STRIDE with the CINRG cohort.

The CINRG DNHS (referred to as CINRG) is the largest prospective multicentre natural history study to date in DMD, and enrolled 440 ambulatory and non-ambulatory DMD patients aged 2 to 28 years at over 20 clinical sites across Europe, the Americas, Asia and Australia (Table C-5).[7] Enrolment began in 2006 with patients followed for 10 years. Data collected includes demographics, genotyping, vital signs, healthcare resource use, strength, and function, as well as quality of life assessments. Patients were included in CINRG based on clearly defined inclusion/exclusion criteria and were subject to a follow-up protocol.[97,125,137]

Table C-5 CINRG DNHS overview

Study name	CINRG DNHS
Objectives	To collect the most comprehensive and largest, prospective, longitudinal natural history data to date on a cohort of DMD patients
Location	Patients were enrolled at 20 centres in nine countries.
Design	Natural history study
Sample size	N=440
Inclusion criteria	• Participants aged 2–4 years with a diagnosis of DMD confirmed by dystrophin immunofluorescence or immunoblot, or both; an out-of-frame deletion; or complete dystrophin gene sequencing in the proband or sibling. • Participants aged 5–29 years with DMD meeting the criteria in (1) or documented clinical symptoms referable to DMD and direct support of the diagnosis by either a positive DNA analysis, a muscle biopsy showing abnormal dystrophin, or a combination of an increased creatine kinase (more than five times the upper limit of normal) in addition to an X-linked pedigree.
Exclusion criteria	• Naive to glucocorticoid treatment and ambulated without assistance past their 13th birthday; or use of glucocorticoid therapy and ambulated without assistance past their 16th birthday. • Patients younger than 16 years were enrolled irrespective of future ambulatory status.
Recruitment	Between May 17, 2006, and July 13, 2009, 340 participants aged 2–28 years with documented DMD were recruited into the CINRG DNHS parent study. An additional 100 participants aged between 4 years and 8 years were recruited from Sept 26, 2012, to Feb 29, 2016.
Procedures	Participants had assessments at baseline and months 3, 6, 9, and 12 (ambulatory), or months 6 and 12 (non-ambulatory). Long-term follow-up visits were at months 18, 24, and annually thereafter. For non-ambulatory patients, age at loss of ambulation was defined precisely by the physician by history and chart review at the time of entry into the study. Historical and current use of glucocorticoid therapy was documented, including medication used, age at onset of use, total duration of use, dose, and dose modification history At each visit, TFTs including time to stand from supine, time to climb four stairs, time to run or walk 10 m, Brooke upper extremity functional rating scale, pulmonary function tests (including spirometry and maximal static airway pressures), and the PODCI HRQL assessment were obtained. Functional milestones were selected to represent sequentially lost abilities associated with disease progression based on prognostic value as described in the literature or milestones affecting published care considerations in DMD.

CINRG collects data from a non-controlled clinical setting comparable to a real-world setting and includes a sufficiently large pool of DMD patients to allow for a propensity score matching approach with ataluren studies that did not have a control arm (e.g., Study 019 and STRIDE).[125,137,138] CINRG serves as a useful comparator to STRIDE and Study 019 because it includes patients receiving BSC who are experiencing the natural course of DMD disease progression. Although the study periods for STRIDE and CINRG do not completely overlap, the populations of both studies represent heterogeneous populations from multiple countries who are representative of the general DMD population. Like CINRG, STRIDE includes patients with a wider range of ages and ambulatory ability than those in clinical trials, meaning that the data are representative of a broader range of real-world patient experiences in comparison with a short-duration randomised placebo-controlled clinical trial with narrowly defined inclusion criteria. In addition, like CINRG, STRIDE and Study 019 also

contribute important data on long-term outcomes such as pulmonary function that are difficult to assess in short-term studies.

A recent study has evaluated the suitability of real-world data (RWD) and natural history data (NHD) for use as external controls in drug evaluations for ambulatory DMD.[139] The analysis included five RWD/NHD sources (n=430 patients) and placebo arm data from six clinical trials in DMD (n=383). Changes in 6MWD were consistent between trial placebo arms and RWD/NHD cohorts subjected to equivalent inclusion/exclusion criteria. There was no evidence that changes in 6MWD were systematically milder in placebo arms compared to RWD/NHD. 6MWD outcomes were also consistent among the different RWD/NHD sources analysed. Based on these findings, the authors conclude that external controls can be suitable for drug evaluations in DMD.[139]

The natural history of DMD has changed over the last five decades, with the introduction of spinal surgery and ventilation between 1970 and 1990, and improvements in cardiac management and use of corticosteroids in the 1990's and early 2000's.[140,141] Patients are living longer, and important milestones such as loss of ambulation and self-feeding are occurring later in life. However, there have been no substantial changes in disease management and commercial availability of treatments that impact disease progression since 2006, other than the conditional approval of Translarna by the European Commission in 2014.[29,142,143]

However, in recognition of the effect of corticosteroid use on DMD milestones and the differences in usage patterns between the ataluren studies and the CINRG study, the propensity score matching model used in the comparison of the two studies included corticosteroid type and duration along with age at first corticosteroid use as covariates. Inclusion of these covariates, along with age at first DMD symptom (or age at diagnosis), effectively controls for any differences between STRIDE/Study 019 and CINRG in the standard of care variables that have been identified as prognostic for clinical outcomes in DMD.[7,16,144]

The following established predictors of disease progression were used in the propensity score matching between STRIDE and CINRG: duration of deflazacort use, duration of other steroid use, age at first symptom and age at initial steroid use.[7]

Age at first symptoms is prognostic for severity of disease: the earlier the age of symptom onset, the more severe and rapid the course of disease progression. A 1-year increase in the age at onset of first symptoms was associated with a 10% reduction in annual risk of LoA for a cohort of patients with either DMD or Becker muscular dystrophy.[54] Analysis of study 019 used the same covariates, however, because age at onset of first symptoms was not recorded in study 019, it was unavailable for use as a covariate. In this analysis, as an alternative assessment, age at diagnosis was used since those data were collected in Study 019. While these two outcomes are not the same, and age at first symptom is a more appropriate predictor of future disease progression, selection of age at diagnosis is a conservative proxy. This allows the matching of slightly older subjects from Study 019 using age of diagnosis data to patients in CINRG that have the earlier age at first symptom profile. The risk assumed in this approach accepts the probability of study 019 patients declining in functional capabilities sooner than those in the CINRG natural history cohort.

Age at first corticosteroid use, duration of corticosteroid use and duration of deflazacort use represent key factors that are known to alter the course of the disease.[97,124] Median age at loss of ambulation was approximately 3 years later in CINRG DNHS patients who were treated with corticosteroids for at least 1 year while they were ambulatory, compared with CINRG DNHS patients who were never treated or treated with corticosteroids for less than 1 year (13.0 vs 10.0 years; n=252

vs 88; patients enrolled between 2006 and 2009).[92] A more recent analysis of CINRG DNHS patients enrolled between 2006 and 2009 or between 2012 and 2016,[97] also showed that the median age at loss of ambulation was later in patients who were treated with corticosteroids for at least 1 year than in those who were never treated or treated with corticosteroids for less than 1 month (13.4 vs 10.0 years; n=329 vs 73). Median age at loss of ambulation was also approximately 3 years later in CINRG DNHS patients who received daily deflazacort than in those who received daily prednisone.[92,97]

A recent review of the literature confirms that age at diagnosis, age at onset of symptoms and glucocorticoid exposure are core prognostic indicators for loss of ambulation.[144] Other indicators included DMD genetic modifiers, DMD mutation type, height, and weight, cardiac medication and orthoses. The STRIDE and CINRG DNHS populations were not matched according to genetic modifiers, mutation type or location. However, most genetic subtypes of DMD present with a similar course and timescale of disease progression. While there is some evidence that certain mutation types may have a milder phenotype, patients with nonsense mutations have a disease progression trajectory similar to other DMD subtypes.[14] The inclusion of patients in CINRG with any DMD genotype rather than only patients with nmDMD should not be considered a source of bias because patients were matched based on several factors that are predictors of disease progression.

Whilst cardiac medication, orthoses, spinal surgery and ventilation support affect the prognosis of patients with DMD, the use of these interventions is now part of standard of care as outlined in international guidelines,[29] and centres included in both the STRIDE/019 and CINRG databases are expected to provide similar levels of care in this respect.

Propensity score matching can only adjust for measured covariates, and thus it cannot be guaranteed that all confounding factors have been removed.[145] However, every effort has been made to ensure key prognostic factors were included in the propensity score matching of the STRIDE/019 and CINRG DNHS datasets, providing populations that were comparable in terms of expected long-term outcomes.

The following outcomes have been assessed in patients receiving ataluren in STRIDE/019 compared to the propensity score matched CINRG population receiving BSC alone:[7,34,37]

- ambulatory outcomes (including the age at loss of ambulation (defined as “full-time wheelchair requirement”) age at time to climb four stairs ≥10 seconds and age at time to stand from supine ≥10)
- pulmonary function outcomes (age at predicted FVC <60%; age at predicted FVC <50%; age at predicted FVC <30% and age at FVC <1 litre).

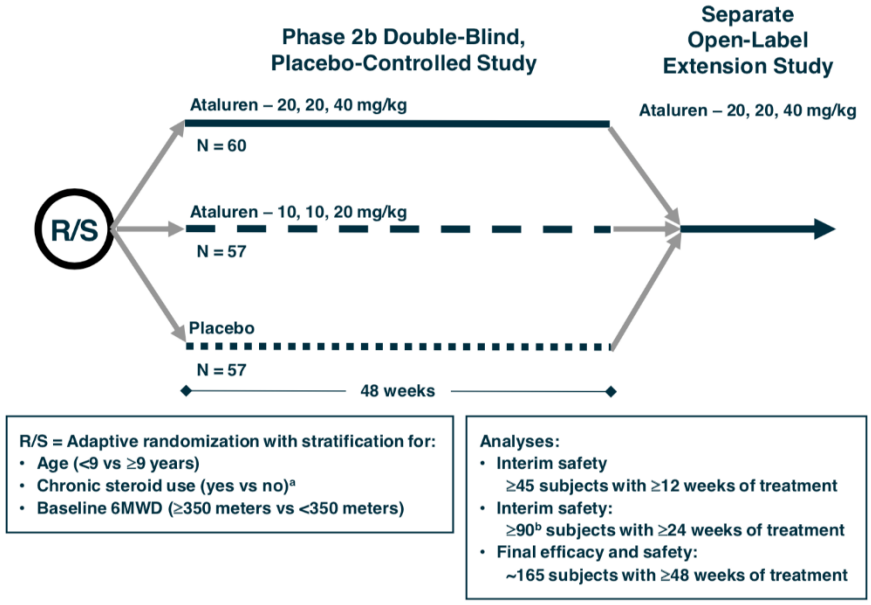
The North Star Clinical Network and database includes information on regular assessments of patients with DMD from 24 paediatric specialist neuromuscular centres regularly followed in the UK. Propensity score matching has also been used to match patients in the MAA with a cohort of patients in the North Star database receiving BSC alone. This is described in section 9.4.1.7. Whilst the North Star database includes a UK patient cohort, it is not as complete as the CINRG database as it does not collect information on patients age at first symptoms which is one of the early predictors for disease severity and used within STRIDE. Also, limitations in patient follow-up resulted in significantly reduced patient numbers informing later data points, contributing to the inability to draw meaningful conclusions from the analysis.

9.4.1.2 Study 007 – Phase 2b efficacy and safety

Study 007 was a randomised, double-blind, placebo-controlled international Phase 2b study in 174 ambulatory patients with nmDMD, aged 5 to 20 years of age. Patients were stratified prospectively by baseline 6MWD (≥350 metres or <350 metres) and randomised to three times a day regimen of ataluren 40 mg/kg/day, 80 mg/kg/day or placebo for 48 weeks. Patients were randomised in a 1:1:1 ratio to either a higher dose of ataluren, a lower dose of ataluren, or placebo, on top of BSC. Patients received ataluren or placebo 3 times per day (at breakfast, lunch, and dinner) for 48 weeks.

Since the licensed dose of ataluren is 40 mg/kg/day, the submission focuses on results for this study arm.

Figure C.3. Overview of study design



R/S, randomisation and stratification
Source: PTC Clinical Study Report, Study 007

Table C-6. Summary of methodology for randomised controlled trial – Study 007

Study name	Study 007 – Phase 2b efficacy and safety
Objectives	To determine the efficacy and safety of ataluren in the treatment of patients with nonsense mutation DMD
Location	Patients were enrolled at 37 sites in 11 countries, including US, Australia, Belgium, Canada, France, Germany, Israel, Italy, Spain, Sweden, UK
Design	Multicentre, randomised, double-blind, placebo-controlled, dose-ranging, phase 2b study efficacy and safety study
Duration of study	48 weeks
Sample size	N=174
Inclusion criteria	• Ability to give written, informed consent (by parents/guardian, if applicable)/consent (if <18 years old). • Male gender. • Age ≥5 years.

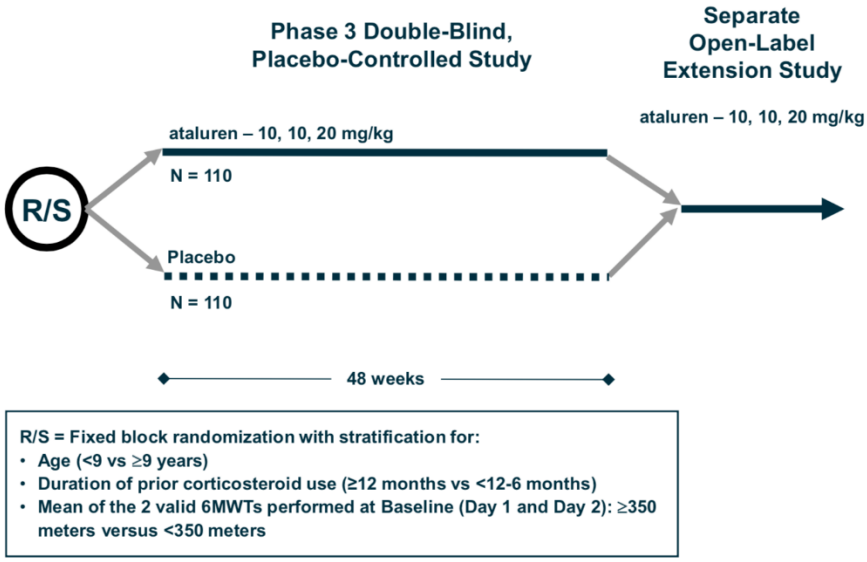
	• Onset of symptoms by age 9. • Phenotypic evidence of DMD due to a nonsense mutation, based on the occurrence of characteristic clinical symptoms or features (e.g., proximal muscle weakness, waddling gait, and Gower's sign) at an age of nine years, increased serum CK concentration, and ongoing walking difficulties. • Evidence of the presence of a nonsense point mutation in the dystrophin gene, as determined by a gene sequence analysis by a certified laboratory. • Ability to walk ≥75 metres unassisted during the 6-MWT at screening. • Evidence that an exit renal 'ultrasound' determination has been performed. • Laboratory tests within normal values (adrenal, renal, and serum electrolyte parameters) • Willingness and ability to comply with planned visits, the drug administration schedule, study procedures, laboratory tests, and study restrictions.
Exclusion criteria	• Treatment with systemic aminoglycoside antibiotics within three months prior to commencement of treatment. • Start of systemic corticosteroid therapy within six months prior to commencement of treatment or a change in treatment with systemic corticosteroids (e.g., start, change in the nature of the drug, dose adjustment not related to body weight change, change in dosage schedule, interruption, discontinuation or restart) within three months prior to commencement of treatment. • Any change (start, change in the nature of the product, dose adjustment, schedule change, interruption, cessation or restart) in the prevention/treatment of congestive heart failure within three months prior to commencement of treatment. • Treatment with warfarin within one month before commencement of treatment. • Earlier treatment with ataluren. • Known hypersensitivity to one of the components or excipients of the study medication. • Exposure to another experimental medicine within two months before the start of treatment. • History of a major surgical operation within 30 days prior to the start of treatment. • Ongoing immunosuppressive therapy (other than corticosteroids). • Ongoing participation in another therapeutic clinical trial. • Expected major surgical intervention (e.g., scoliosis surgery) during the 12-month treatment period. • Need for daytime ventilation assistance. • Clinical symptoms and features of congestive heart failure (American College of Cardiology/American Heart Association stage C or D) or evidence on the echocardiogram of clinically relevant myopathy. • Past or current medical condition (e.g., ancillary disease, psychiatric condition, behavioural disorder, alcoholism, drug abuse), medical history, physical findings, electrocardiogram findings, or laboratory abnormalities that, in the evaluator's judgement, could adversely affect the patient's safety, make it unlikely that the duration of treatment or follow-up testing would be completed, or interfere with the assessment of the results of the study.
Method of randomisation	Patients were randomised in a 1:1:1 ratio to either a higher dose of ataluren, a lower dose of ataluren, or placebo. An Interactive Voice Response/Interactive Web Response (IVR/IWR) system was used to randomise patients. Patients were stratified prospectively by age (<9 or ≥9 years), use

	of glucocorticoids (yes or no), and baseline 6-Minute Walk Distance (6MWD) (≥350 or <350 metres) and were randomised 1:1:1 to the three treatment groups.
Method of blinding	Double-blinded (efficacy and safety data by patients, caregivers, clinic staff, and other study personnel.)
Intervention	• Ataluren 40 mg/kg/day; three times a day • Ataluren 80 mg/kg/day; three times a day • Placebo; three times a day
Baseline differences	There was no significant difference among the 3 arms in any patient characteristic.
Duration of follow-up, lost to follow-up information	One patient discontinued at Week 6 due to non-compliance. The remaining 173 patients completed 48 weeks.
Statistical tests	The sample size was based on the hypothesis that the mean change in 6MWD from baseline to week 48 would be 30 metres (with a standard deviation (SD) of 50 metres) better for ataluren versus placebo. Mixed model repeated-measures (MMRM) were used for the analysis of changes from baseline to week 48. The MMRM model was improved post-hoc by the addition of a baseline visit interaction term. The baseline 6MWD results for one placebo and one 80 mg/kg/day patient was replaced by the screening values because they were much lower than the screening and week 6 values due to lower-limb injury. More specifically, the two patients had suffered lower-limb injuries within 1 or 2 days prior to baseline and had impaired walking ability. These baseline 6MWTs should have been classified as invalid by the clinical evaluator. The analysis was then repeated in the corrected intent-to-treat (cITT) population. Time to persistent 10% 6MWD worsening relative to baseline was an outcome that was defined a priori, i.e., theoretically, prior to empirical observation. In addition, patients were stratified prospectively by age, corticosteroid use and baseline 6MWD (>350 or <350 metres).
Primary outcomes (including scoring methods and timings of assessments)	The primary outcome measure was the change in 6MWD from baseline to week 48.
Secondary outcomes	Secondary endpoints included: i) activity in the community setting, ii) proximal muscle function, iii) muscle strength, iv) muscle v) fragility, vi) biceps muscle dystrophin expression, vii) QoL, viii) cognitive ability, ix) cardiac function, x) frequency of accidental falls during ambulation, xi) treatment satisfaction, xii) safety, xiii) compliance with treatment, and xiv) ataluren pharmacokinetics. Other outcome measures included: i) dystrophin expression, ii) cardiac function, iii) accidental falling during ambulation, iv) parent/caregiver-reported treatment satisfaction.

9.4.1.3 Study 020 – Phase 3 study

Based on results from Study 007 and a greater understanding of the distinct phases of the disease, criteria were developed for Study 020 to enrol a more enriched patient population. In this Phase 3 multicentre, randomised, double-blind, placebo-controlled study conducted in 54 sites and 18 countries, 230 males were treated for 48 weeks. Patients were randomised in a 1:1 ratio to ataluren 10-, 10-, 20-mg/kg dose level or placebo on top of BSC.

Figure C.4. Overview of study design



R/S, randomisation and stratification
Source: PTC Clinical Study Report, Study 020[146]

Table C-7. Summary of methodology for randomised controlled trial - Study 020

Study name	Study 020 – Phase 3 efficacy and safety
Objectives	To determine the efficacy and safety of ataluren in the treatment of patients with nonsense mutation DMD
Location	Patients were enrolled at 54 sites in 18 countries, including US, Australia, Belgium, Brazil, Canada, Chile, Czechia, France, Germany, Israel, Italy, Republic of Korea, Poland, Spain, Sweden, Switzerland, Turkey, UK
Design	Multicentre, randomised, double-blind, placebo-controlled, phase 3 study
Duration of study	48 weeks
Sample size	N=230
Inclusion criteria	• Ability to give written, informed consent (by parents/guardian if applicable)/consent (if <18 years old) • Male gender • Age ≥7 to ≤16 years • Phenotypic evidence of DMD due to a nonsense mutation, based on the occurrence of characteristic clinical symptoms or features (e.g., proximal muscle weakness, waddling gait, and Gower's sign) at an age of nine years, increased serum CK concentration, and ongoing walking difficulties • Evidence of the presence of a nonsense point mutation in the dystrophin gene, as determined by a gene sequence analysis by a certified laboratory, confirmed by a blood sample • Use of systemic corticosteroids (prednisone, prednisolone, or deflazacort) for at least six months prior to the start of the study without any significant change in dosage or dosage regimen (not related to change in body weight) for three months immediately prior to the start of the study and with reasonable consideration that dosages and dosage regimen would not change materially during the study • Ability to walk ≥150 metres unassisted during 6-MWT screening. The 6-MWT had to be ≤80% of the value predicted for age and weight

	• The results of the two 6-MWT baseline measurements had to be determined as valid and the results of the 6-MWT baseline on day 2 had to be within 20% of the 6-MWT baseline on day 1 • The baseline of the 6-MWT (averages of values on day 1 and 2) should not have changed by more than 20% compared to the 6-MWT at screening • Laboratory measurements within normal values (adrenal, renal, and serum electrolyte parameters) • In sexually active patients, willingness to refrain from sexual activity or to use contraception during the use of the study medication and the six-week follow-up periods • Willingness and ability to comply with planned visits, drug delivery schedule, study procedures, laboratory testing, and study restrictions
Exclusion criteria	• Treatment with systemic aminoglycoside antibiotics within three months of starting treatment • Start systemic corticosteroid therapy within six months prior to commencement of treatment • Modification in systemic corticosteroid therapy (e.g., change in the nature of the drug, dose adjustment not related to body weight, schedule change, interruption, discontinuation or restart) within three months prior to commencement of treatment • Any change (start, change in the nature of the drug, dose adjustment, schedule change, interruption, cessation or restart) in the prophylaxis/treatment of congestive heart failure within three months of commencement of treatment • Continued use of coumarin-based anticoagulants (e.g., warfarin), phenytoin, tolbutamide or placlitaxel • Previous treatment with ataluren • Known hypersensitivity to one of the components or excipients of the study medication • Exposure to another experimental drug within three months of starting treatment • History of a major surgical operation within six weeks prior to the start of treatment • Ongoing immunosuppressive therapy (other than corticosteroids) • Ongoing participation in another therapeutic clinical trial • Expected major surgical intervention (e.g., scoliosis surgery) during the 12-month treatment period • Need for daytime ventilation assistance • Clinical symptoms and characteristics of congestive heart failure (American College of Cardiology/American Heart Association Stage C or D) • Past or current medical condition (e.g., ancillary disease, psychiatric condition, behavioural disorder, alcoholism, drug abuse), medical history, physical findings, electrocardiogram findings, or laboratory abnormalities that, in the evaluator's judgement, could adversely affect the patient's safety, make it unlikely that the duration of the treatment or follow-up study would be completed, or evaluate the results of the treatment or follow-up study
Method of randomisation	Patients were randomised in a 1:1 ratio to ataluren or placebo via permuted block randomisation (block size of four) using an interactive voice response or web response system. Randomisation was stratified by age (<9 years vs ≥9 years), duration of previous corticosteroid use (6 months to <12 months vs ≥12 months), and baseline 6MWD (<350 m vs ≥350 m).

Method of blinding	Patients, parents and caregivers, investigational site personnel, PTC Therapeutics employees, and all other study personnel were masked to group allocation until after database lock.
Intervention	• Ataluren 10-, 10-, 20-mg/kg dose level; three times a day • Placebo; three times a day
Baseline differences	Baseline demographic and clinical characteristics, including type of concomitant corticosteroid use, were similar between groups.
Duration of follow-up, lost to follow-up information	The study included a 2-week screening period, a 48-week blinded study drug treatment period, and a 6-week post-treatment follow-up period (only for patients not continuing treatment in the separate extension study. One patient was lost to follow-up (placebo arm).
Statistical tests	The ITT population consisted of all randomised patients. The study was designed with a sample size adequate to detect at least a 30-metre change from baseline to week 48 between ataluren and placebo-treated patients with at least 85% power (alpha = 0.05). An analysis of covariance (ANCOVA) model was used for primary analysis with age, duration of corticosteroid at baseline and baseline 6MWD category as stratification factors and baseline 6MWD as a covariate. If patients were unable to perform 6MWT due to disease progression a value of zero was used. Within-group multiple imputations on the actual scale were applied to handle missing values via the Markov chain Monte Carol method. Secondary endpoints were similarly analysed. If time for TFT exceeded 30 seconds or if patient could not do the test due to disease progression, a value of 30 seconds was used.
Primary outcomes (including scoring methods and timings of assessments)	The primary outcome measure was the change in 6MWD from baseline to week 48.
Secondary outcomes	The secondary outcome measures included i) physical function (TFTs, NSAA), ii) patient and/or parent-reported ADL and disease symptoms, iii) HRQL (PODCI), iv) safety, v) ataluren blood levels, and vi) compliance

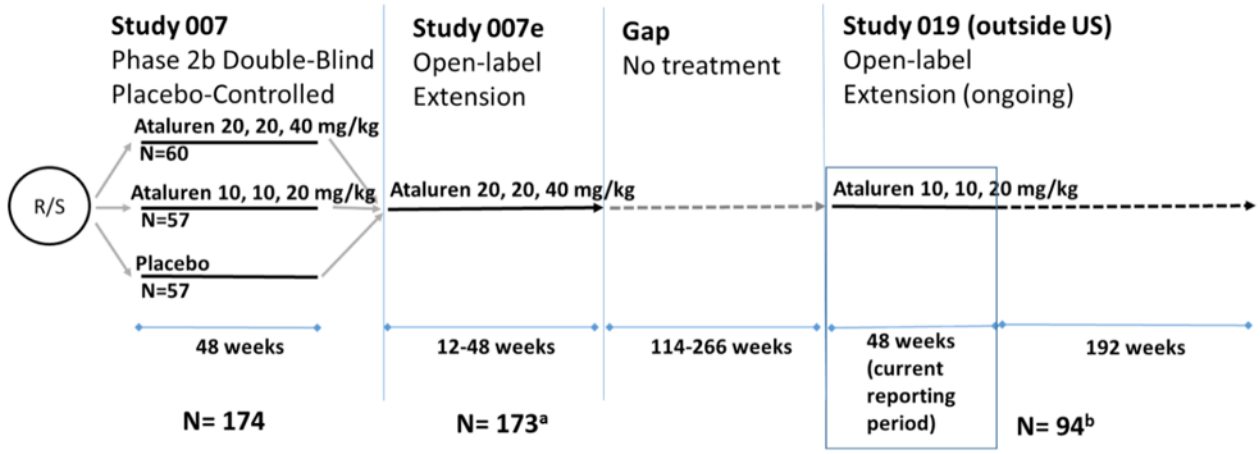
9.4.1.4 Study 019

Study 019 was an open-label, international multicentre study with a primary objective to assess long-term safety of patients who had prior exposure to ataluren in a PTC-sponsored clinical trial outside the US. Not all patients immediately entered Study 019 from a prior ataluren study, and therefore there was a treatment gap between the prior studies and Study 019 (Figure C.5). The secondary objective included the exploration of efficacy of ataluren plus BSC,[147] based on the results of the 6MWT, pulmonary function tests, TFTs, and the NSAA. Patients were considered eligible if they received ataluren in a previous PTC-sponsored study, including Phase 2a Study 004 and Phase 2b Study 007 and their respective extension periods Study 004e and Study 007e. The long-term benefits of ataluren plus BSC beyond the duration afforded by the randomised placebo-controlled studies on the preservation of ambulation and pulmonary function were analysed in a propensity score matched comparison with CINRG.

Notably, this long-term extension study included 240 weeks (i.e., approximately 4.5 years), or in Canada up to 336 weeks, of follow-up, providing an opportunity for exploration of the long-term benefit of ataluren plus BSC beyond the duration afforded by the randomised placebo-controlled studies. CINRG, as described in Section 9.4.1.1, includes longitudinal DMD data from 440 ambulatory and non-ambulatory patients aged 2 to 28 years over a 10-year period (recruited

between 2006 and 2016). It therefore provides a powerful dataset for comparison of subjects receiving BSC alone, with those receiving treatment with ataluren plus BSC.

Figure C.5. History of Ataluren Treatment for Patients Enrolled in Study 019



R/S, randomisation/stratification; US, United States
[a] Ninety-six patients were enrolled in Study 007e at sites outside the United States; 90/96 patients were included in Study 019
[b] Most patients who enrolled in Study 019 had participated in the ataluren phase 2b study (Study 007) and/or the subsequent open-label extension study (Study 007e); patients who had participated in the ataluren phase 2a study (Study 004), or who had no previous exposure to ataluren but had a special exemption, could also have enrolled. One patient did not have previous exposure to ataluren and entered Study 019 through a special exemption.
Note: In Canada Study 019 duration was 336 weeks
Source: Illustration was created by PTC based on Study 019, Study 007, Study 007e design[43]

Table C-8. Study 019 Methodology

Study name	**Study 019 - Long-Term Open-label Safety and Efficacy**
Location	Australia, Belgium, Canada, France, Germany, Israel, Italy, Spain, Sweden, and the UK.
Design	Multicentre, long-term open-label safety and efficacy for patients who participated in one or more prior PTC-sponsored studies of ataluren in nmDMD
Duration of study	Approximately 336 weeks
Sample size	N=94
Inclusion criteria	• Ability to give written, informed consent (by parents/guardian if applicable)/consent (if <18 years old) • Male gender • Patients with a nmDMD who in one or more clinical studies had previously used ataluren • Laboratory tests within normal values (hepatic, adrenal, renal, and serum electrolyte parameters) • In sexually active patients, willingness to refrain from sexual activity or to use contraception during the use of the study medication and the 6-week follow-up periods • Willingness and ability to comply with planned visits, drug administration plan, study procedures, laboratory testing, and study restrictions

Study name	Study 019 - Long-Term Open-label Safety and Efficacy
Exclusion criteria	• Use of any other experimental drug within 1 month of commencement of the study medication • Participation in another clinical trial with ataluren • Known hypersensitivity to any of the components or excipients of the study medication • Continued use of coumarin-based anticoagulants (eg, warfarin), phenytoin, tolbutamide, paclitaxel, or systemic aminoglycoside antibiotics • Medical/surgical condition, electrocardiogram findings, or laboratory abnormalities that, in the evaluator's judgement, could adversely affect patient safety or make it unlikely that the duration of treatment or follow-up studies would be completed
Intervention	Ataluren 10-, 10-, and 20-mg/kg dose level; 3 times a day
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were required to complete a visit at the clinical research facility every 48 weeks. Each patient was to return to the clinical research facility at Week 240 (or Week 336 in Canada) for the end of treatment (EOT) visit. However, study duration could be altered, in which case, the timing of the EOT visit was adjusted appropriately. If the patient terminated the study early because ataluren was commercially available in that country, then the patient only needed to return for the EOT visit. All patients who discontinued ataluren were to return for a Post-Treatment Visit at the investigator site 6 weeks (±7 days) after the last dose of ataluren for final study-related evaluations.
Analysis	The as-treated population in Study 019 consisted of all patients who received at least 1 dose of ataluren.[130] Patients were classed as ambulatory if they had a 10-metre run/walk time that was ≤30 seconds at screening. The long-term benefit of ataluren beyond the duration afforded by the randomised placebo-controlled studies and the preservation of pulmonary function were analysed in a propensity score matched comparison with the CINRG DNHS. Propensity score matching (1:1) was performed to identify CINRG DNHS patients who were similar to Study 019 patients in the following 4 covariates, which are established predictors of disease progression: • Age at onset of first symptoms (using age at diagnosis as a proxy*) • Age at initiation of corticosteroid use • Duration of deflazacort use • Duration of use of other corticosteroids *In Study 019, the age at first symptom was not collected, which makes it unavailable for use as a covariate for propensity score matching against patients with DMD from the CINRG DHNS. As an alternative for this assessment, PTC decided to use age at diagnosis since those data were collected in Study 019. Accepting that these 2 outcomes are not the same, and that age at first symptom is a more appropriate predictor of future disease progression, PTC are confident that selection of age at diagnosis is a conservative proxy. To be eligible for the propensity score matched analysis of age at LoA, patients must have had available data for age at LoA and the 4 aforementioned covariates used for matching. To be eligible for the propensity score matched analysis of age at decline in pulmonary function, patients: • Must have been non-ambulatory and had available data for age at LoA, the 3 pulmonary endpoints described below, and the 4 aforementioned covariates used for matching • Must not have experienced a decline below one of the FVC endpoints listed below before Study 019 entry. Kaplan-Meier analyses were used to estimate the distribution of age at meeting the following endpoints ('events'): LoA; predicted FVC <60%; predicted FVC <50%; and FVC <1 litre. The distribution of age at these endpoints was compared between matched patients from Study 019 and the CINRG DNHS, using a log-rank test stratified by the duration of deflazacort and other corticosteroid use 1 month or treatment naive, ≥1 month to <12 months, and ≥12 months).
Outcomes	• Study assessments was performed at clinic visits during screening, on the first day of ataluren dosing, and then every 48 weeks during the ataluren treatment

Study name	Study 019 - Long-Term Open-label Safety and Efficacy
	period, except for weight, which was measured every 24 weeks at a primary care physician. • The primary outcome measures were the long-term safety and tolerability of ataluren at 240 weeks (approx. 4.5 years). • For ambulatory patients, the endpoints were change from baseline in 6MWD, TFTs, and NSAA. • LoA was defined as a patient having two consecutive vistis in which they took longer than 30s to walk 10m or if a clinician defined a patient as non-ambulant. • For non-ambulatory patients (including those who were ambulatory at study entry) the endpoints were change from baseline in pulmonary function (FVC, FEV1), Peak Expiratory Flow, Peak Cough Flow, and Egen Klassification scale. The Egen Klassification scale measures ADL in patients after LoA.

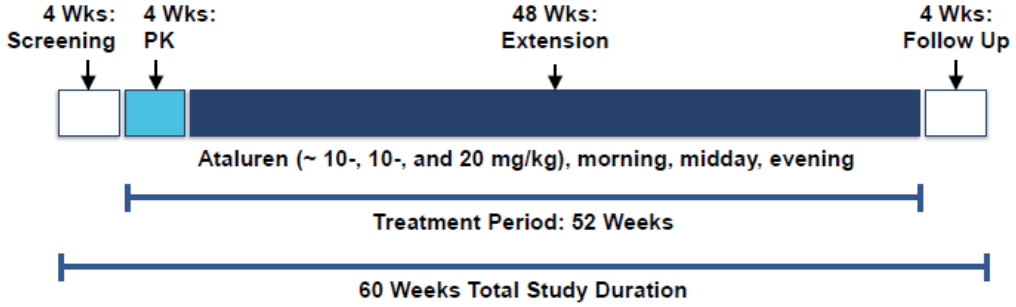
6MWD, 6-minute walk distance; ADL, activities of daily living; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; EOT, end-of-treatment; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LoA, loss of ambulation; nmDMD, nonsense mutation Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; TFT, timed function test; UK, United Kingdom

9.4.1.5 Study 030 - Phase 2 study in children with nmDMD aged ≥2 to <5 years

Study 030 was a Phase 2, open-label, multiple-dose study designed to evaluate the safety and pharmacokinetics of ataluren in boys aged ≥2 to <5 years with nmDMD (Figure C.6 and Table C-9). The study also explored the efficacy of ataluren in this age group. Patients received ataluren at a dose of 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 52 weeks. The study was comprised of a 4-week screening, a 4-week treatment phase, a 48-week extension (treatment period: 52 weeks), and a 4-week follow-up (study duration: 60 weeks). During the treatment period, patients went to the clinical centre on Day 0 and Day 28 for the pharmacokinetic studies and in Weeks 16, 28, 40, and 52 for the safety and efficacy assessments.

The efficacy results of Study 030 were compared with data on the natural history of the disease in 31 untreated DMD patients aged ≥2 and <5 years, identified in the natural history database of the CINRG.

Figure C.6. Overview of Study 030 Design



PK, pharmacokinetics
Source: Tian et al. 2018[131]

Table C-9. Study 030 Methodology

Study name	Study 030 - Phase 2 (age >2 to <5 years)
Location	The study enrolled patients across 6 sites in the US
Design	Multiple-dose, open-label, evaluation of safety, pharmacokinetics, and pharmacodynamics, Phase 2 study
Duration of study	52 weeks
Sample size	N=14
Inclusion criteria	• Males ≥2 to <5 years of age • Body weight ≥12 kg

Study name	Study 030 - Phase 2 (age >2 to <5 years)
	• Diagnosis of DMD • Nonsense mutation in at least 1 allele of the dystrophin gene
Exclusion criteria	• Participation in any other drug or device clinical investigation • Ongoing use of prohibited concomitant medications
Intervention	Ataluren 10-, 10-, and 20-mg/kg dose level; 3 times a day
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	During the treatment period, each subject was to return to the clinical research facility during Week 0 (Visit 2) and Week 4 (Visit 3) for PK testing, and Week 16 (Visit 4), Week 28 (Visit 5), Week 40 (Visit 6), and Week 52 (Visit 7/Early Termination [ET]) All patients were included in the safety and PK populations and completed the PK phase of the study.
Analysis	It is challenging to evaluate efficacy in this young patient population due to the rarity of diagnosed patients with nmDMD in children <5 years of age. In addition, due to growth and maturation, patients in this age group tend to show stabilisation or improvement in measures routinely used to assess muscle function. The rate of maturation in younger patients is also both unpredictable and can vary significantly from patient to patient. In DMD patients between 2 and 5 years of age, the progressive loss of muscle function characteristic of the disease is compensated for by normal growth and development. Therefore, in this age group the loss of motor skills is not yet evident; indeed, there is a progressive acquisition of motor skills rather than deterioration of skills. Therefore, the efficacy of ataluren was evaluated on the basis of improvement in muscle function assessment tests found at Week 28 and Week 52 compared to baseline.
Primary outcome	The primary outcome measure was to evaluate the safety of ataluren in patients aged ≥2 and <5 years with nmDMD (number of abnormal laboratory values and/or AEs).
Secondary outcomes	Secondary outcome measure included i) PK parameters, ii) area under the curve and C min, iii) descriptive assessments of efficacy (TFTs and NSAA), iv) effects on growth parameters.

AE, adverse event; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; nmDMD, NSAA. North Star Ambulatory Assessment; nonsense mutation Duchenne muscular dystrophy; TFT, timed function test; US, United States

9.4.1.6 STRIDE methodology

STRIDE is an ongoing, multicentre, ≥5-year real-world study. STRIDE is a non-imposed post-approval safety study designed to collect information on the safety and effectiveness of ataluren in the real-world setting as part of routine clinical practice. The study was initially designed to enrol approximately 200 patients but was amended to enrol up to 360 patients to reflect continuing enrolment and inclusion of patients aged 2 to less than 5 years. Except for those enrolled after May 2020, patients will be followed for ≥5 years from date of enrolment, and data are collected in conjunction with routine care visits (estimated to occur at 3- to 6-month intervals). For patients who started ataluren prior to enrolment into the registry, data were obtained retrospectively from medical records for the time period between ataluren initiation and enrolment.

The target registry population includes patients for whom the decision to prescribe ataluren (outside of a clinical trial) has already been made. Patients within each prescriber's practice who are or will be receiving treatment with ataluren, and who meet the eligibility criteria and provide informed consent (either by the patient or through authorisation by a legal guardian), are invited to enrol in the registry and be followed according to the protocol. The inclusion criteria are broad, and the exclusion criteria limited, so as to include a representative population of patients treated with ataluren in routine clinical practice.

Comparison with natural history control data

CINRG DNHS, the largest prospective multicentre natural history study to date in DMD, enrolled 440 ambulatory and non-ambulatory DMD patients aged 2 to 28 years.[7]

CINRG DNHS data to 19 March 2018 were used as a historical control to provide context for the effect of ataluren in STRIDE (see section 9.4.1.1). In CINRG and STRIDE, the endpoints were similarly defined, including LoA (full-time wheelchair use).

To eliminate bias and enable a more robust comparison between STRIDE and CINRG, propensity score matching was used to identify a subset of subjects in the CINRG database who were comparable to subjects in the registry according to established predictors of disease progression. The propensity score was created using a logistic regression model with the following covariates: age at first clinical symptoms, age at first corticosteroid use, duration of deflazacort use (<1 month, ≥1 to <12 months, ≥12 months); and duration of other corticosteroid use (<1 month, ≥1 to <12 months, ≥12 months). Once the propensity score was calculated, a local optimal (greedy) algorithm based on the nearest neighbour approaches without replacement was used to find the matching controls.[7] Under the local optimal algorithms approach, both the registry and CINRG subjects were first randomly sorted. The first registry subject was selected to find the closest matching CINRG subject based on the absolute value of the difference between their propensity scores (predicted probability). The CINRG subject with the closest propensity score was selected as the matching control and was no longer available for further matching. This procedure was repeated for all registry subjects for a 1-to-1 match.

Registry data were compared with CINRG data for the overall population and propensity- score-matched population using KM estimates and Cox regression for a number of time-to-event variables. For each time-to-event variable, the median was produced for STRIDE and CINRG separately, along with the 95% CI constructed based on log-log transformation. Distribution of the variables were compared between STRIDE and CINRG using log-rank test stratified by the duration of deflazacort use and the duration of other corticosteroid use calculated up to the time at LoA or the latest time the subject was known to be ambulatory. Gaps between steroid use were excluded and overlap of different steroid use was not double counted. The HR and the corresponding 95% CI (STRIDE versus CINRG) was estimated using a stratified Cox proportional hazard model with study and age at the first symptom as covariates.[7]

Table C-10. STRIDE Methodology

Study name	Study 025 (STRIDE) - Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care
Location	As of 31 January 2021, patients have been enrolled from 13 countries (Austria, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Portugal, Romania, Sweden, UK)
Design	Multicentre, 5-year real-world study
Duration of study	10 years (5 years target follow-up duration)
Patient population	nmDMD
Sample size	Up to 360

Inclusion criteria	Receiving or will be receiving usual care treatment with commercial supply of ataluren (or receiving care within a named patient early access program) Willing to provide written informed consent to allow the study data collection procedures (either by the patient or through authorisation by a legal guardian)
Exclusion criteria	Patients who are receiving ataluren or placebo in a blinded, randomised clinical trial, or ataluren in any other ataluren clinical trial or cohort early access program that prevents participation in this study
Intervention(s) (n =) and comparator(s) (n =)	Translarna, N=286 (as-treated population, 31 January 2021 datacut) There is no comparator however outcomes in patients treated in STRIDE have been compared with those in a matched natural history cohort from the CINRG database (n=398; see section 9.4.1.1)
Baseline differences	Propensity matching of CINRG data yielded a population with no significant differences from the STRIDE population with respect to age at first symptoms, age at first corticosteroid use, duration of deflazacort use, and duration of other corticosteroid use, which provided a relevant basis for comparison.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Data are collected in conjunction with routine care visits (estimated to occur at 3- to 6-month intervals). As of the latest cut-off, subjects in the Evaluable Population have been followed for a median of [redacted] days (range: [redacted]). Most subjects have been on study for at least [redacted] days). [redacted] subjects discontinued Registry participation as of the cut-off date, most frequently ([redacted] were lost to follow-up; [redacted] withdrew consent and [redacted] for reasons categorised as "[redacted]")
Analysis	The following analysis populations are defined for the fifth interim report (31 January 2021): • Screened Population: all subjects who sign informed consent • As-Treated/Safety Population: all screened subjects who receive Translarna • Evaluable Population: male patients who provided informed consent and did not fail screening, and the safety population is defined as all patients who received at least one dose of ataluren. • Effectiveness Population: all subjects in the Evaluable Population excluding those: o with newborn screening or prenatal diagnosis as first symptom o with missing age at first symptoms o with steroid use but missing steroid initiation date

	○ with missing age at LoA • Ambulatory Population: subset of the Evaluable or Effectiveness Population excluding: ○ Subjects who are full-time wheelchair bound or bedridden prior to the date of first recorded commercial or EAP Translarna use ○ Subjects who are in the transition phase defined as greater than or equal to 30 seconds for their first 10-metre run/walk test on or after the date of first recorded commercial or EAP Translarna use. • Non-Ambulatory Population: subset of Evaluable or Effectiveness Population who are full-time wheelchair bound or bedridden on or before first recorded commercial or EAP Translarna use or anytime during the study. Patients who became non-ambulatory during the registry were included in both the ambulatory and non-ambulatory populations. **STRIDE only (not presented in this submission):** To analyse change in clinical outcome measure in the context of this non-interventional study with heterogeneity in assessment timepoints, change from first assessment to last assessment was summarised for all patients with at least 2 assessments at least 48 weeks apart. First assessment was defined as the first data captured in the registry (inclusion, follow-up or retrospective visits) and last assessment was the latest data captured in the registry before the cut-off date. **STRIDE vs. CINRG:** STRIDE data were compared with CINRG data for the overall population and for the propensity score matched population using KM estimates and Cox regression for the time-to-event variables of LoA, TFTs, and pulmonary function. For each time-to-event variable, the median (95% CI) survival time (age at which the survival probability drops to 50% or below) for subjects in STRIDE and CINRG was constructed based on log-log transformation. The distribution of the variables was compared between STRIDE and CINRG using log-rank test stratified by the covariates of duration of deflazacort use (<1 month, ≥1 month and <12 months, ≥12 months) and the duration of other steroid use (<1 month, ≥1 month and <12 months, ≥12 months). The HR and corresponding 95% CI (STRIDE versus CINRG) was estimated using a stratified Cox proportional hazard model with study, age at first symptom, and age at initial steroid usage as covariates.

Outcomes (including scoring methods and timings of assessments)	The registry collects information on the safety, effectiveness, and compliance of ataluren in routine clinical practice. Safety data collected during the registry are spontaneously reported during a clinic visit or derived from hospital records, clinical records, and evaluation checklists. Evaluations that are conducted as per usual care are documented. There are no protocol-mandated procedures or diagnostic tests. However, in response to Regulatory Authority feedback and with the goal of collecting a more robust set of efficacy data for this registry, PTC undertook a multi-faceted approach to increasing consistency and completeness of efficacy data collection. As a result of these initiatives, more complete reporting for efficacy measures was obtained beginning in the subsequent cycle of follow-up visits. In countries where initiation took place in 2017 or 2018, PTC, in agreement with the Steering Committee, requires that sites commit to reporting a minimum set of efficacy assessments for each patient in the registry (including 10-metre walk test, time to rise from floor, FVC), at the time of inclusion and at all follow-up visits. In addition, LoA (defined as "full-time wheelchair use") is always assessed and captured. STRIDE data are being compared with CINRG data for the time-to-event variables of LoA, TFTs, and pulmonary function.

Source: STRIDE 5th Interim Clinical Study Report 2021[148]

9.4.1.7 Managed Access Agreement (MAA) methodology

The MAA collected data on patients in order to compare the ataluren-treated nmDMD patients with DMD patients receiving BSC alone in the North Star registry. The control cohort does not include any nmDMD patients.

The MAA provided data measuring change in the NSAA, over the course of a 3–4-year period. The quality of life of the patients and caregivers was also assessed. The North Star database, used for this analysis, is owned and maintained by the North Star Clinical Network in the UK. The data analysis was performed and validated as a joint effort between North Star Clinical Network and PTC Therapeutics.[149]

Comparison with matched control data (primary analysis)

A propensity score-matching approach was used to minimise the biases of between group comparisons between the ataluren-treated and BSC-only-treated patients.

The propensity scores originally included the following variables: age at baseline, baseline steroid use duration (<1 year, or >1 year), steroid regimen (Daily, Intermittent, Other, & No Steroids), steroid type (Deflazacort, Prednisolone, No Steroids), and baseline NSAA total score.

Following a matching report produced by the North Star registry and interim data on those who had lost ambulation, the propensity score variables were refined and updated to try and account for recent research and publications to minimise the bias:[149]

- age at baseline,

- age at initial use of steroid,
- deflazacort use duration (≤1 month, 1-12 months, ≥12 months) before baseline*
- duration of other steroid use (≤1 month, 1-12 months, ≥12 months) before baseline*,
- steroid use regimen (daily/intermittent and other),
- baseline NSAA total score,
- baseline time to rise from floor.

*Subjects who did not use any steroids would be in the category of other steroids (<1 month) and initial age of steroid use will be imputed to 30.

Once the propensity score was calculated, a local optimal (greedy) algorithm without replacement using both the nearest neighbour and calliper approaches was used to find the matching controls.

Under the local optimal algorithms approach, both the treated and the BSC patients are first randomly sorted. The first treated patient is selected to find the closest control matching BSC patient based on the absolute value of the difference between their propensity scores (logit of the scores). The matching controls were selected utilising both the nearest neighbour matching and a calliper matching approach. It should be noted, that earlier onset age at first signs and symptoms is associated with earlier onset age at loss of ambulation and hence could be used as a measure of disease severity, however these data were not available from the database as a key propensity score matching covariate.[149] Consequently, alternative covariates were used in the matching: age at initial steroid use, baseline NSAA total score and baseline time to rise from floor.

Retrospective analysis

A retrospective comparative analysis of the annualised decline in linearised NSAA for ataluren-treated nmDMD patients relative to BSC-alone-treated DMD patients was undertaken to evaluate whether a correction factor for the prospective analysis was required. The methodology of this analysis is shown in Table C-11. In the retrospective slope analysis that included patients with NSAA records at least two months prior to baseline (median duration to baseline was 638 days and 700 days for ataluren and BSC patients, respectively), there was no significant difference in the rate of decline prior to baseline between the two groups. As there is no meaningful difference in the trajectory of nmDMD patients as compared to the DMD population overall, assuming that both groups are receiving BSC, a correction factor was therefore not needed in the prospective analysis.[149]

Table C-11. MAA Methodology

Name	**Managed Access Agreement - Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)**
Location	England
Design	Data collection
Duration of data collection	Approximately 6 years (March 2016 to January 2022). The median duration of the observation follow-up period was 38 months.
Sample size	N=59 (matched)
Patient eligibility	Patients with nmDMD aged 2 years and older, who are ambulatory must sign up to the MAA and be made aware of the start / stop criteria.[44] **Start criteria:** • Patients must have a confirmed diagnosis of Duchenne muscular dystrophy resulting from an in-frame nonsense mutation in the dystrophin gene. The

Name	Managed Access Agreement - Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)
	presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing. • Patients must be aged 2 years and older and able crawl, stand with support or walk. • Patients should only start once a full set of standard baseline specialist neuromuscular clinical and physiotherapy assessments (including an initial blood test) have been obtained. • Patients / parents will be expected to attend their clinic 2 times a year for assessment within a 14-month period. **Stop criteria:** Patients will become ineligible for further treatment where: • The patient is non-compliant with assessments for continued therapy where non- compliance is defined as fulfilling fewer than 2 attendances for assessment within any 14-month period. • If a patient has lost all ambulation (i.e., can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment. • In such cases as defined above, patients should stop treatment no later than 6 months after becoming fully non-ambulant. • Patients who are taken off treatment will continue to be monitored and supported with normal best standard of care. These patients will continue to be assessed to allow gathering of important information regarding natural history of non-ambulatory patients.
Intervention	Ataluren (MAA patients) BSC (matched North Star cohort)
Outcomes	• NSAA (primary analysis): The NSAA consists of 17 activities, each scored as 0, 1, or 2. The sum of these 17 scores will be used to form a total score. The total score and each of the 17 categories will be summarised. An analysis will be conducted to compare the change in total NSAA scores between the ataluren cohort (ataluren-treated patients) and the matched control cohorts (BSC patients). • HRQL (secondary analysis) o Patient HRQL: Patients in the ataluren cohort will be invited to complete the CHU9D as outlined in the MAA. The questionnaire will be completed twice per year in a timeframe consistent with clinic visits. In addition, control patients will be asked if they are willing to complete the questionnaire. o Caregiver quality of life: At least one caregiver (e.g., parent) of the children in the ataluren cohort will be invited to complete the EQ-5D. Patients will have a confirmed diagnosis of nmDMD and their clinical status will be described – age, level of ambulatory ability, status of non-ambulation (to be fully determined but to include aspects of upper body mobility, level of ventilation support etc). The questionnaire will be completed twice per 14 months in a timeframe consistent with clinic visits and should ideally be completed by the same caregiver(s) each time. In addition, caregivers of the control cohort will be asked if they are willing to complete the EQ-5D.
How were participants followed-up (for example, through pro-active follow-up or passively).	Patients were required to attend clinic twice within any 14-month period for assessment to remain on treatment within the MAA
Analysis/ Statistical tests	The goal is to describe the data collected. No hypothesis testing will be performed on any of the endpoints assessed. Statistical modelling will be employed to obtain the best point estimators (and confidence intervals) to describe the data. All statistical modelling

Name	Managed Access Agreement - Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)
	will be performed based on observed data with no data imputation for the missing data and dropouts. **Primary analysis** The primary analysis will compare the decline in the NSAA score over time in the ataluren-treated group compared to the control cohort. The change in NSAA total score and change in NSAA linear score will be analysed separately using a mixed model for repeated measurement model (MMRM) with factors of treatment (ataluren and BSC), age, time point (6, 12, 18, 24, 30, 36, & 42 months), baseline total score, treatment-by-time point interaction as covariates. Treatment effects, treatment differences, and the corresponding 95% confidence intervals will be estimated for each time point. The sample size would vary by time point and is likely small for later time points. If MMRM modelling is not appropriate (e.g., failed to converge), alternative methods including analysis of covariance with baseline as a covariate by time point may be used. Secondary, descriptive, subgroup analyses will be performed separately to the primary analyses. **Retrospective analysis** A retrospective comparison of the linearised NSAA trajectory for the propensity score matched cohorts will be made. The annual slope of decline of the linearised NSAA before baseline will be calculated over a minimum of 2 years and will be compared to assess if the trajectory is similar between the two cohorts and will be compared to the published data (in particular Ricotti et al). Any correction factor needed for the prospective analysis will be discussed and decided by all parties involved, namely NICE, North Star Group and PTC. **HRQL** HRQL data will be summarised using descriptive statistics or tabulation counts as appropriate by time points.

Source: North Star Clinical Network, MAA Statistical Analysis Plan, v4.2, 2021[149]

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

Table C-12. Ataluren clinical study sources

Study	Primary publication	Additional data sources
Study 007 NCT00592553	Bushby et al. 2014[32]	Study 007 Clinical Study Report[150] Data has also been published in an EMA review by Haas et al[40] and at multiple conferences at shown in Appendix 17.1.
Study 020 (ACT-DMD) NCT01826487	McDonald et al. 2017[33]	Study 020 Clinical Study Report[146] Data has also been published at multiple conferences at shown in Appendix 17.1.
Study 019 NCT01557400	McDonald et al. 2021[130]	Study 019 Clinical Study Report[43]
Study 030 NCT02819557	Tian et al. 2018[131]	Study 030 Clinical Study Report[151]
STRIDE Registry (Study 025o) NCT02369731	Analysis of the STRIDE Registry with data cut 31 January 2021 used to inform the submission has been presented in three conference abstracts/posters: Mercuri et al. 2021[34] Tulinius et al. 2021[37] Muntoni et al. 2021[128] Muntoni et al. 2021[152]	STRIDE 5th Interim Clinical Study Report 2021[36] Earlier data has also been presented by Mercuri et al. 2020[7] (peer-reviewed publication data cut July 2018) and at multiple conferences as shown in Appendix 17.1.

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

The two RCTs, Study 007 and Study 020 were of similar design. One key difference between the trials was the inclusion criterion regarding patients' baseline 6MWD. Study 007 specified boys were aged ≥5 years, with a screening 6MWD ≥75 metres. Study 020 inclusion criteria were stricter, specifying boys aged ≥7 years and ≤16 years, with a 6MWD of both ≥150 metres and ≤80% of that predicted for their age and height. Study 020 also specified that patients should be receiving concomitant stable corticosteroid therapy. This was not specified in the Study 007; nonetheless, 71% of patients recruited were receiving corticosteroids. Patients in both trials received ataluren 40 mg/kg/day or placebo for 48 weeks. Patients in Study 007 who received ataluren 80 mg/kg/day were not included in these meta-analyses.

Study 019 included patients previously treated with ataluren in Study 007 and Study 004. Not all patients immediately entered Study 019 from a prior ataluren study; the mean (SD) treatment gap between the prior studies and Study 019 for the 93 patients who had participated in previous trials was 2.9 (0.5) years. Mean age of enrolled patients at baseline in Study 019 was 12.8 years, representing an older patient population with more advanced disease.

Study 030 investigated ataluren in a younger population with nmDMD, aged ≥2 to <5 years.

STRIDE and the MAA are real-world studies that include patients with a wider range of ages and ambulatory ability than those in clinical trials, meaning that the data are representative of a broader range of patient experiences in clinical practice. STRIDE includes a large cohort of patients that could be propensity score matched using key prognostic covariates, including age at first symptoms. The MAA cohort is considerably smaller (N=59 in the matched analysis), and whilst propensity score matching to a natural history cohort of patients in the UK was possible, factors such as the available patient pool and lack of age at first symptoms as a covariate may have created an imbalance in disease severity in the matched populations.

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

Study 007

Age, corticosteroid use, and baseline 6MWD were pre-specified as stratification factors since these variables were likely to have prognostic significance. The three stratification factors (age [<9 years vs. ≥9 years], corticosteroid use [yes vs. no], and baseline 6MWD [≥350 metres vs. <350 metres]) were included to balance allocation of patients into treatment groups by these potentially important baseline parameters. Subgroup analyses were carried out within the 6 subgroups defined by the 3 stratification factors.[32]

A post-hoc subgroup analysis was conducted after discussion with the CHMP to compare the mean change in the 6MWD from baseline to week 48 measured in placebo-treated patients versus those receiving ataluren who were classified as being in the decline phase. The decline phase subgroup was defined as those aged 7 years to 16 years with a baseline %-predicted 6MWD ≤80%, and to minimise heterogeneity with a baseline of 6MWD ≥150 metres and on a stable dose of corticosteroids.

Study 020

As in Study 007, randomisation was stratified by age (<9 years vs ≥9 years), duration of previous corticosteroid use (6 months to <12 months vs ≥12 months), and baseline 6MWD (<350 metres vs ≥350 metres). A subgroup with baseline 6MWD of ≥300 metres to <400 metres was pre-specified in the statistical analysis plan. Further post-hoc analysis was carried out in patients with baseline 6MWD <300m and ≥400m.[33]

Study 019

In Study 019 at study entry, 50 patients were ambulatory and 44 patients were non-ambulatory. Pulmonary function was only evaluated in non-ambulatory patients.[130]

STRIDE

Two exclusive analytical age subsets of each analysis population are defined for summary and analysis to inform the efficacy and safety of ataluren in younger subjects and facilitate comparisons between STRIDE data and previous ataluren clinical studies:[148]

- Patients ≥2 and <5 years of age at treatment initiation
- Patients ≥5 years of age at treatment initiation

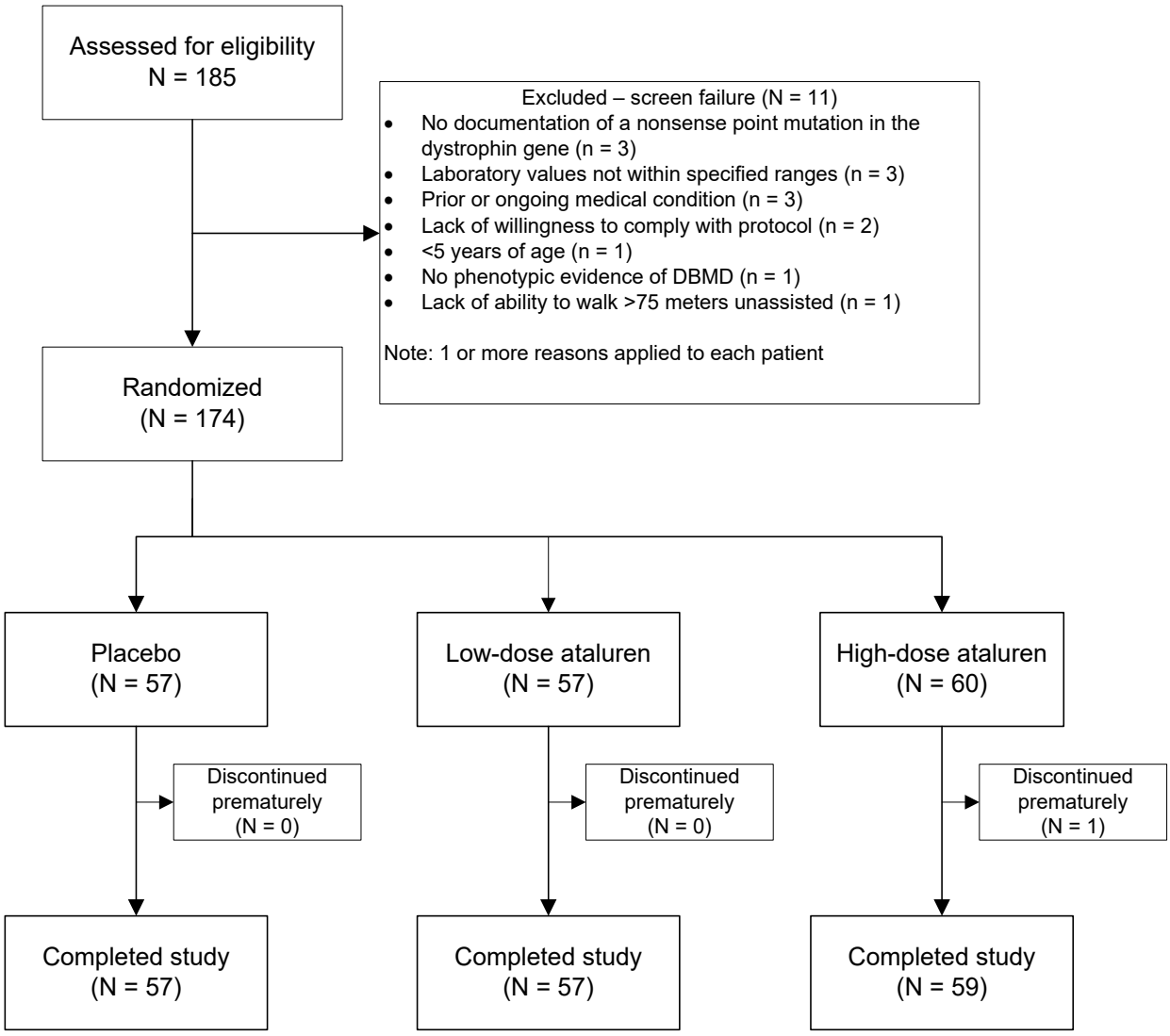
030

No subgroup analyses were completed.

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

9.4.5.1 Patient disposition in Study 007

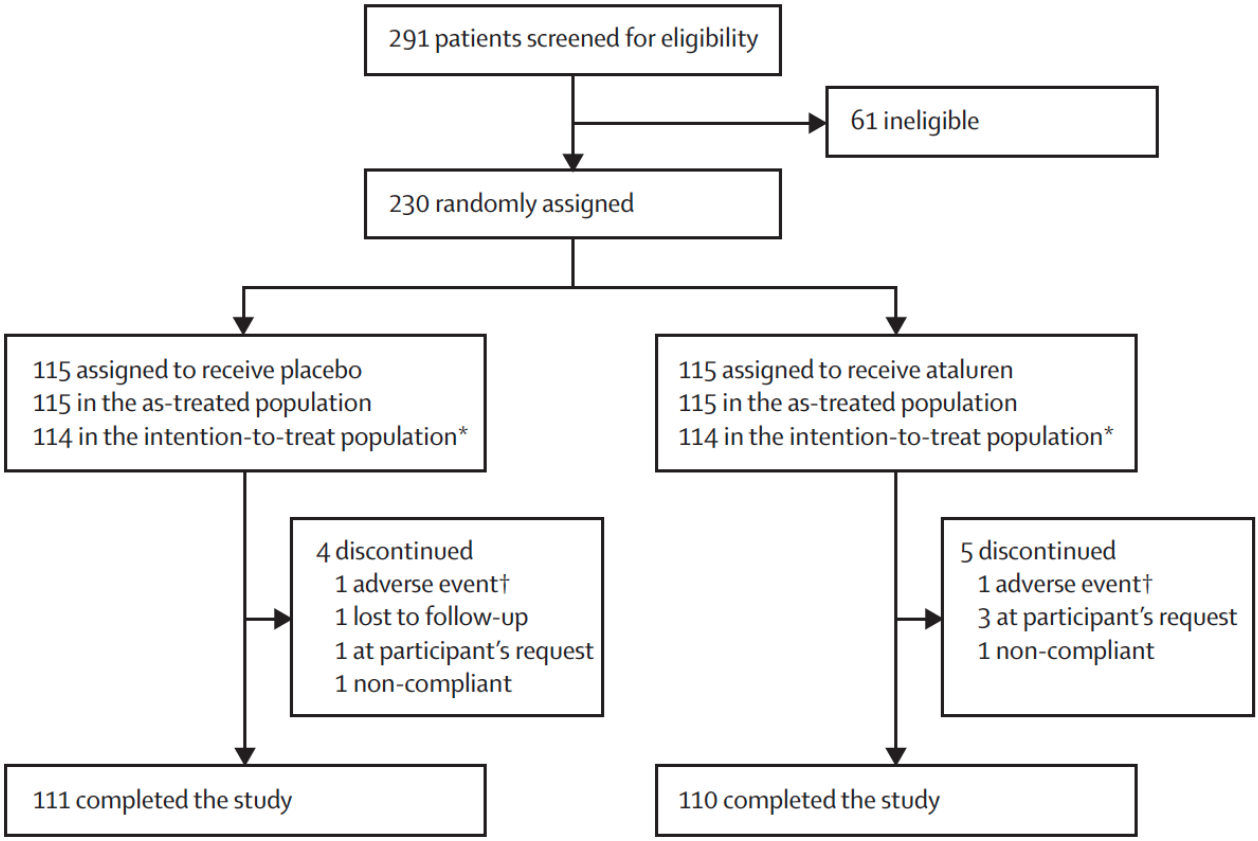
Figure C.7 Patient Disposition, Study 007



Source: Bushy, 2014[32]

9.4.5.2 Patient disposition in Study 020

Figure C.8 Patient Disposition, Study 020



*Two patients from the as-treated population (n=1 per group) were prematurely discontinued when dystrophin gene sequencing did not confirm the presence of a nonsense mutation in the dystrophin gene; these patients therefore did not have at least one valid post-baseline 6-minute walk distance value—a requirement for the intention-to-treat population.
†Adverse events leading to discontinuation were constipation, possibly related to the study drug (n=1 in the ataluren group) and disease progression (n=1 in the placebo group
Source: McDonald 2017[33]

9.4.5.3 Patient disposition in Study 019

A total of 94 boys were included in Study 019, including one patient who did not have previous exposure to ataluren and was enrolled through an institutional review board- and US FDA-approved special exemption. Fifty patients were ambulatory, and 44 patients were non-ambulatory at study entry. Not all patients immediately entered Study 019 from a prior ataluren study; the mean (SD) treatment gap between the prior studies and Study 019 for the 93 patients who had participated in previous trials was 2.9 (0.5) years (range 144–266 weeks).[130]

9.4.5.4 Patient disposition in Study 030

14 patients were screened and enrolled, and all were included in the safety and PK populations, and completed the PK phase of the study.[131]

9.4.5.5 Patient disposition in the STRIDE

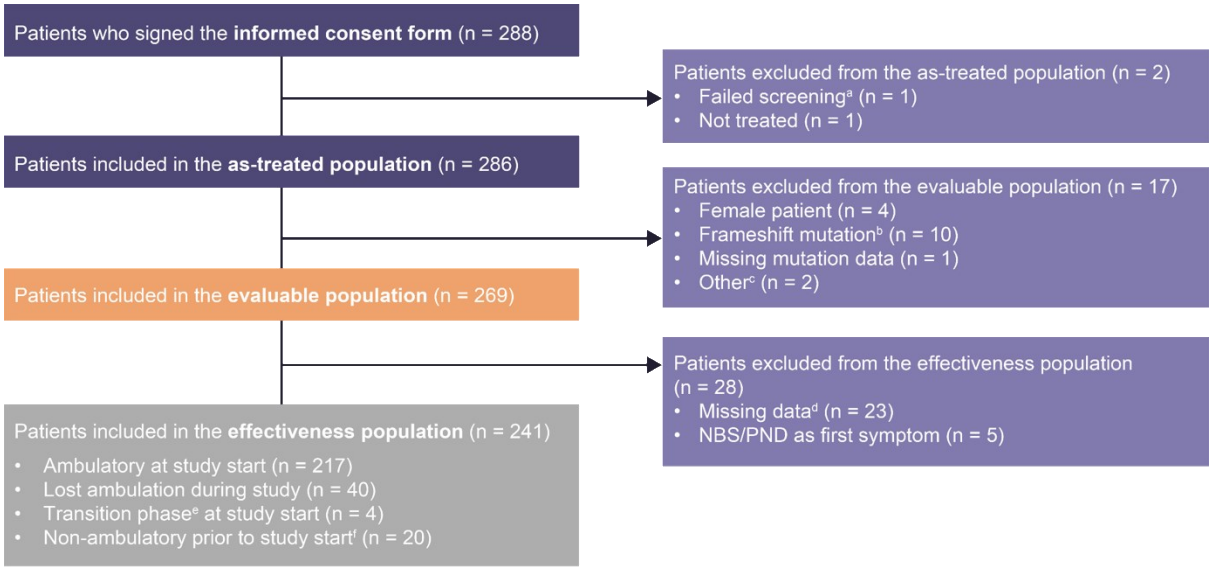
As of 31 January 2021, 288 patients with nmDMD (Figure C.9) from 13 countries with 64 active study sites were enrolled in STRIDE; of these, 286 received at least one dose of ataluren and did not fail screening (as-treated population) and 17 were excluded from the evaluable population (n=269) due to the following reasons: four were female, 10 had a frameshift mutation and three had missing or outstanding mutation data.[34] Of the 269 male patients, 241 with confirmed nmDMD were included in the effectiveness population. The following 28 patients were excluded from the effectiveness population for the stated reasons: 23 patients had missing data for age of LoA or age at first symptoms and five patients had an age at first symptoms equal to 0 years.

Of the 241 patients in the evaluable population, 217 were ambulatory at study entry, 20 were non-ambulatory at the start of study treatment start and four were in the transition phase between being ambulatory and non-ambulatory (they completed the first 10-metre walk/run test in ≥30 seconds).[34]

The mean (95% CI) total exposure to ataluren of the STRIDE effectiveness population was 1197.23 (1126.44, 1268.02) days up to LoA. The propensity-matched STRIDE population had a total exposure to ataluren equivalent to 884.2 patient-years, and 85.5% of patients (206/241) had been receiving ataluren for more than 672 days.[34]

The registry thus provides the opportunity to follow patients with this progressive disease over longer periods of time than afforded by clinical studies designed to show the benefit of treatment in delaying disease progression and loss of muscle function.

Figure C.9: Patient Disposition at Data Cut-Off, as of 31 January 2021



DMD, Duchenne muscular dystrophy; NBS, newborn screening; PND, prenatal diagnosis; STRIDE, Strategic Targeting of Registries and International Database of Excellence

Notes: [a]Screening failure due to a frame shift mutation; [b]Ataluren is not indicated in these patients; ataluren is indicated for the treatment of ambulatory patients with DMD resulting from a nonsense mutation in the dystrophin gene. Patients who do not have a nonsense mutation should not receive ataluren; [c]Critical queries, such as those regarding mutation data, are still outstanding; [d]Data were missing for age at loss of ambulation or age at first symptoms; [e]Patients were in the transition phase if they completed the first 10-metre walk/run test in ≥30 seconds; [f]Non-ambulatory patients were defined as such if using a wheelchair full-time or bedridden; patients who were non-ambulatory "prior to study start" were all ambulatory at ataluren initiation in previous clinical trials.

Source: Mercuri et al. 2021[34]

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

Please see Table C-6 to Table C-11 and section 9.4.5.

9.5 Critical appraisal of relevant studies

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

Table C-13. Critical appraisal of randomised control trials

Study name	**PTC124-GD-007-DMD (Study 007)**		**PTC124-GD-020-DMD (Study 020)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	Response **(yes/no/ not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	An adaptive randomisation using accepted minimisation techniques was utilised to ensure treatment arms were balanced regarding three predefined stratification factors, and patient numbers in each arm. Randomisation was stratified in a 1:1:1 ratio according to age, baseline 6-minute walk distance (6MWD) and use of corticosteroids.	Yes (48-week study period)	Eligible patients were stratified based on age, duration of corticosteroid use, and baseline 6MWD using the permuted block randomisation technique in a 1:1 ratio to receive either ataluren or placebo. After 48 weeks of blinded treatment, all compliant patients were eligible to receive open-label ataluren during a 6-week post-treatment follow-up period.
Was the concealment of treatment allocation adequate?	Yes	An interactive voice response/interactive web response system was used by site representatives to allocate patients.	Yes	An interactive voice response/interactive web response system was used by site representatives to allocate patients.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Randomisation was stratified according to age, baseline 6MWD and use of corticosteroids and therefore treatment arms were well balanced with respect to these prognostic factors. Treatment arms were also similar in terms of other functional characteristics at baseline.	Yes	Randomisation was stratified according to age, duration of corticosteroid use, and baseline 6MWD and therefore treatment arms were well balanced with respect to these prognostic factors. Treatment arms were also similar in terms of other functional characteristics at baseline.

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients, parents/caregivers, investigational site personnel, sponsor and all other study personnel remained blinded to the identity of the treatment assignments until every patient had completed study treatment and the database had been locked. The identity of the study treatments was concealed using a placebo that was identical to the active drug in appearance, taste, odour, packaging, labelling and schedule of administration. Unblinding was only to occur in the case of patient emergencies, if requested by the data monitoring committee (DMC) at the time of the interim analyses, and at the conclusion of the study. During the study, the treatment assignments were to be available only to an independent biostatistician and to the DMC.	Yes	Patients, parents/caregivers, investigational site personnel, sponsor and all other study personnel remained blinded to the identity of the treatment assignments until every patient had completed study treatment and the database had been locked. The identity of the study treatments was concealed using a placebo that was identical to the active drug in appearance, taste, odour, packaging, labelling and schedule of administration. Unblinding was only to occur in the case of patient emergencies, if requested by the DMC at the time of the interim analyses, and at the conclusion of the study. During the study, the treatment assignments were to be available only to an independent biostatistician and to the DMC.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	Only one patient in the ataluren discontinued due to protocol non-compliance at approximately Week 6.	No	The dropout rate was low (4%) in both arms, as only four patients in the placebo arm and five patients in the ataluren arm discontinued prematurely.
Is there any evidence to suggest that the authors measured	No	The study protocol is available, and all outcomes have been reported.	No	The study protocol is available, and all outcomes have been reported.

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	The pre-specified intent-to-treat (ITT) population included all randomised subjects with a valid 6MWD observation available at baseline and ≥1 post-baseline visit. The baseline values for two patients (one placebo-dosed and one treated with ataluren 80 mg/kg/day) were replaced by their screening values, because their baseline 6MWDs were radically lower than their screening and Week 6 values due to lower-limb injuries before the baseline test. This is referred to as the corrected ITT (cITT) population. As predefined in the statistical analysis plan, the primary analysis was repeated using a multiple imputation method for missing 6MWDs to check the effect of missing values on the robustness of the primary analysis. A second pre-specified sensitivity analysis to assess robustness of the primary efficacy results to missing data relied on the last observation carried forward (LOCF) concept, by applying an analysis of covariance (ANCOVA) model to the last available post-baseline 6MWD observation.	Yes	The ITT population included all patients who were randomised, with study drug assignment designated according to initial randomisation, regardless of whether patients received any study drug or received a different study drug from that to which they were randomised. In addition, patients in this population must have had a valid 6MWD baseline value and at least one valid, post-baseline 6MWD value. Siblings were considered as independent subjects. This population was used to analyse all efficacy parameters. As predefined in the study statistical analysis protocol, within-group multiple imputations on the actual scale were applied to handle missing values via the Markov chain Monte Carlo method; 100 imputations were done, which was deemed adequate in view of the anticipated amount of missing data.

Source: Study 007 CSR; Study 020 CSR

Table C-14. Critical appraisal of non-randomised studies – Study 019

	Response	Comments
Section 1: Population		
1.1 Is the source population or source area well described?	++	Patients from 21 sites in defined countries. Outpatients

	Response	Comments
		Demographics adequately described (See CSR Table 14.1.3.1.1)
1.2 Is the eligible population or area representative of the source population or area?	+	Patients had to have a history of exposure to ataluren in a prior PTC-sponsored study in nmDBMD, for which the eligibility is not clearly reported. Recruitment not further reported.
1.3 Do the selected participants or areas represent the eligible population or area?	++	Study includes UK (along with Australia, Belgium, Canada, France, Germany, Israel, Italy, Spain, Sweden) Clear inclusion and exclusion criteria were pre-specified (see 9.3.1. and 9.3.2 of clinical study report (CSR)).
Section 2: Method of allocation to intervention (or comparison)		
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	NA	
2.2 Were interventions (and comparisons) well described and appropriate?	++	A clear description of the intervention is provided. Study was an open-label extension study, so no comparator included.
2.3 Was the allocation concealed?	NA	
2.4 Were participants or investigators blind to exposure and comparison?	NA	Since this was an open-label study, randomisation and blinding were not utilised.
2.5 Was the exposure to the intervention and comparison adequate?	++	Exposure to intervention was adequate - 10 mg/kg, 10 mg/kg, 20 mg/kg ataluren regimen
2.6 Was contamination acceptably low?	NA	
2.7 Were other interventions similar in both groups?	NA	
2.8 Were all participants accounted for at study conclusion?	-	94 enrolled, 37 (39.4%) patients completed the study and 57 (60.6%) patients discontinued (the primary reason for discontinuation was the commercial availability of drug.)
2.9 Did the setting reflect usual UK practice?	++	Outpatient
2.10 Did the intervention or control comparison reflect usual UK practice?	++	Ataluren outpatient - For administration, the powder in the sachet was mixed with water, milk, fruit juice (except apple juice), fruit punch, or in semi-solid food.
Section 3: Outcomes		

	Response	Comments
3.1 Were outcome measures reliable?	++	Efficacy endpoint measurements included NSAA, 6MWT, TFT, spirometry and ADL as measured by the EK scale.
3.2 Were all outcome measurements complete?	+	Some outcomes were not reported for all patients, e.g., only 38/50 (76%) ambulatory patients had baseline measurements for time to rise from supine
3.3 Were all important outcomes assessed?	++	All efficacy and safety endpoints reported on ()
3.4 Were outcomes relevant?	++	The efficacy outcomes reflect a measure of the treatment effect, and adverse events were reported.
3.5 Were there similar follow-up times in exposure and comparison groups?	NA	
3.6 Was follow-up time meaningful?	++	240 weeks, not too long – participants discontinued due to the commercial availability of drug.
Section 4: Analyses		
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NA	
4.2 Was ITT analysis conducted?	NA	
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.4 Were the estimates of effect size given or calculable?	++	The effect sizes are presented
4.5 Were the analytical methods appropriate?	+	95% confidence intervals and mixed model for repeated-measures

	Response	Comments
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	Confidence intervals were provided. The effects were clinically meaningful.
Section 5: Summary		
5.1 Are the study results internally valid (i.e., unbiased)?	+	The study is a single-arm study therefore it is impossible to determine the effect in the absence of the intervention.
5.2 Are the findings generalisable to the source population (i.e., externally valid)?	++	The participants, interventions and outcomes are reflective of that expected in clinical practice.

++ The study satisfies the criterion, + The study partially satisfies the criterion

Table C-15. Critical appraisal of non-randomised studies – Study 030

	Response	Comments
Section 1: Population		
1.1 Is the source population or source area well described?	++	The study was conducted at several clinical research sites in the USA. Outpatient (assumed from "Study subjects were to report to the clinic on the morning of each on-site visit and were to remain in the clinic until released by the Investigator after all the study-related procedures had been completed and the subject and/or parent(s)/caregiver had been instructed regarding drug storage, reconstitution, and administration.") Demographics adequately described (See CSR 11.2 Demographic and Other Baseline Characteristics)
1.2 Is the eligible population or area representative of the source population or area?	++	Subjects were recruited from dystrophinopathy populations who received care or were referred for evaluation at the investigational site, with clear, pre-specified eligibility criteria. The PI or sub-investigator discussed the possibility of participation directly with parent(s)/legal guardian in the clinic.
1.3 Do the selected participants or areas represent the eligible population or area?	++	" The study was conducted at several clinical research sites in the USA." Clear inclusion and exclusion criteria were pre-specified (see 9.3.1. and 9.3.2 of CSR).
Section 2: Method of allocation to intervention (or comparison)		
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	NA	
2.2 Were interventions (and comparisons) well described and appropriate?	++	A clear description of the intervention is provided. Study was open-label, so no comparator included.

	Response	Comments
2.3 Was the allocation concealed?	NA	
2.4 Were participants or investigators blind to exposure and comparison?	NA	Since this was an open-label study, randomisation and blinding were not utilised.
2.5 Was the exposure to the intervention and comparison adequate?	++	Exposure to intervention was adequate - All subjects received approximately 10-, 10-, 20-mg/kg ataluren TID for 4 weeks during the PK portion and for 48 weeks during the extension period.
2.6 Was contamination acceptably low?	NA	
2.7 Were other interventions similar in both groups?	NA	
2.8 Were all participants accounted for at study conclusion?	++	A total of 14 subjects were screened, and all were subsequently enrolled in the study (Section 14.1 Table 14.1.1). There were no screen failures.
2.9 Did the setting reflect usual UK practice?	++	Outpatient (assumed from "Study subjects were to report to the clinic on the morning of each on-site visit and were to remain in the clinic until released by the Investigator after all the study-related procedures had been completed and the subject and/or parent(s)/caregiver had been instructed regarding drug storage, reconstitution, and administration.")
2.10 Did the intervention or control comparison reflect usual UK practice?	++	As above, assumed outpatients, visiting clinics for study assessments
Section 3: Outcomes		
3.1 Were outcome measures reliable?	++	PK parameters, TFTs, NSAA, weight, height, BMI, Ataluren palatability characteristics as determined by a parent/caregiver questionnaire. AEs, dose-limiting toxicities, laboratory tests.
3.2 Were all outcome measurements complete?	++	All subjects were included in the safety population, PK population, and evaluable population. All 14 subjects completed the study, including the PK and extension phases
3.3 Were all important outcomes assessed?	++	All efficacy and safety endpoints reported on, other than weight, height and BMI
3.4 Were outcomes relevant?	++	The efficacy outcomes reflect a measure of the treatment effect, and adverse events were reported.

	Response	Comments
3.5 Were there similar follow-up times in exposure and comparison groups?	NA	
3.6 Was follow-up time meaningful?	++	Yes - 4-week screening period, a 52-week treatment period (the first 4 weeks of which included PK parameters), and a 4-week follow-up period for subjects who completed the treatment period (60 weeks total duration).
Section 4: Analyses		
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NA	
4.2 Was ITT analysis conducted?	NA	
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	
4.4 Were the estimates of effect size given or calculable?	++	The effect sizes are presented
4.5 Were the analytical methods appropriate?	+	Just descriptive statistics: n, mean, SD, median, range, and 95% confidence intervals.
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	Confidence intervals were provided. The effects were clinically meaningful.
Section 5: Summary		
5.1 Are the study results internally valid (i.e., unbiased)?	+	The study is a single-arm study therefore it is impossible to determine the effect in the absence of the intervention.
5.2 Are the findings generalisable to the source population (i.e., externally valid)?	++	The participants, interventions and outcomes are reflective of that expected in clinical practice.

++ The study satisfies the criterion, + The study partially satisfies the criterion

Table C-16 Critical appraisal of observational studies - STRIDE

Study name: STRIDE		
Study question	**Response** **yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients are eligible to participate in STRIDE if they have a confirmed genetic diagnosis of nmDMD and if they are, or will be, receiving usual care treatment with a commercial supply of ataluren (or receiving care within an early access program), and are willing to provide written informed consent for data collection procedures by themselves or a parent/legal guardian. Patients who are receiving ataluren or placebo in an ongoing, blinded, randomised clinical trial or ataluren in any other ongoing clinical trial or early access program that prevents participation in the current registry are not eligible to enrol in STRIDE, although those receiving ataluren can become eligible once they have completed the required follow-up, and fulfilled the conditions of the trial or early access program. Comparative data for STRIDE have been sourced from CINRG, which was designed using the World Health Organisation International Classification of Functioning, Disability and Health. The CINRG DNHS included patients with DMD at 20 centres around the world, collecting the most comprehensive and largest, prospective, longitudinal natural history data to date on a cohort of DMD patients.
Was the exposure accurately measured to minimise bias?	Yes	Enrolled patients in STRIDE were/are or would/will be receiving ataluren at study start and treatment discontinuations had been/are captured across the study period.
Was the outcome accurately measured to minimise bias?	Yes	The study endpoints included well established ambulatory and non-ambulatory outcome measures used across DMDs. All outcomes were assessed following standardised procedures. In the absence of a placebo control, the efficacy results for nmDMD patients in STRIDE were compared to propensity-matched historical controls from CINRG data. This comparison is based on a rigorous propensity score matching method that aligns with the Pharmacovigilance Risk Assessment Committee rapporteur request in the Assessment Report dated 28 February 2019 (procedure EMEA/H/C/002720/MEA 002.4) for analysis with individually matched patients from the CINRG database.

Have the authors identified all important confounding factors?	Yes	Genotype, corticoid use, ambulatory status at baseline are important prognostic and potential treatment effect modifiers and were handled appropriately in the study protocol.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	As per protocol, the efficacy of ataluren was assessed in study populations that accounted for important baseline and prognostic factors. The safety profile of ataluren was presented by corticoid use.
Was the follow-up of patients complete?	No	STRIDE is ongoing and expected to be completed in 2025, when patients would have been followed for at least 5 years. The CINRG natural history study is completed, and its values are sourced as comparative data to that obtained in STRIDE with ataluren.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Latest cut-off-date results from STRIDE were consistent within outcome measures and differences versus data from CINRG reached statistical significance, potentially reflecting the robustness of employing the propensity matching method.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

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

9.6.1.1 Summary of comparative efficacy data

A summary of available comparative data from studies 007, 020, 019 and STRIDE are shown in Table C-17 to Table C-19. Detailed results of each study are shown in sections 9.6.1.2, 9.6.1.3, 9.6.1.4, 9.6.1.6. Results from the single-arm study in patients aged 2 to 5 years (Study 030) are shown in section 9.6.1.5.

Table C-17. Meta-analysis (post-hoc) of Study 007 and Study 020 placebo-controlled RCTs – ambulatory outcomes

Study	LS Mean Difference (95% CI)	p value
Change in 6MWD		
ITT	17.2 (0.2, 34.1)	0.0473
6MWD ≥300 to <400	43.9 (18.2, 69.6)	0.0008
Change in 10-m run/walk		
ITT	1.1 (-2.2, 0.1)	0.0677
6MWD ≥300 to <400	-2.1 (-3.7, -0.4)	0.0149
4-stair climb		
ITT	-1.7 (-2.9, -0.4)	0.0078
6MWD ≥300 to <400	-3.4 (-5.3, -1.5)	0.0004
4-stair descend		
ITT	-1.9 (-3.2, -0.6)	0.0055
6MWD ≥300 to <400	-4.3 (-6.2, -2.3)	<0.0001

LS mean differences between ataluren and placebo groups were assessed by meta-analysis of the ITT and meta-analysis of patients with a baseline 6MWD ≥300–<400 m
6MWD: 6-minute walk distance; ITT: intent-to-treat; LS: Least-squares.
Source: Campbell et al. 2020[41]

Table C-18. Study 019 versus CINRG Propensity-Matched Population – ambulatory and pulmonary function outcomes

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

Source: McDonald et al. 2021[130]

Table C-19. STRIDE versus CINRG Propensity-Matched Population – ambulatory and pulmonary function outcomes

Assessment	STRIDE (ataluren + BSC) N=241	CINRG (BSC alone) N=241
Loss of ambulation		
Median age at event, years (95% CI)	**17.9** (14.4, NA)	**12.5** (11.6, 13.5)
p value[a]	<0.0001	
Hazard ratio (95% CI)[b]	0.374 (0.273, 0.512)	
Loss of time to Climb 4 Stairs ≥10 Seconds		
Median age at event, years (95% CI)	[redacted]	[redacted]
p value	[redacted]	
Hazard ratio (95% CI)	[redacted]	
Loss of Stand from Supine ≥10 Seconds		
Median age at event, years (95% CI)	[redacted]	[redacted]
p value[a]	[redacted]	
Hazard ratio (95% CI)[b]	[redacted]	
Predicted FVC <60%		
Median age at event, years (95% CI)	17.6 (16.2, NA)	15.8 (15.1, 16.5)
p value[a]	0.0051	
Hazard ratio (95% CI)[b]	0.544 (0.343, 0.863)	
Predicted FVC below 50%		
Median age at event, years (95% CI)	[redacted]	[redacted]
p value[a]	[redacted]	
Hazard ratio (95% CI)[b]	[redacted]	
Predicted FVC <30%		
Median age at event, years (95% CI)	NA (NA, NA)	25.4 (20.6, 29.4)
p value[a]	0.0085	

Assessment	STRIDE (ataluren + BSC) N=241	CINRG (BSC alone) N=241
Hazard ratio (95% CI)[b]	0.107 (0.014, 0.813)	
FVC <1 litre		
Median age at event, years (95% CI)	[redacted]	[redacted]
p value[a]	[redacted]	
Hazard ratio (95% CI)[b]	[redacted]	

[a] p value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.
[b] HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE versus CINRG.
Source: PTC Therapeutics Study 025o CSR 2021[153]; Tulinius et al. 2021[37]; Mercuri et al. 2021[34]

9.6.1.2 Study 007

Results for study 007 were provided during the 2015 assessment and are presented again below.

Baseline characteristics

Key patient demographics are shown in Table C-20 and there were no significant differences between the 3 arms. The use of corticosteroids was balanced across groups; no patient discontinued use of corticosteroids and dose changes were minimal.[154]

Table C-20: Patient baseline characteristics in Study 007

	Placebo N=57	Ataluren 40 mg/kg/day N=57	Ataluren 80 mg/kg/day N=60
Age, years Mean (SD) Median Range	 8.3 (2.33) 8.0 5-15	 8.8 (2.91) 8.0 5-20	 8.4 (2.53) 8.0 5-16
Body weight, kg Mean (SD) Median Range	 28.6 (9.1) 25.6 16-55	 31.2 (12.1) 27.0 16-76	 31.9 (12.8) 27.6 17-84
Corticosteroid use, n (%) Yes	 40 (70.2)	 41 (71.9)	 43 (71.7)
Baseline 6MWD, n (%) ≥350 m <350 m	 34 (60) 23 (40)	 32 (56) 25 (44)	 33 (55) 27 (45)

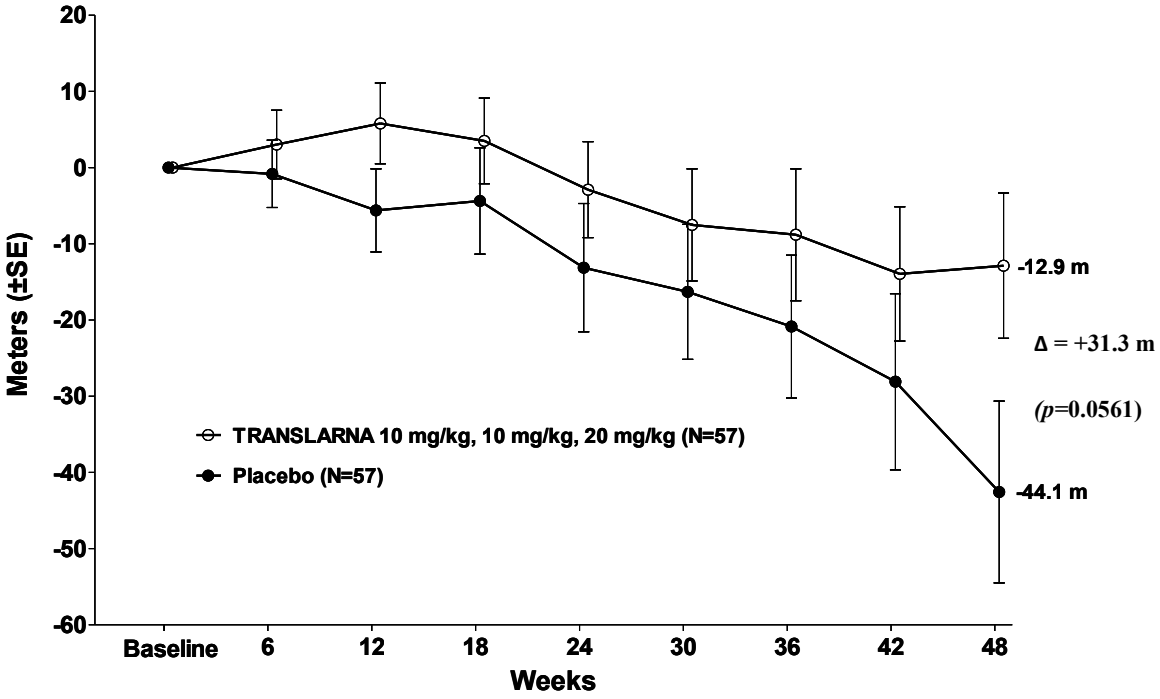
6MWD, 6-minute walk distance; kg, kilogram; mg, milligram; SD, Standard deviation
Source: Bushby et al. 2014[32]

Primary outcome measure results (6MWD)

A clinically meaningful and statistically significant treatment benefit was observed with ataluren. At 48 weeks in the ITT population, the decrease in 6MWD was 42.6 and 12.9 metres for placebo and ataluren, respectively (29.7 metres difference, nominal p=0.149, MMRM on ranks).[32] Furthermore, in the ITT population, the time to persistent 10% worsening in 6MWD analysis showed that 26% of patients in the ataluren arm had progressed at week 48 compared to 44% in the placebo group (HR 0.52, p=0.039).[32] These results show that fewer patients receiving ataluren worsened in the 6MWD over 48 weeks.

In the cITT population, patients receiving ataluren 40 mg/kg/day had a 12.9 metre mean decline in 6MWD and patients receiving placebo had a 44.1 metre mean decline in 6MWD (Figure C.10). The mean change in observed 6MWD from baseline to Week 48 was 31.3 metres less in the ataluren arm than in the placebo arm (p=0.056). Separation of ataluren from placebo was seen at all post-baseline visits.

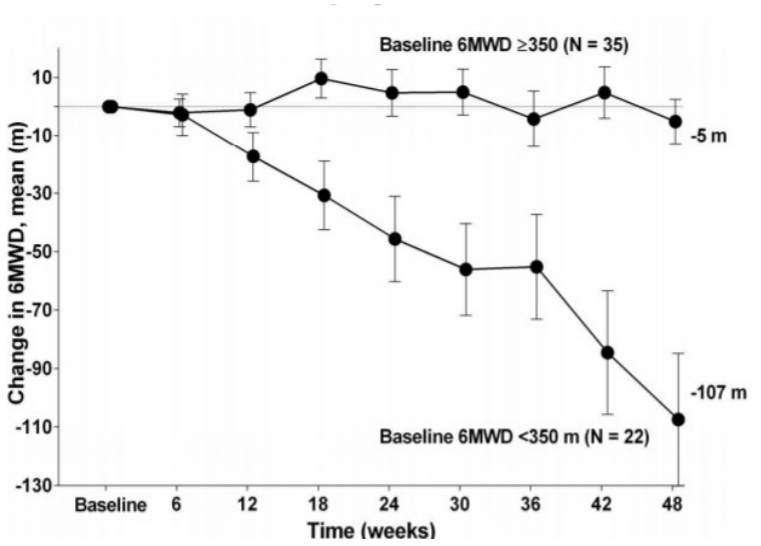
Figure C.10: Mean change in 6MWD over 48 weeks in Study 007 in the cITT population



6MWD, 6-minute walk distance; kg, kilogram; m, metre; mg, milligram; SE, standard error
Source: Illustration was created by PTC based on Busby 2014 [32]

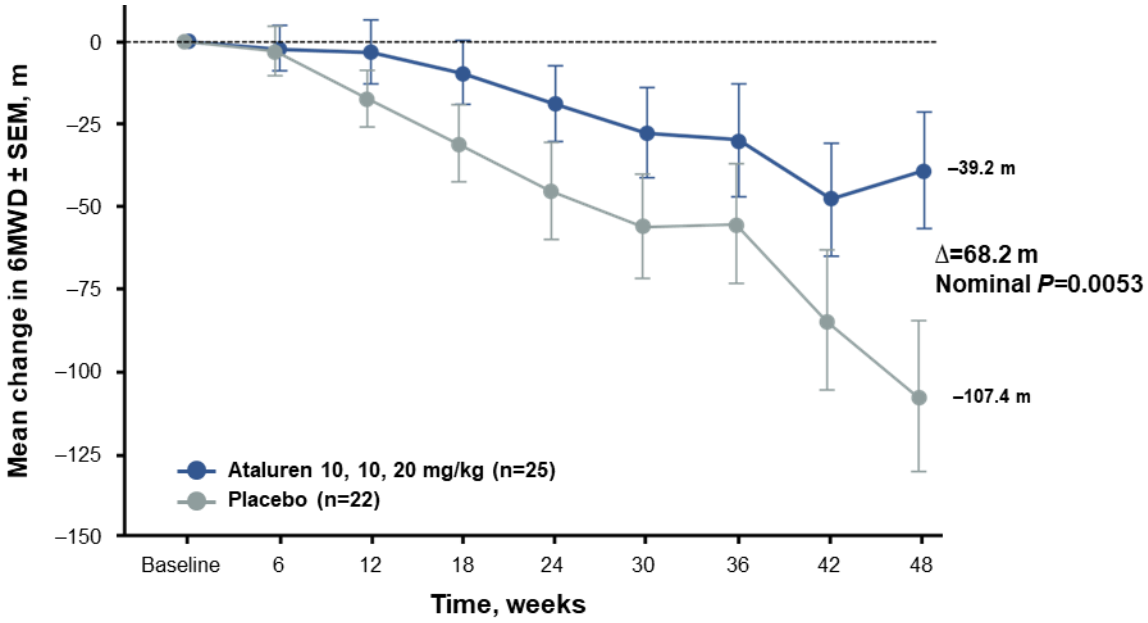
As discussed in section 6.1.3.3, the natural history of changes in ambulation as measured by the 6MWT indicate varied rates of loss of walking ability: whilst patients with a walking distance of greater than 400 metres at baseline generally do not demonstrate substantial changes in their 6MWDs in 48 weeks, those with a 6MWD less than 400 metres tend to have larger declines. In study 007, since a baseline value of 350 metres was a pre-specified stratification factor, an analysis was carried out on this group. Figure C.11 shows that by week 48 in the placebo arm, patients with a baseline 6MWD ≥350 m are stable, losing only 5 metres on average, whereas the patients with mean baseline <350 metres showed a large decline of 107 metres. In the pre-specified group with baseline 6MWD <350 metres (Figure C.12), the mean 6MWD declined by 68.2 metres less in ataluren patients compared to placebo-dosed patients from baseline to week 48 (nominal *p*=0.0053).

Figure C.11: Mean change in 6MWD from baseline to week 48 in Study 007 patients with baseline 6MWD <350 metres versus ≥350 metres subgroups (placebo arm)



6MWD, 6-minute walk distance; kg, kilogram; m, metre; mg, milligram; SE, standard error
Source: PTC Clinical Study Report Study 007[154]

Figure C.12: Mean change in 6MWD over 48 weeks in Study 007 patients with baseline 6MWD <350 metres



6MWD, 6-minute walk distance; SE, standard error
Source: Bushby et al. 2014[32]

Secondary outcome measures

Timed functions tests

The TFTs were a secondary endpoint in Study 007 and consistently demonstrated a trend in favour of ataluren. As shown in Table C-21, the time taken to carry out TFTs increased to a lesser extent for ataluren compared to placebo in time to climb 4 stairs (difference of 2.4 s), time to descend 4 stairs (difference of 1.6 s) and time to run/walk 10 metres (difference of 1.4 s). Importantly, the observed differences are clinically relevant and meaningful to patients (see section 4.1.3). Compared with the TFT results in the cITT, in the pre-specified baseline 6MWD <350 metres subgroup, the results favouring ataluren were even greater (data not shown).

Table C-21. Study 007, changes in TFTs, cITT analysis set

	Placebo		Ataluren		Comparison of change baseline to week 48 ataluren and placebo, mean 95%
Endpoint	Baseline	Week 48	Baseline	Week 48	
Climb 4 stairs, s	6.0	10.8	6.9	9.3	-2.4 (-4.8, 0.0)
	Δ=4.8		Δ=2.4		
Descend 4 stairs, s	5.5	9.6	6.1	8.5	-1.6 (-4.2, 1.0)
	Δ=4.0		Δ=2.4		
Run/walk 10 m, s	6.8	9.8	7.4	9.1	-1.4 (-3.7, 0.9)
	Δ=3.0		Δ=1.7		

cITT, corrected intention-to-treat; mm metre; s, second; TFT, timed function tests

Source: Bushby et al. 2014[32]

Accidental falls

Accidental falls were monitored using patient/caregiver diaries. The relative ratios of the estimated fall rates at week 48 were 0.38 (95% CI, 0.16 to 0.94) for ataluren versus placebo. Positive trends for ataluren versus placebo were also seen across the other secondary outcomes of physical functioning, including activity and wheelchair use in the community and evaluation of muscle strength.

Patient-reported outcome measures

Positive trends were seen in patient-reported HRQL (assessed by the PedsQL) which comprises physical functioning and psychosocial functioning (i.e., emotional functioning, social functioning, and school functioning) scales.

From baseline to week 48, patients in the ataluren group had a higher mean change in the PedsQL physical and school functioning score than placebo-dosed patients (Table C-22).

Table C-22. Patient-reported HRQL (assessed by the PedsQL) in Study 007 (ITT population)

	Placebo		Ataluren		Difference, mean (95% CI)
	Baseline, mean	Δ at week 48, mean	Baseline, mean	Δ at week 48, mean	
Physical	61.9	-1.0	59.3	2.4	3.4 (-5.5 to 12.2)
Emotional	70.1	4.3	73.7	-1.8	-6.1 (-14.3 to 2.1)
Social	63.4	7.8	65.1	3.9	-3.9 (-11.7 to 4.0)
School	64.7	4.1	64.6	6.1	2.1 (-6.0 to 10.1)

CI, confidence interval; HRQL, health-related quality of life; ITT, intention-to-treat; PedsQL, Paediatric Quality of Life Inventory

Source: PTC Study 007 CSR[154]

Interpretation of results

In Study 007, ataluren slowed the rate of decline of walking ability and achieved the pre-specified endpoint (and MCID) of 30 metres in 6MWD at 48 weeks in ambulatory boys with nmDMD.[16,58] In all pre-specified subgroups based on age, baseline 6MWD and glucocorticoid use, ataluren patients performed better than placebo. Results were most pronounced in the patients with advanced disease (i.e., 6MWD <350 metres) who have measurable declines in ambulation.

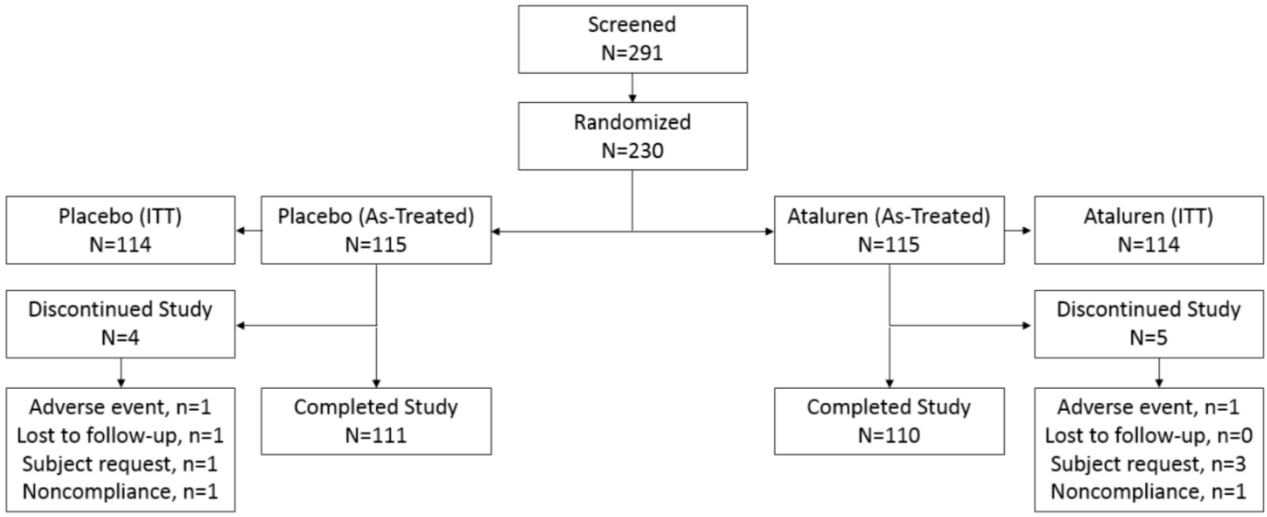
9.6.1.3 Study 020

Results for study 020 were provided during the 2015 assessment and are presented again below.

Baseline characteristics

In Study 020, 230 patients were randomly assigned to receive ataluren (N=115) or placebo (N=115); 228 patients comprised the ITT population.

Figure C.13. Patient disposition



ITT, intention-to-treat
Source: PTC Clinical Study Report, Study 020 [146]

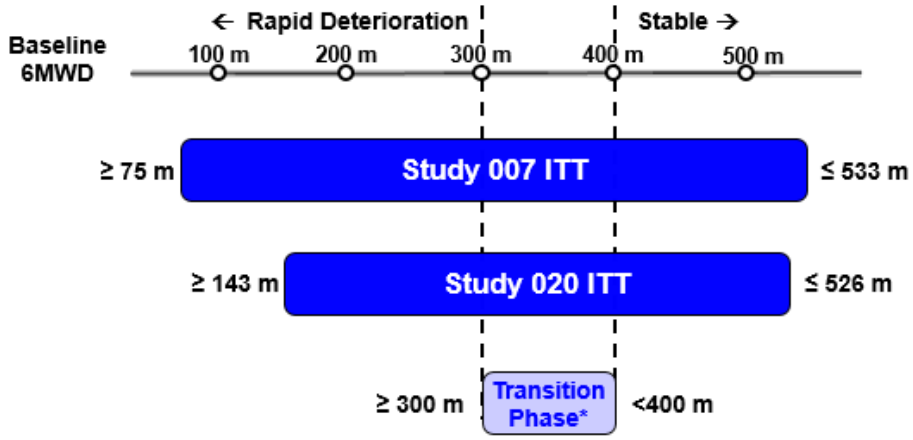
Baseline demographics and characteristics were similar between groups (see Table C-23). The patient population of Study 020 had baseline 6MWDs ranging from 143 to 526 metres, indicating that the overall study population was heterogeneous and included patients in the stable, transition, and accelerated decline phases of the ambulatory stage. Stable patients were not expected to decline during a 48-week study so the goal was to reduce the number of stable patients within the cohorts at baseline. Unfortunately, the 80% of predicted 6MWD inclusion criteria was set too high to adequately exclude these patients. Consequently, many stable patients were included. Figure C.14 shows the range of baseline 6MWD in both Study 007 and Study 020 and the number of patients falling in the transition phase of the disease.

Table C-23. Patient baseline characteristics in Study 020

	Ataluren N=115	**Placebo N=115**
Age (years)	9.0 (7-10)	9.0 (8-10)
Weight (kg)	29.3 (23-37)	27.0 (24-34)
6MWD (m)	375.2 (314-421)	370.5 (314-422)
6MWD Category		
<300 m	25 (22%)	22 (19%)
≥300 m to <400 m	47 (41%)	52 (45%)
≥400 m	43 (37%)	41 (36%)
Corticosteroid use		
Deflazacort	50 (44%)	54 (47%)
Prednisone	38 (33%)	37 (32%)
Prednisolone	29 (25%)	28 (24%)

6MWT, 6-minute walk test, m, metre
Source: McDonald et al. 2017 [33]

Figure C.14. Range of baseline 6MWD in Study 020 and Study 007



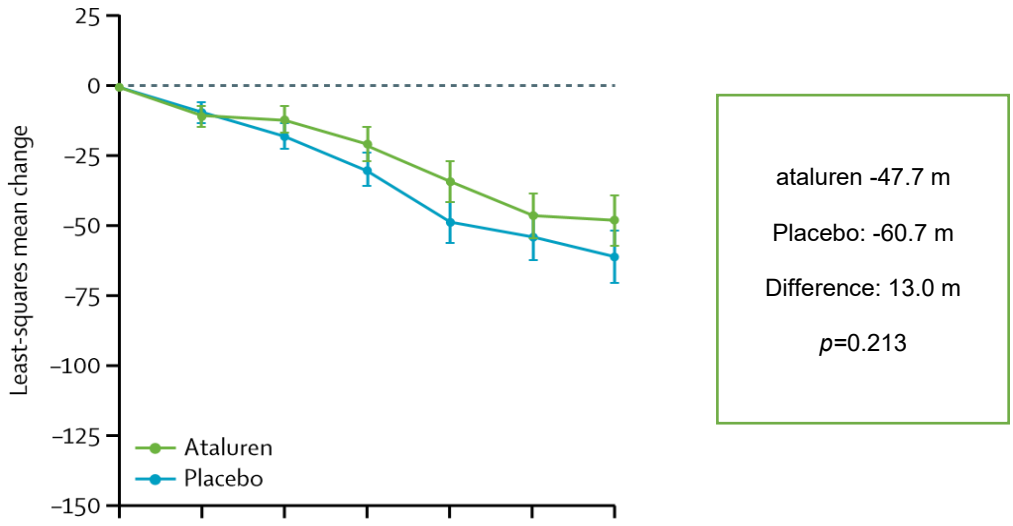
6MWD, 6-minute walk distance; ITT, intention-to-treat; m, metre
Note: Pre-specified analysis subgroup in Study 020
Source: Illustration was created by PTC based on Study 020 and Study 007 [146,154]

Primary outcome results (6MWD)

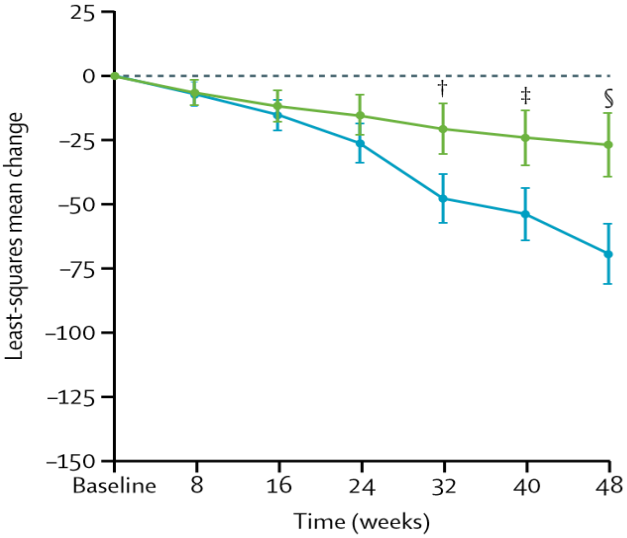
The observed difference between the ataluren and placebo in mean change in observed 6MWD from baseline to week 48 was 15.4 metres in favour of ataluren versus placebo in the ITT population. The least-squares mean change in 6MWD from baseline to 48 weeks was -47.7 metres (standard error [SE] 9.3) for ataluren and -60.7 metres (9.3) for placebo (difference 13.0 metres [SE 10.4], 95% CI, -7.4 to 33.4; p=0.213). As shown in Figure C.15, separation between ataluren and placebo was maintained from week 16 through the end of the study and the effect was more evident in the pre-specified subgroup of patients with 6MWD ≥300 metres to <400 metres with an observed difference of 47.2 metres in favour of ataluren versus placebo. The least-squares mean change in this subgroup was -27.0 metres (SE 12.6) for ataluren and -69.9 metres (12.1) for placebo at week 48 (difference 42.9 metres [SE 15.9], 95% CI, 11.8 to 74.0; p=0.007).

Figure C.15. Least-squares mean change 6MWD baseline to week 48 (ITT and 6MWD ≥300 to <400 populations)

ITT population



Pre-specified 6MWD ≥300 m to <400 m subgroup



ataluren -27.0 m

Placebo: -69.9 m

Difference: 42.9 m

p=0.007

6MWD, 6-minute walk distance; ITT, intention-to-treat; m, metre; †p=0.032. ‡p=0.030. §p=0.007
Source: McDonald et al. 2017 [33]

Secondary outcomes

Timed function tests

Patients in the ataluren group had less of a decline in physical function than did those in the placebo group, as measured by the timed function tests after 48 weeks of treatment; however, only the four-stair descend was statistically significant in the ITT population. This treatment effect was more evident in the subgroup of patients with a baseline 6MWD ≥300 metres to <400 metres.

The results were similar to those in Study 007 and reached the threshold for a clinically meaningful difference (change ~1 to 1.5 seconds, see section 4.1.3). Although stair-climbing and stair-descending were secondary endpoints in Studies 007 and 020, the parallel results in the ITT populations of both these trials support the efficacy of ataluren, especially considering the known limitations of the 6MWT in boys with DMD (see section 6.1.3.1).

Table C-24. Key Secondary Endpoints Consistent with Primary Endpoint in ITT Population

Group	Endpoint	LS mean difference (SE), seconds	p value
ITT	10-m run/walk	−1.1 (0.7)	0.117
	4-stair climb	−1.4 (0.8)	0.058
	4-stair descend	−2.0 (0.8)	0.012
≥300 m to <400 m subgroup	10-m run/walk	−1.8 (1.0)	0.066
	4-stair climb	−3.5 (1.2)	0.003
	4-stair descend	−4.4 (1.2)	<0.001

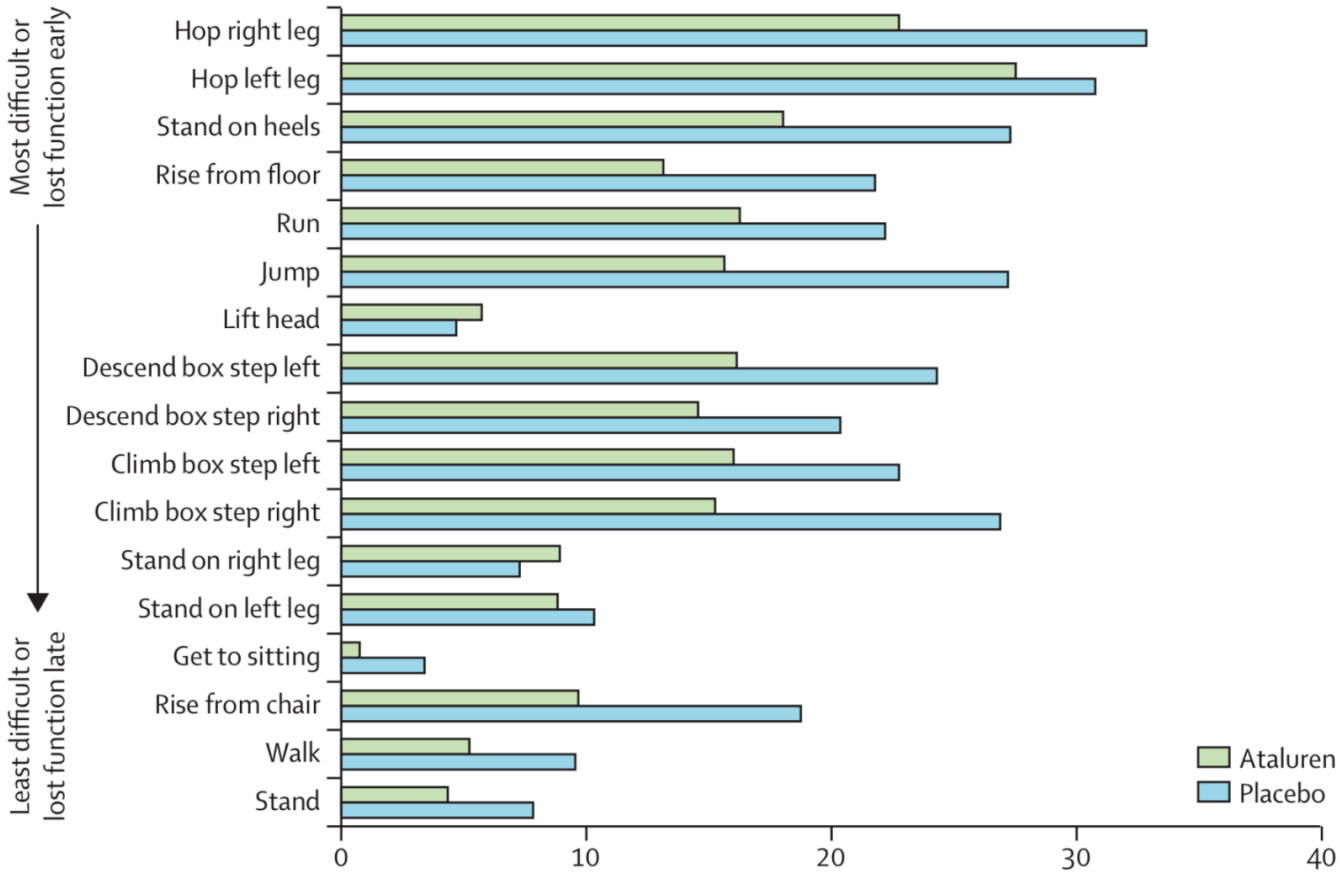
ITT, intention-to-treat; LS, least-squares; m, metre; SE, standard error
Source: McDonald et al. 2017[33]

NSAA

The results for the total NSAA score also support the efficacy of ataluren. There was a least-squares mean treatment different of 0.8 points (SE 0.5, 95% CI, -0.2 to 1.8; p=0.128; ordinal scale) in the pre-specified total NSAA score [33]. This effect was more noticeable in patients with baseline 6MWD ≥300 metres to <400 metres, based on both observed total score (least-squares mean difference 1.7 points [SE 0.8], 95% CI, 0.1 to 3.3; p=0.37) and linear-transformed score (4.2 points [2.1], CI, -0.2 to 8.4; p=0.041).[33]

A 1.0-point difference relates directly to the change from performing an item normally to performing it with compensation, or from performing an item with compensation to inability to perform the function. The results were more striking when comparing the individual functions of the NSAA score that were preserved in ataluren versus placebo-treated patients (Figure C.16). In nearly all measures, muscle function was retained in more patients in the ataluren group compared with the placebo group. The level of preservation was quantified by calculating the proportion of patients who lost the ability to perform individual functions in each treatment arm to obtain the relative risk (RR) of losing a motor function. The relative risk for ataluren versus placebo was 0.69 (p=0.010, post-hoc permutation test) across the 17 functional outcome measures.[33] This means that among patients who could carry out an activity at baseline either normally or with compensation, ataluren-treated patients had a 31% reduction in risk of losing a motor ability. The importance of this result is that it demonstrates that ataluren substantially preserves functions meaningful to patients with nmDMD.

Figure C.16. Proportion of patients who lost ability to perform NSAA item in Study 020 (ITT)



ITT, intention-to-treat; NSAA, North Star Ambulatory Assessment
Source: McDonald et al. 2017[33]

Loss of ambulation

LoA was carried out as a post-hoc analysis in Study 020. In the ITT population, 9 (8%) in the ataluren group lost ambulation compared with 14 (12%) in the placebo group. For patients in the baseline 6MWD ≥300 to <400 metres, none of the 47 patients in the ataluren group lost ambulation after 48 weeks versus four (8%) of 52 patients in the placebo group.[33]

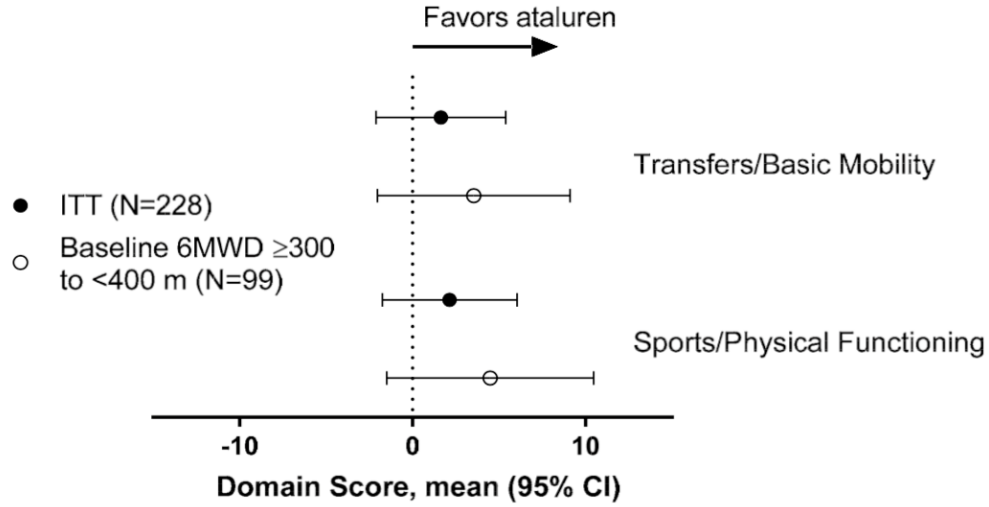
Patients who completed Study 020 were eligible to participate in an ongoing open-label phase 3 extension (Study 020e). On the reference date of 1 February 2016, data were available in the 020e study for a treatment period of at least 48 weeks for a total of 107 patients (53 and 54 randomised

to ataluren and placebo respectively in the 020 study). Among patients who were randomised to ataluren and had 6MWD ≥300 to <400 metres at baseline in Study 020, [redacted] lost ambulation through up to 96 weeks of treatment. In comparison, [redacted] patients who were randomised to placebo and had 6MWD ≥300 to <400 metres at baseline in Study 020 have lost ambulation through up to 96 weeks of treatment, including [redacted] patients during Study 020 (on placebo). [redacted] placebo patients during Study 020e (on delayed ataluren) lost ambulation, and [redacted] had baseline 6MWD <300 metres in Study 020e (PTC Data on file. 020e data cut[155]).

Patient-Reported Outcome Measures

In Study 020, two PODCI domains (transfers/mobility and sports/physical functioning) were evaluated. These two domains are significantly associated with disease progression in patients with DMD; and consequently, were used in Study 020. The transfers/basic mobility domain assesses difficulty experienced in performing routine motor activities in daily life. The sports/physical functioning domain assesses difficulty encountered in participating in more active recreational activities. Each domain is scored from 0 to 100, with 100 representing the highest level of functioning and least pain. Changes in parent/caregiver-reported HRQL, as assessed by the PODCI transfers/basic mobility and sports/physical functioning domain scores, favoured ataluren over placebo in the ITT population and in patients with baseline 6MWD ≥300 to <400 metres (Figure C.17).

Figure C.17. PODCI transfer/basic mobility and sports/physical functioning domain scores



6MWD, 6-minute walk distance, CI, confidence interval, ITT, intent-to-treat, PODCI, Paediatric Outcomes Data Collection Instrument

Source: PTC Clinical Study Report Study 007[146]

Interpretation of results

Although the difference in 6MWD between ataluren and placebo-treated patients in the ITT was not significant, the treatment effect was evident in the pre-specified subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres. The lack of statistical significance in the ITT group was due to the restricted sensitivity of the 6MWT (over 48 weeks) in patients with higher baseline function (i.e., ≥400 metres) and the increased interpatient variability in the patients with baseline <300 metres. Patients with 6MWD ≥ 400 metres accounted for 37% of patients. Nevertheless, fewer patients lost ambulation in the ataluren group than the placebo group in both the ITT and in patients with baseline 6MWD of ≥300 metres to <400 metres. In addition, the TFTs showed a 1.1 to 2.0 seconds benefit in

the ITT population and an even more pronounced benefit in the baseline 6MWD of ≥300 metres to <400 metres subgroup. A 1.0- to 1.5-second treatment effect on a TFT translates to differences in physical and social activities for patients with DMD (see section 4.1.3). A clinical benefit was also seen in the NSAA.

9.6.1.4 Study 019

Baseline Characteristics

A total of 94 boys were included in Study 019, 90 had participated in both the ataluren phase 2b study (Study 007) and the extension study (Study 007e), three had participated in the ataluren phase 2a study (Study 004) and one patient who did not have previous exposure to ataluren and was enrolled through an institutional review board- and US FDA-approved special exemption.[130] Fifty patients were ambulatory, and 44 patients were non-ambulatory at study entry. Not all patients immediately entered Study 019 from a prior ataluren study; the mean (SD) treatment gap between the prior studies and Study 019 for the 93 patients who had participated in previous trials was 2.9 (0.5) years (range 144–266 weeks). Mean age of enrolled patients at baseline in Study 019 was 12.8 years, representing an older patient population with more advanced disease (Table C-25). Corticosteroids were used by 84 patients (89.4%) at baseline. Of the 50 ambulatory patients in Study 019, 47 patients (94%) were using corticosteroids.

Table C-25. Baseline demographics and characteristics for all patients with nmDMD receiving ataluren 40 mg/kg/day plus BSC in Study 019 (as-treated population)

Parameter	Ambulatory	Non-ambulatory	Overall
	n=50	n=44	N=94
Age, years	12.1 (2.1)	13.7 (2.5)	12.8 (2.4)
Age groups, n (%)			
6 to ≤11 years	18 (36.0)	6 (13.6)	24 (25.5)
12 to ≤17 years	31 (62.0)	34 (77.3)	65 (69.1)
≥18 years	1 (2.0)	4 (9.1)	5 (5.3)
Race, n (%)			
Caucasian	46 (92.0)	41 (93.2)	87 (92.6)
Asian	3 (6.0)	1 (2.3)	4 (4.3)
Other	0	2 (4.5)	2 (2.1)
Weight, kg	39.5 (9.5)	53.1 (15.0)	45.8 (14.0)
Height, cm[a]	131.6 (11.1)	135.0 (7.0)	132.1 (10.7)
BMI, kg/m^2	22.8 (4.6)	26.7 (4.8)	23.3 (4.8)
Corticosteroid use, n (%)[b]	47 (94.0)	37 (84.1)	84 (89.4)
Prednisone/prednisolone	14 (28.0)	21 (47.7)	35 (37.2)
Deflazacort	35 (70.0)	16 (36.4)	51 (54.3)
Time to walk/run 10 m, seconds	8.4 (4.7)	37.0 (N/A)[c]	8.9 (6.1)
FVC, L[d,e]	N/A	1.9 (0.5)	N/A
% predicted FVC[d,e]	N/A	72.7 (20.6)	N/A

BMI, body mass index; BSC, best supportive care; FVC, forced vital capacity; N/A, not applicable; SD, standard deviation

Baseline values were the last non-missing numeric value on or before the first dose of study medication.

Data are mean (SD) unless indicated otherwise.

[a] Height values for some non-ambulatory patients were not collected.

[b] Patients could be treated with more than one corticosteroid.

[c] Data for one of the 44 patients were available for the time to walk/run 10 m assessment before the first dose of study treatment was administered. Despite this one patient being defined as non-ambulatory at Study 019 entry as per the definition of taking >30 seconds to run/walk 10 m, he completed baseline assessments intended for ambulatory patients (including time to walk/run 10 m, seconds).

[d] Baseline pulmonary function assessments were only performed for non-ambulatory patients.

[e] One of the 44 non-ambulatory patients had missing baseline FVC and percentage predicted FVC values.

Source: McDonald et al. 2021[130]

Demographics and Characteristics of Propensity Score Matched Patients from Study 019 and CINRG DNHS

Of the 440 patients in CINRG DNHS, 22 had participated in previous clinical trials of ataluren or had received eteplirsen, drisapersen, or tadalafil and were thus excluded before propensity score matching (Table C-26).

Of the 94 patients from Study 019, 60 were eligible for propensity score matching with patients from CINRG DNHS (N=418) for the analysis of age at LoA, according to the criteria (age at onset of first symptoms, age at initiation of corticosteroid use, duration of deflazacort use, duration of use of other corticosteroids), yielding similar populations (N=60) with respect to established predictors of disease progression.[130] Of the 94 patients from Study 019, 45 non-ambulatory patients were eligible for propensity score matching (i.e. they had available data for age at LoA and the four covariates used for propensity score matching) with patients from CINRG DNHS for the analysis of age at decline in pulmonary function, according to the above criteria, yielding similar populations (N=45) with respect to established predictors of disease progression.[130]

Regarding the criteria used in the propensity score matching analysis, it should be noted that in Study 019, the age at first symptom was not collected, which makes it unavailable for use as a covariate for propensity score matching against patients with DMD from CINRG DNHS. As an alternative for this assessment, PTC decided to use age at diagnosis since those data were collected in Study 019. Accepting that these 2 outcomes are not the same, and that age at first symptom is a more appropriate predictor of future disease progression, PTC is confident that selection of age at diagnosis is a conservative proxy.

Table C-26. Baseline demographics and characteristics for all patients in Study 019 and CINRG DNHS, before and after propensity score matching

Assessment	Study 019 N=94	CINRG DNHS N=418	P value
All patients with nmDMD receiving ataluren 40 mg/kg/day plus BSC in Study 019 (as-treated population) and patients with DMD receiving BSC alone in CINRG DNHS, **before propensity score matching**			
Age at first symptoms, years† N Mean (SD)	NA	 405 3.2 (1.7)	0.0634‡
Age at diagnosis, years N Mean (SD)	 93 3.6 (1.9)	 417 4.4 (2.1)	
Age at corticosteroid initiation, years§ N Mean (SD)	 94 13.0 (9.5)	 417 11.5 (9.7)	
Deflazacort duration, n (%)¶ <1 month ≥1 to <12 months ≥12 months	 48 (51.1) 2 (2.1) 44 (46.8)	 249 (59.6) 21 (5.0) 148 (35.4)	0.0800
Other corticosteroid duration, n (%)¶ <1 month ≥1 to <12 months ≥12 months	 66 (70.2) 4 (4.3) 24 (25.5)	 216 (51.7) 35 (8.4) 167 (40.0)	0.0046
Baseline 6MWD, m N Mean (SD)	 90 358.3 (99.1)	 134 350.1 (123.6)	0.5808
Time to climb four stairs at first assessment, seconds#			0.9118

Assessment	Study 019 N=94	CINRG DNHS N=418	P value
N Mean (SD)	92 6.6 (6.9)	250 6.5 (5.4)	
Time to walk/run 10m at first assessment, seconds# N Mean (SD)	 92 7.4 (4.6)	 261 7.5 (3.9)	0.8131
Time to stand from supine at first assessment, seconds# N Mean (SD)	 92 10.5 (10.3)	 230 6.9 (4.8	0.0019
Patients with nmDMD in Study 019 who received ataluren (40 mg/kg/day) plus BSC in at least Study 019 (N=60) and for **propensity score matched** patients with DMD receiving BSC alone in CINRG DNHS (N=60), for the evaluation of LoA			
Age at first symptoms, years† Mean (SD)	 NA	 3.9 (1.7)	0.3859‡
Age at diagnosis, years Mean (SD)	 3.6 (2.0)	 4.9 (2.3)	
Age at corticosteroid initiation, years§ Mean (SD)	 10.9 (8.1)	 10.1 (8.1)	0.6182
Deflazacort duration, n (%)¶ <1 month ≥1 to <12 months ≥12 months	 24 (40.0) 1 (1.7) 35 (58.3)	 27 (45.0) 2 (3.3) 31 (51.7)	0.6865
Other corticosteroid duration, n (%)¶ <1 month ≥1 to <12 months ≥12 months	 37 (61.7) 4 (6.7) 19 (31.7)	 37 (61.7) 2 (3.3) 21 (35.0)	0.6816
Time to climb four stairs at first assessment, seconds# n Mean (SD)	 60 5.3 (5.9)	 31 6.9 (6.5)	0.2247
Time to walk/run 10m at first assessment, seconds# n Mean (SD)	 60 6.6 (4.2)	 33 8.2 (4.5)	0.0851
Time to stand from supine at first assessment, seconds# n Mean (SD)	 60 7.8 (8.5)	 26 7.2 (5.9)	0.7296

6MWD: 6-minute walking distance; BSC, best supportive care; LoA, loss of ambulation; NA, not available; SD, standard deviation

Notes: P values were calculated based on a two-sample t-test for continuous variables or a χ^2 test for categorical variables. Data are mean (SD) unless indicated otherwise.

† The patients' age at first symptoms was not captured in patients in Study 019.

‡ P value is for the comparison between the age at diagnosis for Study 019 patients and age at first symptoms for CINRG DNHS patients.

§ Age at initiation of corticosteroid use for steroid-naïve patients (patients who had never used steroids or used steroids after loss of ambulation) in Study 019 was set to 30 years.

¶ Corticosteroid duration is calculated from starting use of corticosteroid to LoA/censored date.

Time to climb four stairs, walk/run 10 m, and stand from supine at first assessment were determined using baseline values from the prior ataluren studies that the patients were enrolled in, i.e., Study 007/007e or Study 004/004e.

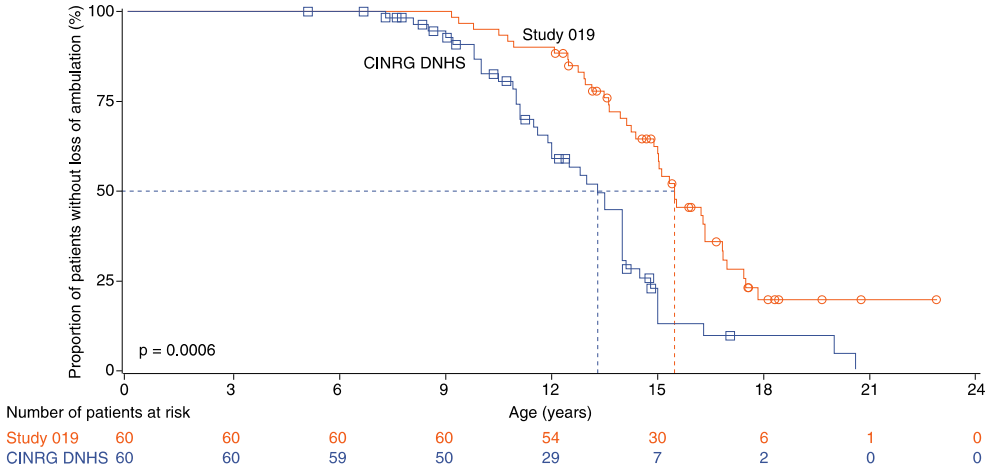
Source: McDonald et al. 2021[130]

Efficacy in Ambulatory Patients (Study 019 Compared to CINRG DNHS)

Comparisons between patients treated with ataluren plus BSC (Study 019) versus BSC alone (CINRG DNHS) were made using a subject-level (propensity score) matching method (see table Table C-8).

In the propensity score matched populations the median age at LoA was 15.5 years for the 60 subjects treated with 40 mg/kg ataluren plus BSC in Study 019 and 13.3 years in the matched CINRG DNHS cohort, representing a statistically significant difference in favour of ataluren plus BSC (p=0.0006) (Figure C.18).

Figure C.18. Age at LoA for Patients with nmDMD Receiving Ataluren 40 mg/kg/day plus BSC in Study 019, and Patients with DMD Receiving BSC Alone in CINRG DNHS (Propensity Score Matched Between the Studies)



BSC, best supportive care; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; LoA, loss of ambulation; nm, nonsense mutation
Note: The median ages at LoA for patients in Study 019 and CINRG DNHS are depicted by the dashed lines.
Source: McDonald et al. 2021[130]

Forced Vital Capacity

In Study 019, FVC was assessed only for non-ambulatory patients, thus only non-ambulatory subjects are included in these analyses. Please see Section 6.1.3.2 for the clinical meaningfulness of each pulmonary endpoint discussed in the next paragraphs.

Ataluren plus BSC was associated with a delay in the age at predicted FVC <60% by 3 years in non-ambulatory patients, compared with BSC alone. The median ages at predicted FVC <60% were 18.1 years and 15.1 years for patients from Study 019 and CINRG DNHS (each N=45), respectively (p=0.0004) (Figure C.19a). Overall, 23 non-ambulatory patients (51.1%) from Study 019 and 32 non-ambulatory patients (71.1%) from the CINRG DNHS experienced a decline to predicted FVC <60%.

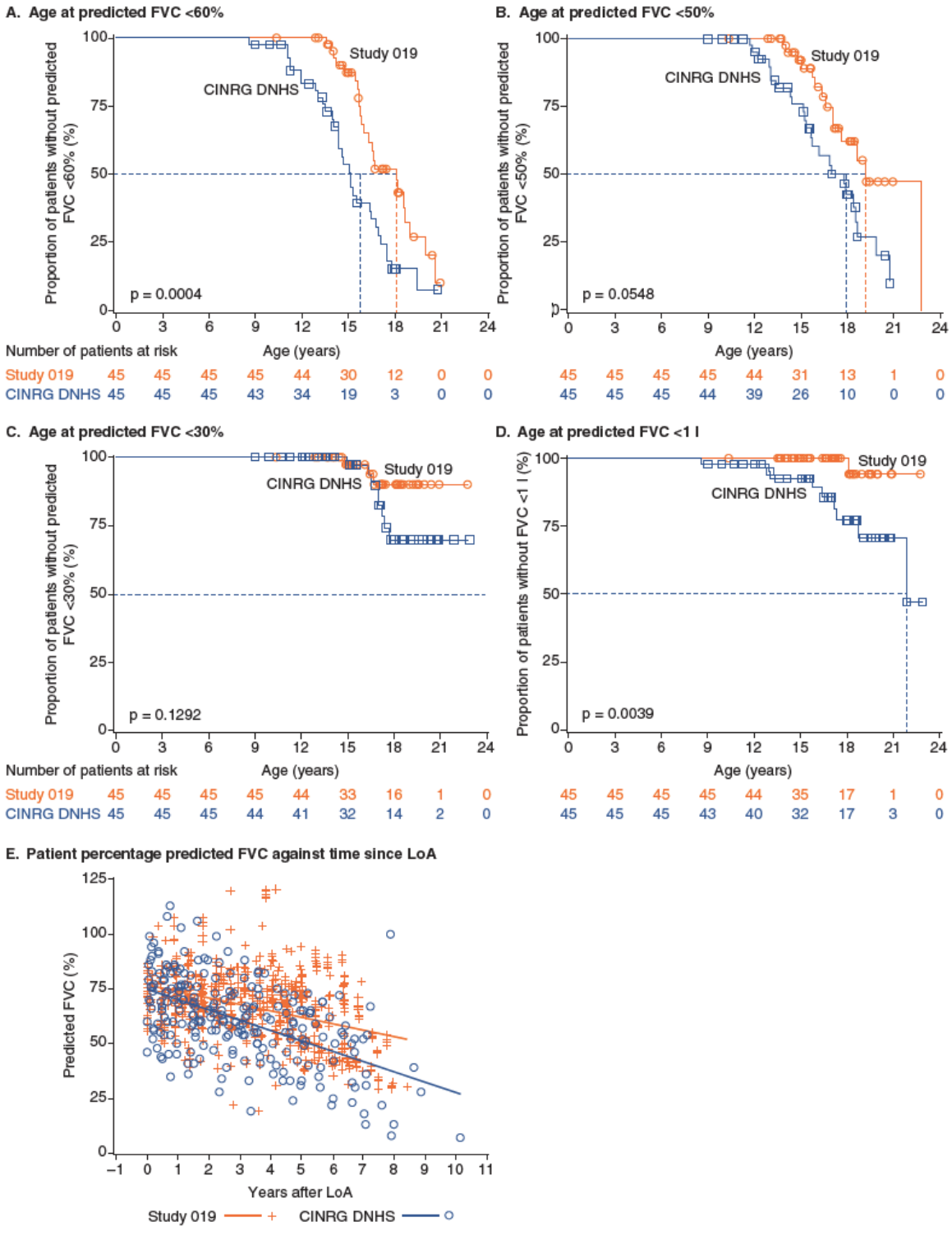
The median ages at predicted FVC <50% were 19.1 years and 17.8 years, respectively (p=0.0548) (Figure C.19b). Overall, 14 non-ambulatory patients (31.1%) from Study 019 and 24 non-ambulatory patients (53.3%) from CINRG DNHS experienced a decline to predicted FVC <50%.

Overall, one non-ambulatory patient (2.2%) from Study 019 and nine non-ambulatory patients (20.0%) from CINRG DNHS experienced a decline to an FVC of 1 litre. The median age at FVC of <1 litre was 21.9 years for non-ambulatory patients from CINRG DNHS (Figure C.19d). Owing to a low number of events, the median age for this advanced stage disease endpoint could not be calculated for the Study 019 non-ambulatory population.

A scatter plot of percentage predicted FVC over time since losing ambulation indicated a more gradual decline in pulmonary function in patients treated with ataluren 40 mg/kg/day plus BSC compared with patients receiving BSC alone in CINRG DNHS (Figure C.19e). This result demonstrates that the observed delay in decline to predicted FVC of <60% with ataluren treatment

is not simply reflective of the 2.2-year delay in LoA. Patients who received ataluren 40 mg/kg/day plus BSC in Study 019 took longer to reach predicted FVC <60% following LoA relative to patients receiving BSC alone in CINRG DNHS (median duration of 4.9 years [n=45] and 3.6 years [n=35], respectively; p=0.2190).

Figure C.19. Age at a) Predicted FVC <60%, b) Predicted FVC <50%, c) Predicted FVC <30%, d) FVC <1 litre and e) the % predicted FVC since loss of ambulation in Study 019 and CINRG DNHS (Propensity Score-Matched)



CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC, forced vital capacity; NC, non-calculable
Note: The median ages at decline in pulmonary function for patients in Study 019 and CINRG DNHS are depicted by the dashed lines.
Source: McDonald et al. 2021[130]

Interpretation of Results

Treatment with ataluren plus BSC significantly delayed LoA by 2.2 years compared with BSC alone. In the propensity score matched populations, the median age at LoA was 15.5 years in Study 019 and 13.3 years in the matched CINRG DNHS cohort, representing a statistically significant, clinically meaningful difference in favour of ataluren plus BSC versus BSC alone. The observed delay in LoA by over 2 years represents not only a highly meaningful prolongation of personal autonomy in daily life, but also a delay in the onset of subsequent disease milestones.

Treatment with ataluren plus BSC significantly delayed loss of pulmonary function, which is clinically relevant given that pulmonary failure is one of the most common causes of death in DMD. The comparative data from Study 019 and the matched CINRG DNHS cohort demonstrates that the dystrophin-restoring mechanism of action of ataluren can be beneficial to patients with nmDMD throughout different stages of disease, regardless of ambulatory status. Ataluren can provide further benefit to that already conferred by corticosteroids and preserve vital functions such as the patients' ability to breathe independently.

9.6.1.5 Study 030

Baseline Characteristics

The demographic and baseline characteristics of the patients recruited into Study 030 are shown in Table C-27. A total of 14 patients were screened, treated with ataluren and completed the study.[131] Despite the mean height and mean weight being slightly higher in patients in Study 030 than in patients of the CINRG DNHS external control group, the BMI of the 2 groups was similar.

Table C-27. Demographics and Baseline Characteristics Study 030

Patient Characteristic Statistic	**Study 030 - 40 mg/kg Ataluren (N=14)**
Age (years)	
N	14
Mean (SD)	3.4 (0.76)
Median	4.0
Min, Max	2, 4
Sex n (%)	
Male	14 (100.0)
Ethnicity, n (%)	
Caucasian	11 (78.6)
African-American	0 (0.0)
Asian	3 (21.4)
Hispanic[a]	3 (21.4)
Other	0 (0.0)
Missing	0 (0.0)
Weight (kg)	
N	14
Mean (SD)	16.99 (3.26)
Median	16.40
Min, Max	13.2, 25.2

Patient Characteristic Statistic	Study 030 - 40 mg/kg Ataluren (N=14)
Height (cm)	
N	14
Mean (SD)	99.43 (5.28)
Median	98.55
Min, Max	88.8, 108.0
BMI (kg/m^2)	
N	14
Mean (SD)	17.09 (2.22)
Median	16.64
Min, Max	14.78, 22.94
Baseline steroid use	
None	8 (57.1)
Prednisone	2 (14.3)
Deflazacort[b]	3 (21.4)
Prednisolone sodium phosphate	1 (7.1)

BMI, body mass index; CSR, clinical study report; Max, maximum; Min, minimum; NSAA, North Star Ambulatory Assessment; SD, standard deviation; TFT, timed function test
[a] In Study 030, patients could be identified as Hispanic or non-Hispanic in addition to Caucasian, African-American, Asian, or Other. All 3 patients who were identified as Hispanic were also identified as Caucasian. [b] One patient in Study 030 who was receiving deflazacort at baseline was excluded from the efficacy analyses because the investigator deemed that the baseline TFT and NSAA assessments were invalid.
Source: Tian et al. 2018,[131] Study 030 Clinical Study Report, 2018[151]

Primary Outcome (Safety)

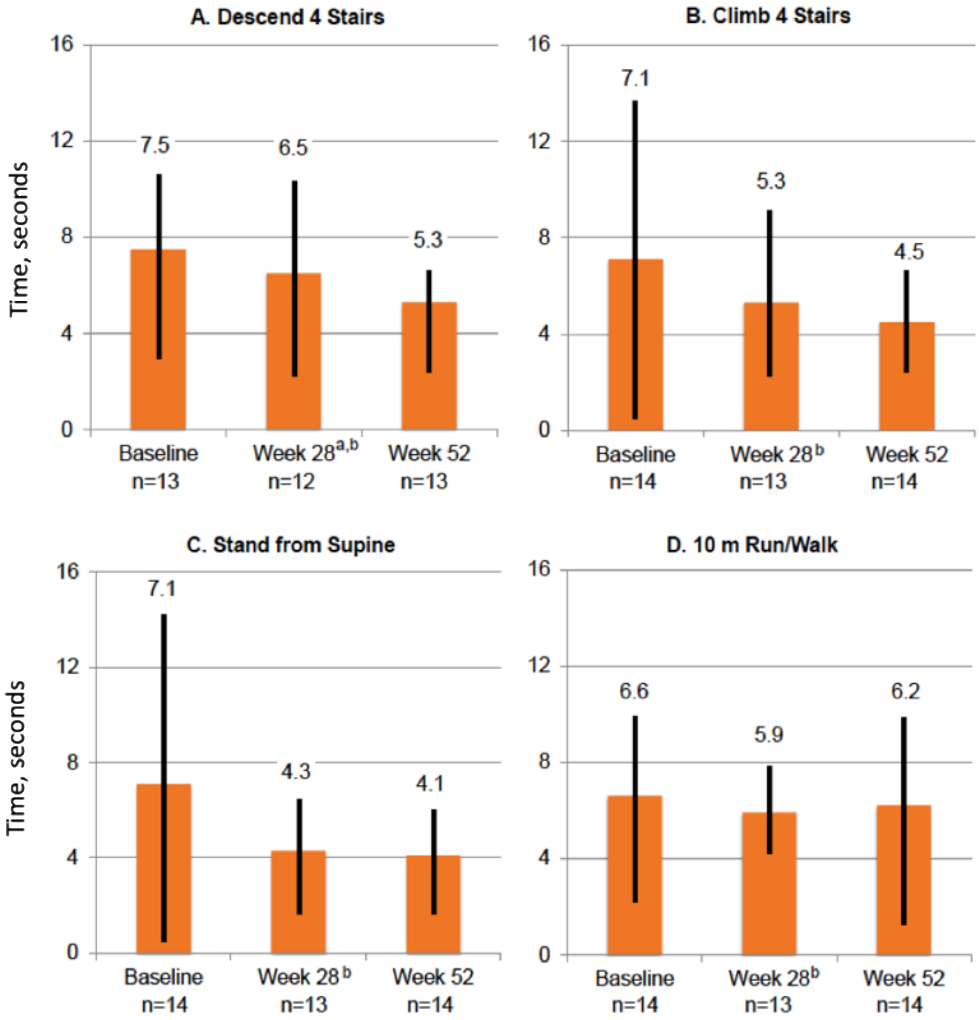
The primary outcome of this study was safety and is reported in Section 9.7.2.4. The adverse event (AE) profile seen in this younger population of patients with nmDMD was similar to that observed in older patients and consistent with the known safety profile of ataluren.[131]

Timed Function Tests (Secondary Outcome)

The time required to descend 4 stairs, to climb 4 stairs, to stand upright from a supine position, and to run or walk 10 metres are TFTs that predict loss of function in DMD, including the loss of ability to walk.[58] In particular, the time taken to stand from the supine position, in addition to being known to an early predictor of disease progression in DMD patients over 7 years old,[156] is clinically relevant in younger children because the loss of the ability to stand up from the supine position is the first crucial event in the evolution of the disease.

The results of all TFTs in patients treated with ataluren showed improvements from baseline at Week 28 and Week 52 (Figure C.20). The improvements at Week 52 in the mean times taken to descend 4 steps, to climb 4 steps and to get up from the supine position, which, although not statistically significant, indicate clinically meaningful improvements, with mean decreases of more than 2 seconds that are of a magnitude similar to the estimated MCID (see section 6.1.3.1).

Figure C.20. TFTs at Baseline, Week 28 and Week 52 in Study 030



TFT, timed function test
[a] Baseline TFT measure for Week 28 timepoint was 7.1.
[b] After the original analysis, TFT results were re-examined with data from 1 subject removed as a result of the data being of questionable reliability due to poor listening.
Source: Tian et al. 2018[131]

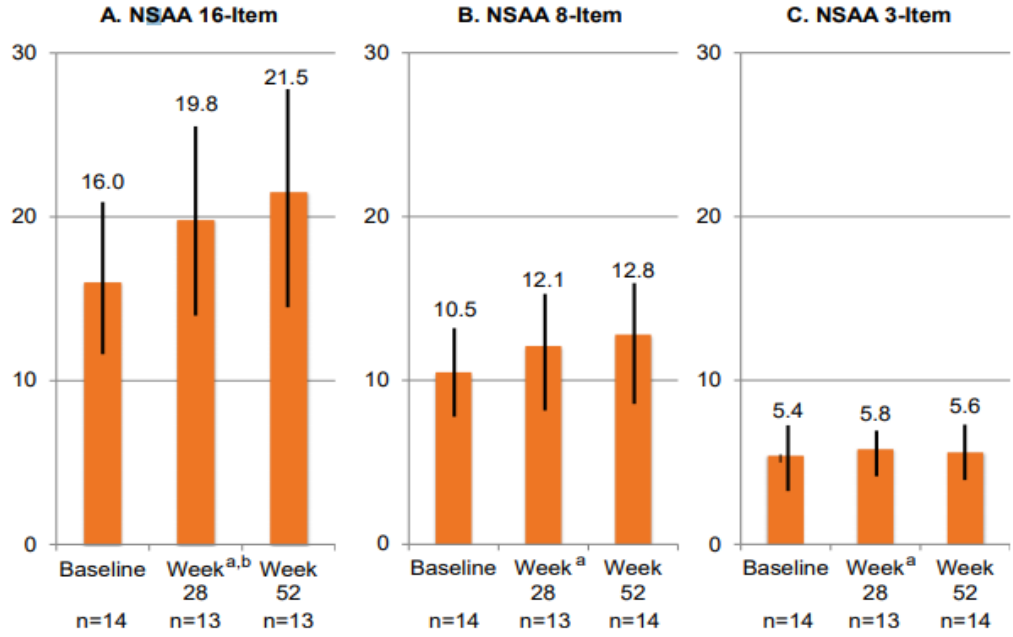
North Star Ambulatory Assessment (Secondary Outcome)

The 16-item NSAA, 8-item NSAA, and 3-item NSAA were used for the evaluation of motor function in patients in Study 030. Clinicians experienced in the disease agree that the modified 8-item NSAA is the most relevant test for assessing motor function because, in the general population, it can be reliably performed by children 4 years of age, which was the mean age of the patients in Study 030.

The scores of all 3 versions of NSAA showed improvements from baseline at Week 28 and Week 52 in patients treated with ataluren (Figure C.21).

Specifically, with regard to the 16-item NSAA and the 8-item NSAA, the improvements at Week 28 and Week 52 were clinically significant, with mean increases in the score of >2 points. As discussed in Section 6.1.3.1, a 1-point difference in NSAA total score is clinically meaningful, as a decrease of this magnitude relates directly to either loss of a motor ability or need for compensation to perform it independently.

Figure C.21. NSAA Results (mean, SD) at Baseline, Week 28, and Week 52 for Study 030



NSAA, North Star Ambulatory Assessment; SD, standard deviation
[a] After the original analysis, NSAA were re-examined with data from 1 subject removed as a result of the data being of questionable reliability due to poor listening.
[b] Mean baseline at Week 28 was 16.2.
Source: Tian et al. 2018[131]

9.6.1.6 STRIDE

Results from STRIDE in comparison to CINRG DNHS were published by Mercuri and colleagues in 2020.[7] Data cut-off date for inclusion in the published analyses was on 09 July 2018.

The STRIDE study is ongoing, and data are currently available up to 31 January 2021. To provide the most complete and up-to-date data for this submission analysis of this dataset has been presented.

Baseline Characteristics

The median age of patients in the evaluable population at consent date in STRIDE was 9.6 years (range: 2.1 to 22.8 years) (Table C-28).[128] More than 88% of patients in the global evaluable population were receiving corticosteroids at any time during STRIDE. Demographic and patient characteristics in the efficacy and ambulatory populations are generally consistent with the evaluable population. In contrast, as would be expected, the non-ambulatory population was older at the time of treatment initiation in STRIDE (median age [redacted] years) than the ambulatory population (median age [redacted] years).[36]

Table C-28. Patient Demographics and Disease Characteristics

	Evaluable (N=269)
Age at consent date (years) Mean (SD) Median (Min, Max)	 9.9 (3.8) 9.6 (2.1, 22.8)
Age at cut-off date (years) Mean (SD) Median (Min, Max)	 13.1 (4.2) 13.1 (3.1, 26.7)
Race, n (%)	

	Evaluable (N=269)
White	194 (72.1)
Arab/Middle Eastern	7 (2.6)
Arab/Middle Eastern, Asian	1 (0.4)
Asian	6 (2.2)
Black	3 (1.1)
Mixed race, black/white	1 (0.4)
North African	1 (0.4)
Latin	1 (0.4)
Unknown	3 (1.1)
Not reported	52 (19.3)
Weight (kg)	
n	222
Mean (SD)	30.2 (13.8)
Median (Min, Max)	25.6 (11.8, 87.0)
Height (cm)	
n	192
Mean (SD)	121.8 (16.8)
Median (Min, Max)	120.0 (84.0, 178.0)
BMI (kg/m^2)	
n	191
Mean (SD)	19.0 (4.4)
Median (Min, Max)	17.6 (13.0, 40.5)
Corticosteroid use, n (%)	
n (%)	237 (88.1)

BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation
Source: Muntoni et al. 2021[128]

Efficacy in STRIDE Compared with DMD Natural History Data

Data from 398 patients in CINRG DNHS were utilised for comparisons with those from patients in STRIDE; [redacted] patients in CINRG DNHS were excluded because they had participated in clinical trials of ataluren or had received eteplirsen, drisapersen, or tadalafil. A further [redacted] patients were excluded because they had missing data for age at LoA and age at first symptoms.[157]

Propensity matching of CINRG DNHS data yielded a population with no significant differences from the STRIDE population with respect to age at first symptoms, age at first corticosteroid use, duration of deflazacort use, and duration of other corticosteroid use, which provided a relevant basis for comparison.

As of the data cut-off of 31 January 2021, 241 patients in the STRIDE effectiveness population have been matched using propensity scoring to CINRG DNHS patients, yielding a comparable population (N=241) with respect to the 4 covariates (age at onset of first symptoms, age at initiation of corticosteroid use, duration of deflazacort use, and duration of other corticosteroid use; Table C-29).

Table C-29. Demographics and characteristics of patients in STRIDE and CINRG DNHS before and after propensity score matching

	Unmatched Population		Propensity score Matched Population	
	STRIDE (N=241)	CINRG DNHS (N=398)	STRIDE (N=241)	CINRG DNHS (N=241)
Age at first symptoms, years				
Mean (SD)	2.74 (1.66)	3.23 (1.68)	2.74 (1.66)	2.78 (1.50)
Median	2.50	3.00	2.50	3.00
Min, Max	0.10, 8.00	0.08, 8.00	0.10, 8.00	0.08, 8.00
p value	0.0004		0.8187	
Age at first corticosteroid use (excluding corticosteroid-naïve patients),[a] years				

	Unmatched Population		Propensity score Matched Population	
	STRIDE (N=241)	**CINRG DNHS (N=398)**	**STRIDE (N=241)**	**CINRG DNHS (N=241)**
n	212	315	212	212
Mean (SD)	6.61 (2.16)	6.74 (2.05)	6.61 (2.16)	6.41 (2.01)
Median	6.18	6.57	6.18	6.22
Min, Max	2.93, 15.31	1.99, 14.25	2.93, 15.31	1.99, 13.89
p value	0.4832		0.3111	
Deflazacort duration,[b] n (%)				
<1 month	124 (51.5)	234 (58.8)	124 (51.5)	120 (49.8)
≥1 to <12 months	12 (5.0)	20 (5.0)	12 (5.0)	12 (5.0)
≥12 months	105 (43.6)	144 (36.2)	105 (43.6)	109 (45.2)
p value	0.1697		0.9322	
Other steroid duration,[b] n (%)				
<1 month	128 (53.1)	204 (51.3)	128 (53.1)	123 (51.0)
≥1 to <12 months	13 (5.4)	35 (8.8)	13 (5.4)	14 (5.8)
≥12 months	100 (41.5)	159 (39.9)	100 (41.5)	104 (43.2)
p value	0.2869		0.8980	

CINRG DNHS, Cooperative International Neuromuscular Research Group; Max, maximum; Min, minimum; NA, not applicable; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence
[a] Treatment naive patients were excluded to calculate the true age at first corticosteroid use. [b] Corticosteroid duration is calculated from the date at which corticosteroid use was started and the loss of ambulation/censor date.
Source: Mercuri et al. 2021[34]

Of these 241 patients included in STRIDE, although a large proportion of patients did not reach a pFVC<50% and below compared with those patients within CINRG, limiting the ability to estimate the accurate rates of decline in pulmonary function. The number of patients who had data available for each motor function or pulmonary outcome, as well as the number of patients who experienced the event are presented below.[36]

Loss of Ambulation - STRIDE versus CINRG

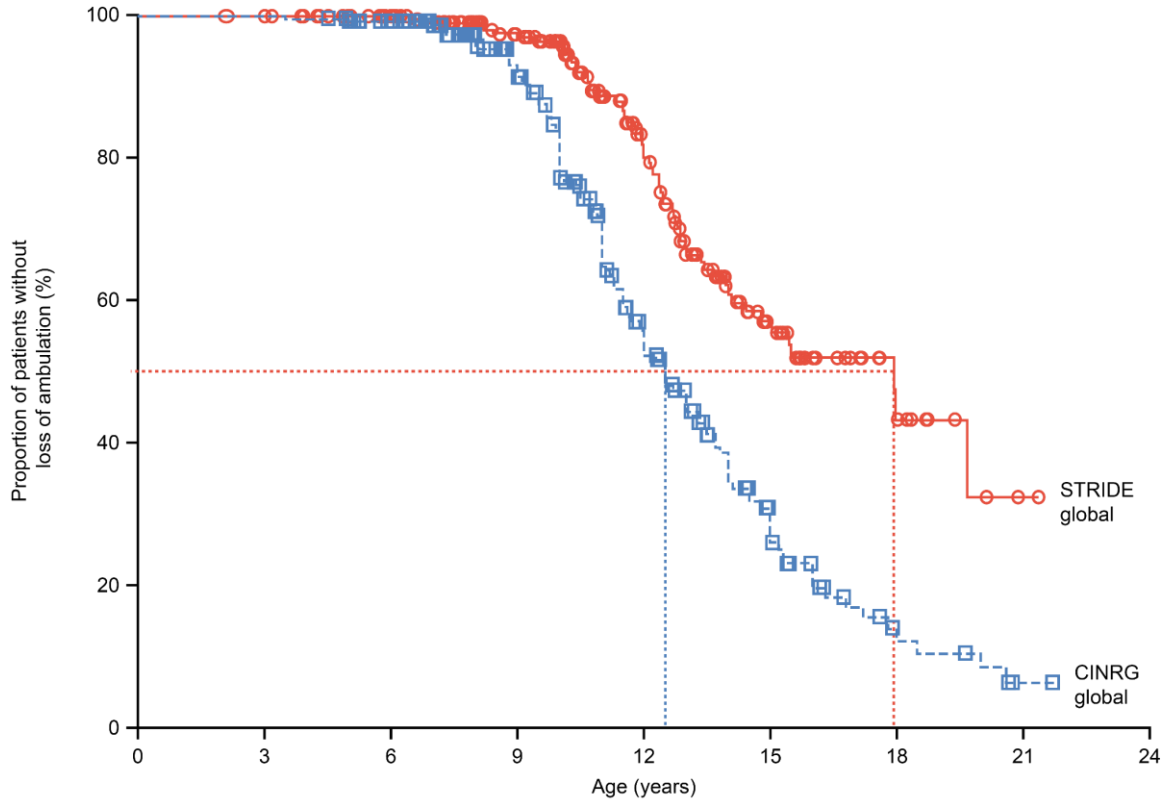
A total of 24.9% of the STRIDE population and 52.7% of the propensity score matched CINRG population lost ambulation (Table C-30 and Figure C.22). The median age at LoA was 17.9 years in the STRIDE population and 12.5 years in the CINRG population, which represents a statistically significant difference in favour of ataluren plus BSC (p<0.0001; HR: 0.374).

Table C-30. Age (years) at LoA in STRIDE versus CINRG Propensity-Matched Population

Assessment	**STRIDE (ataluren + BSC) N=241**	**CINRG (BSC alone) N=241**
Number of patients assessed, n	241	241
Number of patients with events, n (%)	60 (24.9)	127 (52.7)
Number of patients censored, n (%)	181 (75.1)	114 (47.3)
Median age at loss of ambulation,[a] years (95% CI)	**17.9** (14.4, NA)	**12.5** (11.6, 13.5)
Minimum, maximum age of assessed patients[b]	2.1+, 21.4+	3.5, 21.7+
p value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.374 (0.273, 0.512)	

BSC, best supportive care; CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study; HR, hazard ratio; NA, not available; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence
[a] Loss of ambulation was defined as full-time wheelchair use.
[b] Event or censor +Minimum/maximum age of patient who has not yet reached the event; censored at the age of last assessment date.
[c] p value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.
[d] HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE Registry versus CINRG DNHS.
Source: Mercuri et al. 2021[34]

Figure C.22. Kaplan-Meier Analysis of Age at Loss of Ambulation[a] (STRIDE vs CINRG With Propensity Score Matched)



Number of patients[b]									
STRIDE global	241	240	221	184	100	36	10	1	0
CINRG global	241	241	229	171	82	32	8	1	0

CINRG, Cooperative International Neuromuscular Research Group; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence
[a] Loss of ambulation was defined as full-time wheelchair use.
[b] Number of patients at risk of losing ambulation.
Source: Mercuri et al. 2021[34]

Stand from Supine - STRIDE versus CINRG DNHS

STRIDE patients were significantly older than CINRG DNHS propensity score−matched patients (Table C-31 and Figure C.23) when they transitioned to ≥10 seconds to stand from supine (median [redacted] years vs [redacted] years; p=[redacted]; HR [redacted]).[36] Please see Section 6.1.3.1 for the clinical meaningfulness of each endpoint discussed below.

Table C-31. Age at Time to Stand from Supine ≥10 Seconds for Patients in Propensity Score Matched STRIDE and CINRG DNHS Populations

Assessment	STRIDE (ataluren + BSC) N=241	CINRG DNHS (BSC alone) N=241
Number of patients assessed, n	[redacted]	[redacted]
Number of patients with events, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Median age at event, years (95% CI)	[redacted]	[redacted]
Minimum, maximum age of assessed patients, years	4.5[a], 20.1[a]	2.6, 18.7
p value[b]	[redacted]	
Hazard ratio (95% CI)[c]	[redacted]	

BSC, best supportive care; CI, confidence interval; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence

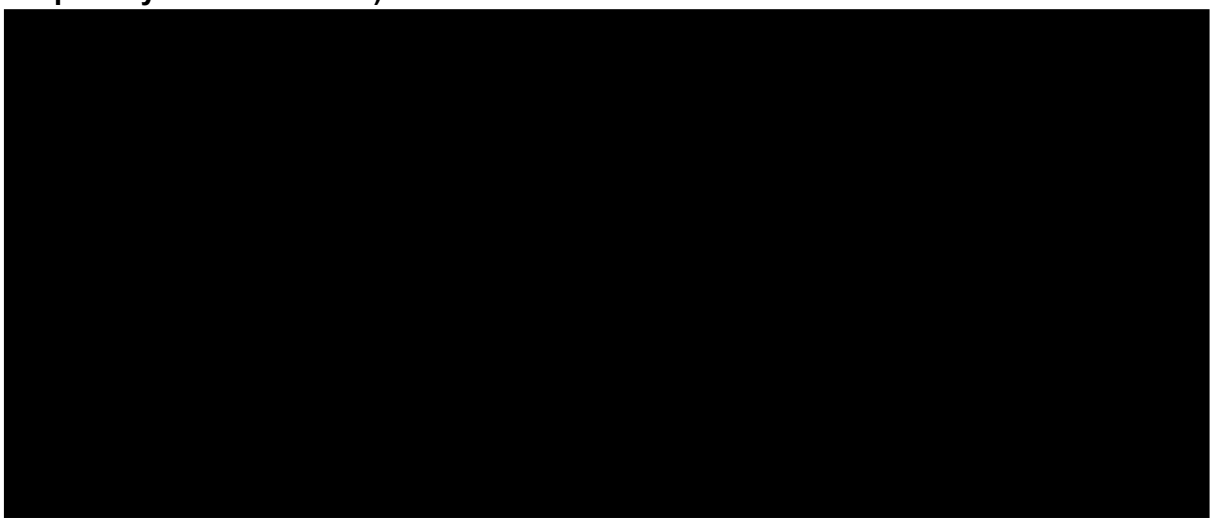
[a] Minimum/maximum age of patient who has not yet reached the event; censored at the age of last assessment date across treatment.

[b] Log-rank test stratified by deflazacort and other steroid usage durations.

[c] Stratified (by durations of deflazacort and other steroid use) Cox regression with covariate age at the first symptoms. Hazard ratio is STRIDE over CINRG DNHS.

Source: STRIDE Clinical study report 2021[36]

Figure C.23. Age at Time to Stand from Supine ≥10 seconds (STRIDE vs CINRG DNHS With Propensity Score Matched)



CONFIDENTIAL. NOT FOR DISTRIBUTION

025, STRIDE; CINRG DNHS/CNG, Cooperative International Neuromuscular Research Group; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence

Source: STRIDE Clinical study report 2021[36]

Climb Stairs- STRIDE versus CINRG DNHS

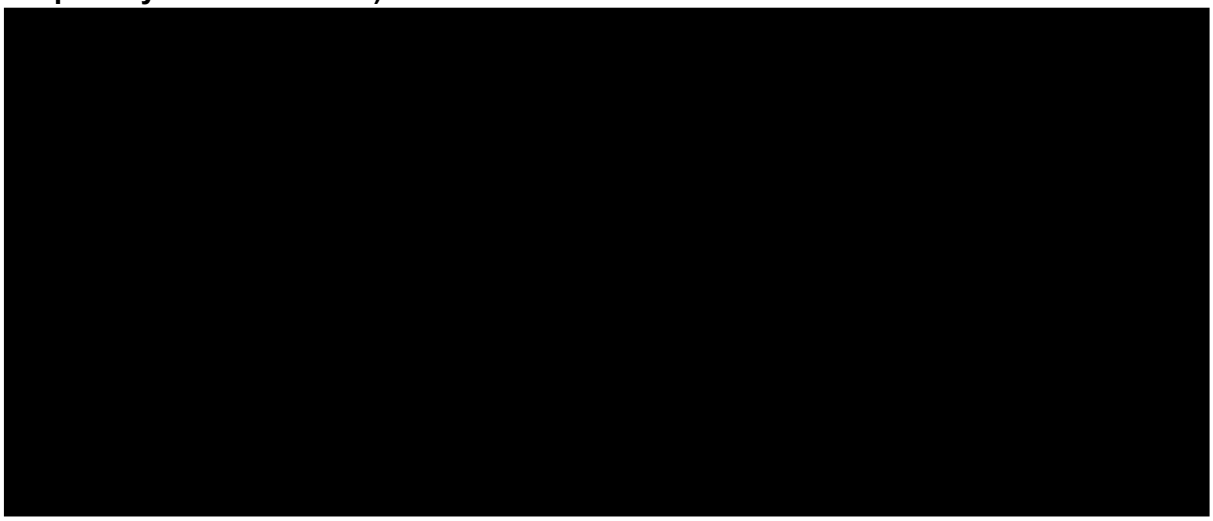
Similarly, Kaplan-Meier analysis showed that STRIDE patients were [redacted] than CINRG DNHS propensity score matched patients when they transitioned to ≥10 seconds to climb 4 stairs, although statistical significance was [redacted] (median [redacted] vs [redacted] years for CINRG DNHS; p=[redacted]; HR [redacted]) (Table C-32, Figure C.24).

Table C-32. Age at Time to Climb 4 Stairs ≥10 Seconds – STRIDE and CINRG DNHS Propensity-Matched Population

Assessment	STRIDE (ataluren + BSC) N=241	CINRG DNHS (BSC alone) N=241
Number of patients assessed, n	[redacted]	[redacted]
Number of patients with events, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Median age at event, years (95% CI)	[redacted]	[redacted]
Minimum, maximum age of assessed patients	[redacted]	[redacted]
p value	[redacted]	
Hazard ratio (95% CI)	[redacted]	

CONFIDENTIAL. NOT FOR DISTRIBUTION
BSC, best supportive care; CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence
[a] Minimum/maximum age of patient who has not yet reached the event; censored at the age of last assessment date across treatment.
Source: STRIDE Clinical study report 2021[36]

Figure C.24. Age at Time to Climb 4 Stairs ≥10 seconds (STRIDE vs CINRG DNHS With Propensity Score Matched)



CONFIDENTIAL. NOT FOR DISTRIBUTION
025, STRIDE; CINRG, Cooperative International Neuromuscular Research Group; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence
Source: STRIDE Clinical study report 2021[36]

Pulmonary Function - STRIDE versus CINRG DNHS

Across all pulmonary function milestones, subjects in STRIDE were older than propensity-matched subjects from the CINRG DNHS database at the time each milestone was reached (Figure C.25, Figure C.26, Figure C.27 and Figure C.28). In the matched populations, a total of 17.2% of STRIDE subjects and 37.5% of the subjects in the CINRG DNHS database had % predicted FVC <60% (Table C-33). The median age at % predicted FVC <60% was 17.6 years for STRIDE subjects and 15.8 years in the CINRG DNHS propensity score matched population (p=0.0051; HR 0.544) [37]. Similar results were observed for the milestones of predicted [redacted]% and <30% [36,37].

[redacted] STRIDE patients assessed had an FVC <1 litre compared with [redacted]%) patients of the CINRG DNHS propensity score matched population. The median age at time of FVC <1 litre was [redacted] in STRIDE patients and was [redacted] years in the CINRG DNHS propensity score matched population (p=[redacted]) (Table C-33)[36]

Table C-33. Age (years) at Pulmonary Function Event in STRIDE versus CINRG DNHS Propensity-Matched Population

Assessment	STRIDE (ataluren + BSC) N=241	CINRG DNHS (BSC alone) N=241
Predicted FVC <60%		
Number of patients assessed, n	169	152
Number of patients with events, n (%)	29 (17.2)	57 (37.5)
Number of patients censored, n (%)	140 (82.8)	95 (62.5)
25% quartile of age at event, years (95% CI)	15.8 (14.1, 17.1)	14.2 (13.2, 14.7)
Median age at event, years (95% CI)	17.6 (16.2, NA)	15.8 (15.1, 16.5)
Minimum, maximum age at event	5.0[a], 20.8[a]	6.0[a], 32.3[a]
p value[b]	0.0051	
Hazard ratio (95% CI)[c]	0.544 (0.343, 0.863)	
Predicted FVC <50%		
Number of patients assessed, n	[redacted]	[redacted]
Number of patients with events, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
25% quartile of age at event, years (95% CI)	[redacted]	[redacted]
Median age at event, years (95% CI)	[redacted]	[redacted]
Minimum, maximum age at event	[redacted]	[redacted]
p value[b]	[redacted]	
Hazard ratio (95% CI)[c]	[redacted]	
Predicted FVC <30%		
Number of patients assessed, n	192	190
Number of patients with events, n (%)	1 (0.5)	25 (13.2)
Number of patients censored, n (%)	191 (99.5)	165 (86.8)
25% quartile of age at event, years (95% CI)	NA (17.5, NA)	20.2 (17.2, 22.5)
Median age at event, years (95% CI)	NA (NA, NA)	25.4 (20.6, 29.4)
Minimum, maximum age at event	5.0[a], 25.5[a]	6.0[a], 32.3[a]
p value[b]	0.0085	
Hazard ratio (95% CI)[c]	0.107 (0.014, 0.813)	
FVC <1 IL		
Number of patients assessed, n	[redacted]	[redacted]
Number of patients with events, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
25% quartile of age at event, years (95% CI)	[redacted]	[redacted]
Median age at event, years (95% CI)	[redacted]	[redacted]
Minimum, maximum age at event	[redacted]	[redacted]
p value[b]	[redacted]	
Hazard ratio (95% CI)[c]	[redacted]	

BSC, best supportive care; CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; NA, not available; NR, not reported; STRIDE, Strategic Targeting of Registries and International Datasets of Excellence

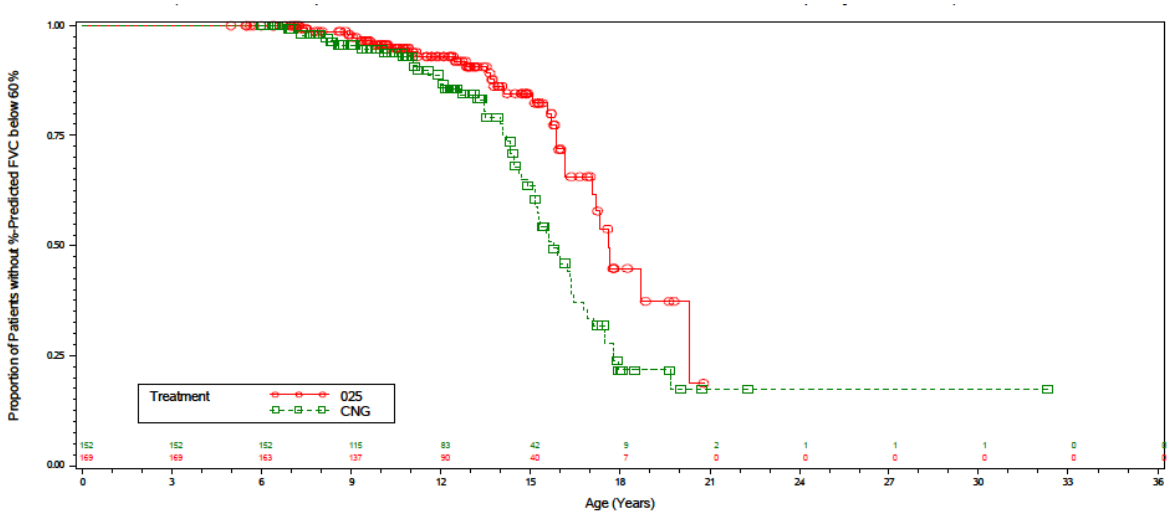
[a] Minimum/maximum age of patient who has not yet reached the event; censored at the age of last assessment.

[b] Log-rank test stratified by deflazacort and other steroid usage durations

[c] Stratified (by durations of deflazacort and other steroid use) Cox regression with covariate age at the first symptoms. Hazard ratio is STRIDE over CINRG DNHS

Source: Tulinius et al. 2021; STRIDE Clinical study report 2021[36,37]

Figure C.25. Age at % Predicted FVC <60% (STRIDE vs CINRG DNHS With Propensity Score Matched)

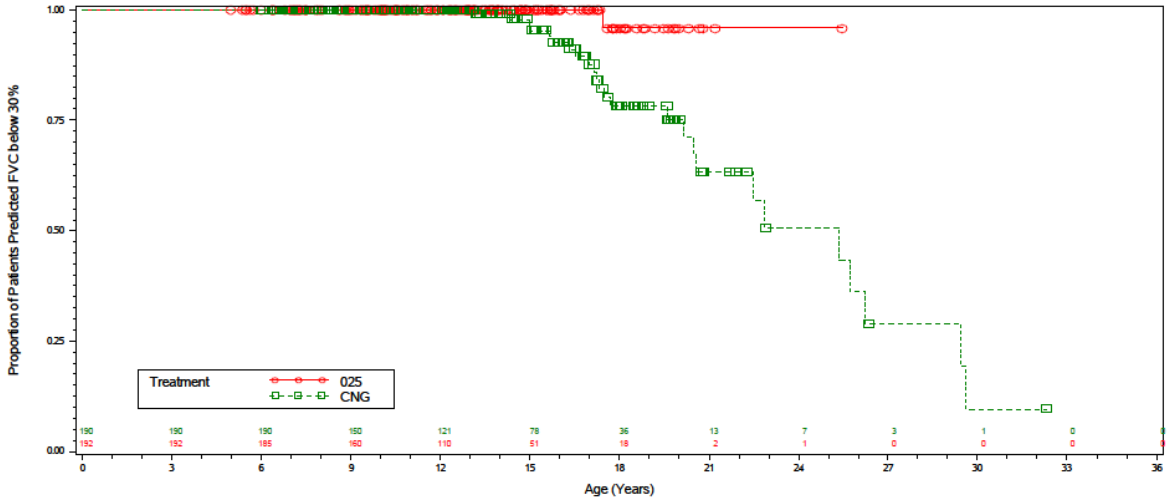


025, STRIDE; 6MWD, 6-minute walk distance; CINRG DNHS/CNG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
Note: Propensity score model covariates include age at first symptom, duration of deflazacort, and duration of steroid other than deflazacort. Censor dates for Study 025o (STRIDE) censored subjects were derived from last assessment date across treatment, physical exam, vital sign, 6MWD, time function tests, North Star Ambulatory Assessments, % predicted FVC, and upper limb function tests. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Numbers at bottom of graph are numbers of patients at risk.
Source: Tulinius et al. 2021; STRIDE Clinical study report 2021[36,37]

Figure C.26. Age at % Predicted FVC <50% (STRIDE vs CINRG DNHS With Propensity Score Matched)

025, STRIDE; 6MWD, 6-minute walk distance; CINRG DNHS/CNG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
Note: Propensity score model covariates include age at first symptom, duration of deflazacort, and duration of steroid other than deflazacort. Censor dates for Study 025o (STRIDE) censored subjects were derived from last assessment date across treatment, physical exam, vital sign, 6MWD, time function tests, North Star
Ambulatory Assessments, % predicted FVC, and upper limb function tests. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Numbers at bottom of graph are numbers of patients at risk.
Source: STRIDE Clinical study report 2021[36]

Figure C.27. Age at % Predicted FVC <30% (STRIDE vs CINRG DNHS With Propensity Score Matched)



025, STRIDE; 6MWD, 6-minute walk distance; CINRG/CNG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
Note: Propensity score model covariates include age at first symptom, duration of deflazacort, and duration of steroid other than deflazacort. Censor dates for Study 025o (STRIDE) censored subjects were derived from last assessment date across treatment, physical exam, vital sign, 6MWD, time function tests, North Star Ambulatory Assessments, % predicted FVC, and upper limb function tests. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Source: Tulinius et al. 2021; STRIDE Clinical study report 2021[36,37]

Figure C.28. Age at FVC <1 litre (STRIDE vs CINRG DNHS with Propensity Score Matched)

[redacted]

025, STRIDE; 6MWD, 6-minute walk distance; CINRG/CNG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
Note: Propensity score model covariates include age at first symptom, duration of deflazacort, and duration of steroid other than deflazacort. Censor dates for Study 025o (STRIDE) censored subjects were derived from last assessment date across treatment, physical exam, vital sign, 6MWD, time function tests, North Star Ambulatory Assessments, % predicted FVC, and upper limb function tests. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Numbers at bottom of graph are numbers of patients at risk.
Source: STRIDE Clinical study report 2021[36]

Summary

STRIDE represents the largest cohort of nmDMD patients ever studied. Data presented here are from the cut-off date 31 January 2021 and the study is still ongoing. An increasingly robust dataset with a longer treatment duration than previously evaluated (median of [redacted] days for the evaluable population) and a rigorously matched comparison to natural history data continues to support the

association of ataluren treatment with the slowing of disease progression in a heterogeneous population of nmDMD subjects across multiple clinically meaningful endpoints.

Kaplan-Meier analysis indicates that ataluren treatment in STRIDE was associated with a delay in the LoA by 5.4 years compared with CINRG DNHS matched control (17.9 years of age vs 12.5 years of age, respectively). Ataluren statistically reduced the risk for LoA by 63% relative to BSC alone in CINRG DNHS (p<0.0001; HR 0.374).

Across all pulmonary function milestones, patients in STRIDE were older than propensity-matched subjects from the CINRG DNHS database at the time each milestone was reached. The median age at % predicted FVC <60% was 17.6 years for STRIDE subjects and 15.8 years in the CINRG DNHS propensity score matched population (p=0.0051; HR 0.544). Similar results were observed for the milestones of % predicted FVC <50%, although the vast majority of patients were censored before reaching this milestone. The median age at the time of FVC<30% and FVC <1 litre were not reached in STRIDE patients due to too few events, although was 24.9 years in the CINRG DNHS propensity score matched population.

These data show that treatment with ataluren in addition to BSC in routine clinical practice may delay disease progression in patients with nmDMD. Nevertheless, future comparative data cuts from STRIDE and CINRG DNHS will provide further real-world insights into the long-term effectiveness of ataluren in the treatment of patients with nmDMD.

9.6.1.7 Managed Access Agreement

Baseline characteristics

Based on the newly defined and agreed protocol, there were 145 potential controls and 60 ataluren-treated patients with complete baseline data for all seven matching factors (Table C-34). Of the 60 ataluren-treated patients, a match was found for 59 patients (98%), and therefore 59 patients in each arm were included in the updated analysis. There were a few ataluren-treated patients included in the re-match who were not included in the original match, and missing data have been filled in since the original match (Table C-35). As a result, the updated analysis included more patients in the matched cohort.

Table C-34. Baseline characteristics before matching (MAA and control cohort)

Summaries mean (standard deviation) and frequency (%)	Potential Controls (N=145)	Ataluren (N=60)	Standardised differences
Age at baseline (years)			
On steroids*			
Age at starting steroids (years)			
Duration of deflazacort prior to baseline# <1 month 1–12 months ≥12 months			
Duration of other steroids prior to baseline# <1 month 1–12 months ≥12 months			
Steroid regime Daily Other None			
NSAA Total score			

Summaries mean (standard deviation) and frequency (%)	Potential Controls (N=145)	Ataluren (N=60)	Standardised differences
Can rise from floor (NSAA rise>0)	[redacted]	[redacted]	
Baseline time to rise from supine, seconds	[redacted]	[redacted]	[redacted]

*For boys not on steroids, age at starting steroids set to 30 years.

#Lower 2 categories combined for matching, so we consider <12 months and ≥12 months. This was done because of small frequencies in some cells and also the 3-level categorisation was felt to be too refined, based on the typical 6 monthly visiting schedule. This was agreed between North Star and PTC.

**Using method of Yange and Dalton, based on dichotomous classification combining lower 2 categories

For information, in the original matching there were 160 potential controls and 70 in the ataluren cohort. Fewer boys are available for matching now the number of matching factors has increased. There are missing rise from supine data and steroid information prior to baseline visit.

Table C-35. Baseline characteristics after matching (MAA and control cohort)

Matching factor	Controls (BSC) (N=59)	Ataluren (N=59)	Standardised differences
Age at baseline (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	
On steroids*	[redacted]	[redacted]	
Age at starting steroids (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	
Duration of deflazacort prior to baseline# <1 month or 1–12 months ≥12 months	[redacted]	[redacted]	[redacted]
Duration of other steroids prior to baseline# <1 month or 1–12 months ≥12 months	[redacted]	[redacted]	[redacted]
Steroid regime Daily Other None	[redacted]	[redacted]	[redacted]
NSAA Total score			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	
Can rise from floor (NSAA rise>0)	[redacted]	[redacted]	
Baseline time to rise from supine, seconds			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	

*For boys not on steroids, age at starting steroids set to 30 years.

#Lower 2 categories combined for matching, so we consider <12 months and ≥12 months. This was done because of small frequencies in some cells and also the 3-level categorisation was felt to be too refined, based on the typical 6 monthly visiting schedule. This was agreed between North Star and PTC.

Source: PTC MAA Data Tables[158]

The propensity score matching was performed using the seven covariates listed above as agreed between, NICE, North Star and PTC. However, likely due to the relatively small sample size, the BSC group was a mean [redacted] years younger and took [redacted] second less to rise from floor on average. NSAA is a composite endpoint, with 17 functions assessed and scored individually. It has been used successfully in randomised clinical trials, yielding comparable groups at baseline. However, identifying a comparable matched control group from real-world studies seems to be more challenging. For several items on the NSAA a higher percentage of patients on ataluren had already lost function at baseline, including for example the ability to run, suggesting patients on ataluren

were [redacted] (Figure C.29). Together, these data suggest that patients in the ataluren group were [redacted] at baseline.

A further examination of the age group indicated that [redacted]%) of the boys in the BSC group were 7 years or younger compared to [redacted] Since boys with DMD are known to gain motor function up to the age of 7 years, and concordantly NSAA increases,[15] the effect of ataluren in this group is not as observable compared to those in the declining phase (see section 6.1.3.1). This is also reflected in the retrospective analysis of the NSAA prior to baseline, which shows considerable heterogeneity, with increasing NSAA scores observed in younger patients and declining NSAA after the age of 7 years (Figure C.30).

Figure C.29. Number of patients who lost functions at baseline (a score of 0)

[redacted]

Figure C.30. Retrospective Analysis – NSAA vs age at visit by subject

[redacted]

Source: PTC NICE MAA Results Summary February 2022[159]

Efficacy analysis

Data from a total of [redacted] clinical visits ([redacted] from patients in the control group and [redacted] from ataluren-treated patients) were analysed, with a median follow-up period of [redacted] months.

The significant number of subjects who did not have valid NSAA scores after 1 year, 2 years and 3 years (Figure C.31), and the resultant lack of longitudinal data make it difficult to draw conclusions between the two groups, especially for 42 months and after. Only data from the first 3 years were included for the change in NSAA score and change in NSAA linear score mixed model analysis.

Figure C.31. Number of patients with NSAA score over time

BSC, best supportive care; NSAA, North Star Ambulatory Assessment.

Source: PTC NICE MAA Results Summary February 2022[159]

Patients on ataluren had numerically [redacted] NSAA score from Months 24–36 (Figure C.32) and among the subjects who had functions at baseline (a score of 1 or 2), [redacted] patients lost functions over 36 months: [redacted] patients on BSC lost ability to climb box step (Left: [redacted] & Right: [redacted]%) and Descend Box Step (Left: [redacted]% & Right: [redacted]%) at Month 36 (Figure C.33). These data suggest that ataluren tended to slow down disease progression compared to BSC alone.

Figure C.32. Change in NSAA over 36 months

NSAA

NSAA linear

Source: PTC NICE MAA Results Summary February 2022[159]

Figure C.33. Number of patients who lost function over 36 months

Source: PTC NICE MAA Results Summary February 2022[159]

Amongst patients who completed 36 months of treatment and who had NSAA data for all timepoints, treatment with ataluren demonstrated a slowing of disease progression. This benefit was demonstrated both by the results in change in NSAA and NSAA linear curves throughout the 36 months (Figure C.34). In this analysis, the change from baseline over 3 years in linear NSAA was a mean (SD) [redacted]points for ataluren and a mean (SD) [redacted]) points for BSC.

Figure C.34. Change in NSAA in 36-months completers

NSAA

NSAA linear

Source: PTC NICE MAA Results Summary February 2022[159]

Analysis of individual items on the NSAA, including time to rise from the floor was also carried out. Time to rise from the floor is a key parameter used to predict disease progression and LoA. At baseline, the data for time to rise from the floor were not normally distributed, and to meet a modelling assumption it was therefore transformed using the reciprocal. In this case higher values mean less time to complete the task. As shown in Figure C.35, ataluren [redacted] the disease progression compared to BSC

Figure C.35. Reciprocal of Time to Rise from Floor

Observed Means ± SE

Model adjusted Means ± SE

Source: PTC NICE MAA Results Summary February 2022[159]

HRQL data

A summary of responses to the CHU9D is shown in Table C-36. Following conversations with experts from ScHARR, PTC have yet been unable to convert the CHU9D results into health state utility values associated with DMD. It is understood that it is theoretically possible to map the CHU9D results into utility values should further supportive evidence be required when considering the patient health state utility values, although at this stage it is not possible to establish if there are any underlying limitations with the analysis.

A summary of caregiver responses to the EQ-5D-5L is shown in Table C-37. For those with multiple records, the last one was chosen. The mean EQ-5D visual analogue scale (VAS) score (n=53) was). The mean EQ-5D-5L utility (n=50) was .

Table C-36. Summary of responses to the CHU9D

CHU9D dimensions and levels	ataluren (n=54)
1. worried (%)	
I don't feel worried today	[redacted]
I feel a little bit worried today	[redacted]
I feel a bit worried today	[redacted]
I feel quite worried today	[redacted]
I feel very worried today	[redacted]
2. sad (%)	
I don't feel sad today	[redacted]
I feel a little bit sad today	[redacted]
I feel a bit sad today	[redacted]
I feel quite sad today	[redacted]
I feel very sad today	[redacted]
3. pain (%)	
I don't have any pain today	[redacted]
I have a little bit of pain today	[redacted]
I have a bit of pain today	[redacted]
I have quite a lot of pain today	[redacted]
I have a lot of pain today	[redacted]
4. tired (%)	
I don't feel tired today	[redacted]
I feel a little bit tired today	[redacted]
I feel a bit tired today	[redacted]
I feel quite tired today	[redacted]
I feel very tired today	[redacted]
5. annoyed (%)	
I don't feel annoyed today	[redacted]
I feel a little bit annoyed today	[redacted]
I feel a bit annoyed today	[redacted]
I feel quite annoyed today	[redacted]
I feel very annoyed today	[redacted]
6. school work/homework (such as reading, writing, doing lessons) (%)	
I have no problems with my schoolwork/homework today	[redacted]
I have a few problems with my schoolwork/homework today	[redacted]
I have some problems with my schoolwork/homework today	[redacted]
I have many problems with my schoolwork/homework today	[redacted]
I can't do my schoolwork/homework today	[redacted]
7. sleep (%)	
Last night I had no problems sleeping	[redacted]

Last night I had a few problems sleeping	[redacted]
Last night I had some problems sleeping	[redacted]
Last night I had many problems sleeping	[redacted]
Last night I couldn't sleep at all	[redacted]
8. daily routine (things like eating, having a bath/shower, getting dressed) (%)	
I have no problems with my daily routine today	[redacted]
I have a few problems with my daily routine today	[redacted]
I have some problems with my daily routine today	[redacted]
I have many problems with my daily routine today	[redacted]
I can't do my daily routine today	[redacted]
9. able to join in activities (things like playing out with your friends, doing sports, joining in things) (%)	
I can join in with any activities today	[redacted]
I can join in with most activities today	[redacted]
I can join in with some activities today	[redacted]
I can join in with a few activities today	[redacted]
I can join in with no activities today	[redacted]

Source: PTC MAA Data Tables[158]

Table C-37. Summary of responses to the EQ-5D-5L

EQ-5D-5L Dimensions and Levels	Ataluren (N=53)
1. MOBILITY (%) NO PROBLEMS SLIGHT PROBLEMS MODERATE PROBLEMS SEVERE PROBLEMS UNABLE TO WALK ABOUT	[redacted]
2. SELF-CARE (%) NO PROBLEMS SLIGHT PROBLEMS MODERATE PROBLEMS SEVERE PROBLEMS UNABLE TO WALK ABOUT	[redacted]
3. USUAL ACTIVITIES (%) NO PROBLEMS SLIGHT PROBLEMS MODERATE PROBLEMS SEVERE PROBLEMS UNABLE TO WALK ABOUT	[redacted]
4. PAIN/DISCOMFORT (%) NO PROBLEMS SLIGHT PROBLEMS MODERATE PROBLEMS SEVERE PROBLEMS	[redacted]

UNABLE TO WALK ABOUT	
5. ANXIETY / DEPRESSION NO PROBLEMS SLIGHT PROBLEMS MODERATE PROBLEMS SEVERE PROBLEMS UNABLE TO WALK ABOUT	[redacted]

Source: PTC MAA Data Tables[158]

Summary

Overall, the NSAA scores show that patients who received ataluren maintained higher NSAA scores from months 24 onwards and fewer ataluren patients lost function across the individual mobility measures. Despite this, the results of the MAA analysis struggled to demonstrate meaningful treatment effect due to a number of underlying limitations of the analysis.

The baseline age for the matched cohorts were not well balanced. The median age for ataluren patients was [redacted] years compared to [redacted] years for the control cohort. Natural history data suggests that mobility functionality improves in children with DMD until approximately 7 years of age, before the patients enter the “transition” phase of ambulation. The median age of the control cohort indicates the majority of patients were younger than 7 years old at baseline and are therefore likely to experience increased or stable mobility functionality for the first period of follow-up. An older median age in the ataluren cohort suggests patients are starting later in the disease progression and are therefore more likely to experience a greater rate of decline throughout the follow-up duration.

Additionally, age of first symptom, a key prognostic indicator, was not available as a matching covariate as it was not recorded as part of the NorthStar registry data collection. The absence of this parameter makes it difficult to establish whether the predicted rate of disease progression at baseline was comparable between the individuals within each cohort.

Finally, the analysis suffered from a rapid decline in available patient numbers in later follow-up timepoints, due to the nature of real-world data collection, and the fact that patients began treatment on different start dates. It is therefore difficult to draw meaningful conclusions from the later timepoints given the low patient numbers, but also it is not known whether those patients with longer follow-up data available differ significantly on any of the key prognostic indictors included as matching covariates than the full ITT population.

Overall, it is difficult to form any meaningful conclusions based on the results of the NorthStar data, and more emphasis should be given to the results of the STRIDE analysis, in which the majority of the MAA patients are included.

9.6.1.8 Additional studies

Qualitative caregiver survey

As previously discussed in section 7.1, a recent qualitative study has reported on the symptoms and impacts of nmDMD in ambulatory individuals prior to the initiation of ataluren. This study also explored their experience with ataluren.

Qualitative interviews were conducted with caregivers of individuals with nmDMD treated with ataluren in the UK. An interview guide, developed with input from clinical experts and patient advocacy groups, explored key concepts (symptoms and impacts) associated with ambulatory individuals with nmDMD before and after treatment with ataluren. Ten interviews were conducted with parents of individuals with nmDMD aged 4-19 years.[22]

Several caregivers reported that they had noticed positive changes in their son's symptoms or level of function since they had started taking ataluren. This included improved muscle strength, improvements in the length of time they could walk, reduced fatigue/increased energy levels and improvements in concentration. Improvements in impacts were also reported, with some caregivers reporting that their social interactions improved and others noticing an improvement in their son's emotional wellbeing. Other caregivers said that they had not noticed any changes since their son had started taking ataluren, however this was most often perceived as stability of symptoms and a positive sign. Some caregivers reported that their son's symptoms and physical function had declined since starting ataluren, but this was generally attributed to the natural course of nmDMD. One caregiver said that even though their son's nmDMD had progressed, they still thought that ataluren had delayed the progression. Overall, most caregivers said they would recommend ataluren.[22]

Long-term treatment with ataluren in Sweden

Methodology

Long-tern treatment outcomes with ataluren have been investigated in a retrospective longitudinal case-series study of all male DMD patients who have been treated with ataluren and followed at the Queen Silvia Children's Hospital in Gothenburg, Sweden, since 2008.[129]

All patients had a genetically verified nonsense mutation leading to a premature stop codon. Most patients initially received ataluren as part of their enrolment in prospective, controlled clinical trials. As part of these trials, patients' treatment periods with ataluren varied, and five patients had 'off treatment' periods between trials. Since 2017, all patients have been enrolled in the STRIDE Registry.

Upon initiation of ataluren treatment, all patients were followed in a prospective, systematic manner, either as part of their enrolment in a clinical trial or as part of regular follow-ups to assure continued medical surveillance and disease monitoring. The follow-ups included physical examination and physiotherapeutic evaluation every 24 weeks. Since 2013, lung function tests were added to the follow-ups, twice per year. For this study, data were also retrospectively collected from the patients' medical records using a case report form (CRF) which is available upon request. Data included age

at symptom onset, age of corticosteroid start and dosage, muscle biopsy and genetic results, comorbidities, other medications, hospitalisations and number of infections per year. For the pulmonary and motor function tests, the time period 1st January 2013 to 1st November 2020 was used, to have a more homogenous set of data.

Baseline characteristics

A total of 11 male DMD patients were included. All were on daily corticosteroid treatment with a stable, weight appropriate dosage, starting at a median age of 4 years. All patients had different age and disease duration when initiated on ataluren. They were clinically followed to a median age of 16.2 years (12.2 - 26.45 years). The patients started ataluren treatment at a median age of 8.4 years (5.2 - 14.4 years) and the median exposure to ataluren was 2312 days (1472 – 3413 days). Treatment with ataluren was discontinued in four patients, at a median age of 17.6 years (14.2 -25.5 years), all were non ambulant at the time of termination. One patient could not perform reliably on the pulmonary and motor function tests throughout the study due to neuropsychiatric disorder and was thus excluded from the analyses.

Ambulatory outcomes

Four of 10 patients were ambulatory at last follow-up. Loss of ambulation occurred at a median age of 13.2 years (8.5 - 18.1 years). Three patients who lost ambulation prior to 13.2 years of age had received ataluren for a median period of 5 years (4 -8.25 years). Six patients who continued to be ambulatory after 13.2 years of age had received ataluren for a median period of 6.5 years (5.25 - 9.35 years) until loss of ambulation or last follow-up if ambulatory. One ambulatory patient was 12.2 years old at last follow-up and was therefore not included in the estimations above. Two patients lost ambulation while they were off treatment between trials for 2.5 years. One patient started on ataluren off-label at 8 years of age and lost ambulation only after 6 months. This was the most severely affected patient in the cohort as shown in all motor and respiratory measurements.

Pulmonary function outcomes

All patients except one maintained a pulmonary decline above the expected over time. Two of 10 patients declined in predicted FVC % lower than 50% at the age of 17 and 17.5 years respectively.

All ambulatory patients increased in their predicted FVC with 2.8 to 8.2% annually. Following loss of ambulation, 5 of 6 patients declined in predicted FVC, with annual rate of decline varying from 1.8 to 21.1%.

Study conclusions

This is the first study that presents long-term cumulative treatment outcomes over a median period of 6.3 years on ataluren treatment. The authors conclude that the results indicate a delay in loss of ambulation similar to that seen in STRIDE, as well as a slower decline in FVC and in upper limb motor function. The treatment was considered safe and well tolerated, while there were no treatment-related issues of non-compliance.

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

Not applicable.

9.7 Adverse events

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

Studies reporting adverse events were identified and described in sections 9.1 to 9.5. Safety results of the studies identified are presented below.

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

9.7.2.1 Overview of Placebo-Controlled Clinical Trial Adverse Reactions

The safety profile of ataluren is based on pooled data from two randomised, double-blinded, 48-week placebo-controlled studies conducted in a total of 232 male patients with nmDMD aged 5 to 20 years treated at the recommended dose of 40 mg/kg/day (N=172) or at a dose of 80 mg/kg/day (N=60), compared to placebo (N=172).[1] The 80 mg/kg/day dose of ataluren is not an approved dose.

The spectrum and severity of AEs were consistent across the two trials (Table C-38 and Table C-39).[41] In brief, the majority of patients experienced AEs that were mild to moderate in severity (phase 2b trial: ataluren, 82.5%; placebo, 82.5%; Study 020: ataluren, 83.5%; placebo, 79.1%). AEs were considered possibly or probably related to the study drug in a similar proportion of patients across both trials (phase 2b: ataluren, 45.6%; placebo, 52.6%; Study 020: ataluren, 33.9%; placebo, 20.9%). No individuals discontinued owing to AEs in Study 007; two patients discontinued owing to AEs in Study 020 (ataluren, n=1 [constipation]; placebo, n=1 [disease progression]). No deaths were reported in either trial.

The most common adverse reactions in the 2 placebo-controlled studies were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients (Table C-40 and Table C-41). In both studies, 1/232 (0.43%) patients treated with ataluren discontinued due to an adverse reaction of constipation and 1/172 (0.58%) placebo patients discontinued treatment due to an adverse reaction of disease progression (LoA).[1]

The adverse reactions reported in patients with nmDMD treated with the recommended daily dose of 40 mg/kg/day ataluren in the 2 placebo-controlled studies are presented in Table C-38. Adverse reactions reported in >1 patient in the 40 mg/kg/day group at a frequency greater than that of the placebo group are presented by MedDRA System Organ Class, Preferred Term, and frequency. Frequency groupings are defined to the following convention: very common (≥1/10) and common (≥1/100 to <1/10).[1]

Adverse reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these two studies.

Table C-38. Adverse Reactions Reported in >1 Ataluren-Treated Patient With nmDMD at a Frequency Greater Than Placebo In the 2 Placebo-Controlled Studies (Pooled Analysis)

System Organ Class	Very Common	Common	Frequency Not Known
Metabolism and nutrition disorders		Decreased appetite, hypertriglyceridemia	Change in lipid profile (increased triglycerides and cholesterol)
Nervous system disorders		Headache	
Vascular disorders		Hypertension	
Respiratory, thoracic, and mediastinal disorders		Cough, epistaxis	
Gastrointestinal disorders	Vomiting	Nausea, upper abdominal pain, flatulence, abdominal discomfort, constipation	
Skin and subcutaneous tissue disorders		Rash erythematous	
Musculoskeletal and connective tissue disorders		Pain in extremity, musculoskeletal chest pain	
Renal and urinary disorders		Haematuria, enuresis	Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C)
General disorders and administration site conditions		Pyrexia, weight decreased	

Source: Translarna SPC[1]

Table C-39. Overview of TEAEs in Study 007 and Study 020 (Both As-Treated Population)

	Study 007			Study 020	
Parameter, n (%)	**Placebo (N=57)**	**Ataluren 40 mg/kg/day (N=57)**	**Ataluren 80 mg/kg/day (N=60)**	**Placebo (N=115)**	**Ataluren 40 mg/kg/day (N=115)**
Patients with ≥1 adverse event	56 (98.2)	55 (96.5)	57 (95.0)	101 (88)	103 (90)
Adverse events by severity					
Grade 1 (mild)	21 (36.8)	16 (28.1)	20 (33.3)	54 (47)	61 (53)
Grade 2 (moderate)	26 (45.6)	31 (54.4)	27 (45.0)	37 (32)	35 (30)
Grade 3 (severe)	9 (15.8)	8 (14.0)	10 (16.7)	9 (8)	7 (6)
Grade 4 (life-threatening)	0	0	0	0	0
Adverse events by relatedness					
Unrelated	14 (24.6)	8 (14.0)	11 (18.3)	47 (41)	44 (38)
Unlikely	16 (28.1)	17 (29.8)	13 (21.7)	30 (26)	20 (17)
Possible	20 (35.1)	25 (43.9)	29 (48.3)	18 (16)	27 (23)
Probable	6 (10.5)	5 (8.8)	4 (6.7)	6 (5)	12 (10)
Discontinuations due to adverse events	0	0	0	NR	NR
Serious adverse events	3 (5.3)	2 (3.5)	2 (3.3)	4 (3.4)	4 (3.4)
Deaths	0	0	0	0	0

Source: Bushby 2014[32]; McDonald 2017[33]

Table C-40. TEAEs With a Patient Frequency of ≥5%, Study 007

MedDRA System Organ Class/ Preferred Term[a]	**Treatment Arm**		
	Placebo	**Ataluren 40 mg/kg/day**	**Ataluren 80 mg/kg/day**
	N=57, n (%)	**N=57, n (%)**	**N=60, n (%)**
Gastrointestinal disorders	37 (64.9)	42 (73.7)	44 (73.3)
Vomiting	22 (38.6)	32 (56.1)	27 (45.0)
Diarrhoea	14 (24.6)	11 (19.3)	17 (28.3)
Abdominal pain upper	9 (15.8)	9 (15.8)	13 (21.7)
Nausea	7 (12.3)	8 (14.0)	10 (16.7)
Abdominal pain	4 (7.0)	7 (12.3)	10 (16.7)
Flatulence	4 (7.0)	5 (8.8)	7 (11.7)
Stomach discomfort	0	4 (7.0)	5 (8.3)
General disorders	21 (36.8)	23 (40.4)	20 (33.3)
Pyrexia	12 (21.1)	14 (24.6)	7 (11.7)
Disease progression	6 (10.5)	4 (7.0)	5 (8.3)
Asthenia	2 (3.5)	3 (5.3)	4 (6.7)

MedDRA System Organ Class/ Preferred Term[a]	Treatment Arm		
	Placebo	Ataluren 40 mg/kg/day	Ataluren 80 mg/kg/day
	N=57, n (%)	N=57, n (%)	N=60, n (%)
Infections and infestations	43 (75.4)	38 (66.7)	39 (65.0)
Nasopharyngitis	13 (22.8)	13 (22.8)	10 (16.7)
Upper respiratory tract infection	10 (17.5)	9 (15.8)	11 (18.3)
Influenza	8 (14.0)	6 (10.5)	7 (11.7)
Gastroenteritis	4 (7.0)	9 (15.8)	3 (5.0)
Rhinitis	2 (3.5)	6 (10.5)	3 (5.0)
Ear infection	3 (5.3)	3 (5.3)	4 (6.7)
Gastroenteritis viral	3 (5.3)	4 (7.0)	3 (5.0)
Injury, poisoning and procedural complications	26 (45.6)	28 (49.1)	31 (51.7)
Fall	7 (12.3)	11 (19.3)	6 (10.0)
Procedural pain	7 (12.3)	6 (10.5)	8 (13.3)
Contusion	3 (5.3)	6 (10.5)	4 (6.7)
Joint sprain	1 (1.8)	4 (7.0)	4 (6.7)
Investigations	4 (7.0)	10 (17.5)	6 (10.0)
Weight decreased	1 (1.8)	5 (8.8)	3 (5.0)
Metabolism and nutrition disorders	3 (5.3)	7 (12.3)	6 (10.0)
Decreased appetite	2 (3.5)	5 (8.8)	5 (8.3)
Musculoskeletal and connective tissue disorders	19 (33.3)	25 (43.9)	28 (46.7)
Pain in extremity	6 (10.5)	7 (12.3)	8 (13.3)
Back pain	5 (8.8)	9 (15.8)	6 (10.0)
Arthralgia	2 (3.5)	2 (3.5)	6 (10.0)
Muscle spasms	5 (8.8)	3 (5.3)	1 (1.7)
Muscular weakness	1 (1.8)	3 (5.3)	5 (8.3)
Nervous system disorders	17 (29.8)	25 (43.9)	18 (30.0)
Headache	14 (24.6)	22 (38.6)	15 (25.0)
Dizziness	4 (7.0)	3 (5.3)	3 (5.0)
Respiratory, thoracic and mediastinal disorders	18 (31.6)	20 (35.1)	22 (36.7)
Cough	11 (19.3)	9 (15.8)	13 (21.7)
Nasal congestion	4 (7.0)	5 (8.8)	6 (10.0)
Oropharyngeal pain	4 (7.0)	6 (10.5)	4 (6.7)
Rhinorrhoea	6 (10.5)	4 (7.0)	0
Skin and subcutaneous tissue disorders	18 (31.6)	19 (33.3)	14 (23.3)
Rash	5 (8.8)	4 (7.0)	8 (13.3)
Scar	3 (5.3)	4 (7.0)	5 (8.3)

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 have 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.
Source: Ataluren Study 007 CSR; Bushby 2014 [32]

Table C-41. TEAEs With a Patient Frequency of ≥5%, Study 020

MedDRA System Organ Class/ Preferred Term	Placebo	Ataluren 40 mg/kg/day
	N=115, n (%)	N=115, n (%)
Gastrointestinal disorders	48 (42)	52 (45)
Vomiting	21 (18)	26 (23)
Diarrhoea	10 (9)	20 (17)
Abdominal pain upper	13 (11)	9 (8)
Nausea	7 (6)	7 (6)
Abdominal pain	7 (6)	7 (6)
Constipation	10 (9)	3 (3)
General disorders	32 (28)	29 (25)
Pyrexia	12 (10)	16 (14)
Disease progression	14 (12)	9 (8)
Infections and infestations	50 (43)	63 (55)
Nasopharyngitis	22 (19)	24 (21)
Upper respiratory tract infection	6 (5)	11 (10)
Rhinitis	4 (3)	8 (7)
Injury, poisoning and procedural complications	34 (30)	35 (30)
Fall	20 (17)	21 (18)
Musculoskeletal and connective tissue disorders	32 (28)	32 (28)
Pain in arm, leg or both	14 (12)	10 (9)
Back pain	8 (7)	11 (10)
Nervous system disorders	23 (20)	28 (24)
Headache	21 (18)	21 (18)
Respiratory, thoracic and mediastinal disorders	30 (26)	34 (30)
Cough	13 (11)	19 (17)
Oropharyngeal pain	6 (5)	7 (6)

Source: McDonald 2017[33]

9.7.2.2 Study 020e

The primary objective of the extension phase was to obtain long-term ataluren safety data to augment the ataluren safety. A total of 68 patients completed 144 weeks of treatment in Study 020e.

The most frequently reported TEAEs (≥ 15%) included nasopharyngitis (26.1%), disease progression (25.7%), fall (22%), headache (19.3%), and vomiting (17.0 %). Based on exposure-adjusted event rates, headache (23.2%), nasopharyngitis (19.8%), fall (15.2%) and vomiting (14.2%), were the most frequently reported TEAEs.[160]

There were no TEAEs leading to fatal outcomes; one TEAE (anxiety) of mild intensity led to study discontinuation. Forty-four serious TEAEs were reported in 24 patients (11%), none of which were considered related to study drug. Sixteen (7.3%) patients had serious TEAEs that were also severe (Grade 3) in intensity and 2 patients had life-threatening events, including hypoxia, femur fracture, hypotension, bradycardia, acute respiratory distress syndrome, and pneumonia aspiration, all of which resolved. Thirty-five patients had 51 adrenal, hepatic or renal TEAEs that were mild to moderate in intensity except for 1 event each of nephrolithiasis and haematuria, that were severe (Grade 3) in intensity. A total of 68 TEAEs in 44 (20.2%) patients were reported as being related to study medication. Haematuria (n=11) was the only related preferred term occurring in ≥5% of patients.[160]

Small mean increases in LDL, total cholesterol, and triglycerides levels were observed; but were not considered clinically relevant.[160]

9.7.2.3 Safety in Long-Term Open-Label Study 019

The safety profile of ataluren observed up to 336 weeks in Study 019 was consistent with other ataluren studies, and no new ataluren risks were identified. Overall, 91 of 94 patients (96.8%) experienced a total of 1282 TEAEs (Table C-42). The majority of TEAEs were mild or moderate in severity (54/94 [57.4%]) and TEAEs that were considered drug related were observed in 26 of 94 patients (27.7%). There were no life-threatening TEAEs. Thirty-one patients (33.0%) experienced serious adverse events (SAEs): the SAEs in all but one of these patients were considered by the investigator unrelated to ataluren. Two patients experienced two SAEs each that led to death; none of these events were considered by the investigator related to the study drug.[130]

Table C-42. Treatment-emergent adverse events experienced by patients in the as-treated population of Study 019 (N=94)

TEAEs	Corticosteroid use		Overall (N=94)
	Yes (n=84)	No (n=10)	
Number of TEAEs†	1199	83	1282
Patients with at least one of the following			
TEAE	82 (97.6)	9 (90.0)	91 (96.8)
TEAE related to ataluren	23 (27.4)	3 (30.0)	26 (27.7)
TEAE leading to discontinuation of ataluren	2 (2.4)	1 (10.0)	3 (3.2)
SAE	29 (34.5)	2 (20.0)	31 (33.0)
TEAE with maximum severity‡,§			
Mild	21 (25.0)	2 (20.0)	23 (24.5)
Moderate	26 (31.0)	5 (50.0)	31 (33.0)
Severe	34 (40.5)	1 (10.0)	35 (37.2)
Life-threatening	0 (0)	0 (0)	0 (0)
Fatal	1 (1.2)	1 (10.0)	2 (2.1)
Patients with at least one of the following‡,¶,#			
Infections and infestations‡	63 (75.0)	5 (50.0)	68 (72.3)
Gastrointestinal disorders‡	48 (57.1)	6 (60.0)	54 (57.4)
Injury, poisoning and procedural complications‡	48 (57.1)	3 (30.0)	51 (54.3)

TEAEs	Corticosteroid use		Overall (N=94)
	Yes (n=84)	No (n=10)	
General disorders and administration site conditions‡	46 (54.8)	4 (40.0)	50 (53.2)
Musculoskeletal and connective tissues disorders‡	41 (48.8)	7 (70.0)	48 (51.1)
Respiratory, thoracic and mediastinal disorders‡	31 (36.9)	5 (50.0)	36 (38.3)
Nervous system disorders‡	32 (38.1)	1 (10.0)	33 (35.1)
Investigations‡	17 (20.2)	4 (40.0)	21 (22.3)
Cardiac disorders‡	16 (19.0)	2 (20.0)	18 (19.1)
Skin and subcutaneous tissue disorders‡	17 (20.2)	1 (10.0)	18 (19.1)
Metabolism and nutrition disorders‡	9 (10.7)	2 (20.0)	11 (11.7)
Psychiatric disorders‡	10 (11.9)	0 (0)	10 (10.6)
Renal and urinary disorders‡	7 (8.3)	0 (0)	7 (7.4)
Surgical and medical procedures‡	6 (7.1)	1 (10.0)	7 (7.4)
Eye disorders‡	6 (7.1)	0 (0)	6 (6.4)
Ear and labyrinth disorders‡	5 (6.0)	0 (0)	5 (5.3)
Vascular disorders‡	3 (3.6)	0 (0)	3 (3.2)
Endocrine disorders‡	2 (2.4)	0 (0)	2 (2.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)‡	1 (1.2)	0 (0)	1 (1.1)
Reproductive system and breast disorders‡	1 (1.2)	0 (0)	1 (1.1)

†TEAE is defined as any AE that occurred or worsened in the period extending from the day of a patient's first dose of ataluren to 6 weeks after the last dose of ataluren in this study.
‡TEAE categories.
§For patients with two or more AEs, the event with the maximum severity was reported. The order of severity is: 'Mild', 'Moderate', 'Severe', 'Life-threatening' and 'Fatal'.
¶AEs were coded using the Medical Dictionary for Regulatory Activities (version 20.1)
#A patient who reported two or more AEs with the same preferred term was counted only once for that term. A patient who reported two or more AEs with different preferred terms within the same organ class was counted only once in the system organ class
AE: adverse events; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: McDonald 2021[130]

9.7.2.4 Safety in Patients ≥2 to <5 Years of Age

Study 030 was a Phase 2, open-label, multiple-dose study designed to evaluate the PK and safety in boys aged ≥2 to <5 years with nmDMD.[42] TEAEs classified as possibly related to ataluren were rash, flatulence, nausea and vomiting and all were classified as mild (except for 1 occurrence of vomiting that was moderate) in severity. No patient experienced a TEAE considered to be severe (or greater) in intensity, a SAE, or prematurely discontinued ataluren due to a TEAE. A higher frequency of malaise (7.1%), pyrexia (42.9%), ear infection (28.6%), and rash (21.4%) were reported in patients aged 2 to 5 years compared with patients 5 years of age and older. Safety data from 28

weeks of therapy showed a similar safety profile of ataluren in patients 2 to 5 years as compared with patients aged 5 years and older.[1]

9.7.2.5 STRIDE

In this long-term observational study of ataluren in nmDMD, interim safety results continue to be consistent with the known safety profile of ataluren. With longer term routine clinical use, there was no cumulative toxicity or late occurring unexpected events with ataluren, and the AE profile tended to reflect the progression of the underlying DMD disease process.

Results from STRIDE with a data cut-off on 09 July 2018 were published by Mercuri and colleagues in 2020.[7] Data presented in this section relate to the most recent cut-off on 31 January 2021.[36]

Summary of Adverse Events

Safety outcomes were consistent with the known safety profile of ataluren (Table C-43).

Seven patients (2.4%) experienced a TEAE deemed related to ataluren, and 13 patients (4.5%) experienced a TEAE that led to discontinuation of ataluren.[128] Twenty-three patients (8.0%) had a total of 34 SAEs, which were considered not related to the study medication (n=31); of unknown relationship to study medication (n=2); or the relationship to the study medication was not reported (n=1). The majority of TEAEs were mild to moderate in severity, and no life-threatening TEAEs were reported.[128]

Safety information is presented for the 266 subjects in the ≥5 years subgroup and for 20 subjects in the ≥2 to <5 years subgroup (Table C-43).[36]

Table C-43: Overview of Treatment-Emergent Adverse Events (As-Treated Population; 31 January 2021 Cut-Off)

	As-Treated Population ≥5 Years Subgroup			As-Treated Population ≥2 to <5 Years Subgroup			As-treated (All)		
	Corticosteroid Use			Corticosteroid Use			Corticosteroid Use		
	Yes	No	All	Yes	No	All	Yes	No	All
	n=240	n=26	n=266	n=10	n=10	n=20	n=250	n=36	n=286
Number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	278	41	319
Patients with 1 or more (n, %):									
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100 (40.0)	14 (38.9)	114 (39.9)
TEAE related to ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (2.4)	1 (2.8)	7 (2.4)
TEAE leading to discontinuation of ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (4.4)	2 (5.6)	13 (4.5)
SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19 (7.6)	4 (11.1)	23 (8.0)
TEAE with a maximum severity:[a]									
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (4.0)	0 (0.0)	10 (3.5)
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (2.4)	2 (5.6)	8 (2.8)
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39 (15.6)	4 (11.1)	43 (15.0)
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34 (13.6)	5 (13.9)	39 (13.6)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (4.4)	3 (8.3)	14 (4.9)
Life-threatening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)	0 (0.0)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Note: TEAE is defined as any adverse event with an end date on or after the first ataluren use date. Events with missing severity are considered Not reported.
[a] For subjects with 2 or more adverse events, the event with the maximum severity was reported in this summary. The order of the severity is 'Not Reported', 'Unknown', 'Mild', 'Moderate', 'Severe', and 'Life-threatening
Source: PTC STRIDE CSR 2021; Muntoni 2021[36,128]

Display of Adverse Events

The TEAEs in the subjects ≥5 years of age most often were due to [redacted] (Table C-44). The most common individual TEAEs (occurring in ≥3% of all subjects) were [redacted] ([redacted] subjects).

The TEAEs reported in the ≥2 to <5 years subgroup included upper respiratory infection [redacted] and gastroenteritis, respiratory tract infection, subdural hematoma, and idiopathic intracranial hypertension[redacted]; Table C-45).

Table C-44. Treatment-Emergent Adverse Events ≥1% of All Subjects (As-Treated Population ≥5 Years Subgroup); 31 January 2021 Cut-Off)

	Corticosteroid Use		
System Organ Class	**Yes**	**No**	**All**
Preferred Term[a]	**n=240**	**n=26**	**(n=266)**
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]

	Corticosteroid Use		
System Organ Class	**Yes**	**No**	**All**
Preferred Term[a]	**n=240**	**n=26**	**(n=266)**
Fall	[redacted]	[redacted]	[redacted]
Off-label	[redacted]	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Humerus fracture	[redacted]	[redacted]	[redacted]
Laceration	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Gait inability	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Myoglobinuria	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Cataracts	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
TEAE is defined as any adverse event with an end date on or after the first ataluren use date. A subject who reported 2 or more occurrences with the same preferred term was counted only once for that term.
[a] Adverse Events were coded using MedDRA, Version 20.1.
Source: PTC STRIDE CSR 2021[36]

Table C-45. Treatment-Emergent Adverse Events in 1 or More Patients (As-Treated Population ≥2 to <5 Years; 31 January 2021 Cut-Off, As-Treated

	Corticosteroid Use		
System Organ Class	**Yes**	**No**	**All**
Preferred Term[a]	**n=10**	**n=10**	**(n=10)**
Patients with at least 1 of the following (n, %)			
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Subdural hematoma	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Idiopathic intracranial hypertension	[redacted]	[redacted]	[redacted]

MedDRA, Medical Dictionary for Regulatory Activities, TEAE, treatment-emergent adverse event

a Adverse Events were coded using MedDRA, Version 20.1.
Note: TEAE is defined as any adverse event with an end date on or after the first ataluren use date. A subject who reported 2 or more occurrences with the same preferred term was counted only once for that term.
Source: PTC STRIDE CSR 2021[36]

Serious Adverse Events

deaths have been reported as of the data cut-off of 31 January 2021.

A total of subjects in the ≥5 years subgroup experienced SAEs during participation (with corticosteroid use and with no corticosteroid use) (Table C-43). SAEs in all subjects were considered unrelated to ataluren treatment, and led to discontinuation of treatment. The most common events involved .

subjects in the ≥2 to <5 years subgroup, both with corticosteroid use, experienced SAEs during Registry participation. All SAEs were considered unrelated to ataluren treatment, and none led to discontinuation of treatment.[36]

Drug Related Adverse Events

subjects in the ≥5 years subgroup (with corticosteroid use and with no corticosteroid use) had at least 1 TEAE considered by the investigator to be related to ataluren (Table C-43). The TEAEs considered related to ataluren included: in 1 subject each. treatment-related events were mild or moderate in severity.

of the TEAEs in the ≥2 to <5 years subgroup were considered related to treatment.[36]

Adverse Events by Severity

Where TEAE severity was known, most subjects in the ≥5 years subgroup had events of mild (subjects) or moderate (subjects) severity. TEAEs in patients were considered severe (used corticosteroids and did not). TEAEs considered severe included .

severe TEAE was reported in the ≥2 to <5 years subgroup (.[36]

Laboratory Results

Laboratory assessments were performed and collected as determined by routine clinical practice. Clinically significant laboratory abnormalities were infrequent, and no clinically meaningful trends were observed in laboratory assessments.

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

In clinical trials and long-term studies, the observed safety and tolerability profile of ataluren is comparable to that of BSC alone. The most common reported adverse reactions were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients. These adverse reactions generally did not require medical intervention and few patients discontinued ataluren treatment due to any adverse reaction.

In the long-term observational study of ataluren in nmDMD (STRIDE), interim safety results continue to be consistent with the known safety profile of ataluren. With longer term routine clinical use, there was no cumulative toxicity or late occurring unexpected events with ataluren, and the AE profile tended to reflect the progression of the underlying DMD disease process.

9.8 Evidence synthesis and meta-analysis

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

9.8.1.1 Meta-analyses of studies 007 and 020

The Study 020 statistical analysis plan included a meta-analysis with data from the ITT population of Study 020 and a subgroup of patients from the intention-to-treat population of the Phase 2b trial (who met the ACT-DMD entry criteria). This analysis was provided during the original assessment and was published by McDonald et al. in 2017.[33] In brief, this analysis showed that when 6MWD data were combined, a 21.1-m (SE 9.0, 95% CI 3.4–38.8) treatment benefit was observed for ataluren-treated versus placebo-treated patients over 48 weeks. Similarly, when data for TFTs were combined, patients in the ataluren group had less of a decline than did those in the placebo group (–1.4 to –2.0 across the three tests, SE 0.6–0.7; 95% CI −3.4 to −0.2).

A meta-analysis on the entire ITT populations has also been conducted to provide additional data with a more conservative approach, including a larger and more heterogeneous population than the meta-analysis specified in the Study 020 statistical analysis plan. This analysis provided consistent results and is described in detail in this section.

9.8.1.2 Post-hoc meta-analysis of studies 007 and 020

Methodology

Data from the two completed RCTs (Studies 007 and 020) of ataluren in nmDMD were combined to examine the ITT populations and 2 patient subgroups (baseline 6MWD ≥300 to <400 metres or <400 metres).[41] Meta-analyses examined 6MWD change from baseline to Week 48.

The meta-analyses of Studies 007 and 020 were performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines, where applicable.[41] Because these meta-analyses included only two randomised, placebo-controlled studies, and no significant treatment–study interaction or treatment heterogeneity across the two studies was observed, the standard fixed-effects model approach was utilised.

Outcomes for the 6MWT and TFTs are reported as the LS mean difference ±95% CIs. Time to persistent 10% 6MWD worsening is reported as the HR with 95% CI, indicating the risk of persistent worsening.

The meta-analyses were conducted in three populations: i) the entire ITT populations of the 2 trials; ii) patients from the ITT populations with a pre-specified baseline 6MWD of ≥300 to <400 metres; and iii) the ITT population with a baseline 6MWD of <400 metres.

Quality assessment of the two studies is provided in Table C-13.

Inclusion/Exclusion Criteria Differences

The two trials, Study 007 and Study 020 were of similar design. One key difference between the trials was the inclusion criterion regarding patients' baseline 6MWD. Study 007 specified boys were aged ≥5 years, with a screening 6MWD ≥75 metres. Study 020's inclusion criteria were stricter,

specifying boys aged ≥7 years and ≤16 years, with a 6MWD of both ≥150 metres and ≤80% of that predicted for their age and height. Study 020 also specified that patients should be receiving concomitant stable corticosteroid therapy. This was not specified in the Study 007; nonetheless, 71% of patients recruited were receiving corticosteroids.

Patients in both trials received ataluren 40 mg/kg/day or placebo for 48 weeks. Patients in Study 007 who received ataluren 80 mg/kg/day were not included in these meta-analyses.

Outcome measures

The meta-analyses evaluated the change in 6MWT and TFTs from baseline beyond 48 weeks between ataluren and placebo-treated patients.

Baseline Characteristics

These meta-analyses included data from all patients who received ataluren 40 mg/kg/day or placebo in Study 007 (ataluren, n=57; placebo, n=57) and Study 020 (ataluren, n=114; placebo, n=114).[41]

- The meta-analysis of the ≥300 to <400 metres 6MWD patient subgroup was based on 44 patients in Study 007 (ataluren, N=22; placebo, N=22) and 99 patients in Study 020 (ataluren, N=47; placebo, N=52) who had a baseline 6MWD ≥300 to <400 metres.
- The meta-analysis of the <400 metres 6MWD subgroup included 72 patients from Study 007 (ataluren, N=37; placebo, N=35) and 144 patients in Study 020 (ataluren, N=71; placebo, N=73).

Baseline demographics and characteristics of boys included in both trials were similar, except for the baseline 6MWD inclusion criterion previously described, and were balanced between the ataluren and placebo-treated groups. The mean (standard deviation [SD]) age of patients in both trials was comparable (ataluren vs placebo: Study 007, 8.8 [2.9] vs 8.3 [2.3] years; Study 020, 8.9 [1.8] vs 9.0 [1.7] years). The majority of patients in both trials were Caucasian (ataluren vs placebo: Study 007, 93.0% [53/57] vs 94.7% [54/57]; Study 020, 77.4% [89/115] vs 74.8% [86/115]). At baseline, mean (SD) 6MWD was slightly lower for patients in the Study 007 (ataluren, 350.0 [97.6] m; placebo, 359.6 [87.7] m) than in Study 020 (ataluren, 364.0 [73.3] m; placebo, 362.7 [81.4] m).

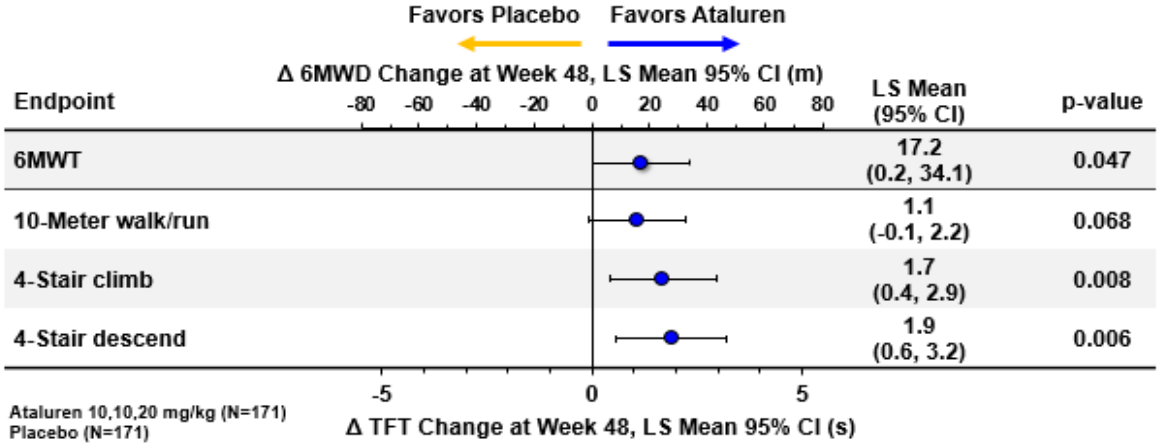
The efficacy results are presented for each subgroup below; between trial differences were not statistically significant for any endpoint in each subgroup justifying combining the data in these analyses.

9.8.1.3 Results

As shown in Figure C.36 and Table C-46, the combined results from the two ITT populations demonstrated a significant favourable change in 6MWD from baseline to Week 48 with ataluren than with placebo (LS mean difference [95% CI], +17.2 [0.2 to 34.1] metres; p=0.0473). Combined results also revealed statistically significant benefits in patients receiving ataluren versus placebo (LS mean [95% CI]) in time to climb 4 stairs (−1.7 [−2.9 to −0.4] s; p=0.0078) and descend 4 stairs (−1.9 [−3.2 to −0.6] s; p=0.0055).

Patients who received ataluren also had a statistically significantly reduced risk of persistent 10% worsening of 6MWD versus placebo (HR [95% CI], 0.68 [0.48 to 0.94]; p=0.0215).[41]

Figure C.36. Meta-Analysis of Study 020 and Study 007 (ITT Population)



6MWT, 6-minute walk test, LS, least-squares; TFT, timed function test
Source: Illustration was created by PTC based on Campbell et al. 2020[41]

In the ≥300 to <400 metres 6MWD patient subgroup, the meta-analysis demonstrated a statistically significant difference in change in 6MWD between ataluren-treated and placebo-treated patients, favouring ataluren (+43.9 [18.2 to 69.6] metres; p=0.0008). Statistically significant benefits in patients receiving ataluren versus placebo in this subgroup were also seen in time to run/walk 10 metres (−2.1 [−3.7 to −0.4] seconds; p=0.0149), climb 4 stairs (−3.4 [−5.3 to −1.5] seconds; p=0.0004), and descend 4 stairs (−4.3 [−6.2 to −2.3] seconds; p<0.0001). There was no significant difference in risk of persistent 10% 6MWD worsening in ataluren versus placebo-treated patients (0.66 [0.39 to 1.11]; p=0.1162).[41]

In the <400 metres 6MWD patient subgroup, the difference in change in 6MWD between ataluren and placebo-treated patients was also statistically significant, favouring ataluren (+27.7 [6.4 to 49.0] metres; p=0.0109. Statistically significant benefits in patients receiving ataluren versus placebo were also seen in time to run/walk 10 metres (−1.7 [−3.2 to −0.3] seconds; p=0.0197), climb 4 stairs (−2.6 [−4.3 to −1.0] seconds; p=0.0013), and descend 4 stairs (−2.8 [−4.3 to −1.1] seconds; p=0.0015). Furthermore, patients who received ataluren experienced a statistically significant reduced risk of persistent 10% 6MWD worsening relative to those who received placebo (0.62 [0.45 to 0.85]; p=0.0028).[41]

Improved TFT results were statistically significant in all patient subgroups; in the full ITT population ataluren had a benefit of 1.1 to 1.9 seconds versus placebo across the three tests and a greater benefit was observed in the 6MWD ≥300 to <400 metres (2.1 to 4.3 seconds) and <400 metres (1.7 to 2.8 seconds) subgroups.

Summary

Meta-analyses of Study 007 and Study 020 confirmed that ataluren slows disease progression versus BSC alone in patients with nmDMD over 48 weeks and that the observed statistical trends in studies 007 and 020 can be attributed to their small sample sizes when analysed separately.

Table C-46. Meta-analysis (post-hoc) of Study 007 and Study 020 placebo-controlled RCTs

Analysis Subgroup	Study	LS Mean Difference (95% CI)	p value
Change in 6MWD			
ITT	007 All patients (placebo n=57, ataluren, n=57)	26.4 (-4.2, 57.1)	0.0905
	020	13.0 (-7.4 to 33.4)	0.213
	Meta-analysis	17.2 (0.2, 34.1)	0.0473
6MWD ≥300 to <400	007	45.9 (0.1, 91.8)	0.0496
	020	42.9 (11.8 to 74.0)	0.007
	Meta-analysis	43.9 (18.2, 69.6)	0.0008
6MWD <400	007	34.0 (-3.3, 71.3)	0.0735
	020	24.6 (-1.6, 50.7)	0.0650
	Meta-analysis	27.7 (6.4, 49.0)	0.0109
Change in 10-m run/walk			
ITT	007	-1.1 (-3.4, 1.2)	0.3509
	020	−1.1 (-2.4, 0.3)	0.117
	Meta-analysis	1.1 (-2.2, 0.1)	0.0677
6MWD ≥300 to <400	007	-2.7 (-5.9, 0.5)	0.1000
	020	−1.8 (-3.8, 0.1)	0.066
	Meta-analysis	-2.1 (-3.7, -0.4)	0.0149
6MWD <400	007	-1.9 (-4.7, 0.9)	0.1823
	020	-1.7 (-3.4, 0.0)	0.0050
	Meta-analysis	-1.7 (-3.2, -0.3)	0.0197
4-stair climb			
ITT	007	-2.4 (-4.8, 0.0)	0.0488
	020	−1.4 (-2.9, 0.1)	0.058
	Meta-analysis	-1.7 (-2.9, -0.4)	0.0078
6MWD ≥300 to <400	007	-3.3 (-6.8, 0.3)	0.0715
	020	−3.5 (-5.7, -1.2)	0.003
	Meta-analysis	-3.4 (-5.3, -1.5)	0.0004
6MWD <400	007	-3.7 (-6.5, -0.8)	0.0116
	020	-2.1 (-4.1, -0.2)	0.0340
	Meta-analysis	-2.6 (-4.3, -1.0)	0.0013
4-stair descend			
ITT	007	-1.6 (-4.2, 1.0)	0.2268
	020	−2.0 (-3.5, -0.4)	0.0120
	Meta-analysis	-1.9 (-3.2, -0.6)	0.0055
6MWD ≥300 to <400	007	-4.0 (-7.8, -0.1)	0.0419
	020	−4.4 (-6.6, -2.1)	<0.001
	Meta-analysis	-4.3 (-6.2, -2.3)	<0.0001
6MWD <400	007	-2.6 (-5.7, 0.5)	0.1018
	020	-2.9 (-5.0, -0.8)	0.0070
	Meta-analysis	-2.8 (-4.3, -1.1)	0.0015

LS mean differences between ataluren and placebo groups were assessed by meta-analysis of the ITT. meta-analysis of patients with a baseline 6MWD ≥300–<400 m and meta-analysis of patients with a baseline 6MWD <400 m
6MWD: 6-minute walk distance; ITT: intent-to-treat; LS: Least-squares.
Source: Campbell et al. 2020[41]

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

Not applicable.

9.9 Interpretation of clinical evidence

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

Treatment with ataluren plus BSC significantly delays loss of ambulation compared to BSC alone

In Phase 2 and 3 clinical studies (007 and 020), ataluren reduced the decline in 6MWD over 48 weeks compared with BSC alone, and consistently demonstrated benefit across multiple measures of muscle strength and function.[32,33]

Although the primary endpoint was not met in Study 007 or Study 020, a clinically meaningful benefit in the decline in 6MWD was observed Study 007.[32,40] Following completion of Study 007, patients with a baseline 6MWD of ≥300 to <400 metres were identified as the optimal group as these patients have a considerable loss of walking ability, but still have enough muscle mass in their lower limbs to be able to show a drug effect on 6MWD over 48 weeks.[33] The treatment effect was evident in the pre-specified subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres in Study 020, with a statistically significant LS mean difference of 42.9 metres between the two groups (p=0.007).[33]

In addition, a pre-specified meta-analysis of the studies was conducted to increase the sample size resulting in statistically significant treatment effects on the 6MWT.[33] Further analysis that combined results from the two ITT populations demonstrated a difference in change in 6MWD from baseline to Week 48 between ataluren- and placebo-treated patients, which was statistically significant in favour of ataluren (LS mean difference [95% CI], +17.2 [0.2 to 34.1] metres; p=0.0473) that was more pronounced in the ≥300–<400 metre group (43.9 (18.2 to 69.6) metres; p=0.0008).[41] The meta-analyses also demonstrated improved TFT results that were statistically significant in all patient subgroups; in the ITT population, ataluren had a benefit of 1.1 to 1.9 seconds versus placebo across the three tests. Moreover, an even greater benefit was observed in the ≥300–<400 metre (2.1–4.3 seconds) and <400 metre (1.7 to 2.8 seconds) subgroups across all three TFTs.[41]

Ataluren treatment in STRIDE was associated with a delay in LoA by 5.4 years compared with CINRG DNHS matched controls (17.9 years of age vs 12.5 years of age, respectively). Ataluren statistically reduced the risk for LoA by 63% relative to BSC alone in CINRG DNHS (p<0.0001,

HR 0.374).[35] Ataluren-treated patients also retained their ability to stand from supine for longer, with a [redacted] lower risk of reaching a time to rise from supine in more than 10 seconds compared to matched patients in CINRG DNHS ([redacted]).[36]

In Study 019, treatment with ataluren plus BSC significantly delayed LoA by 2.2 years compared with the CINRG DNHS matched control. In the propensity score matched populations, the median age at LoA was 15.5 years in Study 019 and 13.3 years in the matched CINRG DNHS cohort, representing a statistically significant, clinically meaningful difference in favour of ataluren versus BSC alone.

The observed delay in LoA represents not only a highly meaningful prolongation of personal autonomy in daily life, but also a delay in the onset of subsequent disease milestones (see section 9.9.3).

Treatment with ataluren plus BSC significantly delays loss of pulmonary function compared to BSC alone

Across all pulmonary function milestones, patients in STRIDE were older than propensity-matched subjects from the CINRG DNHS database at the time each milestone was reached. The median age at % predicted FVC <60% was 17.6 years for STRIDE subjects and 15.8 years in the CINRG DNHS propensity score matched population (p=0.0051; HR 0.544). Similar results were observed for the milestones of % predicted FVC [redacted] and <30%. The median age at the time of FVC <1 litre was not reached in STRIDE patients due to too few events and was 24.9 years in the CINRG DNHS propensity score matched population.

In Study 019 there was a 3-year delay in decline of predicted forced vital capacity to <60% in non-ambulatory patients (p=0.0004).[130]

Ataluren is well tolerated in nmDMD patients as young as 2 years old

In clinical trials and long-term studies, the observed safety and tolerability profile of ataluren is comparable to that of BSC. In the two placebo-controlled studies the most common reported adverse reactions were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients.[1] These adverse reactions generally did not require medical intervention and few patients discontinued ataluren treatment due to any adverse reaction. Adverse reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these two studies.[1] The safety profile of ataluren observed up to 336 weeks in Study 019 was consistent with other ataluren studies.[130] Safety data from 28 weeks of therapy showed a similar safety profile of ataluren in patients 2–5 years as compared with patients aged 5 years and older.[1]

In the long-term observational study of ataluren in nmDMD (STRIDE), interim safety results continue to be consistent with the known safety profile of ataluren. With longer term routine clinical use, there was no cumulative toxicity or late occurring unexpected events with ataluren, and the AE profile tended to reflect the progression of the underlying DMD disease process.

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

There have been a limited number of large, randomised studies in DMD and, through the ataluren trial programme, PTC Therapeutics are pioneering clinical trial research in this disease area. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials. STRIDE is the first drug registry for patients with DMD and is the largest real-world study of patients with nmDMD to date. STRIDE provides data on patterns of ataluren use and long-term patient outcomes in real-world routine clinical practice.

Study 007 and Study 020 were placebo-controlled studies, reflecting the lack of available efficacious treatments other than ataluren for boys with nmDMD. The choice of placebo for the reference arm was justified, as ataluren represents a first-in-class approach to DMD treatment where no approved standard therapy exists. Prior to regulatory approval of ataluren for the treatment of nmDMD, the only management options for this devastating disease were supportive in nature and did not address the underlying cause of the condition, i.e., the loss of dystrophin. Without dystrophin, muscles progressively weaken and deteriorate, leading to complete loss of ambulation, cardiac and pulmonary insufficiency, and death. Ataluren is the first disease-modifying treatment option for nmDMD that can be used early in life.

During Study 007 all patients continued to receive the BSC they were on when they entered the study including, in many cases, corticosteroid treatment. Similarly, all patients in Study 020 were receiving BSC, including corticosteroids. The studies therefore provide a comparison of efficacy and safety of ataluren compared to established clinical management without ataluren.

The challenges associated with the use of the 6MWT in patients with DMDs can undermine the statistical power of properly designed trials. Performance tends to improve with time in very young patients whereas performance tends to worsen with time in older patients, and there can be a floor effect of losing ambulation in older patients with more advanced disease.[98] It is now known that patients with a baseline 6MWD ≥400 metre remain relatively stable in physical functioning over 48 weeks, whereas patients with a 6MWD <300 metre are at highest risk of rapid decline in and loss of ambulation over the same period of time. The variability in the 6MWD over 48 weeks in this disease was unknown at the time Study 007 was designed. Considerable heterogeneity in the rate of disease progression contributed to the higher-than-anticipated standard deviation and meant that the study was underpowered.[32] The entry criteria used in Study 020 were selected to enrich for patients likely to be in ambulatory decline; however, these criteria allowed for inclusion of a subset of study patients with a broad baseline 6MWD (142.5–526.0 metres) and ultimately failed to enrich for patients in ambulatory decline.

Due to those challenges, the treatment effect of ataluren was demonstrated in suitable subgroup populations of studies 007 and 020. Although neither trial met its primary endpoint, both reported a numerical benefit for ataluren-treated patients compared to those treated with placebo, as measured by the 6MWT; in the Phase 3 trial Study 020, this difference was statistically significant in the pre-specified subgroup with baseline 6MWD ≥300 to <400 metres (patients in the 'ambulatory transition' phase) but not in the overall ITT population.[33] More stringent entry criteria with regard to baseline 6MWD subgroups would likely have increased the overall effect observed, as noted for patients with a baseline 6MWD of 300 metres or more to less than 400 metres. The EMA and US FDA guidelines

recommend stratifying patients by functional status.[78,161] Additionally, because of the slowly progressive nature of the disorder, a longer treatment duration is recommended in current DMD regulatory guidelines,[78,161] which were not available when this study was designed.[33]

Rare disease clinical trials such as these are limited by the inclusion of relatively low numbers of participants, which can be overcome using meta-analysis. The efficacy of ataluren in nmDMD based on all the available evidence was therefore assessed by conducting meta-analyses using the ITT populations of patients from both trials (receiving ataluren 40 mg/kg/day or placebo), and then using subgroups categorised by pre-specified baseline 6MWD values. These meta-analyses support previous evidence for ataluren in slowing of disease progression compared to placebo in nmDMD patients over 48 weeks. Treatment benefit was most evident in patients with a baseline 6MWD ≥300 to <400 metres (the ambulatory transition phase).[41]

STRIDE enrolled patients who were, or who would be, receiving usual care treatment and a commercial supply of ataluren; as a registry there was no treatment control arm. CINRG DNHS serves as a useful comparator to STRIDE because it includes patients receiving BSC who are experiencing the usual course of DMD disease progression. Propensity score matching is a method used to estimate the effect of receiving treatment when random assignment of patients to treatments is not possible. As described in section 9.4.1.1, to eliminate bias and to enable a robust comparison between STRIDE and CINRG DNHS, propensity score matching was performed to identify a subset of patients in CINRG DNHS who were comparable to patients in STRIDE according to established predictors of disease progression.[7]

STRIDE represents the largest cohort of nmDMD patients ever studied. Data presented here are from the cut-off date 31 January 2021 and the study is still ongoing. An increasingly robust dataset with a longer treatment duration than previously evaluated (median of [redacted] days for the Evaluable Population) and a rigorously matched comparison to natural history data continues to support the association of ataluren treatment with the slowing of disease progression in a heterogeneous population of nmDMD subjects across multiple clinically meaningful endpoints.

STRIDE includes patients with a wider range of ages and ambulatory ability than those in clinical trials, meaning that the data is representative of a broader range of real-world patient experiences in comparison with a short-duration randomised placebo-controlled clinical trial with narrowly defined inclusion criteria. STRIDE also contributes important data on long-term outcomes such as pulmonary function.

PTC Therapeutics has contributed to the project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis), a collaboration between Duchenne UK, and pharmaceutical companies developing medicines to treat DMD, to increase the chances of patients with DMD of accessing innovative treatments. The project was started in recognition of the challenges of trial design and data collection in this very rare condition, and development of the evidence required for HTA submissions. The project is bringing together possibly the largest collection of clinical data on DMD to develop increased understanding of the disease area with the following focus areas:

- A natural history model
- The development of a DMD specific utility metric
- An observational study to determine the burden of illness
- A health economic model

The MAA collected data from ataluren-treated nmDMD patients in order to compare with DMD patients receiving BSC alone in the North Star registry. Whilst a propensity score-matching approach was used to minimise the biases of between group comparisons between the ataluren-treated and BSC-only-treated patients data for the key prognostic covariate, age at first symptoms, were not available for matching.[149] Together with the relatively small and heterogenous population in the analysis, this may have limited the comparability of the two cohorts at baseline. Aspects of the data suggest that patients in the ataluren group had more [redacted] disease at baseline. Despite this, the data suggest that ataluren tended to [redacted] disease progression compared to BSC alone.

The NSAA was chosen as the clinical outcome measure in the 2016 MAA, as, unlike the 6MWT, can be administered in routine clinical practice in the UK. The following expectation was outlined: "*Using similar extrapolations to those seen in study 020, as well as the natural history data as published by Ricotti et al. 2015, and considering the composition of the cohort to be similar to study 020, the cohort of patients receiving ataluren is expected to have a decline over the initial 2 years of the MAA by [redacted] linearised points on the NSAA scale, a numeric difference of around [redacted] points from the matched control cohort which is expected to have declined by [redacted] points over the same period*". In the MAA at 24 months the mean change from baseline was [redacted] for the ataluren-treated patients compared to [redacted] for the control cohort, therefore the declines were not as substantial as those expected which may have impacted the ability to determine a treatment effect. This may have been impacted by the inclusion of significant proportion of boys under the age of 7 years, who are known to gain motor function.[15] As discussed in 9.6.1.7, the retrospective analysis of the NSAA prior to baseline reflects this considerable heterogeneity, with increasing NSAA scores observed in younger patients and declining NSAA after the age of 7 years (Figure C.30). As the NSAA results were based on length of follow-up from baseline, rather than the age of the patients, the difference in baseline age between the cohorts is introducing potential bias into the analysis.

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

Motor function and loss of ambulation

Comparison of the efficacy results of STRIDE with patients from the natural history study CINRG DNHS, who received BSC only, further supports and extends the findings from the prior clinical studies that found ataluren treatment can stabilise or slow disease progression in nmDMD.[32,33] Patients with nmDMD face a relentless and devastating disease. Stabilisation or slowing of disease progression is considered an important benefit of therapy by the DMD patient community.[120]

In STRIDE, patients treated with ataluren lost ambulation at a later age than those receiving BSC alone.[35,130] In clinical trials, ataluren consistently demonstrated clinically meaningful benefits across multiple measures of muscle strength and function.[32,33]

The delay in loss of motor functions associated with ataluren is not only clinically important but is highly meaningful to patients and their families, as the loss of a function milestone is irreversible. Preservation of motor function impacts a patient's autonomy as it postpones the loss of basic daily functions such as climbing and descending stairs and walking short distances independently. Prolonging ambulation is particularly important; the ability to walk allows a patient to be independent to go to the bathroom, to feed themself, to go upstairs without assistance, or simply to be able to

transfer from a wheelchair to a bed. Moreover, the time of loss of one function predicts the onset of subsequent disease milestones indicative of disease progression.[33,60]

- Maintenance of ambulatory capacity is associated with delayed onset and reduced severity of scoliosis.[60,62,63] Although early scoliosis may be noted in the late ambulatory stage of DMD, it almost invariably progresses during puberty. Children that lose ambulation at a later age are at lower risk of developing scoliosis altogether and are at lower risk of developing progressive scoliosis that requires major surgery.[60,76]
- LoA is associated with deterioration of the lungs and heart.[4] The age at LoA has been shown to be predictive of onset of moderate and severe pulmonary insufficiency. In groups of children that lost ambulation at a mean age of 7.1, 9.3 and 12.0 years, the age of severe pulmonary insufficiency occurred at a mean age of 14.7, 18.1 and 22.1 years, respectively ($p<0.001$, between group comparison). FVC parameters were also significantly correlated with the age at LoA and were statistically different between the groups.[60]
- Several studies have shown a correlation between age at LoA and mortality risk.[60,77,101]

In a degenerative disease with progressive loss of functions, that eventually leads to death, stopping or slowing the progression of the disease is considered meaningful to patients as this would preserve their abilities and delay the next loss of function. This is illustrated in quotes from a UK qualitative interview study,[22] aimed at understanding the impact of ataluren treatment on people with nmDMD and their caregivers:

"Yesterday again, for example, he got out of his all-terrain hopper and he walked for I would say a good 20 minutes or more yesterday. Without Translarna, I don't think he would be able to do that"

"It's just good to see that [he] can be stable. Obviously, we know that things will change at some point but it's a much slower decline so it gives you just more time to play with really and it's just positive all round"

"It's getting it across that, just because he's not able to run a marathon now, doesn't mean it's not working. Maintaining the function is just as important"

Pulmonary function

Ataluren therapy is associated with a significant delay in pulmonary function decline. The preservation of pulmonary function is critical since pulmonary failure is the most common cause of death in patients with DMD.[162] Disease milestones indicative of increasing deterioration in pulmonary function and disease progression are percentage predicted FVC of <60%, <50% and <30%, and absolute FVC of <1 litre.[20,21,60,72,94] Predicted FVC of <60% is indicative of the first need for intervention using lung volume recruitment, when patients require mechanical ventilation to preserve lung function.[72] Predicted FVC of <50% is indicative of the need for assisted coughing techniques and nocturnal-assisted ventilation; non-invasive ventilation is strongly recommended.[72] Once patients with DMD have declined to a predicted FVC of <30% they are considered to have severe pulmonary insufficiency, for which non-invasive ventilation is necessary.[60,94] Absolute FVC decline to <1 litre is a threshold that is strongly predictive of mortality within 3 years and is associated with a four-fold increased risk of death.[20,21]

Across all pulmonary function milestones, patients in STRIDE were older than propensity-matched subjects from the CINRG DNHS database at the time each milestone was reached.[37] Similar results were observed in Study 019.

The comparative data from STRIDE and Study 019 compared to CINRG DNHS demonstrates that the dystrophin-restoring mechanism of action of ataluren can be beneficial to patients with nmDMD throughout different stages of disease, regardless of ambulatory status. Ataluren can provide further benefit to that already conferred by corticosteroids (given as part of BSC) and preserve vital functions for longer such as the patients' ability to breathe independently.

Impact of early treatment

By promoting formation of full-length functional dystrophin protein, ataluren addresses the underlying cause of nmDMD. Initiation of dystrophin restoration therapy at a younger age, prior to substantial muscle loss, may maximise benefit, helping to slow or stabilise disease progression in patients with nmDMD.[33,163,164] Early intervention in the disease process of nmDMD, prior to muscle loss and fibrosis, is of critical importance. Given the obstacles to directly assessing efficacy in the younger population, plasma levels comparable to those seen in older children are the primary means to demonstrate comparable efficacy. In Study 030 all patients in the ≥2 to <5 year age group had ataluren exposure within the target range for C_{ave} based on previous pharmacokinetic-pharmacodynamic analyses.

Notably, while TFTs and the NSAA were assessed, the study was not designed to evaluate efficacy, considering the intrinsic issues of directly demonstrating efficacy in this population. In addition to the challenges presented by the rarity of diagnosed patients with nmDMD in this age group, children under the age of 5, as a result of growth and maturation, tend to show stabilisation or improvement in the measures routinely used to assess muscle function. As a result, directly assessing efficacy in this population in a clinical trial setting would require a significantly larger and longer study.

However, data from Study 030 for these functional endpoints do provide additional and supportive evidence of clinical benefit in younger patients. Ataluren-treated patients in Study 030 evidenced improvement across multiple endpoints, including time to run or walk 10 metres, to climb four standard stairs, and to rise from supine, the developmentally appropriate 8- and 3-item scales for the NSAA, the full 17-item NSAA total score, and the NSAA linear score.

Given the established impact of preserving the earliest loss of functions on the entire DMD disease process, it is expected that these younger patients will continue to show the benefit of slowed disease progression as they enter the decline phase of the disease.

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

The ataluren study populations are comparable to the patients that will be treated in clinical practice in England. The MAA includes all patients treated with ataluren in clinical practice in England following the NICE assessment in 2016.

The STRIDE Registry includes patients who have been treated in the UK (n[redacted]) including those receiving treatment under the MAA. However, it should be noted that in STRIDE, in countries other than the UK, patients may have continued to receive ataluren following LoA.

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

Ataluren should be used within its licensed indication. No additional criteria are expected to be used to select patients suitable for treatment.

10 Measurement and valuation of health effects

Patient experience

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

Patients with DMD experience diminishing physical ability and later reduced respiratory capacity as part of their disease, due to the absence of functional dystrophin protein. While their disease is characterised by additional aspects such as cognitive and behavioural problems, the aspects of the condition that most affect patient's quality of life are:

A lowered capacity to engage in physical activity from an early age

When children diagnosed with DMD are young (~3-12 years) they cannot keep up with their peers, have problems walking, hopping, running, climbing stairs and fall frequently. Frequent falls can result in fractures that cause further incapacitation and may even lead to permanent wheelchair dependence.[59,102] Up to 60% of boys with DMD will have low-trauma extremity fractures even without steroid treatment and the risk doubles when receiving steroid treatment.[165] Boys with DMD rarely have the chance to fully engage in physical activities normal for their age: running around and playing games with friends, playing football or riding a bike.

Quality of life deteriorates as the disease progresses as observed by a decrease in parent-reported HRQL in boys in the early ambulatory stage and late ambulatory stage.[24,114] In the qualitative interview study by Williams et al. an analysis of the impact of nmDMD at different stages of ambulation showed that, as individuals with nmDMD lose ambulation, their decline in physical function can lead to impairments in other areas of life including daily activities, social activities and emotional wellbeing, which can impact their HRQL and that of their caregivers.[166] Participants completed a background questionnaire with questions which enabled categorisation into one of three ambulatory health states (early ambulatory: can rise from supine, stand and walk 10 metres; late ambulatory: can stand and walk 10 metres; intermediate: can stand). Worsening health state severity was related to a decrease in physical function, including the ability to walk, run/jump, climb stairs and get up off the floor, as well as fine motor skills. This impacted the affected individuals ability to take part in daily and social activities, which had a subsequent impact on their emotional wellbeing.[166] In addition, the declining physical function was reflected in an increased level of care and emotional burden reported by caregivers.[166]

Loss of ambulation

Losing the ability to walk and permanent dependence on use of a wheelchair is a key milestone in the lives of boys and is associated with a large detrimental reduction in quality of life.[24,114]

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

Once a child is fully wheelchair bound, home modifications are required. These are both expensive and not always readily available, further limiting the child's environment and ability to carry out daily tasks, and severely impacting on the quality of life of the family. Likewise, transport needs are dramatically affected. If a child can no longer walk, they are dependent on others in order to have access to their school, friends, and extended family members.

Loss of upper body function

In non-ambulatory boys and young men, there is gradual loss of upper limb, trunk and neck functions, so that grooming, toileting, bathing, dressing, sitting unsupported and eating become impaired or impossible to perform by oneself – severely affecting the quality of life of patients, their caregivers and families.[10,24,114]

Loss of respiratory function

Children with DMD suffer from a progressive decline in pulmonary function leading to breathing difficulties and ultimately the need for ventilation, further impacting on their quality of life.[10,114] As respiratory function initially declines ventilation support is provided during the night, usually with a mouthpiece. Dependence on permanent ventilation (day and night-time), which may require tracheostomy, usually occurs before 23 years of age.[18,19]

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

As described above, the HRQL of patients with DMD decreases dramatically over the course of disease progression. In the study by Landfeldt et al.[24,114] the HUI-derived utility decreased through the four stages (early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory). The mean patient utility dropped from 0.75 in early ambulatory patients (approximate age 5–7 years) to 0.15 in late non-ambulatory patients (approximately 16 years of age or older) ($p<0.001$).[114]

Similarly, HRQL declines as pulmonary function declines and patients require ventilation.[114,167]

HRQL data derived from clinical trials

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

- Method of elicitation.
- Method of valuation.

- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals

The instruments used in clinical studies to measure patient HRQL were the PedsQL (Study 007), PODCI (Study 020) and CHU9D (MAA). These are described in section 7.1.3.

- In Study 007, the PedsQL was completed at each visit: screening, baseline and every 6 weeks until Week 48.[150] Positive trends were seen in the PedsQL which comprises physical functioning and psychosocial functioning (i.e., emotional functioning, social functioning, and school functioning) scales. From baseline to week 48, patients in the ataluren group had a higher mean change in the PedsQL physical and school functioning score than placebo-dosed patients (Table C-22, section 9.6.1.2).
- In Study 020, the PODCI was completed at each visit: screening, baseline and every 8 weeks until Week 48. Changes in the PODCI transfers/basic mobility and sports/physical functioning domain scores favoured ataluren over placebo in the ITT population and in patients with baseline 6MWD ≥300 to <400 metres (Figure C.17, section 9.6.1.3).

Data from the clinical trials was not used in the economic model. PedsQL has been validated for use in DMD.[114] However, the PedsQL components are only weakly correlated with clinical outcome measures that have been validated in DMD, such as the 6MWT and the 10-metre run/walk.[16,168] It is possible to map the PedsQL to the EQ-5D,[116] however due to the limited sensitivity and the limitations of capturing changes in QoL for a progressive, lifelong condition within the short time period of the trial (48 weeks), as well as lack of data in the non-ambulatory disease states, this was not carried out. PODCI scores correlate strongly with the 6MWT and the 10-metre run/walk test, and changes in PODCI scores after one year are more strongly correlated with changes in the 6MWT after one year than PedsQL scores.[16] However, in addition to a lack of data in the non-ambulatory disease states, no mapping techniques are available to generate a utility value from the PODCI.

CHU9D utility data was collected for children receiving ataluren in the MAA, which provides a generic preference-based measure of HRQL, suitable for children and adolescents aged seven to 17 years old. Patient HRQL data collected as part of the MAA was not available, and therefore has not been used to inform the economic model.

Mapping

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

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

Not applicable.

HRQL studies

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

An SLR was conducted to identify studies reporting HRQL in DMD that could be used to inform health state utility values.

The eligibility criteria specified in Table C-47 was used to inform the inclusion of studies at first and second pass stages of the review. The review included studies of patients with DMD of any type receiving no disease-modifying treatment (i.e., BSC alone with/without corticosteroid use) or ataluren. The review was broad to identify any studies that could inform utility estimates in the cost-effectiveness modelling.

The search strategy is shown in Appendix 5 (section 17.5).

Table C-47 Eligibility criteria for the original and update QoL reviews

	Inclusion	Exclusion
Population	• People with DMD of unspecified form • People with nmDMD	• People without DMD including, but not limited to, variations such as Becker muscular dystrophy • Studies that report only on people with mutations other than nmDMD
Intervention/comparators	• No treatment • Corticosteroid (e.g., prednisone, prednisolone, deflazacort) • Translarna (ataluren)	Any disease-modifying drugs other than Translarna or corticosteroid (e.g., exon-skipping therapies (such as eteplirsen and drisapersen), gene therapies)
Outcomes	• Disease-specific measures of quality of life o PedsQL neuromuscular o PODCI/POSNA o Muscular Dystrophy Child Health Index of Life with Disabilities (MDCHILD) o SOLE • Generic measures of quality of life o EQ-5D o HUI (1/2/3) o Short form (e.g., SF-36 or SF-10) o PedsQL o CHU-9D o World Health Organisation Quality of Life-BREF (WHOQOL-BREF)	All other outcomes
Study design	No restriction; any study type reporting the outcomes of interest	

Geographical location	No restriction; any geographical location
Language	No restriction; any language
Publication date	No restriction; any study date

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

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

In the original review (searches conducted on 8 June 2019) 54 references related to 36 individual studies were included. These studies are listed in Table 21 of Appendix 5 (section 17.5).

For the updated review (searches conducted on 10 September 2021) an additional 31 references related to 28 individual studies were included. These studies are listed in Table 22 of Appendix 5 (section 17.5).

Data from all identified studies were extracted and presented in Tables 25 to 30 of Appendix 5 (section 17.5).

The reasons for selection of studies for the economic model is provided in section 11.2.1.

The study by Landfeldt et al. is the key study informing utility values in the economic model (Table C-49). The first publication of this study was in 2014, and utility values were used in the original submission to NICE in 2015. Since then, there have been several further publications related to this study:

- Landfeldt et al. (2016a[115]); Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational cross-sectional study
- Landfeldt et al. (2016b[114]); Quantifying the burden of caregiving in Duchenne muscular dystrophy

- Landfeldt et al. (2017[167]); Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis
- Landfeldt et al. (2020[169]); Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy

The Landfeldt study measured HRQL in DMD patients enrolled in registries in the UK, Germany, Italy and the United States. Patient quality of life was measured online using the HUI whilst caregiver quality of life was measured using the EQ-5D-3L. A total of 2,346 were invited to participate in the study and 770 patient-caregiver responses were received (response rate = 42%). Of these, 191 patients were from the UK and 98% of the caregivers were parents to the patient.

In a separate study by Landfeldt et al. (2020[169]), improvements in health status and utility associated with ataluren for the treatment of nmDMD were investigated through a Delphi panel.

For a detailed summary of Landfeldt et al. 2017 and 2020, see section 12.3.2. Landfeldt et al. 2017 was identified in the economic section of the SLR as opposed to the HRQL section. The HRQL SLR identified Landfeldt 2016a and 2016b, which have been used to inform the utilities reported in Landfeldt et al. 2017.

Landfeldt et al. 2020[169]

Landfeldt et al. 2020 conducted a Delphi panel of clinicians in Sweden with experience of treating patients with ataluren. A mix of clinicians was chosen including two paediatric neurologists, one adult neurologist, one specialist nurse, and two specialist physiotherapists. Combined, the clinicians had 140 patient-years experience in treating ataluren-receiving DMD patients. Consensus was reached on the HUI-3 and the VAS in ambulatory (assuming 13 years) and non-ambulatory (assuming 17 years) nmDMD patients treated with ataluren in combination with best standard of care and best standard of care alone. Patients were described as neither suffering from scoliosis or utilising ventilation support. The study assumed ambulatory ataluren and BSC alone patients had a 6MWT result of 410 and 316 metres, respectively. Three Delphi rounds were necessary before a consensus had been reached, defined as an 80% level agreement for the HUI3. These values were converted to utilities using the HUI Mark III algorithm with t-tests used to compare HUI-derived estimates. The results are presented in Table C-48. The results highlight that there is a significant difference in utility values between BSC alone and ataluren in addition to BSC in favour of ataluren.

Table C-48. Delphi panel-derived utility values

	Ataluren in addition to BSC	BSC alone	Difference	P value
Ambulatory stage	0.9315	0.6174	0.3140	<0.001
Non-ambulatory stage (“b” and “c” on question 10: “ability to use hands and fingers”)	0.3179	0.1643	0.1536	0.021
Non-ambulatory stage (“c” and “d” on question 10: “ability to use hands and fingers”)	0.2672	0.0913	0.1759	0.009

Source: Landfeldt et al. 2020[169]

Table C-49. Studies reporting utility data used in the economic model

	Landfeldt 2014, 2016a, 2016b (& 2017)	Landfeldt 2020
Population in which health effects were measured.	770 DMD patients (and one of their caregivers) Median patient age was 12 years (interquartile range 9–17).	Patients with nmDMD Values provided through a Delphi panel of six experts, consisting of two paediatric neurologists, one adult neurologist, one specialist nurse, and two specialist physiotherapists.
Information on recruitment.	Patients were from Germany, Italy, the UK, and the USA identified through national DMD registries that form part of the global TREAT-NMD Neuromuscular Network.	Clinical experts for the Delphi panel were identified and recruited from the only two neuromuscular centres in Sweden with experience in using ataluren for the treatment of nmDMD
Interventions and comparators.	None	Ataluren (plus BSC) BSC alone
Sample size.	n=770	n=6
Response rates.	Overall study response rate was 42%	NR
Method of elicitation/valuation	Patient HRQL was self-reported and proxy-assessed by primary caregivers, using PedsQL and HUI, respectively. Caregiver HRQL was assessed using EQ-5D, VAS and SF-12	Consensus among the participating experts using the Delphi technique was sought for the health status of patients with nmDMD as measured using the HUI Mark III[12] and a VAS.]
Description of health states	**Model I** consisted of 25 health states based on the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT), a patient-reported outcome instrument comprising eight questions in four domains (arm function, mobility, transfers and ventilation status) measuring functional ability in patients with DMD on an interval scale ranging from 0 to 23, where higher scores represent higher functional. **Model II** was based on stages of disease as specified in the international DMD clinical care guidelines, defined first in terms of ambulatory status and second in terms of age. It included five states: (1) early ambulatory (approximately age 5–7 years); (2) late ambulatory (approximately age 8–11 years); (3) early non-ambulatory (approximately age 12–15 years); (4) early non-ambulatory (approximately age 16 years or older); and (5) an absorbing state for dead. **Model III** was based on patients' ventilation status, which marks key clinical disease milestones and staging for interventions, and comprised four states: (1) no ventilation support; (2) night-time ventilation support; (3) day- and night-time ventilation support; and (4) an absorbing state for dead	Consensus was sought for two specific cohorts, or disease stages, of nmDMD: i) ambulatory patients; and ii) non-ambulatory patients. In non-ambulatory, patients were specified to not have scoliosis or require ventilatory support for survival. Panellists were instructed to assess health status for the ambulatory stage assuming a mean patient age of 13 years, which corresponds to the median age for patients receiving best supportive care in this stage. For the non-ambulatory disease stage, the corresponding median patient age considered was 17 years. Based on the observed and extrapolated efficacy data of ataluren, patients' functional ability, as measured using the 6-minute walk test, was specified at 410 metres for those treated with ataluren and 316 metres for patients receiving BSC alone in the ambulatory disease stage.

Results with confidence intervals. **Uncertainty around values.**	See section 10.1.9.	See section 12.3.2. Ataluren in addition to best supportive care • Ambulatory stage: 0.9315 • Non-ambulatory stage: 0.3179 • Non-ambulatory stage: 0.2672 Best supportive care alone • Ambulatory stage: 0.6174 • Non-ambulatory stage: 0.1643 • Non-ambulatory stage: 0.0913
Consistency with reference case.	High – utility data in relevant population and health states.	Low – utility data reported in relevant health states. Small number of participants all based in Sweden

	MAA	**Delphi report**
Population in which health effects were measured.	A cohort of ambulatory nmDMD patients aged 2 years and above treated with ataluren and a cohort of DMD patients receiving BSC. Mean (SD), range Baseline age, years BSC (n=59): [redacted] Ataluren (n=59): [redacted]	Patients with nmDMD Delphi panel of [redacted] clinical experts, with a mean (range) in years of experience of treating patients with DMD of [redacted]) and a mean (range) number of patients they have treated with ataluren of [redacted]). Taken together, the panellists' combined experience of ataluren for the treatment of nmDMD encompassed more than [redacted] patient-years.
Information on recruitment.	The MAA collected data on patients to compare the ataluren-treated nmDMD patients with DMD patients receiving BSC alone in the NorthStar registry, owned and maintained by the NorthStar Clinical Network in the UK. The control cohort does not include any nmDMD patients. **Ataluren cohort** All patients starting treatment with ataluren before December 31st 2017 with a baseline visit at one of the NorthStar Clinical Network sites before starting treatment were included in the ataluren cohort. **Control cohort** Eligible control patients were selected using information from their first clinic visit after the date of the start of the MAA (1st August 2016).	Candidate clinical experts for the Delphi panel were identified and recruited by PTC Therapeutics. To be considered eligible for this study, all experts had to meet the following inclusion criteria: • Act as the coordinating/specialist physician to patients with DMD; and • Have experience of ataluren for the treatment of nmDMD.
Interventions and comparators.	Ataluren (MAA patients) BSC (matched NorthStar cohort)	Ataluren (plus BSC) BSC alone
Sample size.	Total planned sample size: 59 (matched analysis)	n=[redacted]

Response rates.	NR	[redacted] additional eligible experts were asked to take part in the study, but chose to not participate or were not available
Method of elicitation/valuation	NSAA data was collected from all patients when they start ataluren treatment and at all subsequent clinic visits and entered into the NorthStar database. The NSAA consists of 17 activities, each scored as 0, 1, or 2. The sum of these 17 scores is used to form a total score. Patients in the ataluren cohort and control patients were invited to complete the CHU9D twice per year in a timeframe consistent with clinic visits. At least one caregiver (e.g. parent) of the children in the ataluren cohort and control cohort were invited to complete the EQ-5D on behalf of the patient as a proxy utility estimate.	Consensus among the participating experts using the Delphi technique was sought for the health status and HRQL of patients treated with ataluren on top of BSC versus BSC alone using the HUI and a VAS. Consensus for ordinal/nominal question was pre-specified to have been achieved when at least 80% of participating experts (rounded to the nearest integer) agreed of the appropriate response level/category
Description of health states	Patients 2 years and older and able crawl, stand with support or walk.	Excluding mobility (only asked for ambulatory patients), emotion, pain and dexterity questions were asked in the context of the following health states: • Ambulatory patients 10 years of age; • Non-ambulatory patients not yet requiring ventilation support; • Non-ambulatory patients at the time when initiating night-time ventilation support; and • Non-ambulatory patients at the time when initiating full-time ventilation support.
Results with confidence intervals. **Uncertainty around values.**	**Mean (SD), (95% CI) EQ-5D-5L Utility Index Summary** Treated Population, Ataluren Cohort patient proxy [redacted]	**Consensus HUI utilities estimates: Ataluren + BSC** • Ambulatory state: [redacted] • Non-ambulatory state, no ventilation: [redacted] • Non-ambulatory state, night-time ventilation: [redacted] • Non-ambulatory state, full-time ventilation[redacted] **BSC** • Ambulatory state: [redacted] • Non-ambulatory state, no ventilation: [redacted] • Non-ambulatory state, night-time ventilation: [redacted] • Non-ambulatory state, full-time ventilation: [redacted] **Consensus VAS scores** <u>Ambulatory state:</u>

		Ataluren on top of BSC: [redacted] BSC alone: [redacted] <u>Non-ambulatory state, no ventilation</u> Ataluren on top of BSC: [redacted] BSC alone: [redacted] <u>Non-ambulatory state, night-time ventilation</u> Ataluren on top of BSC: [redacted] BSC alone: [redacted] <u>Non-ambulatory state, full-time ventilation</u> Ataluren on top of BSC: [redacted] BSC alone: [redacted] Estimates of average mortality across stages of the disease (Proportion (%) of all patients reaching this disease stage that die in this stage) Ambulatory: [redacted] Non-ambulatory, no ventilation support: [redacted] Non-ambulatory, night-time ventilation support [redacted] Non-ambulatory, full-time ventilation support: [redacted]
Consistency with reference case.	Medium – Whilst patients from the MAA were matched to the NorthStar patients using a robust methodology, the relatively small and heterogenous MAA cohort, absence of key prognostic baseline data from the NorthStar patients, and missing data at later timepoints limit the ability to make conclusions from the analysis.	Medium – utility data reported in relevant health states. Small number of participants unclear where based.

Sources: PTC MAA Data Tables[158]; North Star Clinical Network, MAA Statistical Analysis Plan, v4.2, 2021[149]; Draft manuscript (Delphi panel)[170]

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

The clinical trials reported PedsQL HRQL data, however these data were not mapped and used to generate utilities due to the limitations previously mentioned (see section 10.1.3). Therefore, no comparison could be made to the literature derived from the SLR.

Adverse events

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

In clinical trials and long-term studies (e.g., MAA, STRIDE), the observed safety and tolerability profile of ataluren is comparable to that of placebo (see section 9.6.1.6 and section 9.6.1.7). The most common reported adverse reactions were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients.[1] These adverse reactions generally did not require medical intervention and few patients discontinued ataluren treatment due to any adverse reaction.

No specific HRQL data is available for adverse events, from clinical trials, long-term studies (e.g., MAA, STRIDE) or Landfeldt et al. studies. Given the comparability of the safety profiles of the intervention and placebo, it is anticipated that adverse events have a negligible impact on HRQL and therefore disutilities resulting from adverse events were not modelled.

Quality of life data used in cost-effectiveness analysis

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

Table C-50. Summary of quality of life values for cost-effectiveness analysis

State	Utility values (confidence interval)			Justification
	Patient		Caregiver	
	Ataluren + BSC	BSC		
Ambulatory	0.9315 (0.745, 1.000)	0.6174 (0.494, 0.741)	0.839 (0.671, 1.000)	See justification below
Non-ambulatory, predicted FVC >50%	0.3179 (0.254, 0.381)	0.1643 (0.131, 0.197)	0.837 (0.670, 1.000)	
Non-ambulatory, predicted FVC <50%	0.3179 (0.254, 0.381)	0.1643 (0.197, 0.131)	0.775 (0.620, 0.930)	
Non-ambulatory, predicted FVC <30%	0.3179 (0.381, 0.254)	0.1643 (0.197, 0.131)	0.774 (0.619, 0.929)	
References: Landfeldt et al. 2020 (patient utilities); Landfeldt et al. 2017 (caregiver utilities)				

Patient utility values were informed by published literature (Landfeldt et al. 2020).[169] These patient utilities are based on consensus from six Swedish clinicians, who concluded that patients receiving ataluren in combination with BSC experienced greater QoL versus patients receiving BSC alone, for patients in the same health state. These findings are consistent with the unpublished Delphi panel study with [redacted] clinicians from the UK and Europe [redacted], and represents the most recent patient utility data.

For further information on the publications, see section 10.1.6, which provides a summary of the publication and utility values used to inform the cost-effectiveness analysis.

It should be noted that the two independent Delphi panels support the assumption that ataluren patients will on average have a better QoL within the same health state. This provides further validation that ataluren patients within the economic analysis are expected to experience better QoL than the BSC comparative patients, within the same health state. Both sources were considered as the base-case utility values to inform the analysis. The utility value from the global Delphi panel for ambulatory ataluren patients was equal to [redacted], this value appears to be to unrealistically high for a severe debilitating condition DMD. For this reason, the Swedish Delphi panel was deemed a more appropriate source for the utilities in the base-case analysis.

As an attempt to mitigate the issues of unrealistically high utility values elicited as part of the global Delphi panel, a scenario is presented where the treatment benefit in QoL associated with ataluren is applied to the utility values presented in Landfeldt 2017. This is referred to as the Delphi panel/Landfeldt 2017 hybrid approach.

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

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

Clinical experts for the Delphi panel conducted in Sweden (Landfeldt et al. 2020) were identified and recruited from the only two neuromuscular centres in Sweden with experience in using ataluren for the treatment of nmDMD (Table C-49). Landfeldt et al. 2020 conducted a Delphi panel of clinicians in Sweden with experience of treating patients with ataluren. A mix of clinicians was chosen including

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

two paediatric neurologists, one adult neurologist, one specialist nurse, and two specialist physiotherapists. Combined, the clinicians had 140 patient-years experience in treating ataluren-receiving DMD patients. Consensus was reached on the HUI-3 and the VAS in ambulatory (assuming 13 years) and non-ambulatory (assuming 17 years) nmDMD patients treated with ataluren in combination with best standard of care and best standard of care alone. Patients were described as neither suffering from scoliosis or utilising ventilation support. The study assumed ambulatory ataluren and BSC alone patients had a 6MWT result of 410 and 316 metres, respectively. Three Delphi rounds were necessary before a consensus had been reached, defined as an 80% level agreement for the HUI3. These values were converted to utilities using the HUI Mark III algorithm with t-tests used to compare HUI-derived estimates.

An international Delphi panel study was used to evaluate the face validity of the ataluren cost-effectiveness model (CEM) to strengthen the reliability and acceptability of estimated cost-effectiveness results and investigate clinical expert consensus of the health status and HRQL of patients with nmDMD treated with ataluren.[170]

The study population comprised of [redacted] clinical experts from the UK and Europe ([redacted] To be considered eligible for this study, all experts had to meet the following inclusion criteria:

- Act as the coordinating/specialist physician to patients with DMD; and
- Have experience of ataluren for the treatment of nmDMD.

Candidate clinical experts for the Delphi panel were identified and recruited by PTC Therapeutics. A total of [redacted] clinical experts participated in the study. The panellists' combined experience of ataluren for the treatment of nmDMD encompassed more than [redacted] patients.

The study employed a series of questionnaires, administered iteratively, to collect data from a panel of selected experts. In each iteration, participants were provided feedback, which allowed and encouraged the panellists to re-assess their initial judgements about the information provided in previous iterations.

The panel was engaged to assess the health status and HRQL of patients treated with ataluren on top of BSC versus BSC alone using the HUI and a VAS. In this study, only questions of relevance to DMD, as elicited in a previous Delphi panel[169], were included in the Delphi panel questionnaire. These include:

- Emotion (which one of the following best describes how the patient has been feeling?);
- Pain (which one of the following best describes the pain and discomfort the patient has experience?);
- Mobility (which one of the following best describes the ability of the patient to walk?); and
- Dexterity (which one of the following best describes the ability of the patient to use their hands and fingers?).

As a complement to the classification of health states through the HUI, a single-item VAS scale was employed as a measure of proxy-assessed global patient HRQL. The VAS was shown as a continuous scale ranging from 0 to 100, where a higher value represents higher HRQL. The scale was 10 centimetres in length.

Excluding mobility (only asked for ambulatory patients), emotion, pain and dexterity questions were asked in the context of the following health states:

- Ambulatory patients 10 years of age;
- Non-ambulatory patients not yet requiring ventilation support;
- Non-ambulatory patients at the time when initiating night-time ventilation support; and
- Non-ambulatory patients at the time when initiating full-time ventilation support.

In the international Delphi panel study, consensus for ordinal/nominal question was pre-specified to have been achieved when at least 80% of participating experts (rounded to the nearest integer) agreed of the appropriate response level/category. For continuous outcomes, consensus was pre-specified to have been achieved when all ratings fell within a range of ±20% (e.g., ±20 points on a scale from 0 to 100), or when at least 80% of participating experts (rounded to the nearest integer) agreed to an exact value.

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

The cost-utility model has been structured to reflect the natural history of patients with DMD and is structured into six health states to reflect key milestones in the disease (see section 12.1.3). Due to the nature of DMD, as the disease progresses, an affected child's functional ability diminishes, causing extensive morbidity, disability and a greater need for care (see section 10.1.1 for further details). Patients would therefore experience greatest HRQL in the earliest stage of the disease (i.e. ambulatory health state), when they are most functional with the ability to engage in physical and social activities with peers, as well as carry out daily tasks. As their disease progresses to more advanced stages of the disease (e.g., non-ambulatory health states), DMD patients would experience diminishing HRQL alongside their reduced functional, pulmonary and cognitive abilities. Patients HRQL will be greatly impaired in the final stages of disease before death, in which they are non-ambulatory and require day- and night-time ventilation support (i.e., predicted FVC <30% health state) as well as assistance from professional and informal caregivers. HRQL would likely vary in specific health states, however the functionality of the economic analysis does not allow for this to be easily explored, although has been partially accounted for through the application of treatment specific utility values.

The consensus formed by clinicians as part of two independent Delphi panels suggest that patients receiving ataluren will on average spend a longer time experiencing a better QoL within the same health states than control patients, due to the wide range of possible levels of disease severity a health state such as the "ambulatory" health state represents. It was also concluded that due to reaching more severe disease milestones later in life, patients have benefited from improved opportunities for personal development due to better functionality in their teenage years. This again results in improved QoL for treated patients within the same non-ambulatory health states. As a result, the panel agreed that utility values would be on average higher for ataluren patients compared to untreated controls within the same health state (see section 10.1.10).

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

The original SLR identified a total of 54 references, relating to 36 individual studies. The updated SLR identified a total of 31 references, relating to 27 individual studies (section 10.1.5). For all studies identified in the original and updated SLR, see Appendix 5 (section 17.5).

Of the 54 publications reported in the original SLR, a total of six publications reported utility values based on three studies (Cavazza et al. 2016,[26] Translational Research in Europe-Assessment and Treatment of Neuromuscular Diseases [TREAT-NMD],[114,115] Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe [BURQOL-RD][171,172]). Cavazza et al.[26] reported one utility value for UK DMD patients with a mean age of 21.1 years, this utility value was equal to -0.08. Given that the utility value was reported for adult DMD patients, with no indication of their pulmonary status, it could not be attributed to a specific health state, likewise, there was no utility data reported for other stages in the disease. Pentek et al. (2014, 2016)[171,172] reported utility values for children and adults with DMD, where 38% of children and 50% of adults were using wheelchairs, and 2% of children and 0% of adults were on non-invasive mechanical ventilation. The utilities reported in this study did not differentiate by disease stage and was not able to provide sufficient data for health states in the model.

A number of other identified studies also reported HRQL scores, however values were not reported for specific stages of the disease and therefore did not provide the level of granularity required to provide utilities specific to the model health states. Two publications based on one study (CARE-NMD) were identified in the original SLR, in which HRQL data was reported by relevant health states, informed by PedsQL.[173,174] This study (CARE-NMD) was conducted in the UK with a total of 321 participants, for early and late ambulatory health states, and early and late non-ambulatory health states.

Another 11 publications were also identified in the SLR, however they were not extracted as they reported associations of QoL with other factors, but contained no actual QoL values, and therefore did not contribute to the analysis.

Of the 31 publications identified in the update SLR, a total of seven reported utility values based on five studies.[175-181]

Gallop et al.[179] reported mean time tradeoff (TTO) utility values for 100 UK patients and caregivers, according to hand-to-mouth function (HTMF) and pulmonary function, where pulmonary function was defined as FVC. Rowen et el. (2021[180]) was also identified in the updated SLR, in which 1,043 participants from the UK general population completed an online discrete choice experiment survey. Rowen et al. reported preferences for health states described by the classification system, which were informed by nine discrete choice experiment surveys, from 1,043 participants from the UK general population. Szabo et al. (2021[181]) and Audhya et al. (2021[175]) reported HUI2 and HUI3 utility values for 61 and 60 boys with DMD, however once again, did not differentiate by stage in disease, but rather explored the correlation between patient outcomes and disease characteristics (i.e., ambulation, emotional status).

Crossnohere et al. 2021a and 2021b reported utility by early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory health states, based on online survey responses from 367 participants (2020[176]), and 263 participants (2021[178]) globally (Austria, Belgium, Canada, France,

Italy, Netherlands, UK and the US). Crossnohere et al. 2019 also reported utility values for patients (N=22), however did not specify health states of participating patients.

A number of studies identified in the updated SLR report HRQL such as PedsQL and SF-36, for social participation and functional abilities,[182-192] however the utility values were reported for health states that were not appropriate for the analysis in section 12.

A remaining 12 publications were identified in the updated SLR, however were not extracted as they reported associations of QoL with other factors but contained no actual QoL values.

The original and updated SLRs identified the Landfeldt study reported in several publications (2014[24], 2016a[115], 2016b[114]), which inform the patient utility values reported in Landfeldt et al. 2017[167]. The Landfeldt study is based on a multinational cross-sectional study of 770 patient-caregiver pairs, capturing the HRQL burden of DMD study, which are mapped to health states that are most closely aligned to health states used in the model, and therefore was considered the most appropriate. Overall, the Landfeldt publications were considered more appropriate for the analysis, due to the greater patient population size and the alignment to the health states in the model. In addition to this, using Landfeldt et al. 2017[167] utility values have allowed us to use a consistent source for patient utilities, caregiver utilities and the economic data informing disease management costs in the model.

The updated SLR also identified Landfeldt et al. 2020[169], which reports utility values for each of the health states, informed by a Delphi panel study of six Swedish clinical experts. Utility values from this study have been used to inform scenario analyses only.

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

Not applicable.

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

Patients with nmDMD are expected to experience diminishing HRQL as the disease progresses. Patients' functional ability diminishes rapidly, and affected children become non-ambulatory usually in their early teens. In later, non-ambulatory stages of the disease upper limb function deteriorates progressively, and patients eventually need assistance to carry out the most basic activities of daily living.

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

Utility values informing the base-case economic analysis were taken directly from published literature and have not been altered.

Treatment continuation rules

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

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Ataluren is a long-term chronic therapy. Currently, under the conditions of the Managed Access Agreement, treatment may be continued until patients lose ambulation, as follows: If a patient has lost all ambulation (i.e., can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment. In such cases, patients should stop treatment no later than 6 months after becoming fully non-ambulant.[2]

Based on input received by PTC from clinical experts in England, treatment with ataluren should continue beyond loss of ambulation, until full-time ventilation is required (i.e., patients require ventilation >16 hours per day), which is around the time predicted FVC falls below 30%.[3]

In the economic model base-case, ataluren treatment is continued until patients are non-ambulatory with a predicted FVC <50%. The selection of this stopping criteria takes into consideration the input from clinicians suggesting that genuine treatment benefit can be received until full-time ventilation is required, however a very limited number of patients reached this stage of disease progression whilst receiving ataluren. For this reason, the clinical evidence base more closely aligns with a treatment stopping criteria of predicted FVC<50%, i.e., most patients remained on treatment after LoA, however almost all patients have not received ataluren post predicted FVC<50%. It is therefore difficult to establish whether further treatment benefit is to be expected in patients who continue ataluren beyond achieving a predicted FVC<50%. The model currently adopts a conservative approach in which a proportion of the established delay in disease progression is assumed to translate into a delay in reaching future disease milestones.

PTC also recognise that continuing to reimburse a specialised treatment in patients who are non-ambulatory and require night-time ventilation, who have a very poor level of QoL, with little to no

chance of recovery, is an inefficient use of NHS resources. For these reasons it is proposed that the most appropriate stopping criteria in clinical practice is when patients require night-time ventilation support, i.e., when their respiratory function reaches a pFVC<50%.

D Value for money and cost to the NHS and personal social services

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

11 Existing economic studies

11.1 Identification of studies

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

The objective of the health economic SLR was to identify economic evaluation studies in DMD and to identify the costs associated with DMD.

Searches were conducted in several databases to identify literature published from database inception to present.

The original review searches were conducted on the 10th June 2019 in MEDLINE and Embase, and 11th June 2019 in The Cochrane Library and EconLit.

For the update review, searches were conducted on the 10th September 2021. The update searches were conducted without date limits to identify literature published from database inception to present, then deduplicated against the original review's EndNote library in order to remove the publications already assessed in the original review along with the usual removal of duplicate publications picked up through searching multiple databases.

For further details and information relating to the search strategies and databases used to inform the SLR obtaining economic studies, refer to the Appendices in section 17.

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

Table D-1. Selection criteria used for health economic studies

Inclusion Criteria	
Population	• People with DMD of unspecified form People with nmDMD
Interventions	No restriction; any intervention
Outcomes	• Quality-adjusted life years • Life years

	• Lifetime costs • Cost-effectiveness results • Cost-utility results • Budget impact results • Healthcare resource utilisation: medical costs (such as hospitalisation, A&E visits, wheelchair use, ventilation assistance, hours of care) • Cost of illness • Non-medical costs Indirect costs
Study design	No restriction; any study type reporting the outcomes of interest
Language restrictions	No restriction; any languages
Search dates	No restriction; any study date
Exclusion Criteria	
Population	• People without DMD including, but not limited to, variations such as Becker muscular dystrophy Studies that report only on people with mutations other than nmDMD
Interventions	No restriction; any intervention
Outcomes	All other outcomes
Study design	No restriction; any study type reporting the outcomes of interest
Language restrictions	No restriction; any languages
Search dates	No restriction; any study date

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

The PRISMA diagrams illustrated in Figure D.1 and Figure D.2, for the original and update reviews respectively, presents how clinical references were reviewed and extracted.

In the original review, of the 593 titles and abstracts screened 486 did not meet the criteria. Hence, full texts of the remaining 107 references were retrieved and reviewed based on the eligibility criteria. Including publications identified in the grey literature search, 66 references were about studies that met the eligibility criteria and were considered for extraction. The 66 references related to 59 individual studies.

In the update review, of the 150 titles and abstracts screened 114 did not meet the criteria. Hence, full texts of the remaining 36 references were retrieved and reviewed based on the eligibility criteria. Including publications identified in the grey literature search, 21 references were about studies that

met the eligibility criteria and were considered for extraction. The 21 references related to 19 individual studies.

Figure D.1. PRISMA - original review

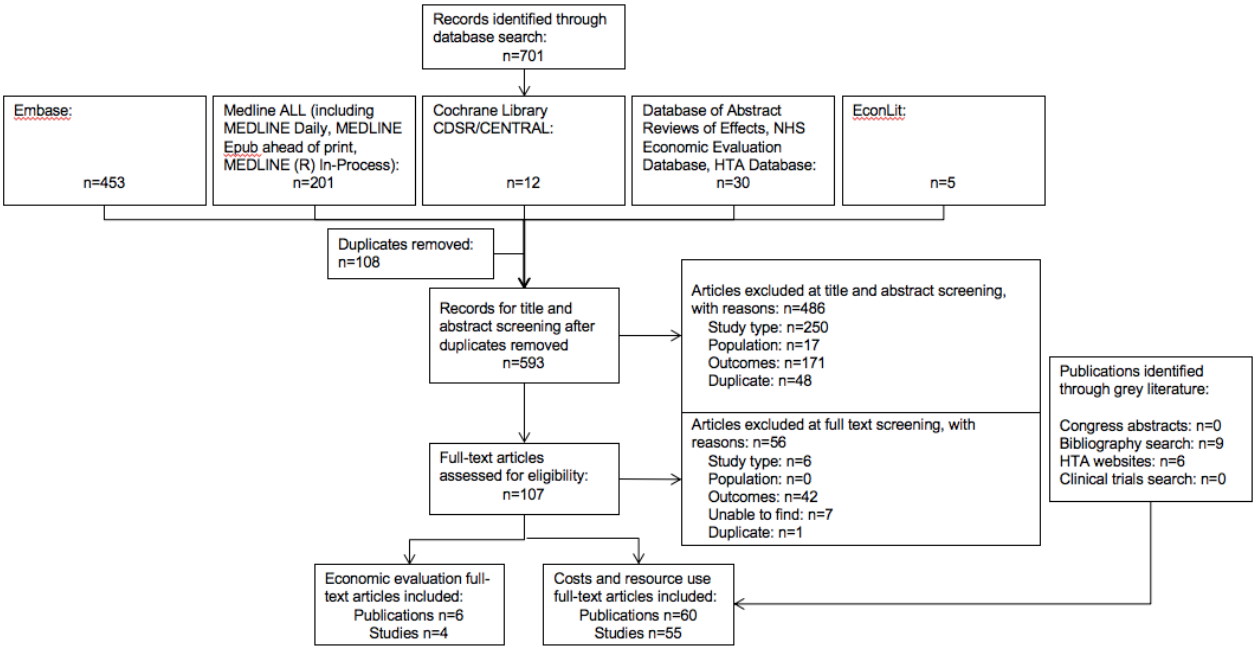
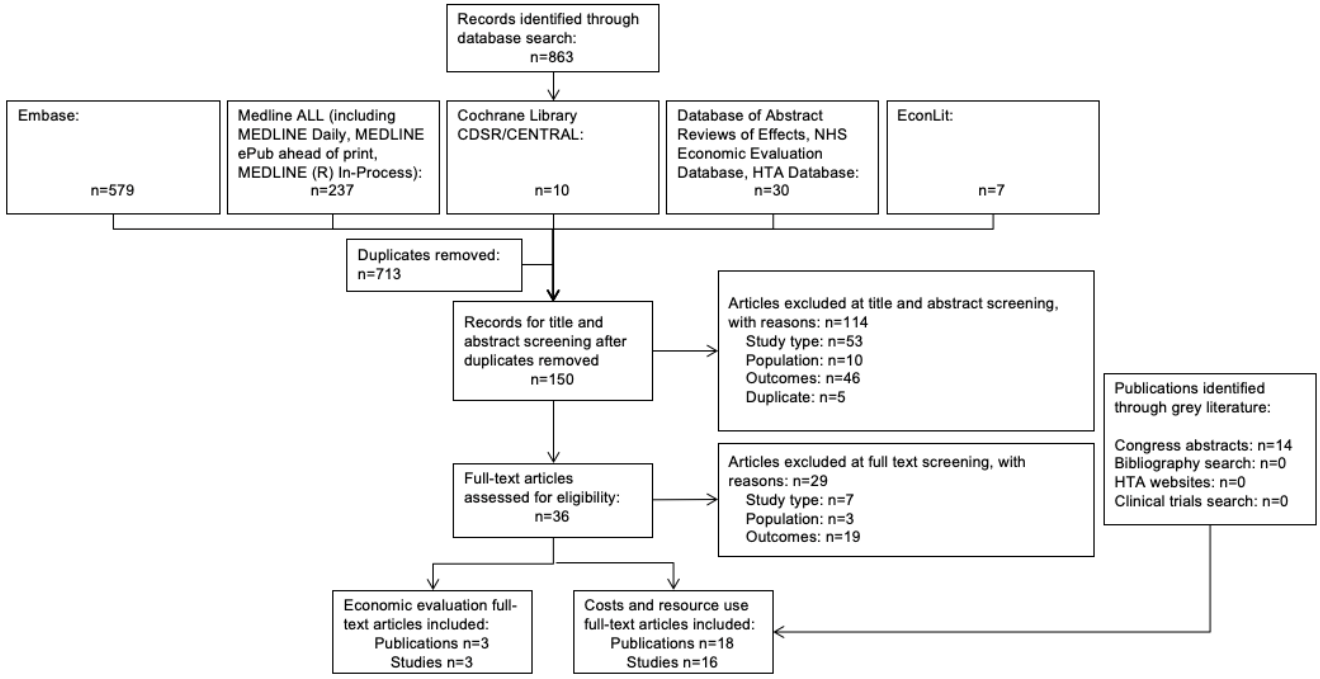


Figure D.2. PRISMA - updated review



11.2 Description of identified studies

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

The original review identified a total of six health economic publications encompassing four studies. Carlton et al. (2018a,[193] 2018b[194]) assessed the economic impact of deflazacort for the treatment of DMD, specifically in the US, and therefore was not considered relevant to the submission due to its geographical focus. Likewise, Fabriani et al. (2014[195]) assessed the cost of illness in DMD in Italy, and was also not relevant for the submission. Two publications on the cost-effectiveness of ventricular assist device destination therapy for advanced heart failure in DMD were also identified,[196,197] however were excluded from the submission due to their focus on heart failure therapy in DMD, as opposed to DMD itself.

Three health economic publications were identified in the updated SLR, none of which were considered relevant to informing the economic model structure or inputs. Agboola et al. (2020[198]) assessed the effectiveness and value of Deflazacort and Exon-skipping therapies for DMD in the US, likewise Quach et al. (2019[199]) assessed the cost-effectiveness of deflazacort in the US. Nelson et al. (2020[200]) was an abstract reporting lifetime cost model (state transition cohort model), however did not provide data to inform the submission.

Costs reported by Landfeldt et al. (2017[167]) have been used to inform the costs of disease management in DMD in the model. This paper was identified in the original SLR. The study assessed the economic burden of DMD, based on survey responses from 770 patient-caregiver pairs. The study reports the direct and indirect costs associated with the disease, for further details on the study objective and outcomes (costs) see section 12.3.2.

Table D-2. Summary list of all evaluations involving costs

Carlton et al. 2018a[193] **Carlton et al. 2018b**[194]	USA	The study design was an economic model to estimate the budget impact of deflazacort for the treatment of patients with DMD in a hypothetical US health plan	Hypothetical commercial health plan with 1,000,000 members, 16 patients aged 5-24 years were estimated to have DMD	The estimated incremental per-member-per-month pharmacy cost due to deflazacort was $0.008/$0.012/$0.0116 for years 1/2/3.	NR	Due to lower costs associated with delays in scoliosis surgery, loss of ambulation and onset of cardiomyopathy, and less need for nocturnal ventilation, the total annual cost per patient treated with deflazacort was approximately $17,000 less than patients who were not treated Based on a deflazacort market uptake of 10%/15%/20% in years 1/2/3, deflazacort budget impact was a savings of $28,299/$42,262/$56,226 in years 1/2/3, with 3-yr cumulative total budget impact of $126,786; corresponding total per-member-per-month budget impact was -$0.002, -$0.004, -$0.005 for years 1, 2, and 3
Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population**	**Costs**	**Patient outcomes**	**Results (annual cost savings, annual savings per patient, incremental cost per QALY)**

Fabriani et al. 2014[195]	Italy	The study design was a probabilistic prevalence-based cost of illness model to estimate the average annual direct and indirect costs associated with DMD in Italy considering both National Health System and societal perspective All the costs were determined through a survey that families completed online Human capital approach was used to determine loss of productivity due to absenteeism, while the bottom up approach	NHS and family perspective has been analysed dividing the patients into three age groups (<8, 8–16 and >16). Further patient population details were not reported.	NR	NR	**Indirect costs per year** €474,634,836 (95%CI: €300,028,168 - €698,965,090) **Direct health care costs** are €7,475,596 (95%CI: €5,124,369,29* - €10,263,785) non-medical costs €12,944,879 (95% CI: €7,925,699 - €19,175,331) Patients over 16 years spend more than those between 0 and 7 years old, and even more than those between 8 and 15 **Private expenditure** Direct costs: €2,910,506 (95%CI: €345,231.83 - €718,786*) Non-medical costs: €185,333,744 (95%CI: €114,177,282 -

		was used to calculate direct costs. A probabilistic sensitivity analysis was performed				€273,446,219) for the non-medical costs ** Appears to be an error but as reported in the publication*
Landfeldt et al. 2017[167]	UK	The study design was a cost-effectiveness model based on the DMD Functional Ability Self-Assessment Tool (DMDSAT), a new rating scale created specifically to measure disease progression in clinical practice and trials and model DMD in economic evaluations, and compare it with two alternative model structures. The model were used to evaluate the cost-effectiveness of a	All cohorts were followed from the age of 5 years until death (or an age of 100 years)	**NOTE:** model cost inputs are also presented in the publication (Table 1). Model 1 (DMDSAT) Intervention (hypothetical) Intervention cost: £1,547,110 Direct medical costs: £190,840 Direct non-medical costs: £184,330 Patient indirect costs: £69,000 Caregiver indirect costs: £125,850 Total Healthcare perspective cost: £1,737,690	**Utilities, mean (SE) presented for patient and caregiver respectively:** **Model 1 (DMDSAT)** Initial: 0.879 (0.037); 0.862 (0.016) Per lost score (multiplier): 0.905 (1.003) 0.995 (1.001) **Model 2 (ambulatory status)** Early ambulatory: 0.699 (0.036) 0.858 (0.017) Late ambulatory:	**Incremental cost-effectiveness ratio (ICER)** **Model 1 (DMDSAT)** Healthcare perspective: £1,442,710 Societal perspective: £1,266,510 **Model 2 (ambulatory status)** Healthcare perspective: £1,939,590 Societal perspective: £1,760,650

		hypothetical intervention for DMD versus standard of care in a UK setting. See Table C-49 for information on the cost-effectiveness frameworks (see section 10.1.6).		Total societal perspective cost: £2,117,140 Comparator (BSC) Intervention cost: £0 Direct medical costs: £217,510 Direct non-medical costs: £201,290 Patient indirect costs: £69,000 Caregiver indirect costs: £136,440 Total Healthcare perspective cost: £217,510 Total societal perspective cost: £624,240 Model 2 (ambulatory status) Intervention (hypothetical) Intervention cost: £1,547,110 Direct medical costs: £221,250	0.607 (0.029) 0.839 (0.017) Early non-ambulatory: 0.224 (0.014) 0.784 (0.021) Late non-ambulatory: 0.146 (0.010) 0.810 (0.018) **Model 3 (ventilation status)** None: 0.518 (0.027) 0.837 (0.014) Night-time: 0.129 (0.017) 0.775 (0.030) Day- and night-time: 0.051 (0.010) 0.774 (0.033) **Quality-adjusted life years (QALY)**	**Model 3 (ventilation status)** Healthcare perspective: £3,574,770 Societal perspective: £3,121,890

				Direct non-medical costs: £194,520 Patient indirect costs: £69,000 Caregiver indirect costs: £139,490 Total Healthcare perspective cost: £1,768,370 Total societal perspective cost: £2,171,380 Comparator (BSC) Intervention cost: £0 Direct medical costs: £244,120 Direct non-medical costs: £204,830 Patient indirect costs: £69,000 Caregiver indirect costs: £145,560 Total Healthcare perspective cost: £244,120 Total societal perspective cost: £663,500	**Model 1 (DMDSAT)** Intervention Patient QALYs: 8.13 Caregiver QALYs: 12.93 Comparator (BSC) Patient QALYs: 7.07 Caregiver QALYs: 12.80 **Model 2 (ambulatory status)** Intervention Patient QALYs: 7.96 Comparator (BSC) Patient QALYs: 7.17	

				Model 3 (ventilation status) Intervention (hypothetical) Intervention cost: £1,547,110 Direct medical costs: £262,050 Direct non-medical costs: £204,580 Patient indirect costs: £69,000 Caregiver indirect costs: £150,150 Total Healthcare perspective cost: £1,809,160 Total societal perspective cost: £2,232,890 Comparator (BSC) Intervention cost: £0 Direct medical costs: £284,640 Direct non-medical costs: £207,080	**Model 3 (ventilation status)** Intervention Patient QALYs: 6.39 Comparator (BSC) Patient QALYs: 5.96	

				Patient indirect costs: £69,000 Caregiver indirect costs: £153,130 Total Healthcare perspective cost: £284,640 Total societal perspective cost: £713,840		
Magnetta et al. 2018[197] **Magnetta et al. 2016**[196]	USA	Markov-state transition model to compare survival, costs, and QoL between medical management and continuous-flow destination ventricular assist device (DT-VAD) therapy in a hypothetical cohort of patients with DMD and advanced heart failure	Hypothetical cohort of patients with DMD and advanced heart failure.	Total costs for the DT-VAD and medical management strategies were $435,602 and $125,696 Cost inputs: VAD implantation cost $250,000 VAD replacement cost $133,993 VAD replacement rate 0.5%/month VAD re-hospitalisation cost $3231 VAD re-hospitalisation rate 22%/month	DT-VAD - 1.99 QALYs Medical management - 0.26 QALYs Survival gains on average 3.13 and 0.6 life years, for DT-VAD and medical management, respectively.	The ICER for DT-VAD compared with medical management was $179,086/ QALY. Only when the cost of VAD implantation was <$113,142 did DT-VAD fall below the $100,000/QALY willingness-to-pay threshold. For all other sensitivity analyses, DT-VAD was estimated to cost more than $100,000/QALY gained, including wide variations in overall survival estimates of up to +/- 50% and best-case and worst-case survival

				DMD costs (VAD) $2891/month DMD costs (medical management) $9297/month End-of-life cost $60,040 All costs were adjusted to 2016 US Dollars using the Consumer Price Index		
Agboola 2020 (ID4)	International	The model evaluated the lifetime cost-effectiveness of treatments using a de novo 5-state partitioned survival model informed by key clinical trials, cohort studies, and previous relevant economic modelling in DMD. The 5 health states in the model were early ambulatory, late ambulatory,	The model used a hypothetical cohort of patients with DMD who began treatment at the age of 5 years. Patients were partitioned into relevant health states based on a previous comprehensive analysis of international clinical trial data involving steroid treatment for DMD.	**Discounted** Health sector perspective Total Cost $ Prednisone[a]: 464,000 Deflazacort[a]: 1,010,000 Modified societal perspective Total Cost $ Prednisone[a]: 1,240,000 Deflazacort[a]: 1,830,000	**Discounted** Health sector perspective QALYs Prednisone[a]: 6.88 Deflazacort[a]: 8.40 LYs Prednisone[a]: 15.05 Deflazacort[a]: 16.64 Modified societal perspective QALYs Prednisone[a]: 6.88 Deflazacort[a]: 8.40 LYs	**Deflazacort versus Prednisone** Health sector perspective Cost per QALY Gained, $: 344,000 Cost per LY Gained $: 361,000 Modified societal perspective Cost per QALY Gained, $: 371,000 Cost per LY Gained $: 390,000 Eteplirsen and Golodirsen Versus Supportive Care. There was insufficient evidence to guide assumptions about the magnitude of beneficial

		early non-ambulatory, late non-ambulatory, and death. The model was developed with 2 base cases under ICER's ultra-rare disease value framework, a health care sector perspective and a societal perspective.			Prednisone[a]: 15.05 Deflazacort[a]: 16.64	treatment effects. However, given that the price for eteplirsen is available, we were able to perform threshold analyses to determine how effective the treatment would need to be in order to achieve different levels of cost-effectiveness. Even under the extreme threshold assumption that eteplirsen restores all patients with DMD to perfect health for an additional 40 years of life, at the current annual cost of $1,002,000, the cost per QALY was calculated to be $1,110,000 and cost per life year gained was $1,450,000, far exceeding commonly accepted thresholds for cost-effectiveness. If one assumes that golodirsen will have the same costs as eteplirsen, then the

						threshold analyses would be the same for golodirsen as for eteplirsen.
Nelson 2020 (ID95)	Not clearly reported. Author affiliations are the UK and USA.	A lifetime cost model was constructed based on a state transition cohort model (adapted from Landfeldt et al.) containing four disease stages of DMD: early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory. DMD treated with corticosteroids and symptom management acts as the base-case in the model, and the impact of a hypothetical treatment given in the early ambulatory stage, which reduces the risk of progression to	NR	NR	In the base-case, loss of ambulation occurs at age 13 years (median). Reducing the risk of disease progression from early to later disease stages by 80-100% increases this to age 42-80 years. Compared to the base-case, this results in a gain of 19-37 work years.	NR

		later disease stages, is shown.				
Quach 2019 (ID108)	USA	A Partitioned Survival Model (PartSA) was developed based on a previous research effort that measured time to loss of ambulation and death fromDMD patients on corticosteroids using Kaplan-Meier curves, and on previous survey-based evidence regarding supportive care costs and health utility for ambulatory and non-ambulatory DMD patients. As a conservative assumption, a highly favourable but still evidence-based treatment effect that shifted both	The analysis took a United States health sector perspective and a modified societal perspective over a lifetime time horizon and used a 3% discount rate.	NR	NR	Even with very favourable assumptions regarding treatment effects for deflazacort, the ICERs were $790,000/QALY gained and $829,000/QALY gained for the health sector perspective and modified societal perspective, respectively. Treatment effect, deflazacort drug cost, and ambulatory health utility were the most sensitive in the DSA. In the PSA, deflazacort had a 0% probability of being cost-effective at a willingness-to-pay threshold of $150,000/QALY gained and a 2.79% probability at $500,000/QALY gained.

		the ambulation survival curve and mortality curve by two years was used to estimate changes in quality-adjusted life years (QALYs) and direct medical costs for deflazacort. The analysis took a United States health sector perspective and a modified societal perspective over a lifetime time horizon and used a 3% discount rate. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analyses (PSA) were also performed.				

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

Table D-3. Quality assessment of health economic studies

Study name Landfeldt 2017		
Study design	**Three Markov cohort state transition models to evaluate the cost-effectiveness of a hypothetical intervention for DMD versus standard of care in a UK setting. Model I was based on the DMDSAT, model II on stages of disease as defined in the DMD clinical care guidelines and model III on patients' ventilation status**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To synthesize the authors' previously published health economic evidence and develop a model framework for the assessment of the cost-effectiveness of treatments for DMD based on the DMDSAT, a new rating scale created specifically to measure disease progression in clinical practice and trials and model DMD in economic evaluations. For comparison, they also developed two models based on conventional staging of the disease.
2. Was the economic importance of the research question stated?	Yes	Cost-effectiveness of treatments
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Results for the healthcare and societal perspective scenario for each model
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Hypothetical treatment versus standard of care – the study developed a framework for cost-effectiveness analysis as opposed to conducting an analysis of specific treatments

5. Were the alternatives being compared clearly described?	No	A lifelong hypothetical intervention that reduced the probability of disease progression across all model states by a conservative (but realistic) 25%, in agreement with (but in addition to) the efficacy of glucocorticoid treatment observed in clinical practice
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness Markov cohort state transition models
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Cost-effectiveness model for the assessment of the cost-effectiveness of treatments for DMD
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	"The efficacy of glucocorticoid treatment observed in clinical practice [15]." 15. Wang RT, Silverstein Fadlon CA, Ulm JW, Jankovic I, Eskin A, Lu A, et al. Online self-report data for Duchenne muscular dystrophy confirms natural history and can be used to assess for therapeutic benefits. PLoS Curr. 2014.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Partial	Some results given as follows, and design can be found in the linked paper (retrospective review of registry data - DuchenneConnect), but not clearly described in the report. "To showcase the models, we specified a base-case scenario of a lifelong hypothetical intervention that reduced the probability of disease progression across all model states by a conservative (but realistic) 25%, in agreement with (but in addition to) the efficacy of glucocorticoid treatment observed in clinical practice [15]. For reference, at this efficacy level patients would on average become non-ambulatory at an age of 17 years instead of 14 years (i.e. a mean delay of 3 years). Two alternative treatment durations were explored in sensitivity analysis“

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Model input data were collated through a targeted literature review in PubMed and Web of Science (details are provided in the Electronic Supplementary Material Appendix) and from the DMD experts, but efficacy data was based on the one study.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Model outcomes comprised total lifetime costs, number of life years, and number of quality-adjusted life years (QALYs). Lifetime cost and QALY estimates were used to calculate the incremental cost (DC) per incremental QALY (DE), known as the incremental cost-effectiveness ratio (ICER) (DC/DE).
12. Were the methods used to value health states and other benefits stated?	Yes	HUI Mark 3, standard gamble method and a visual analogue scale [19]. Caregivers, EQ-5D [20] UK value set, time-tradeoff method. [21]
13. Were the details of the subjects from whom valuations were obtained given?	Yes	HUI Mark 3, standard gamble method and a visual analogue scale from 256 randomly selected members of the general population in Hamilton, Ontario, Canada [19]. Caregivers, EQ-5D [20] derived using the UK value set, which is based on preference data collected through the time-tradeoff method from 2997 randomly selected members of the non-institutionalised adult general population in England, Scotland, and Wales [21]
14. Were productivity changes (if included) reported separately?	Yes	See table 1 and 2 of publication
15. Was the relevance of productivity changes to the study question discussed?	Yes	Given the low life expectancy in DMD and the fact that our estimates of informal care costs, caregiver indirect costs and caregiver loss in HRQL only concern the primary caregiver (e.g., one parent), we assumed that all patients had at least one caregiver for the duration of the simulation (while alive). In fact, as reported in our previous work, informal care and

		indirect costs together account for approximately 47% of total costs of illness in the UK [10]. In the context of HTA, this finding emphasises the importance of considering all costs, not only those attributed to formal care, in evaluations of treatments for chronic childhood diseases such as DMD to allow for a meaningful appraisal of treatment benefits.
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Direct medical and non-medical costs of DMD were calculated using data on resource use and national reference prices [1-3]. Costs for medical aids and devices were obtained through input from experts within the Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) network.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Source cost estimates were converted from US dollars to Great British pounds using an exchange rate of 0.634 and inflated from 2012 to 2015 values using consumer price data from the Organisation for Economic Co-operation and Development (OECD).
20. Were details of any model used given?	Yes	Cost-effectiveness Markov cohort state transition models
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	See Section 2.1. For example: The DMDSAT exhibits excellent psychometric properties and has been shown to have good clinical validity. It is currently the only tool that measures functional ability across the entire trajectory of disease. The framework of model II was based on stages of disease as specified in the international DMD clinical care guidelines.

		Model III was based on patients' ventilation status, which marks key clinical disease milestones and staging for interventions.
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime - All cohorts were followed from the age of 5 years until death (or an age of 100 years).
23. Was the discount rate stated?	Yes	Costs and QALYs were discounted at 3.5%. Sensitivity analysis discount rate 0% and 5%.
24. Was the choice of rate justified?	Yes	Base-case used 3.5%, additional discount rates were run in scenario analyses
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	Deterministic one-way scenario analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	Investigating the impact (from a healthcare perspective) of assuming different discount rates, starting treatment at 10 years of age, different treatment durations and efficacy on mortality. In addition, to help understand to which variables the ICER was most sensitive, and thereby identity which input data are most important for the different model frameworks, we ran deterministic sensitivity analysis in which key model parameters were altered (one-way) by ±50%.
29. Were the ranges over which the parameters were varied stated?	Yes	Deterministic sensitivity analyses were run with key model parametrics, which were altered (one-way) by ±50%.

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	DC difference in total costs, DE difference in total QALY gains, and ICERs reported.
33. Was the answer to the study question given?	Yes	The introduction of the hypothetical treatment, which was assumed to delay disease progression by 25%, resulted in a patient QALY gain of 1.05 due to maintained HRQL, a reduction in direct medical costs of 26,670 and an ICER of £1,442,710 (£1,520,450/1.05) assuming an annual drug cost of £100,000 (equal to £1,547,110 during the lifetime of the patient)
34. Did conclusions follow from the data reported?	Yes	Discussion – page 257 in the publication
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations described, for example, where some input data were not available so was based on clinical experience and was identified by a targeted literature review, as opposed to a full systemic review.
36. Were generalisability issues addressed?	Partial	The study discussed the strengths and limitations of the cost-effectiveness frameworks. No specific discussion was made on generalisability, however the study focused on the disease area and was informed by survey data from 770 patient-caregiver pairs across a number of countries.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

12 Economic analysis

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

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

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

12.1 Description of the de novo cost-effectiveness analysis

The original HST submission for ataluren in nmDMD included a cost-utility analysis based on a multi-state Markov model. Since then, a new model has been developed in the form of a partition survival model, in order to provide a stronger cost-utility analysis. The model structure was updated so as to align to the HERCULES natural history model (Figure D.4) and therefore the advances in knowledge of DMD and patient outcomes. HERCULES provides a robust natural history model based on patient progression observed in placebo clinical trial arms by multiple pharmaceutical companies, which highlights key milestones in DMD, including loss of ambulation and diminishing FVC capacity, to represent the progressive and chronic nature of DMD. Updating the structure of the model also allowed the use of long-term real-world data from the STRIDE Registry, including the survival curves for time to loss of ambulation and time to predicted FVC <50%, which was not available in the original submission. By using data on LoA, the model does not rely on 6MWD data and avoids the challenges associated with its use in relatively short clinical trials (see section 6.1.3.3). The new model is outlined and discussed in the remainder of section 12.

Patients

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

The cost-utility analysis of ataluren is conducted within its licensed indication of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged two years and older.[1] Ambulation is defined as patients who were not full-time wheelchair bound or bedridden prior to first recorded dose of ataluren.

STRIDE was used to inform the economic model. The STRIDE dataset is the largest international nmDMD observational cohort which includes 269 patients (evaluable population, as at 31st January 2021), who have been propensity score matched to patients in the Cooperative International Neuromuscular Research Group (CINRG) DNHS (section 9.4.1.6). These patients have been matched using four covariates: age at onset of first symptoms, age at initiation of corticosteroid use, duration of deflazacort use, and duration of other corticosteroid use. As of the data cut-off of 31 January 2021, 241 patients in the STRIDE effectiveness population have been matched using

propensity scoring to CINRG DNHS patients. The following number of patients had data available and were assessed for each modelled outcome from the 31 January 2021 data cut:

- Age at loss of ambulation, n=241
- Age at predicted FVC < 50%, n=182
- Age at FVC < 1 litre, n=173

Ataluren and best supportive care

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

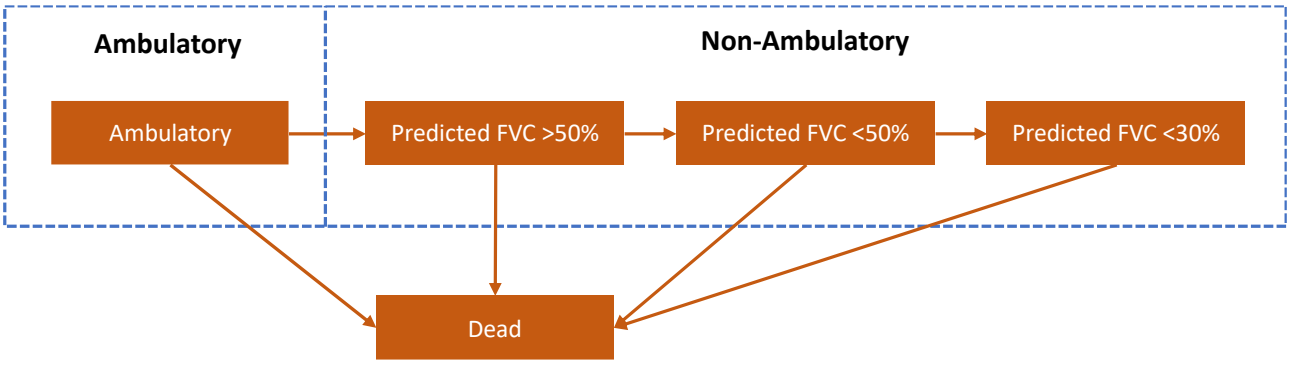
The comparator used in the CEM is aligned with the final NICE scope – established clinical management without ataluren, i.e., BSC.

There are currently no other licensed therapies available for the treatment of nmDMD. Ataluren has been studied in people receiving BSC and is expected to be initiated in ambulatory nmDMD patients in combination with BSC including use of corticosteroids. The comparator arm of the model is based on a natural history cohort receiving BSC, reflecting UK clinical practice.

Model structure

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

Figure D.3. Model Schematic



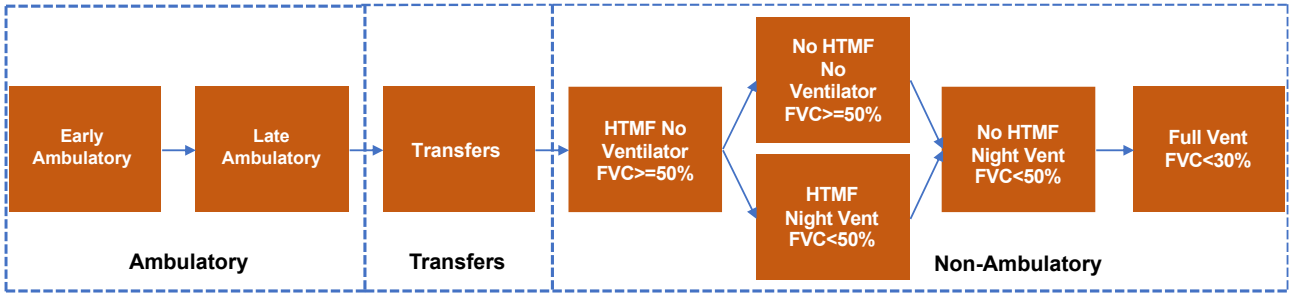
12.1.4 Justify the chosen structure in line with the clinical pathway of care.

HERCULES Natural History Model

The model structure was informed by the work of the HERCULES collaborative workstreams.[75] A key workstream of this project was the development of a natural history model by The University of Leicester. This involved a patient-centric analysis of placebo arm clinical trial data provided by multiple pharmaceutical companies to understand the progression of DMD. The natural history model characterises DMD by three encompassing descriptions: ambulatory, transfers and non-ambulatory (Figure D.4).

The ambulatory state is split into early and late, respectively. The transition between early and late ambulatory is defined by the loss of the ability to stand from supine, synonymous with the ability to walk 10 metres. The transfer state is derived from patient and caregiver input and reflects the ability of DMD patients to bear weight; although they have lost the ability to ambulate. This health state has significance to the patient as it means that they can support themselves whilst standing, allowing them to transfer from chair to bed, toilet, car etc thus helping to maintain their independence. In the non-ambulatory states, progression is defined by pulmonary and HTMF (defined by the Brooke score used to describe arm and hand function) where patients see a progressive decline in both respective functions. Pulmonary function declines from the initial predicted FVC >50% (i.e., no ventilator) to the need for full ventilation (day and night) support when predicted FVC is <30%.

Figure D.4. HERCULES Natural History Model



The HERCULES natural history model and its derivation is, as yet, unpublished and unvalidated. However, the updated natural history reflects the current knowledge on DMD and has been developed in conjunction with clinical experts, patient organisations, health technology assessment bodies, pharmaceutical companies, academia and external research organisations. The submitted economic model is based on an adjusted version of the HERCULES natural history model to represent the available ataluren data. Specifically, the model does not include hand-to-mouth function (HTMF), as given by the Brooke score, as these data have not been collected for ataluren. Additionally, the model includes a combination of the two ambulatory states and uses loss of ambulation data to inform the transition between ambulatory and non-ambulatory states with the exclusion of the transfer state as there are no ataluren data to inform this.

Cost-utility Model Structure

The model is developed as a partitioned survival model to reflect the heterogenous and progressive nature of DMD. The model, presented in Figure D.3 and summarised in Table D-1, consists of five health states: ambulatory, predicted FVC >50%, predicted FVC <50%, predicted FVC <30% and dead. These health states are derived from the HERCULES natural history model. Patients progress into the non-ambulatory states when they have lost ambulation, defined by when they reach a state of being fully wheelchair bound. Patients continue to progress to a predicted FVC <50% and the final two health states which includes predicted FVC <30% and dead. The model includes an absorbing state: dead. Patients can enter the absorbing state (dead) as a result of background mortality from any health state. Predicted FVC <1L is a prognostic indicator of death, with published evidence stating that all patients die within three years of entering the final non-ambulatory health state.[20] Clinicians as part of a Delphi panel concluded that a predicted FVC<30% has very similar mortality prognostics as an FVC<1L, therefore the economic analysis assumes patients will survive for 3 years after entering the pFVC<30% health state.

Patients enter the model in the ambulatory state and progress through the health states as presented in Figure D.3. Patients are modelled from the age of two years onwards, as per the licensed indication, and survival curves are used to determine patient movements in a progressive manner, following a partitioned survival modelling framework. Survival curves from STRIDE (ataluren), propensity score matched to CINRG DNHS (BSC) for age at loss of ambulation, age at predicted FVC <50% and age at predicted FVC <30%, were used to represent the rate of disease progression in patients receiving ataluren. Further detail of the survival analysis conducted is outlined in section 12.2.1 and section 12.2.2. Overall survival was derived from Office for National Statistics (ONS) published mortality data by age and sex.[201]

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

The model assumptions with justifications are outlined in Table D.4.

Table D.4. Model Assumptions

Assumption	Justification
Early treatment (i.e. at 2 versus 5 years of age) results in a further delay in reaching DMD milestones. This includes loss of ambulation, predicted FVC<50% and precited FVC <30%. All patients are assumed to start treatment at 2 years old.	This assumption was validated as part of the global Delphi panel (see section 12.3.2). The values provided are: Delay in loss of ambulation: [redacted] Delay in predicted FVC<50%: [redacted] Delay in predicted FVC<30%: [redacted] Starting treatment at two years of age aligns with the licensed indication.
All patients are assumed to weight equal to that of the average UK based STRIDE patient for the whole time horizon.	UK patients within the STRIDE registry are at various different ages and stages of disease progression, and therefore represent a realistic cohort of eligible patients' weights within the UK.
4-year delay in predicted FVC <30% with ataluren.	Due to the immature time to predicted FVC <30% data from STRIDE, this data could not be extrapolated and therefore could not be used to inform the economic model. The model assumes that patients receiving ataluren will experience a 4-year delay to predicted FVC <30% compared to patients receiving BSC. This assumption is based on the median delay observed in LoA for ataluren patients compared with BSC patients as part of the STRIDE/CINRG analysis, where ataluren patients experienced greater than 5 year median delay in LoA. Clinicians agreed that a delay in LoA would likely result in a delay in reaching future disease milestones, however the relationship may not be linear, hence the value of 4 years was assumed.

Upon losing ambulation, patients enter the predicted FVC>50% health state.	Pulmonary function forms the basis of the non-ambulatory health states. The predicted FVC>50% health state denotes all patients that have yet to experience a decline in FVC. This assumption has been validated as part of the global Delphi panel.
Patients with predicted FVC<50% are assumed to require night-time ventilation support, and those with predicted FVC<30% are assumed to require full-time ventilation support.	This is validated by clinicians as part of project HERCULES[75]
Predicted FVC<30% mortality. Patients entering the final health state (predicted FVC <30%) die within three years.	There is published evidence that FVC<1 litre is a prognostic indicator of mortality.[20] Clinicians confirmed that FVC <1 litre is comparable to predicted FVC <30%. Upon reaching this health state, all patients progress to 'dead' within three years. This assumption has been validated as part of the global Delphi panel (see section 12.3.2).
Appropriate survival curves were selected based on both goodness of fit statistics and the plausibility of the long-term extrapolation.	Standard process for selecting survival curves.
The base-case analysis applies a re-based approach where the parametric survival models are fit to the observed survival data, ignoring the first few years in which very few events are observed.	Improves the fit of the survival curves by focusing the analysis during the period where most events are observed.
Ambulatory and non-ambulatory patients are assumed to have two caregivers.	This was validated by a global Delphi panel (see section 12.3.2) and confirmed by UK clinicians.
Bereavement assumes life expectancy for a non-SMR adjusted population.	Implementation of standardised mortality ration (SMR) adjusted bereavement would be difficult to implement in the model structure.

Treatment compliance rates of 95.0% and 85.0% are assumed for ambulatory and non-ambulatory patients receiving ataluren.	This was validated by a global Delphi panel (see section 12.3.2).

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

The cost-utility model has been structured to reflect the natural history of patients with DMD and the progressive nature of the disease. The model captures this with two key clinical measures, loss of physical function due to muscle deterioration (i.e., ability to walk and loss of ambulation) and subsequent weakening in pulmonary function (predicted FVC).

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table D4.

Table D.5. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime (70 years)	DMD is a rare and progressive condition which affects patients throughout their lives.	Assumption
Discount of 3.5% for costs	3.5% discount rate for costs	NICE reference case.	NICE, Reference Case. 2013. Accessed on: 24 November 2021. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword
Perspective (NHS/PSS)	NHS and PSS	NICE reference case.	NICE, Reference Case. 2013. Accessed on: 24 November 2021. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword
Cycle length	3 months	The model adopts a three-month cycle length to capture patient movements, resource use, costs and utilities, as DMD can progress quickly.	Assumption
DMD: Duchenne muscular dystrophy; NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

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

STRIDE and CINRG survival curves

Time-to-event data from the propensity-matched STRIDE and CINRG data was used to estimate parametric survival curves representing the rate of disease progression by transition through the health states. KM data was mature enough for survival curves to be estimated for the rate of LoA for both the STRIDE and CINRG cohorts. Despite an immature data set for STRIDE patients, survival curves for age to reach pFVC<50% were estimated directly using the KM for both STRIDE and CINRG cohorts.

Insufficient patients within the STRIDE cohort have declined to pFVC<30% to estimate the rate of transition to the final pFVC health state. The time to reach pFVC<30% for BSC patients in the CINRG cohort is used to inform the rate of transition to the final pFVC health state for both treatment arms, with an assumption that ataluren patients reach this stage of disease progression four years later than BSC patients. This calculation is based on the assumption that a delay in achieving earlier stages of disease progression contributes to a delay in achieving future disease milestones. This assumption is supported by clinicians and a value of four years was decided upon.

Ataluren discontinuation

The model applies a treatment discontinuation rate of [redacted]% per three-month cycle. Discontinuation of ataluren is informed by global STRIDE data. [redacted] patients out of the total of [redacted] discontinued ataluren treatment over a period of [redacted] years, equivalent to a [redacted]% discontinuation rate per modelled three-monthly cycle.[36]

Patients who discontinued treatment within STRIDE were continued to be followed within the analysis, as per the analysis protocol. Therefore, the effectiveness data from STRIDE is representative of patients discounting at 0.94% per three-month-cycle, so discontinuation is applied only to the cost calculations to appropriately reflect the change in treatment costs

Patient weight

Ataluren dosing is based on the weight of the patient. In the base-case analysis, the mean weight for the UK STRIDE patients is used to inform all patient weight throughout the time horizon. A scenario is presented where the weight of the patients is informed by healthy children growth charts, rescaled by the mean reduction in DMD patient weight compared to healthy controls of [redacted]%.

The estimated weight reduction compared to healthy patients was calculated as the mean difference in UK STRIDE patient weights compared to median healthy weight for a child of the same age. [202]

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Since the available data does not cover a lifetime horizon, extrapolation was required before use in the health economic model. Specifically, parametric models were fitted to Kaplan-Meier data, as recommended when censoring is present. This allows the total area under the curve to be estimated

and utilised in the partitioned survival approach implemented here. The parametric models fitted included: Exponential, Weibull, Gompertz, log-logistic, log normal, generalised gamma and gamma.

Parametric models were fitted to the individual Kaplan-Meier curves for loss of ambulation, predicted FVC <50% and predicted FVC <30%. Independent, re-based STRIDE and CINRG DNHS survival curves were utilised in the base-case.

Curve re-basing was performed in an attempt to improve the curve fits. Re-basing operates by fitting the parametric survival curves to truncated period of available follow-up, which aims to ignore the period at the beginning of follow-up where very few events are expected to take place. This allows for a more precise fit during the time period in which most of the events are observed. Five and 3.5 years were chosen as starting points for STRIDE (ataluren) and CINRG (BSC) curves respectively, as these were points prior to observation of events, and considered to be a reasonable assumption as to the 'earliest time at which an event could occur'. Independent non re-based survival curves are used in scenario analyses.

Selection of parametric models was based on the following criteria:

- Assessment of statistical goodness of fit through Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC);
- Visual inspection of curve fit to trial period and expected extrapolated period;

Please refer to Appendix 6 for additional information.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

There is published evidence that FVC <1L (that closely approximates predicted FVC<30%) is a prognostic indicator of mortality.[20] The model assumes that upon reaching this health state, patients progress to 'dead' within three years.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not included in the cost-effectiveness analysis, see section 10.1.8 for further details of adverse events in DMD.

12.2.5 Provide details of the process used when the sponsor's clinical advisors assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

A Delphi panel study (as described in section 10.1.10) was used to evaluate the face validity of the ataluren CEM. The study population comprised of [redacted] clinical experts. To be considered eligible for this study, all experts had to meet the following inclusion criteria:

- Act as the coordinating/specialist physician to patients with DMD; and
- Have experience of ataluren for the treatment of nmDMD.

Candidate clinical experts for the Delphi panel were identified and recruited by PTC Therapeutics. A total of [redacted] clinical experts participated in the study. The panellists' combined experience of ataluren for the treatment of nmDMD encompassed more than [redacted] patients.

Consensus among participating experts was sought for key clinical parameters and assumptions underlying the ataluren CEM. The following assumptions were validated by participating clinicians:

- Patients are assumed to have a predicted FVC ≥50% at the time of loss of ambulation;
- Patients with predicted FVC <50% are assumed to require night-time ventilation support, and those with predicted FVC <30% (or FVC <1L) are assumed to require full-time ventilation support;
- Patients who start treatment with ataluren at two years of age are assumed to become non-ambulatory [redacted] (on average) compared with those who start treatment at five years of age;
- Life expectancy when patients reach FVC <1 litre (predicted FVC <30%) is assumed to be [redacted] on average

For full details and questions asked during the Delphi panel, see section 10.1.10.

Further validation with UK clinicians was conducted to validate key model assumptions. PTC Therapeutics held telephone discussions with [redacted] and [redacted], in which the following assumptions and model inputs were validated:[3]

- Extending the treatment stopping rule with ataluren beyond LoA
- Delay in time to predicted FVC <30% based on delay in reaching earlier milestones
- Improved quality of life in patients receiving ataluren plus BSC, versus BSC alone
- Average number of caregivers per patient
- Compliance for ambulatory and non-ambulator patients receiving ataluren
- Weight variation in nmDMD patients
- The clinical plausibility of the selected survival curves

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in below.

Table D.6. Summary of clinical variables applied in the cost-effectiveness model

Parameter	Value	Source
Baseline Age	2 years	Translarna SmPC, 2020
Mean weight of ambulatory UK STRIDE patients	[redacted]kg	STRIDE 025 Study
Mean weight of non-ambulatory UK STRIDE patients	[redacted]kg	STRIDE 025 Study
Weight variation compared to healthy children	[redacted]%	STRIDE 025 Study (patients have lower than average weight versus age matched healthy children; average -4.70% difference)
Ambulatory Transitions, Data Source	BSC: CINRG DNHS 2021 (effectiveness population, independent curves, re-based analyses) Ataluren: STRIDE 2021 (effectiveness population, independent curves, re-based analyses)	STRIDE 025 Study; CINRG DNHS Base-case used KM curves in combination with parametric models
Ambulatory Transitions, Parametric Curve	Log logistic	Best-fitting parametric curve (section 12.2.1)
Early Treatment (2–5-year-olds) Delay to Loss of Ambulation (Ambulatory Transitions)	[redacted]	Assumption; if broad indication is selected (≥2 years), it is assumed that the LoA curve will shift by this additional number of years compared to BSC
Non-ambulatory transitions – predicted FVC <50%, Data Source	BSC: CINRG DNHS 2021 (effectiveness population, independent curves, re-based analyses) Ataluren: STRIDE 2021 (effectiveness population, independent curves, re-based analyses)	STRIDE 025 Study; CINRG DNHS Base-case used KM curves in combination with parametric models
Non-ambulatory Transitions – predicted FVC <50%, Parametric Curve	Log logistic	Best-fitting parametric curve (section 12.2.1)
Early Treatment Delay (Non-Ambulatory; predicted FVC<50%)	[redacted]	Validated assumption; if broad indication is selected (≥2 years), it is assumed that the FVC<50% curve will shift by this additional number of years compared to BSC
Non-Ambulatory Transitions – predicted FVC <30%, Data Source	CINRG DNHS 2021 (effectiveness population, independent curve, re-based analyses)	CINRG DNHS Base-case used KM curves in combination with parametric models

Parameter	Value	Source
Non-ambulatory Transitions – predicted FVC <30%, Parametric Curve	Log normal	Best-fitting parametric curve (section 12.2.1)
Delay in time to predicted FVC <30% for ataluren	4 years	Validated by UK based clinical validation
Early Treatment (2-5 years olds) Delay (Non-Ambulatory; predicted FVC <30%)	[redacted]	Validated assumption; (treatment in ≥2 years), it is assumed that the predicted FVC<30% curve will shift by this additional number of years compared to BSC
Treatment Stopping Rule	Predicted FVC <50%	Most closely aligns with available clinical data for STRIDE
Ataluren compliance, Ambulatory	[redacted]%	Validated as part of global Delphi panel and by UK clinicians
Ataluren compliance, Non-ambulatory	[redacted]%	Validated as part of global Delphi panel and by UK clinicians
Number of caregivers per patient	2	Qualitative study conducted in UK; validated as part of global Delphi panel
DMD Mortality, Time to death following transition to predicted FVC <30%	3 years	Published literature[20,21]

CI: confidence interval; DMD: Duchenne Muscular Dystrophy; FVC: forced vital capacity; kg: kilogram LoA: loss of ambulation

12.3 Resource identification, measurement, and valuation

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is no specific Healthcare Resource Group (HRG) for the clinical management of DMD. The economic model allocates disease management costs associated with DMD, based on health states in the model. Disease management costs by health state are outlined in Table D-6 (section 12.3.2).

Resource identification, measurement, and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria and consider published and unpublished studies.

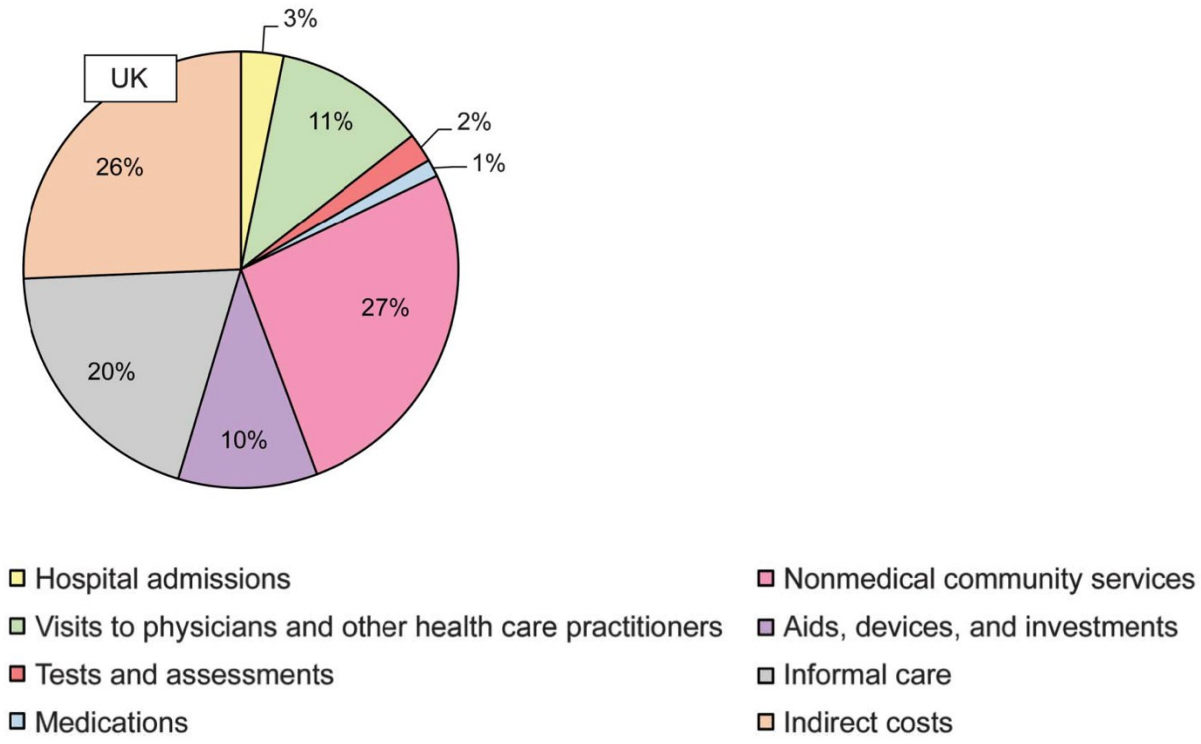
Details of the SLR, including search terms and results, are provided in Appendix (see section 17).

Two HRQL and economic studies containing resource cost were identified in the SLRs. These studies and their methods are briefly described below.

Landfeldt et al. 2014[24]

Landfeldt et al. 2014 estimated the economic burden of DMD including 191 patient-caregiver pairs from the United Kingdom, from a total of 770 patient-caregiver pairs, using an online questionnaire delivered as part of the Translational Research in Europe-Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) registries. The following eligibility criteria applied: male, DMD diagnosis, and age five years or older. Eligible patients and one of their caregivers completed the online questionnaire based on recall. Reference prices were applied for the direct costs of illness. The human capital approach was used to calculate productivity losses. Informal care also used the human capital approach and applied to the caregivers' leisure time as determined by the Work Productivity and Activity Impairment (WPAI) Questionnaire and compared to Organisation for Economic Co-operation and Development for a standard adult in the general population. Each hour of leisure time was conservatively valued at 35% of the country-specific national mean gross wage. Indirect costs, non-medical community services and informal care were the three largest contributors to economic burden (Figure D.5).

Figure D.5 Components of annual cost of DMD



Landfeldt et al. 2017[167]

Landfeldt et al. 2017 estimated total cost and HRQL for different disease stages. Three alternative state transition models were developed. Model I is based on the DMDSAT, Model II is based on the ambulatory state and comprises of the following health states: early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory. Finally, Model III consists of no ventilation support, night-time ventilation support and night- and daytime ventilation support. Table D-4 presents these values.

Table D-4. Annual Mean Cost and Utility Values per Patient

GBP 2015 Mean Costs	Direct Costs (£)		Indirect (productivity) Costs (£)	
	Medical	Non-medical	Patient	Caregiver
Early Ambulatory	10,670	9,740	0	7,180
Late Ambulatory	11,190	11,420	0	8,340
Early non-ambulatory	16,490	17,860	0	12,810
Late non-ambulatory	27,590	16,810	14,230	11,240
None	11,520	12,660	14,230	9,160
Night-time	31,710	14,610	14,230	10,490
Day- and night-time	36,390	15,500	14,230	12,860

Note: Costs were inflated to 2021 prices using ONS CPIH Detailed indices annual averages: 2008 to 2021.

Source: **Landfeldt et al. 2017[167]**

12.3.3 Provide details of the process used when clinical advisors assessed the applicability of the resources used in the model[2].

Not applicable. Resources used in the model have not been validated by clinical assessors.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

Ataluren sachet size	Price	Source
125 mg	£84.40	BNF [203]
250 mg	£168.80	BNF [203]
1,000 mg	£675.20	BNF [203]

BNF: British National Formulary

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

The cost-effectiveness model uses the list price. A PAS in the form of a simple discount of [redacted] has also been applied to the model. Results are provided for the list price and PAS price, where applicable.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost-effectiveness model. A suggested format is provided in Tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

As the model compares treatment with ataluren in combination with BSC, versus BSC alone. The cost of BSC was not included in the analysis, as the cost of BSC is the same whether is it treated in combination with ataluren, or alone.

Table D-5. Costs per treatment/patient associated with the technology in the cost-effectiveness model (List price and PAS price)

Items	Value (per 3-month cycle)	Source

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

Price of the technology per ambulatory patient, based on average weight 35.5kg (assuming 95% compliance)	£80,536	BNF, 2021; Translarna SPC
Price of the technology per non-ambulatory patient, based on average weight 39.5kg (assuming 85% compliance)	£78,609	BNF, 2021; Translarna SPC
Price of the technology per ambulatory patient, based on average weight 35.5kg (assuming 95% compliance), PAS discount applied	[redacted]	BNF, 2021; Translarna SPC, PAS discount applied
Price of the technology per non-ambulatory patient, based on average weight 39.5kg (assuming 85% compliance), PAS discount applied	[redacted]	BNF, 2021; Translarna SPC, PAS discount applied
Administration cost	£0	Translarna SPC
Training cost	£0	Translarna SPC
Other costs (monitoring, tests etc)	£0	Translarna SPC
Total cost per ambulatory patient	£80,536	BNF, 2021; Translarna SPC
Total cost per non-ambulatory patient	£78,609	BNF, 2021; Translarna SPC
Total cost per ambulatory patient	[redacted]	BNF, 2021; Translarna SPC, PAS discount applied
Total cost per non-ambulatory patient	[redacted]	BNF, 2021; Translarna SPC, PAS discount applied

Health state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in Section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Direct and indirect costs reported by Landfeldt et al. 2017 have been used to inform the disease management costs of DMD, by health state in the model. Direct costs represent medical and non-medical costs. Direct medical costs include hospital admissions, emergency care, respite care, visits to physicians and other healthcare practitioners (i.e. nurses, general practitioners, specialist physicians, psychologists, therapists, physiotherapists, occupational therapists, care coordinators/care advisors, dentists, dietitians/ nutritionists and speech/language/swallowing therapists), tests and assessments, medications, medical aids, devices and investments, and community services (e.g., home help and personal assistants). Direct non-medical costs include non-medical aids, devices and investments, and costs associated with informal care. Indirect costs represent patient (≥18 years) and caregiver productivity costs (valued according to the human capital approach at the cost of employment). See Table D-4 (see section 12.3.2) for costs reported by Landfeldt 2017, used to inform health state costs in Table D-6.

In the base-case analysis, due to adopting an NHS and PSS perspective (as per the reference case) indirect costs are not included in the calculations. A scenario analysis is presented where a wider societal perspective is adopted, and indirect costs are included in the analysis.

Table D-6. List of health states and associated costs in the cost-effectiveness model (List price)

Health states	Items	Value (per 3-month cycle)	Reference
Ambulatory	Technology cost	£80,536	Based on average weight 35.5 kg and 95% compliance rate; BNF, 2021; Translarna SPC.
Non-Ambulatory		£78,609	Based on average weight 39.5 kg and 85% compliance rate; BNF, 2021; Translarna SPC.
Ambulatory (PAS discount applied)	Technology cost	[redacted]	Based on average weight 35.5 kg and 95% compliance rate; BNF, 2021; Translarna SPC. (PAS discount applied)

Non-Ambulatory (PAS discount applied)		[redacted]	Based on average weight 39.5 kg and 85% compliance rate; BNF, 2021; Translarna SPC. (PAS discount applied)
Ambulatory	Direct healthcare costs	£6,450	Landfeldt et al. 2017
	Indirect healthcare costs	£2,379	Landfeldt et al. 2017
Non-Ambulatory, predicted FVC >50%	Direct healthcare costs	£6,897	Landfeldt et al. 2017
	Indirect healthcare costs	£6,672	Landfeldt et al. 2017
Non-Ambulatory, predicted FVC <50%	Direct healthcare costs	£13,213	Landfeldt et al. 2017
	Indirect healthcare costs	£7,051	Landfeldt et al. 2017
Non-Ambulatory, predicted FVC <30%	Direct healthcare costs	£14,802	Landfeldt et al. 2017
	Indirect healthcare costs	£7,727	Landfeldt et al. 2017

Direct and indirect healthcare costs derived from Landfeldt et al. 2017 are inflated from 2015 to 2021 prices, using ONS CPIH Detailed indices annual averages: 2008 to 2021 (2015=100).

Adverse event costs

12.3.8 Complete Table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer term use of the technology.

The cost-effectiveness analysis does not include costs associated with adverse events.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

There are no additional costs and cost savings included in the model.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Experts cited that the costs during the ambulation disease state would progress over time. They stated that ataluren is likely to reduce the costs in the early stages of a patient being non-ambulant as they are likely to still be able to use a self-propelled wheelchair, which costs considerably less than an electric wheelchair. Due to the limited data available on specific costs, this factor has not been taken into account in the cost-consequence model. Therefore, it is likely that treatment costs are slightly underestimated by simplifying the health states to ambulatory and non-ambulatory.

By delaying the time to loss of ambulation, ataluren is increasing the probability of patients reaching a working age and obtaining a job. Not only would enabling employment increase the mental wellbeing of DMD patients, but they would also be contributing to society through taxation. It has not been possible to quantify this benefit due to limited data.

An additional factor that will have costs and consequences that has not been included in the model is the impact of ataluren on the reduction of falls. Boys with DMD have been found to have decreased bone density and an increased risk of fractures.[59] Falls are common in DMD patients and can lead to a wide range of consequences and subsequent costs for the patient and carer. Loss of function often follows a fracture (32 out of 71 cases).[59] Lower extremity post-fracture recovery often includes prolonged periods of non/partial weight bearing with increased amounts of time spent sitting in wheelchairs, increasing the risk of contractures and disuse weakness. The impact that ataluren has shown in the reduction in number of falls is expected to reduce the number of falls and the subsequent morbidity, and therefore reduce the burden on carers and healthcare system.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-effectiveness analysis.

The model structure has been developed based on the HERCULES natural history model (Figure D.4), see section 12.1 for further details. The model structure, inputs and assumptions have been validated by UK clinicians. To investigate uncertainties, one-way sensitivity analyses and probabilistic sensitivity analyses have been run. To further investigate potential uncertainties, scenario analyses have been presented.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic and probabilistic sensitivity analyses are included as part of the economic evaluation. For the deterministic sensitivity analysis, each variable was varied individually using a ±20% variation.

For the probabilistic sensitivity analyses, each model parameter was given a probability distribution with the standard error of the distribution set according to any distributional information provided. For utilities, a shifted negative gamma distribution was used (bounded negative infinity to one), for costs and resource use estimates, a gamma distribution was fitted (bounded zero to infinity) and beta for all proportions (bounded zero to one). This was performed simultaneously for each parameter with the incremental results recorded for 1,000 iterations and presented on a Cost-Effectiveness Plane (CEP) and in a Cost-Effectiveness Acceptability Curve (CEAC) using different values of willingness-to-pay (WTP).

12.4.3 Complete Table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Variables included in the deterministic one-way sensitivity analyses (OWSA) have been varied by ±20.0%.

Table D-7. Variables used in one-way scenario-based deterministic sensitivity analysis

Parameter	Description	Base-Case	Upper bound value	Lower bound value	Bounds source
Settings					
Ambulatory compliance	The compliance rate applied to ambulatory patients	[redacted]	[redacted]	[redacted]	±20.0%
Non-ambulatory compliance	The compliance rate applied to non-ambulatory patients	[redacted]	[redacted]	[redacted]	±20.0%
Discontinuation rate	Ataluren treatment per cycle discontinuation	[redacted]	[redacted]	[redacted]	±20.0%
Weight variation ambulatory	% difference in weight for ambulatory compared to general population	[redacted]	[redacted]	[redacted]	±20.0%
Weight variation non-ambulatory	% difference in weight for non-ambulatory compared to general population	[redacted]	[redacted]	[redacted]	±20.0%
Number of caregivers to be applied	The number of caregivers required by DMD patients	2.000	2.400	1.600	±20.0%
Bereavement QALY adjustment	Adjustment applied to QALY loss due to bereavement based on HST7	0.090	0.108	0.072	±20.0%
Mortality adjustment	Excess mortality applied to all states except the last health state	1.000	1.200	0.800	±20.0%

Parameter	Description	Base-Case	Upper bound value	Lower bound value	Bounds source
Mean ambulatory weight STRIDE	Mean weight for ambulatory patients from STRIDE	[redacted]	[redacted]	[redacted]	±20.0%
Mean non-ambulatory weight STRIDE	Mean weight for non-ambulatory patients from STRIDE	[redacted]	[redacted]	[redacted]	±20.0%
Ambulatory early treatment delay	Delay in loss of ambulation due to early treatment with ataluren	[redacted]	[redacted]	[redacted]	±20.0%
Predicted FVC <50% early treatment delay	Longer time spent in FVC<50% due to early treatment with ataluren	[redacted]	[redacted]	[redacted]	±20.0%
Last transition (Predicted FVC<30%) early treatment delay	Longer time spent in last health state due to early treatment with ataluren	[redacted]	[redacted]	[redacted]	±20.0%
Time to death following last transition	The number of years spent in the last health state before mortality	3.000	3.600	2.400	±20.0%
Utilities					
Ataluren ambulatory patient utilities	Late ambulatory utilities for patients receiving ataluren	0.932	1.000	0.745	±20.0%
Ataluren predicted FVC>50% patient utilities	Predicted FVC>50% utilities for patients receiving ataluren	0.318	0.381	0.254	±20.0%
Ataluren predicted FVC<50% patient utilities	Predicted FVC<50% utilities for patients receiving ataluren	0.318	0.381	0.254	±20.0%
Ataluren predicted FVC<30% patient utilities	Predicted FVC<30% utilities for patients receiving ataluren	0.318	0.381	0.254	±20.0%
BSC ambulatory patient utilities	Late ambulatory utilities for patients receiving BSC	0.617	0.741	0.494	±20.0%
BSC predicted FVC>50% patient utilities	Predicted FVC>50% utilities for patients receiving BSC	0.164	0.197	0.131	±20.0%

Parameter	Description	Base-Case	Upper bound value	Lower bound value	Bounds source
BSC predicted FVC<50% patient utilities	Predicted FVC<50% utilities for patients receiving BSC	0.164	0.197	0.131	±20.0%
BSC predicted FVC<30% patient utilities	Predicted FVC<30% utilities for patients receiving BSC	0.164	0.197	0.131	±20.0%
Ataluren ambulatory caregiver utilities	Late ambulatory utilities for caregivers of patients receiving ataluren	0.839	1.000	0.671	±20.0%
Ataluren predicted FVC>50% caregiver utilities	Predicted FVC>50% utilities for caregivers of patients receiving ataluren	0.837	1.000	0.670	±20.0%
Ataluren predicted FVC<50% caregiver utilities	Predicted FVC<50% utilities for caregivers of patients receiving ataluren	0.775	0.930	0.620	±20.0%
Ataluren predicted FVC<30% caregiver utilities	Predicted FVC<30% utilities for caregivers of patients receiving ataluren	0.774	0.929	0.619	±20.0%
BSC ambulatory caregiver utilities	Late ambulatory utilities for caregivers of patients receiving BSC	0.839	1.000	0.671	±20.0%
BSC predicted FVC>50% caregiver utilities	Predicted FVC>50% utilities for caregivers of patients receiving BSC	0.837	1.000	0.670	±20.0%
BSC predicted FVC<50% caregiver utilities	Predicted FVC<50% utilities for caregivers of patients receiving BSC	0.775	0.930	0.620	±20.0%
BSC predicted FVC<30% caregiver utilities	Predicted FVC<30% utilities for caregivers of patients receiving BSC	0.774	0.929	0.619	±20.0%
Management costs					

Parameter	Description	Base-Case	Upper bound value	Lower bound value	Bounds source
Ambulatory direct healthcare costs	Late ambulatory direct healthcare costs	£6,449.50	£7,739.40	£5,159.60	±20.0%
Predicted FVC>50% direct healthcare costs	Predicted FVC>50%% direct healthcare costs	£6,897.35	£8,276.81	£5,517.88	±20.0%
Predicted FVC<50% direct healthcare costs	Predicted FVC<50%% direct healthcare costs	£13,212.78	£15,855.34	£10,570.22	±20.0%
Predicted FVC<30% direct healthcare costs	Predicted FVC<30% direct healthcare costs	£14,801.62	£17,761.95	£11,841.30	±20.0%

Table D-8. Variable values used in probabilistic sensitivity analysis

Parameter	Base-Case	SE	Alpha	Beta	Distribution
Settings					
Ambulatory compliance	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Non-ambulatory compliance	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Weight variation- ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	Normal
Weight variation- non-ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	Normal
Number of caregivers to be applied	2.000	0.400	25.000	0.080	Gamma
Bereavement QALY adjustment	0.090	0.018	22.660	229.118	Beta
Mortality adjustment	1.000	0.200	25.000	0.040	Gamma
Mean ambulatory weight STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	Lognormal
Mean non-ambulatory weight STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	Lognormal

Parameter	Base-Case	SE	Alpha	Beta	Distribution
Ambulatory early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Predicted FVC <50% early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Last transition (predicted FVC<30%) early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Time to death following last transition	3.000	0.600	25.000	0.120	Gamma
Utilities					
Ataluren ambulatory patient utilities	0.932	0.186	0.135	0.507	Shifted Negative Gamma
Ataluren predicted FVC>50% patient utilities	0.318	0.064	115.095	0.006	Shifted Negative Gamma
Ataluren predicted FVC<50% patient utilities	0.318	0.064	115.095	0.006	Shifted Negative Gamma
Ataluren predicted FVC<30% patient utilities	0.318	0.064	115.095	0.006	Shifted Negative Gamma
BSC ambulatory patient utilities	0.617	0.123	9.601	0.040	Shifted Negative Gamma
BSC predicted FVC>50% patient utilities	0.164	0.033	646.794	0.001	Shifted Negative Gamma
BSC predicted FVC<50% patient utilities	0.164	0.033	646.794	0.001	Shifted Negative Gamma
BSC predicted FVC<30% patient utilities	0.164	0.033	646.794	0.001	Shifted Negative Gamma
Ataluren ambulatory caregiver utilities	0.839	0.168	0.921	0.175	Shifted Negative Gamma

Parameter	Base-Case	SE	Alpha	Beta	Distribution
Ataluren predicted FVC>50% caregiver utilities	0.837	0.167	0.948	0.172	Shifted Negative Gamma
Ataluren predicted FVC<50% caregiver utilities	0.775	0.155	2.107	0.107	Shifted Negative Gamma
Ataluren predicted FVC<30% caregiver utilities	0.774	0.155	2.131	0.106	Shifted Negative Gamma
BSC ambulatory caregiver utilities	0.839	0.168	0.921	0.175	Shifted Negative Gamma
BSC predicted FVC>50% caregiver utilities	0.837	0.167	0.948	0.172	Shifted Negative Gamma
BSC predicted FVC<50% caregiver utilities	0.775	0.155	2.107	0.107	Shifted Negative Gamma
BSC predicted FVC<30% caregiver utilities	0.774	0.155	2.131	0.106	Shifted Negative Gamma
Management costs					
Ambulatory direct healthcare costs	£6,449.50	£1,289.90	25	257.9801	Gamma
Predicted FVC>50% direct healthcare costs	£6,897.35	£1,379.47	25	275.8938	Gamma
Predicted FVC<50% direct healthcare costs	£13,212.78	£2,642.56	25	528.5112	Gamma
Predicted FVC<30% direct healthcare costs	£14,801.62	£2,960.32	25	592.0649	Gamma

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

No parameters or variables were omitted.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base-case incremental cost-effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D1.

In the model base-case, discounted model results are presented in Table D-9 for list price and Table D-10 for PAS price. Using a lifetime time horizon, the incremental total LYs gain of ataluren versus BSC was [redacted] years. The discounted incremental costs of [redacted] and incremental QALYs of [redacted] resulted in an ICER of £336,555 versus BSC. When the PAS discount is applied the incremental cost is [redacted] which results in an ICER of [redacted]. The 2022 NICE manual specifies a decision modifier to the £100,000 per QALY threshold for technologies appraised via the HST process whereby higher weights are applied depending on the number of (undiscounted) QALYs gained. As the base-case analysis indicates that over 23 undiscounted QALYs are gained, a weight of 2.3 may be applied to the ICER so that the results can be interpreted with reference to the £100,000 per QALY threshold. Applying the decision modifier [204] results in [redacted] incremental QALYs, a list price ICER of £145,514, and a PAS discounted ICER of £[redacted]. Therefore, at a £100,000 per QALY threshold, ataluren is a cost-effective use of NHS resources based on the PAS discounted price.

The economic results presented for the remainder of this section consider the impact of the decision modifier so that they can be interpreted using the £100,000 per QALY threshold rather than multiple thresholds depending on the incremental number of QALYs.

Table D-9. Base-case results (List price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Ataluren + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£336,555
Ataluren + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,514
*Total incremental QALYS are weighted using the HST decision modifier [204] ICER: Incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years							

Table D-10. Base-case results (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Ataluren + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total incremental QALYS are weighted by the HST decision modifier [204] ICER: Incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years							

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The following clinical outcomes were modelled:

- Time to LoA
- Time to predicted FVC <50%
- Time to predicted FVC <30% (BSC only)

Clinical outcomes from the model are the extrapolated STRIDE survival curves, propensity score matched to the CINRG registry data.

These outcomes could not be compared to clinical trial outcomes, as long-term data was not available.

Table D-11. Summary of model results

Outcome (median survival)	Economic model	
	Ataluren plus BSC	BSC
Median time to LoA	[redacted]	[redacted]
Median time to predicted FVC <50%	[redacted]	[redacted]
Median time to predicted FVC <30%	[redacted]	[redacted]

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of patients in the ambulatory, non-ambulatory predicted FVC >50%, predicted FVC <50% and predicted FVC <30% health states are shown in Table D-5for ataluren plus BSC, and in Table D-6 for BSC alone.

Figure D.5. Proportion of patients in each state - ataluren and BSC

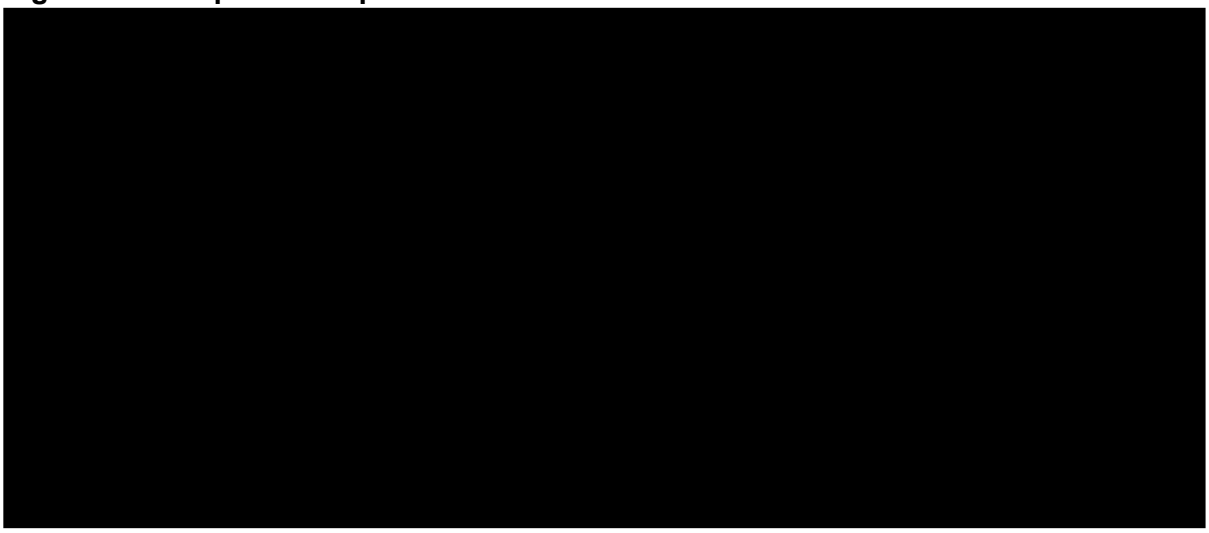


Figure D.6. Proportion of patients in each state – BSC

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs accrued over time for the first 10 years are presented in Table D-12 for both ataluren plus BSC and BSC alone.

Table D-12. Accrued QALYs (first 10 years)

Year	Ataluren and BSC*	BSC*
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]

*Please note that the QALYs generated each year are greater than one due to the addition of caregiver QALYs

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

It was not possible to estimate the LYG and QALYs for each clinical outcome, Table D-13 shows these outcomes for each health state in the model.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Discounted QALYs by health state, for ataluren and BSC versus BSC alone are presented in Table D-13.

Table D-13. Summary of discounted QALY gain by health state

Health state		Ataluren and BSC, QALYs	BSC, QALYs	Increment
Patient				
Ambulatory		[redacted]	[redacted]	[redacted]
Non-ambulatory	**Predicted FVC >50%**	[redacted]	[redacted]	[redacted]
	Predicted FVC <50%	[redacted]	[redacted]	[redacted]
	Predicted FVC <30%	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]
Caregiver				
Ambulatory		[redacted]	[redacted]	[redacted]
Non-ambulatory	**Predicted FVC >50%**	[redacted]	[redacted]	[redacted]
	Predicted FVC <50%	[redacted]	[redacted]	[redacted]
	Predicted FVC <30%	[redacted]	[redacted]	[redacted]
Bereavement		[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]
Patient and Caregiver				
Total		[redacted]	[redacted]	[redacted]
Incremental QALYs weighted using the HST decision modifier		[redacted]	[redacted]	[redacted]

BSC: best supportive care; HST: Highly specialised technology; QALYs: quality-adjusted life years

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Undiscounted QALYs by health state, for ataluren and BSC versus BSC alone are presented in Table D-14.

Table D-14. Summary of undiscounted QALY gain by health state

Health state		Ataluren and BSC, QALYs	BSC, QALYs	Increment
Patient				
Ambulatory		16.41	7.14	9.27
Non-ambulatory	1.42	0.92	0.50	0.50
	2.28	0.84	1.44	1.44
	0.95	0.49	0.46	0.46
Total		21.06	9.39	11.67
Caregiver				
Ambulatory		29.55	19.40	10.16
Non-ambulatory	7.49	9.38	-1.89	-1.89
	11.14	7.93	3.21	3.21
	4.63	4.64	-0.01	-0.01
Total		52.81	41.35	11.46
Patient and Caregiver				
Total		73.87	50.74	23.13

BSC: best supportive care; QALYs: quality-adjusted life years

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table D15.

Table D-15. Summary of costs by category of cost per patient (List price)

Costs	Ataluren and BSC	BSC	Increment (versus BSC)	Absolute increment
Direct healthcare costs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BSC: best supportive care				

Table D-16. Summary of costs by category of cost per patient (PAS price)

Costs	Ataluren + BSC	BSC	Increment (versus BSC)	Absolute increment
Direct healthcare costs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BSC: best supportive care				

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table D13.

Direct healthcare costs, by health state are presented in **Table D-17**. However, discounted treatment costs by health state were not reported in the model, as such these outcomes cannot be presented.

Table D-17. Summary of costs by health state per patient

Health state		Ataluren and BSC	BSC	Increment (versus BSC)	Absolute increment
Direct healthcare costs					
Ambulatory		[redacted]	[redacted]	[redacted]	[redacted]
Non-ambulatory	**Predicted FVC >50%**	[redacted]	[redacted]	[redacted]	[redacted]
	Predicted FVC <50%	[redacted]	[redacted]	[redacted]	[redacted]
	Predicted FVC <30%	[redacted]	[redacted]	[redacted]	[redacted]
BSC: best supportive care					

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table D14.

Not applicable. Cost of adverse events was not included in the analyses.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results of the deterministic one-way sensitivity analysis (OWSA) are presented in **Error! Reference source not found.** for list price and Table D-19 for the PAS price.

Table D-18. Results of deterministic OWSA (List price)

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
Settings					
Ambulatory compliance	[redacted]	[redacted]	£151,926.54	£121,144.70	£24,368.96
Non-ambulatory compliance	[redacted]	[redacted]	£149,233.91	£141,297.37	£4,216.29
Discontinuation rate	[redacted]	[redacted]	£137,444.86	£153,715.25	£8,201.59
Weight variation ambulatory	[redacted]	[redacted]	£145,513.66	£145,513.66	£0.00
Weight variation non-ambulatory	[redacted]	[redacted]	£145,513.66	£145,513.66	£0.00
Number of caregivers to be applied	2.400	1.600	£123,055.83	£174,782.83	£29,269.17
Bereavement QALY adjustment	0.108	0.072	£144,960.90	£146,070.65	£556.99
Mortality adjustment	1.200	0.800	£145,513.66	£145,513.66	£0.00
Mean ambulatory weight STRIDE	[redacted]	[redacted]	£167,667.25	£123,360.06	£22,153.60
Mean non-ambulatory weight STRIDE	[redacted]	[redacted]	£152,540.80	£140,243.30	£7,027.14
Ambulatory early treatment delay	[redacted]	[redacted]	£141,588.35	£147,553.30	£3,925.31
Predicted FVC <50% early treatment delay	[redacted]	[redacted]	£145,421.29	£145,529.73	£92.37

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
Last transition (predicted FVC<30%) early treatment delay	[redacted]	[redacted]	£132,185.03	£155,692.02	£13,328.63
Time to death following last transition	3.600	2.400	£145,353.63	£145,746.75	£233.09
Utilities					
Ataluren ambulatory patient utilities	1.000	0.745	£128,686.03	£212,807.64	£67,293.98
Ataluren predicted FVC>50% patient utilities	0.381	0.254	£141,932.70	£149,231.89	£3,718.23
Ataluren predicted FVC<50% patient utilities	0.381	0.254	£140,296.47	£151,027.91	£5,514.25
Ataluren predicted FVC<30% patient utilities	0.381	0.254	£143,500.54	£147,569.89	£2,056.23
BSC ambulatory patient utilities	0.741	0.494	£171,889.66	£124,849.22	£26,376.00
BSC predicted FVC>50% patient utilities	0.197	0.131	£148,091.77	£143,002.46	£2,578.11
BSC predicted FVC<50% patient utilities	0.197	0.131	£147,678.84	£143,395.75	£2,165.18
BSC predicted FVC<30% patient utilities	0.197	0.131	£146,693.64	£144,347.87	£1,179.98
Ataluren ambulatory caregiver utilities	1.000	0.671	£86,487.51	£308,307.97	£162,794.31
Ataluren predicted FVC>50% caregiver utilities	1.000	0.670	£128,467.43	£166,810.85	£21,297.19
Ataluren predicted FVC<50% caregiver utilities	0.930	0.620	£122,517.65	£175,664.61	£30,150.95
Ataluren predicted FVC<30% caregiver utilities	0.929	0.619	£136,095.28	£155,956.22	£10,442.56
BSC ambulatory caregiver utilities	1.000	0.671	£232,765.66	£98,451.98	£87,252.00
BSC predicted FVC>50% caregiver utilities	1.000	0.670	£174,477.04	£122,691.00	£28,963.38

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
BSC predicted FVC<50% caregiver utilities	0.930	0.620	£168,031.30	£127,236.89	£22,517.64
BSC predicted FVC<30% caregiver utilities	0.929	0.619	£157,227.57	£135,062.88	£11,713.91
Management costs					
Ambulatory direct healthcare costs	£7,739.40	£5,159.60	£146,177.51	£144,849.81	£663.85
Predicted FVC>50% direct healthcare costs	£8,276.81	£5,517.88	£145,302.67	£145,724.65	£210.99
Predicted FVC<50% direct healthcare costs	£15,855.34	£10,570.22	£145,706.11	£145,321.20	£192.46
Predicted FVC<30% direct healthcare costs	£17,761.95	£11,841.30	£145,385.84	£145,641.48	£127.82

Table D-19. Results of deterministic OWSA (PAS Price)

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
Settings					
Ambulatory compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ambulatory compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight variation ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight variation non-ambulatory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of caregivers to be applied	2.400	1.600	[redacted]	[redacted]	[redacted]
Bereavement QALY adjustment	0.108	0.072	[redacted]	[redacted]	[redacted]

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
Mortality adjustment	1.200	0.800	[redacted]	[redacted]	[redacted]
Mean ambulatory weight STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean non-ambulatory weight STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ambulatory early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predicted FVC <50% early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last transition (predicted FVC<30%) early treatment delay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to death following last transition	3.600	2.400	[redacted]	[redacted]	[redacted]
Utilities					
Ataluren ambulatory patient utilities	1.000	0.745	[redacted]	[redacted]	[redacted]
Ataluren predicted FVC>50% patient utilities	0.381	0.254	[redacted]	[redacted]	[redacted]
Ataluren predicted FVC<50% patient utilities	0.381	0.254	[redacted]	[redacted]	[redacted]
Ataluren predicted FVC<30% patient utilities	0.381	0.254	[redacted]	[redacted]	[redacted]
BSC ambulatory patient utilities	0.741	0.494	[redacted]	[redacted]	[redacted]
BSC predicted FVC>50% patient utilities	0.197	0.131	[redacted]	[redacted]	[redacted]
BSC predicted FVC<50% patient utilities	0.197	0.131	[redacted]	[redacted]	[redacted]
BSC predicted FVC<30% patient utilities	0.197	0.131	[redacted]	[redacted]	[redacted]
Ataluren ambulatory caregiver utilities	1.000	0.671	[redacted]	[redacted]	[redacted]
Ataluren predicted FVC>50% caregiver utilities	1.000	0.670	[redacted]	[redacted]	[redacted]

Parameter	Upper bound value	Lower bound value	ICER at upper bound value	ICER at lower bound value	Maximum Outcome Difference
Ataluren predicted FVC<50% caregiver utilities	0.930	0.620	[redacted]	[redacted]	[redacted]
Ataluren predicted FVC<30% caregiver utilities	0.929	0.619	[redacted]	[redacted]	[redacted]
BSC ambulatory caregiver utilities	1.000	0.671	[redacted]	[redacted]	[redacted]
BSC predicted FVC>50% caregiver utilities	1.000	0.670	[redacted]	[redacted]	[redacted]
BSC predicted FVC<50% caregiver utilities	0.930	0.620	[redacted]	[redacted]	[redacted]
BSC predicted FVC<30% caregiver utilities	0.929	0.619	[redacted]	[redacted]	[redacted]
Management costs					
Ambulatory direct healthcare costs	£7,739.40	£5,159.60	[redacted]	[redacted]	[redacted]
Predicted FVC>50% direct healthcare costs	£8,276.81	£5,517.88	[redacted]	[redacted]	[redacted]
Predicted FVC<50% direct healthcare costs	£15,855.34	£10,570.22	[redacted]	[redacted]	[redacted]
Predicted FVC<30% direct healthcare costs	£17,761.95	£11,841.30	[redacted]	[redacted]	[redacted]

The OWSA tornado diagrams are presented in Figure D.7and Figure D.8 for list price and PAS price, respectively.

Figure D.7. OWSA tornado diagram (List price)

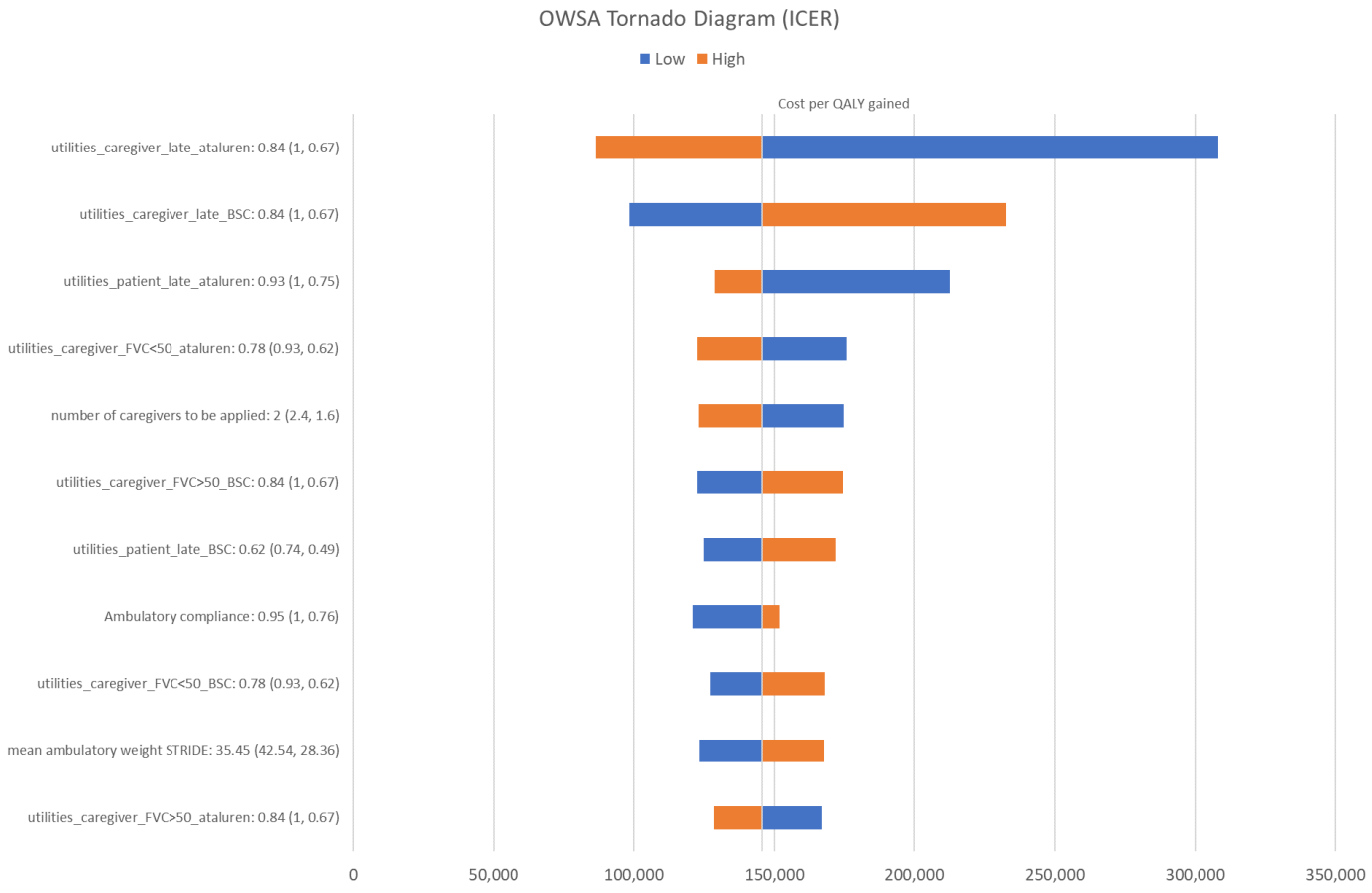
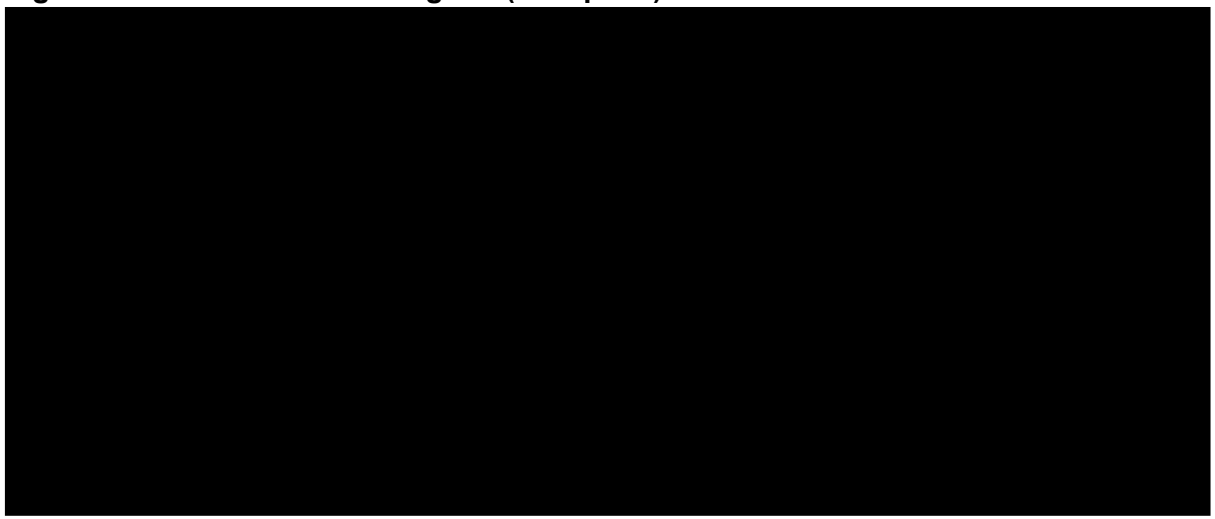


Figure D.8. OWSA tornado diagram (PAS price)



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Results of the scenario analyses are presented in Table D-20 for the list price and Table D-21 for the PAS price.

Table D-20. Deterministic multi-way scenario analysis results (List Price)

Scenario	Ataluren and BSC, total costs (£)	Ataluren and BSC, total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	£145,514
Societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	£145,897
Use RCHCP weight data source (healthy child median weight by age)	[redacted]	[redacted]	[redacted]	[redacted]	£160,007
Discount rate (1.5% for health effects)	[redacted]	[redacted]	[redacted]	[redacted]	£99,955
Delphi panel utilities (International)[170]	[redacted]	[redacted]	[redacted]	[redacted]	£170,362
Delphi panel/Landfeldt 2017 hybrid	[redacted]	[redacted]	[redacted]	[redacted]	£191,489
Exclude bereavement due to loss of a child	[redacted]	[redacted]	[redacted]	[redacted]	£148,342

Treatment stopping rule 6 months post LoA	[redacted]	[redacted]	[redacted]	[redacted]	£135,546
Treatment stopping rule predicted FVC < 30%	[redacted]	[redacted]	[redacted]	[redacted]	£154,659
Effectiveness population, not re-based	[redacted]	[redacted]	[redacted]	[redacted]	£146,553
Kaplan-Meier piece-wise analysis	[redacted]	[redacted]	[redacted]	[redacted]	£178,035

Table D-21. Deterministic multi-way scenario analysis results (PAS price)

Scenario	Ataluren + BSC, total costs (£)	Ataluren + BSC, total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use RCHCP weight data source	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate (1.5% for health effects)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delphi panel utilities[170]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Delphi panel/Landfeldt 2017 hybrid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude bereavement due to loss of a child	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule 6 months post LoA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule predicted FVC < 30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effectiveness population, not re-based	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier piece-wise analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

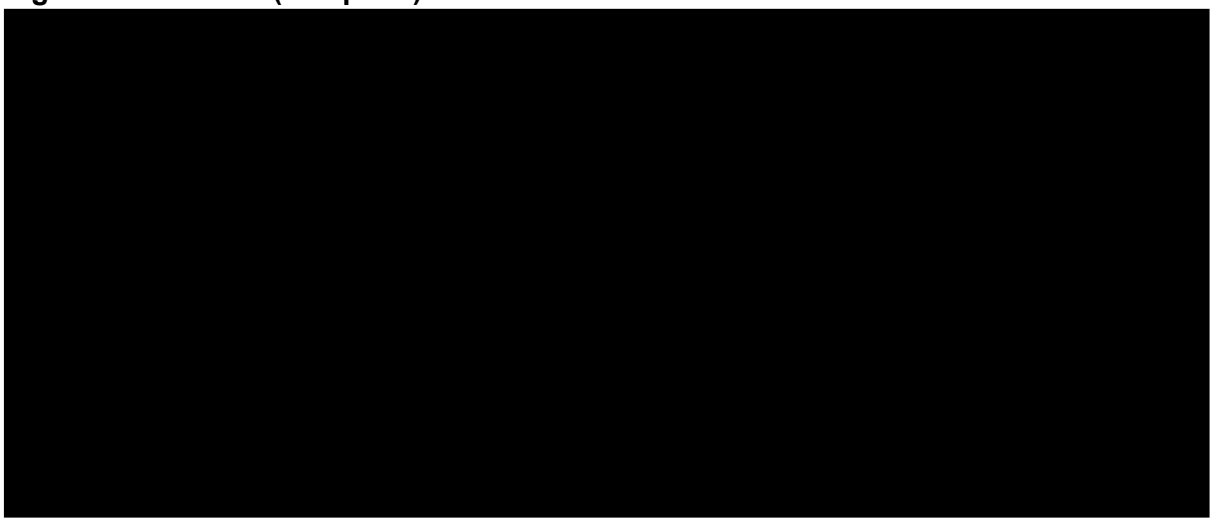
PSA – List Price

PSA simulations were plotted on the cost-effectiveness plane (Figure D.9) and a CEAC was generated (Figure D.10). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving the probabilistic ICER of £142,883. The proportion of simulations considered cost-effective at a threshold of £100,000 per QALY was [redacted]%.

Figure D.9. Cost-effectiveness plane (List price)

*Note: the yellow dotted line represents the WTP threshold of £100,000 per QALY gained

Figure D.10. CEAC (List price)

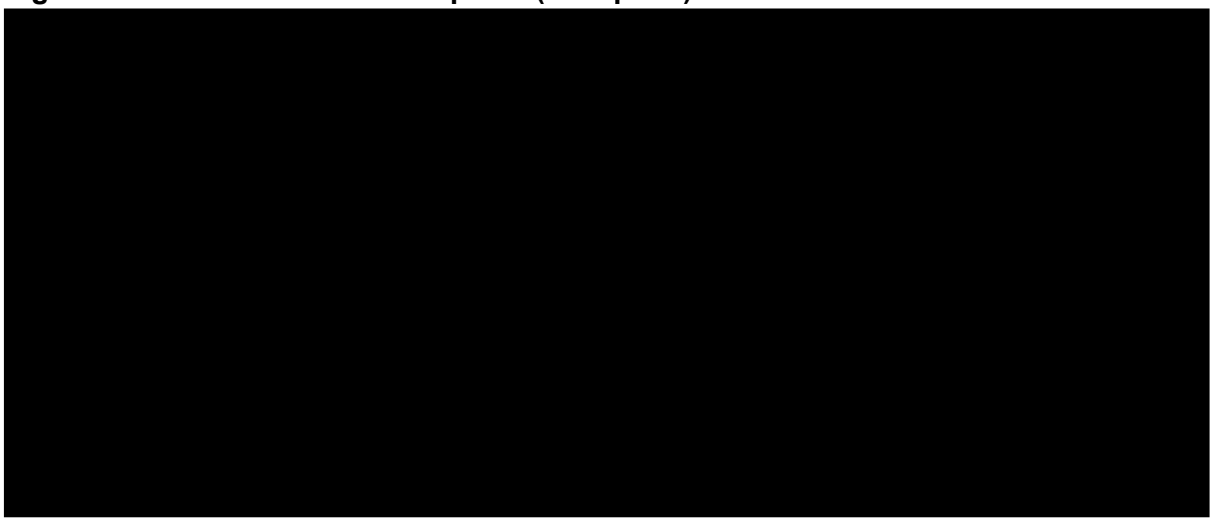


PSA – PAS Price

With the simple PAS discount of [redacted], the average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving the probabilistic ICER of [redacted]. The cost-

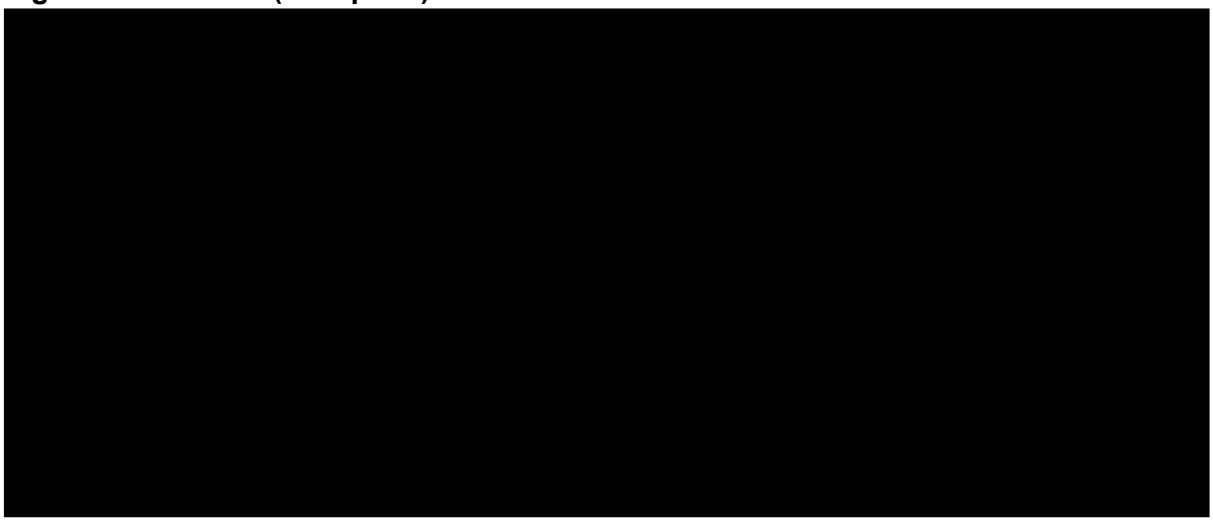
effectiveness plane and CEAC are presented in Figure D.11**Error! Reference source not found.** and Figure D.12, respectively. The proportion of simulations considered cost-effective at a threshold of £100,000 was [redacted]%.

Figure D.11. Cost-effectiveness plane (PAS price)



*Note: the yellow dotted line represents the WTP threshold of £100,000 per QALY gained

Figure D.12. CEAC (PAS price)



12.5.14 What were the main findings of each of the sensitivity analyses?

The PSA indicates that at PAS price, ataluren is cost-effective in the majority of iterations at a willingness-to-pay threshold of £100,000. The sensitivity analyses also indicate that the model is robust to variations in model inputs.

12.5.15 What are the key drivers of the cost results?

As shown in Table D-19 and Figure D.8, patient and caregiver utilities, treatment compliance, and patient weights are key drivers of the cost results.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analyses were conducted as part of the analyses. This is due to the lack of identified subgroups and the small patients' numbers available in the data.

12.6.2 Define the characteristics of patients in the subgroup(s)

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The economic model, key inputs and assumptions have been validated by UK clinicians (see section 12.2.5). In addition to this, key model assumptions (detailed in section 12.1.5) have been validated as part of a Delphi panel study with [redacted].

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Landfeldt et al. 2017[167] conducted a cost-effectiveness analysis of a hypothetical intervention versus SoC. The study developed three model structures, each of which were run over a lifetime horizon to report the total costs and QALYs of the hypothetical intervention versus SoC (see section 12.3.2 for further details). The study and the economic model in this evidence submission are informed by the same direct costs (costs informing our model have been inflated to 2021 prices), as well as the same caregiver utilities. However, patient utility values used in this evidence submission are informed by Landfeldt et al. 2020[169] as opposed to Landfeldt et al. 2017. The ICERs reported by the literature are larger than those reported in section 12.5. Firstly, the published literature is informed by different clinical data, Landfeldt et al. applied efficacy data that "reduced the probability of disease progression across all model states by a conservative (but realistic) 25%, in agreement with (but in addition to) the efficacy of glucocorticoid treatment observed in clinical practice".

The cost-effectiveness model structure has been developed based on the HERCULES natural history model, which captures the key milestones of nmDMD (LoA, reduction in pulmonary capacity). The model is informed by STRIDE registry data, which has been propensity score matched to data from the CINRG registry, therefore providing robust comparative data. The model is reflective of treatment with ataluren, for the indicated population and therefore reports the expected costs and outcomes of treatment with ataluren for patients in England. Therefore, the cost-effectiveness analyses in the published literature are not comparable to this analysis.

12.8.2 Is the cost-effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes. The cost-effectiveness analysis is relevant for all eligible nmDMD patients.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The cost-effectiveness analysis is informed by the best available data on the clinical progression of nmDMD patients receiving treatment with ataluren. The STRIDE dataset is the largest international nmDMD observational cohort which includes 269 patients (evaluable population, as of 31st January 2021). STRIDE data has been propensity score matched with patients in the CINRG registry, providing comparative data. In addition to this, the model structure has been informed by the HERCULES model, a robust natural history model based on patient progression and key milestones in DMD, which has been validated by clinicians.

Despite best efforts to obtain clinical data for all relevant inputs in the model, due to the ultra-orphan nature of nmDMD, not all inputs could be obtained from clinical trials or real-world evidence. Therefore, a number of key model inputs and assumptions have been informed/validated by clinicians.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

PTC Therapeutics are currently conducting a phase III, randomised clinical trial to characterise the long-term effects of ataluren in patients with nmDMD. This trial is split into a 72-week study and 72-week open-label phase. The study phase is a randomised, double-blind, placebo-controlled phase, in which patients receive either ataluren or placebo. Study 041 is expected to finish in July 2023, following completion of the HST submission. Preliminary results of the 72-week study phase are expected to be available in April/May 2022, which will report rate of change in 6-minute walk distance over 72 weeks (primary outcome) as well as other secondary outcome measures (change from baseline in 6-minute walk distance, time to loss of ambulation, time to loss of stair-climbing and stair-descending and more; over 72 weeks).

STRIDE registry is ongoing, which collects data on patients receiving ataluren. Patient data is collected for time to LoA and time to predicted FVC <50%, which we have used to inform the cost-effectiveness analysis.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also, present results for the subsequent 5 years.

Currently in England there are [redacted] patients being treated with ataluren under the MAA (as at December 2021). For the budget impact analyses, we have used this value to inform the number of prevalent patients in the model, as it is representative of the number of eligible patients receiving ataluren in England.

A 2013 study estimated DMD incidence to be 19 per 100,000 males.[205] Based on the number of live births in England (613,936), 51% of which are males, there are an estimated 58 incident DMD patients per year.[206] Data from the TREAT-NMD DMD Global database, which contains over 7,000 mutations, has found that 10% of patients have nmDMD.[207] Therefore, there are 6 incident nmDMD patients per year.

Table D-22. Calculation of incidence estimates

Patient population	Incidence
DMD	1 out of 5,135 male births (Moat, 2013)
nmDMD	10% of DMD (Bladen, 2015)
Patients per year	6 new per annum

In the budget calculation data from the cost-effectiveness model for the mortality rate and the rate of patients reaching predicted FVC <50% (per year) have also been applied, [redacted] and [redacted] respectively. This has been derived from the cost-effectiveness model based on a median survival of [redacted] and a median age at predicted FVC <30% of [redacted].

This results in an eligible patient population, i.e., in line with the marketing authorisation for ataluren, of [redacted] patients in Year 1 increasing to [redacted] patients in Year 5.

Table D-23. Eligible patients for ataluren over the next five years in England

	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Prevalence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	6	6	6	6	6	6
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule (predicted FVC <50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The expected market uptake with ataluren is 100%. It is expected that the demand for ataluren will remain constant, therefore the budget impact analysis assumes a 100% market uptake for all years.

The model also applied a compliance rate of 95%, based on a Delphi panel study of [redacted].

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Not applicable.

13.4 Describe any estimates of resource savings associated with the use of the technology.

No resource savings are associated with the use of ataluren.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

None.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The budget impact analysis over the next 5 years is shown in Table D-24.

Table D-24. Budget impact for ataluren (List price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Cost (per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table D-25. Budget impact for ataluren (PAS price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Cost (per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The incidence figure in the budget impact calculations is based on a Welsh newborn bloodspot screening programmes for DMD which is one of the longest running in the world (Moat, 2013[205]). In this programme, newborn bloodspots were collected routinely as part of the Wales newborn screening programme. Specific consent was obtained for this test separately from the other tests. During the 21-year period, 369,780 bloodspot cards were received from male infants, of these 343,170 (92.8%) were screened using a bloodspot CK assay following parental consent. DMD was confirmed in 56 cases by genotyping/muscle biopsy studies. The incidence of DMD in Wales of 1:5136 during this period is lower than that of 1:4046 before commencement of screening in Wales. It was concluded that screening had reduced the diagnostic delay enabling reproductive choice for parents of affected boys and earlier administration of current therapies. It would mean that one would expect the incidence of DMD to continue to decline over time and thus the figure of 1:5136 is likely to be an overestimate of the incidence.

An annual background mortality rate of [redacted] has been applied and a rate for reaching predicted FVC <50% [redacted] based on data from the cost-effectiveness model. There may be a survival benefit with ataluren, however this has not been assumed for the 5-year budget impact calculation.

Compliance is assumed to be 95%, as with the cost-effectiveness analysis. This is based on a recent Delphi panel study of [redacted] clinical experts from the [redacted], see section 10.1.10 for further details.

E Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

A substantial proportion of the benefits of ataluren treatment are incurred outside of the NHS and personal social services. Due to its early onset and rapid progression, DMD results in severe disability and consequent lack of independent living by the early twenties with death usually occurring before the age of 30. As a result, adults with DMD rarely succeed in participating in a working life or contributing to society. Only a very small proportion of patients are reported to be in employment and the burden on caregivers results in substantial losses in productivity.

Landfeldt et al. (2014[24]) estimated the total economic burden of DMD to society and caregiver households across a number of countries. Patients with DMD from Germany, Italy, United Kingdom, and United States were included in the study (770 patient-caregiver pairs) (described in detail in sections 10.1.6 and 12.3.2). Demographics of caregivers showed that in the UK 98% of caregivers were parents, 79% of whom were female. Informal care (caregivers' nonprofessional paid care and the proportion of caregivers' leisure time devoted to provide informal care) was extensive in all countries. In the UK, 55% of caregivers were employed whereas 49% had reduced working hours or had stopped working completely because of their relative's DMD. For employed caregivers, the mean overall work impairment (loss in work time and productivity while working) was estimated at 29% (95% CI 24–35%) for the UK sample. Labour-force participation among patients was very low (4%). A further study has reported on the demographics and care of adults with DMD in the UK compared to other European countries.[208] In this study 42 patients aged over 18 responded to the survey (18.6% of the total UK respondents). All were non-ambulatory and none were in employment, with 25.6% still in education (secondary school, special needs school, vocational training, or university). Most of the UK adults were living at home (92.9 %), which was higher than elsewhere in Western Europe.[208]

Costs associated with DMD-related health care resource use, informal care, and production losses (indirect costs) are presented in Table E-1. The largest cost component was indirect costs in Germany, Italy, and the US, and non-medical community services in the UK.[24] The total annual cost of illness of DMD in the UK was estimated as 72,870 US dollars (GBP £53,325) per patient. Of this at least 46% related to the cost of informal care and loss of productivity and therefore not incurred by the NHS/ Personal Social Services. It is also expected that a large proportion of non-medical community care, as well as adaptations to the home is paid for privately by families.

In a cross-sectional study of patients with DMD from Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK, based on questionnaires completed by patients or their caregivers (N=422), the average annual total cost per person in 2012 was €34,658 in the UK.[26] Direct non-healthcare costs were the main component of total costs (89% in the UK), and informal care was the main driver of non-healthcare costs. Main informal carer and other informal carer cost was mean €17,123 and €11,893, respectively, per annum in the UK. The mean per patient annual household economic burden of DMD, calculated for households in which the patients with DMD currently lived, is presented in Table E-2.

The cost of illness (including both direct medical cost, cost of informal care and indirect costs) increases as patients enter the non-ambulatory stages of disease. In the UK the cost of illness almost doubled between the early and late stages of being non-ambulatory (from approximately 66,000 to 129,000 US dollars/per patient/annum).[24] Patients in the late ambulatory, early non-ambulatory, and late non-ambulatory classes had 38% (relative risk [RR]: 1.38, 95% CI: 1.20–1.59), 181% (RR: 2.81, 95% CI: 2.41–3.27), and 191% (RR: 2.91, 95% CI: 2.54–3.34) higher annual household economic burden compared with their early ambulatory counterparts. Similar results were seen in a separate study of patients in Germany where both direct medical and non-medical cost of illness increased with disease severity.[23]

Estimates of the total economic burden of DMD, including a monetary value of the loss in patient and caregiver quality of life (intangible costs) were also calculated by Landfeldt et al. Using the DMD prevalence estimates, the national burden of DMD in the UK was estimated at $200,478,000 per annum (GBP £146,705,080).[24]

A treatment that changes the course of nmDMD by slowing disease progression enables children and adults with nmDMD to maintain their independence for longer. This in turn would mean that that caring for their children would be less intensive for parents/ caregivers and may allow them to stay in paid work for longer. It may also mean that children with nmDMD can participate in education for longer, remain more self-sufficient and have an increased chance of employment in adulthood.

Ataluren treatment delays loss of ambulation and delaying progression to the non-ambulatory stage of disease would delay the occurrence of the associated higher costs, of which a large proportion are made up of costs to households incurred outside of the NHS and personal social services.

The estimation of the impact of ataluren treatment on from a societal perspective is shown in section **Error! Reference source not found.**, as part of scenario analyses.

Table E-1 Components of annual cost of Duchenne muscular dystrophy (UK)

Component	Percentage of cost of illness	Per patient cost (US dollars, 2012)	Per patient cost (GBP 2014)[e]
Hospital visits[a]	3%	2,300 (1,500–3,720)	1,683
Visits to physicians and other health care practitioners	11%	8,230 (6,360–13,150)	6,023
Tests and assessments	2%	1,580 (1,450–1,750)	1,156
Medications	1%	930 (820–1,070)	681
Non-medical community services[b]	27%	19,250 (13,240–28,670)	14,087
Aids, devices and investments[c]	10%	7,520 (5,690–9,790)	5,503
Informal care	20%	14,340 (13,030–15,990)	10,494
Indirect costs (production losses)	26%	18,700 (16,280–21,150)	13,684
Total annual cost of illness	-	72,870 (64,350–84,150)	53,325
Intangible costs[d]	-	46,080 (42,360–50,050)	33,720
Total burden of illness	-	118,950 (108,280–132,710)	87,045

Data presented as mean (95% confidence interval), rounded to nearest 10.

[a] Including emergency and respite care.

[b] Home help, personal assistants, nannies, and transportation services.

[c] Include investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).

[d] cost (costs due to pain, anxiety, social handicap, etc.) was estimated by assigning a monetary value to the loss in quality of life for patients and caregivers in relation to the age- and sex-specific mean quality of life in the general population.

[e] Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

Source: Landfeldt, 2014[24]

Table E-2 Per patient annual household burden of DMD in the UK

	Cost (in 2012 US dollars)	Per patient cost (GBP 2014)[b]
No. (%) living with caregiver	188 (98)	138
Total out-of-pocket payments	3,490 (2,220–5,570)	2,554
Insurance premiums	10 (0–30)	7
Copayments for medical services	60 (30–140)	44
Copayments for medications	100 (60–140)	73
Copayments for community services	140 (60–290)	102
Out-of-pocket payments for investments[a]	3,180 (2,020–5,710)	2,327
Income loss	750 (440–1,200)	549
Loss of leisure time	13,590 (12,410–14,980)	9,945
Intangible costs	45,770 (42,070–49,670)	33,493
Total per patient annual household burden	63,600 (58,790–68,370)	46,541

DMD, Duchenne muscular dystrophy.

Data presented as mean (95% confidence interval), rounded to nearest 10, if not otherwise stated.

[a] Include non-reimbursed payments for medical and non-medical aids and devices, as well as investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility).

[b] Converted to GBP using PPPs and inflated to 2014 using the consumer price index (multiplied by 0.731776454 to get 2014 GBP costs)

Source: Landfeldt et al. 2014[24]

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is anticipated that treatment with ataluren could result in cost savings to the following government departments or budgets:

Education budget – a child with DMD will receive a statement of special educational needs, which will usually involve the cost of classroom assistance and adaptations to the fabric of the school (for example, to widen spaces to accommodate a wheelchair). These costs may be reduced, or postponed, if the patient derives clinical benefit from treatment with ataluren.

Local Government budget – cost savings may accrue (in terms of reduced Disabled Facilities Grant payments, for example) if fewer adaptations need to be made to a patient's home, or if the adaptations needed are less costly.

Welfare budget – the more independent and capable the patient is, the less dependent they – or their caregivers – are on respite care, or on disability and other welfare payments.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Costs borne by patients/ caregivers include:

- Out-of-pocket expenses, e.g., travel expenses
- Non-reimbursed payments for medical and non-medical aids and devices, as well as investments to and reconstructions of the home (e.g., adaptations for wheelchair accessibility)
- Patient loss of quality of life, leisure time, a normal education and ability to contribute to society
- Caregiver loss of quality of life, leisure time, earnings
- Non-reimbursed payments for home help, personal assistants, nannies, and transportation services

Please also refer to Table E-2.

In the study by Landfeldt et al. (2014[24]) patients in the late ambulatory, early non-ambulatory, and late non-ambulatory classes had 38% (relative risk [RR]: 1.38, 95% CI: 1.20–1.59), 181% (RR: 2.81, 95% CI: 2.41–3.27), and 191% (RR: 2.91, 95% CI: 2.54–3.34) higher annual household economic burden compared with their early ambulatory counterparts. Depending on the patients' current health and mental status, between 17% and 62% reported that they did not have enough money to take care of the patient.[27]

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

A considerable amount of time is spent by family members in providing care. Landfeldt et al (2016[115]), in their study of 770 patient-caregiver pairs, reported hours of leisure time devoted to informal care: 35% spent >50 hours a week, 26% spent 25-50 hours per week, and the remaining 38% spent <25 hours per week.

The mean number of hours of informal care per week has been estimated at 63 hours in the UK.[27] Given that parents provide care throughout their child's lifetime, the burden is substantial.

The majority of caregivers are parents (98%).[115] In addition to helping their children with daily activities such as getting around, dressing and washing, time is spent each day at home on stretching exercises and physiotherapy. Caregivers in the UK report that caring for the individual with nmDMD took up a substantial amount of time, not only because they needed to look after the individual, but also because they needed to attend a large number of medical appointments. This time impact had a subsequent impact on their social activities and relationships.[109] This becomes even more acute when patients transition to adult services when care is generally more fragmented necessitating multiple visits.

Many DMD caregivers terminate their employment or reduce their working hours to find the time needed to care for their sons, and those who do continue to work have markedly impaired productivity with high levels of absenteeism.[115] UK caregivers also reported that they had needed to take time off work due to back pain or anxiety and stress.[109] Given that the physical and emotional

impacts of caring for an individual may worsen as the individual's physical abilities decline, there is the potential for this impact on the caregiver's work also to worsen.

Indeed, the time spent providing informal care increases with disease progression. In the German study by Schreiber-Katz et al, DMD non-working relatives' total care efforts was estimated at a mean of 9.4 (SD 10.9) hours per day, with a notable increase in more severe clinical stages.[23] In this study the cost of informal care was around €8,000 per year in the non-ambulatory stages, which rose to €19,532 in the early non-ambulatory stage, €31,490 in the late non-ambulatory stage and €44,443 when adults were confined to bed.[23] This indicates that parents spend at least double the time caring for their children following loss of walking ability and that this again increases substantially in the late non-ambulatory stage as the boys lose upper body function. Since the German health care system provides long-term nursing care insurance, the time spent on care by parents in the UK may be even higher.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Ataluren is an innovative, first-in-class drug and is the first specific approved therapy for nmDMD that addresses the underlying cause of the disease. Since ataluren received conditional regulatory approval by the EMA in 2014, no other treatments for DMD have been approved in Europe, highlighting the challenges of developing an effective treatment and conducting clinical trials in this condition.

There have been a limited number of large, randomised studies in DMD, and, through the ataluren trial programme, PTC Therapeutics are pioneering clinical trial research in this disease area. Despite the challenges of generating clinical evidence in areas of (ultra)-rare slowly progressing diseases, PTC has accumulated data on over 995 patients with nmDMD by conducting the largest clinical program in nmDMD to date[32,33,52] and developing the largest international nmDMD observational cohort for clinical effectiveness and safety (STRIDE Registry).[7,128]

The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials. Study 007 was the first study for registration in DMD and through its entire pre-clinical and clinical development programme PTC Therapeutics has been a pioneer in this field. At the time of the initial study design there were no established primary or secondary endpoints from a regulatory perspective, and there was limited DMD natural history data available. Completion of this trial has provided a better understanding of the natural history of DMD using the 6MWD and has established the 6MWD as a validated primary endpoint in DMD clinical trials; in addition, the data from this trial has helped to identify the best secondary endpoints in DMD trials and has provided the clinical trial groundwork for future therapies for this devastating and life-limiting condition. STRIDE provides data on patterns of ataluren use and long-term patient outcomes in real-world routine clinical practice.

Under the MAA, in total 100 patients with nmDMD have been treated with ataluren, with data being collected on ambulatory outcome and HRQL. It is expected that most of these patients are also enrolled in STRIDE.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

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

The number of large, randomised studies in DMD has been limited and through the ataluren trial programme and STRIDE Registry PTC Therapeutics has, and continues to, pioneer clinical trial research in this area. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials of treatments for this devastating and life-limiting condition. This has led to other companies (including British based ones) investing in developing treatments for DMD. Together this leads to further advances in the treatment of DMD and ensures expertise and clinical experience in the UK are retained.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

Not applicable – the STRIDE Registry is established and ongoing.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Ataluren has a conditional marketing authorisation from the EMA. Additional data will be generated post-authorisation in the confirmatory phase 3 study PTC124-GD-041-DMD (Study 041) which is expected to report initial results during Q3 2022 (see section 4).

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The marketing authorisation for ataluren states that treatment should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Not applicable, as ataluren is already used in clinical practice.

F Managed Access Arrangements

15 Managed Access Arrangement

Section not applicable.

16 References

1. Translarna SPC. *Summary of product characterisitcs. Translarna 125 mg, 250 mg and 500 mg granules for oral suspension. Available at: https://www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information_en.pdf.* 2021.
2. National Institute for Health and Care Excellence (NICE). *Managed Access Agreement 2016: Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD).* https://www.nice.org.uk/guidance/hst3/resources/managed-access-agreement-july-2016-pdf-2553024061.
3. PTC Therapeutics. *UK Clinical expert opnion recieved on economic model inputs.* February 2022.
4. Passamano L, Taglia A, Palladino A, et al. Improvement of survival in Duchenne Muscular Dystrophy: Retrospective analysis of 835 patients. *Acta Myologica.* 2012;31(OCTOBER):121-125.
5. Blake DJ, Weir A, Newey SE, Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiological reviews.* 2002;82(2):291-329.
6. Klingler W, Jurkat-Rott K, Lehmann-Horn F, Schleip R. The role of fibrosis in Duchenne muscular dystrophy. *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology.* 2012;31(3):184-195.
7. Mercuri E, Muntoni F, Osorio AN, et al. Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *J Comp Eff Res.* 2020;9(5):341-360.
8. NHS. Health A to Z, Muscular dystrophy types. 2020; https://www.nhs.uk/conditions/muscular-dystrophy/types/. Accessed 05 October, 2020.
9. van Ruiten HJa, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. *Archives of Disease in Childhood.* 2014;99(12):1074-1077.
10. European Medicines Agency. *Briefing Document: Antisense oligonucleotide-mediated exon skipping therapy development for Duchenne muscular dystrophy (DMD) - A COST/SCOPE-DMD meeting hosted by the European Medicines Agency. Available at: https://exonskipping.eu/wp-content/uploads/2015/04/Briefing-Document-COST-and-SCOPE-DMD-EMA-meeting-April-2015-FINAL-VERSION.pdf. Accessed 02 August 2021.* 2015.
11. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. *The Lancet. Neurology.* 2010;9(1):77-93.
12. McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. *Muscle & nerve.* 2010;41(4):500-510.
13. Arora H, Willcocks RJ, Lott DJ, et al. Longitudinal timed function tests in Duchenne muscular dystrophy: Imaging DMD cohort natural history. *Muscle Nerve.* 2018;58(5):631-638.

14. Bello L, Morgenroth LP, Gordish-Dressman H, et al. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. *Neurology.* 2016;87(4):401-409.

15. Ricotti V, Ridout Da, Pane M, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. *Journal of Neurology, Neurosurgery & Psychiatry.* 2016;87:149-155.

16. Henricson E, Abresch R, Han JJ, et al. The 6-minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: Longitudinal comparisons and clinically-meaningful changes over one year. *PLoS currents.* 2013;5.

17. Mayer O. Advances in Pulmonary Care in Duchenne Muscular Dystrophy. *US Neurology.* 2017;13(1):35-41.

18. Ishikawa Y, Miura T, Ishikawa Y, et al. Duchenne muscular dystrophy: Survival by cardio-respiratory interventions. *Neuromuscular Disorders.* 2011;21(1):47-51.

19. Kieny P, Chollet S, Delalande P, et al. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. *Annals of Physical and Rehabilitation Medicine.* 2013;56(6):443-454.

20. McDonald CM, Gordish-Dressman H, Henricson EK, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids. *Neuromuscular Disorders.* 2018;28(11):897-909.

21. Phillips MF, Quinlivan RCM, Edwards RHT, Calverley PMA. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. *American Journal of Respiratory and Critical Care Medicine.* 2001;164(12):2191-2194.

22. Williams K, Davidson I, Rance M, Boehnke A, Buesch K, Acaster S. Symptoms and impacts of ambulatory nonsense mutation Duchenne muscular dystrophy: a qualitative study and the development of a patient-centred conceptual model. *J Patient Rep Outcomes.* 2021;5(1):75.

23. Schreiber-Katz O, Klug C, Thiele S, et al. Comparative cost of illness analysis and assessment of health care burden of Duchenne and Becker muscular dystrophies in Germany. *Orphanet Journal of Rare Diseases.* 2014;9(1):210.

24. Landfeldt E, Lindgren P, Bell CF. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. *Neurology.* 2014;83:529-536.

25. Pangalila RF, van den Bos GAM, Stam HJ, van Exel NJa, Brouwer WBF, Roebroeck ME. Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. *Disability and Rehabilitation.* 2012;34(12):988-996.

26. Cavazza M, Kodra Y, Armeni P, et al. Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. *European Journal of Health Economics.* 2016;17:1-11.

27. Landfeldt E, Edstrom J, Buccella F, Kirschner J, Lochmuller H. Duchenne muscular dystrophy and caregiver burden: a systematic review. *Dev Med Child Neurol.* 2018;60(10):987-996.

28. Duchenne UK. About Project HERCULES. Accessed 10 September 2020. 2020; https://hercules.duchenneuk.org/about-project-hercules/.

29. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet. Neurology.* 2018;17(3):251-267.

30. Torgan C. Optimizing Steroid Treatment for Duchenne Muscular Dystrophy. *National Institute of Arthritis and Musculoskeletal and Skin Diseases.* 2018.

31. Agency MHpR. Ataluren. 2021; https://cms.mhra.gov.uk/pip/mhra-100098-pip01-21-m01-update.

32. Bushby K, Finkel R, Wong B, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle & Nerve.* 2014;50(4):477-487.

33. McDonald CM, Campbell C, Torricelli RE, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet.* 2017;390(10101):1489-1498.

34. Mercuri E, Muntoni F, Buccella F, Desguerre I. Poster EP.142: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Duchenne Natural History Study: a matched cohort analysis. Paper presented at: 26th International Annual Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24. 2021.

35. McDonald C, Muntoni F, Rance MJ, Jiang J, Kristensen A. Ataluren delays loss of ambulation and decline in pulmonary function in patients with nonsense mutation Duchenne muscular dystrophy. Presented at the 2021 MDA virtual clinical & scientific conference March 15–18, 2021 2021.

36. PTC Therapeutics Clinical Study Report. *(Fifth Interim Report) PTCT124-GD-0250-DMD. Long-term observational study of Tranlsarna safety and effectivenees in usual care.* 2021.

37. Tulinius M, Buccella F, Desguerre I, Kirschner J. Poster EP.144: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Duchenne Natural History Study: a matched cohort analysis. Paper presented at: 26th International Annual Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24. 2021.

38. !!! INVALID CITATION !!! 40.

39. !!! INVALID CITATION !!! 29.

40. Haas M, Vlcek V, Balabanov P. European Medicines Agency review of ataluren for the treatment of ambulant patients aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. *Neuromuscular Disorders.* 2015;25:5-13.

41. Campbell C, Barohn R, Bertini E, Chabrol B, Muntoni F, on behalf of the PTC124-GD-007-DMD Study Group ADSG, & the Clinical Evaluator Training Groups. Meta-analyses of ataluren randomized controlled trials in nonsense mutation Duchenne muscular dystrophy. *Journal of Comparative Effectiveness Research.* 2020;9(14):973-984.

42. Tian C FJ, O'Mara E, Trifillis P, McIntosh J, Renfroe J. Ataluren in patients aged ≥ 2 to < 5 years with nonsense mutation Duchenne muscular dystrophy (nmDMD): 28-week results from a Phase 2 study. Abstract. International Congress on Neuromuscular Disease; July 6-10, 2018; Vienna, Austria.

43. PTC Clinical Study Report. *PTC124-GD-019-DMD. An open-label study for previously treated ataluren patients with nonsense mutaiton dystrophinopathy.* August 26 2018.

44. National Institute for Health and Care Excellence (NICE). Contract Variation Agreement No. 1 to Managed Access Agreement for Ataluren (TranslarnaTM) for treating nonsense mutation Duchenne muscular dystrophy. 2021. Accessed 22 November, 2021.

45. Williams K, Davidson I, Rance M, Buesch K, Acaster S. A qualitative study on the impact of caring for an ambulatory individual with nonsense mutation Duchenne muscular dystrophy. *J Patient Rep Outcomes.* 2021;5(1):71.

46. European Medicines Agency. Translarna: Assessment report. 2019; https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-ii-0049-epar-assessment-report-variation_en.pdf.

47. European Medicines Agency. Translarna - Procedural steps taken and scientific information after the authorisation. 2021. Accessed 28 May, 2021.

48. Consortium SM. Medicines advice - Ataluren (Translarna). 2021; https://www.scottishmedicines.org.uk/medicines-advice/ataluren-translarna-uo-pathway-smc2327/.

49. Petrof BJ, Shrager JB, Stedman HH, Kelly aM, Sweeney HL. Dystrophin protects the sarcolemma from stresses developed during muscle contraction. *Proceedings of the National Academy of Sciences of the United States of America.* 1993;90(8):3710-3714.

50. Welch EM, Barton ER, Zhuo J, et al. PTC124 targets genetic disorders caused by nonsense mutations. *Nature.* 2007;447(7140):87-91.

51. Pichavant C, Aartsma-Rus A, Clemens PR, et al. Current status of pharmaceutical and genetic therapeutic approaches to treat DMD. *Molecular Therapy.* 2011;19(5):830-840.

52. Finkel RS, Flanigan KM, Wong B, et al. Phase 2a study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. *PLoS ONE.* 2013;8(12).

53. Muntoni F, Domingos J, Manzur AY, et al. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. *PLoS One.* 2019;14(9):e0221097.

54. Ciafaloni E, Kumar A, Liu K, et al. Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker Muscular Dystrophy: Data from the MD STARnet. *J Pediatr Rehabil Med.* 2016;9(1):5-11.

55. Aartsma-Rus A, Hegde M, Ben-Omran T, et al. Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy. *J Pediatr.* 2019;204:305-313.e314.

56. Goemans N, van den Hauwe M, Wilson R, van Impe A, Klingels K, Buyse G. Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. *Neuromuscular Disorders.* 2013;23(8):618-623.

57. Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. *Neurology.* 2011;77(3):250-256.

58. McDonald CM, Henricson EK, Abresch RT. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle and Nerve.* 2013;48(3):343-356.

59. Vestergaard P, Glerup H, Steffensen BF, Rejnmark L, Rahbek J, Moseklide L. Fracture risk in patients with muscular dystrophy and spinal muscular atrophy. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine.* 2001;33(4):150-155.

60. Humbertclaude V, Hamroun D, Bezzou K, et al. Motor and respiratory heterogeneity in Duchenne patients: Implication for clinical trials. *European Journal of Paediatric Neurology.* 2012;16(2):149-160.

61. Archer JE, Gardner AC, Roper HP, Chikermane AA, Tatman AJ. Duchenne muscular dystrophy: The management of scoliosis. *J Spine Surg.* 2016;2(3):185-194.

62. Kinali M, Messina S, Mercuri E, et al. Management of scoliosis in Duchenne muscular dystrophy: a large 10-year retrospective study. *Developmental medicine and child neurology.* 2006;48(6):513-518.

63. Yilmaz Ö, Karaduman a, Topaloğlu H. Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. *European Journal of Neurology.* 2004;11(8):541-544.

64. Finder J, Mayer OH, Sheehan D, et al. Pulmonary endpoints in Duchenne muscular dystrophy. A workshop summary. *American journal of respiratory and critical care medicine.* 2017;196(4):512-519.

65. Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. *American family physician.* 2014;89(5):359-366.

66. Buyse GM, Voit T, Schara U, et al. Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. *Lancet (London, England).* 2015;385(9979):1748-1757.

67. Connolly AM, Florence JM, Zaidman CM, et al. Clinical trial readiness in non-ambulatory boys and men with duchenne muscular dystrophy: MDA-DMD network follow-up. *Muscle Nerve.* 2016;54(4):681-689.

68. Connolly AM, Malkus EC, Mendell JR, et al. Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy. *Muscle Nerve.* 2015;51(4):522-532.

69. Khirani S, Ramirez A, Aubertin G, et al. Respiratory muscle decline in Duchenne muscular dystrophy. *Pediatr Pulmonol.* 2014;49(5):473-481.

70. Mayer OH, Finkel RS, Rummey C, et al. Characterization of pulmonary function in Duchenne Muscular Dystrophy. *Pediatric Pulmonology.* 2015;50(5):487-494.

71. Meier T, Rummey C, Leinonen M, et al. Characterization of pulmonary function in 10–18 year old patients with Duchenne muscular dystrophy. *Neuromuscular Disorders.* 2017;27(4):307-314.

72. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Respiratory, cardiac, bone health, and orthopaedic management. *The Lancet Neurology.* 2018;17(4):347-361.

73. LoMauro A, Romei M, Gandossini S, et al. Evolution of respiratory function in Duchenne muscular dystrophy from childhood to adulthood. *Eur Respir J.* 2018;51(2).

74. Ryder S, Leadley RM, Armstrong N, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet journal of rare diseases.* 2017;12(1):79.

75. Duchenne UK. About Project HERCULES. Accessed 10 September 2020. 2020; https://hercules.duchenneuk.org/about-project-hercules/.

76. Eagle M, Bourke J, Bullock R, et al. Managing Duchenne muscular dystrophy - The additive effect of spinal surgery and home nocturnal ventilation in improving survival. *Neuromuscular Disorders.* 2007;17(6):470-475.

77. Rall S, Grimm T. Survival in Duchenne muscular dystrophy. *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology.* 2012;31(2):117-120.

78. European Medicines Agency. Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf (Accessed 17 June 2021). 2015; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf.

79. Food and Drug Administration. Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment. Guidance for industry. https://www.fda.gov/media/92233/download (Accessed 17 June 2021). 2018; https://www.fda.gov/media/92233/download.

80. Bushby K, Connor E. Clinical outcome measures for trials in Duchenne muscular dystrophy: Report from International Working Group meetings. *Clinical investigation.* 2011;1(9):1217-1235.

81. Escolar DM, Hache LP, Clemens PR, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. *Neurology.* 2011;77(5):444-452.

82. Bendixen RM, Lott DJ, Senesac C, Mathur S, Vandenborne K. Participation in daily life activities and its relationship to strength and functional measures in boys with Duchenne muscular dystrophy. *Disabil Rehabil.* 2014;36(22):1918-1923.

83. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: Reliability, concurrent validity, and minimal clinically important differences from a multicenter study. *Muscle and Nerve.* 2013;48(3):357-368.

84. European Medicines Agency. Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. 2015; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf.

85. Mayhew AG, Cano SJ, Scott E, et al. Detecting meaningful change using the North Star Ambulatory Assessment in Duchenne muscular dystrophy. *Developmental Medicine & Child Neurology.* 2013;55(11):1046-1052.

86. Mazzone E, Messina S, Vasco G, et al. Reliability of the North Star Ambulatory Assessment in a multicentric setting. *Neuromuscular Disorders.* 2009;19(7):458-461.

87. Ekici B, Ergül Y, Tatlı B, et al. Being ambulatory does not secure respiratory functions of Duchenne patients. *Annals of Indian Academy of Neurology.* 2011;14(3):182-184.

88. Ergul Y, Ekici B, Nisli K, et al. Evaluation of the North Star Ambulatory Assessment scale and cardiac abnormalities in ambulant boys with Duchenne muscular dystrophy. *Journal of paediatrics and child health.* 2012;48(7):610-616.

89. Larkindale J, Abresch R, Aviles E, et al. Duchenne regulatory science consortium meeting on disease progression modeling for Duchenne muscular dystrophy. Paper presented at: Duchenne Regulatory Science Consortium2017.

90. McDonald C ME, Muntoni F, Selby K, Jin F, Panaghie-Meltzer G, ., et al. *Long-term pulmonary function outcomes in non-ambulatory patients with nonsense mutation duchenne muscular dystrophy treated with ataluren: 240-week data from an open-label extension study', in 15th International Child Neurology Congress, ICNC 2018 . Hotel Grand Hyatt, M: International Child Neurology Congress.* 2018.

91. Muntoni F, Desguerre I, Guglieri M, et al. Ataluren use in patients with nonsense mutation Duchenne muscular dystrophy: patient demographics and characteristics from the STRIDE Registry. *J Comp Eff Res.* 2019.

92. Bello L, Gordish-Dressman H, Morgenroth LP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology.* 2015;85(12):1048-1055.

93. Bello L, Kesari A, Gordish-Dressman H, et al. Genetic modifiers of ambulation in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study. *Ann Neurol.* 2015;77(4):684-696.

94. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *The Lancet Neurology.* 2010;9(2):177-189.

95. Straub V, Mercuri E, Aartsma-Rus A, et al. Report on the workshop: Meaningful outcome measures for Duchenne muscular dystrophy, London, UK, 30–31 January 2017. *Neuromuscular Disorders.* 2018;28(8):690-701.

96. Ricotti V, Muntoni F, Voit T. Challenges of clinical trial design for DMD. *Neuromuscul Disord.* 2015;25(12):932-935.

97. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *The Lancet.* 2018;391(10119):451-461.

98. Food and Drug Administration. Duchenne muscular dystrophy and related dystrophinopathies: Developing drugs for treatment. 2018; https://www.fda.gov/media/92233/download.

99. Pane M, Mazzone ES, Sivo S, et al. Long Term Natural History Data in Ambulant Boys with Duchenne Muscular Dystrophy: 36-Month Changes. *PLoS ONE.* 2014;9(10):e108205-e108205.

100. Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. *Neuromuscular Disorders.* 2010;20(11):712-716.

101. Essen AJV, Verheij JBGM, Reefhuis J, Fidler V, Jacobus H. The natural history of Duchenne muscular dystrophy . Analysis of data from a Dutch survey and review of age related events. *PhD thesis.* 1997.

102. McDonald CM. Physical Activity, Health Impairments, and Disability in Neuromuscular Disease. *American journal of physical medicine & rehabilitation.* 2002;81(11):108-120.

103. Bendixen RM, Senesac C, Lott DJ, Vandenborne K. Participation and quality of life in children with Duchenne muscular dystrophy using the international classification of functioning, disability, and health. *Health and Quality of Life Outcomes.* 2012;10(1):43.

104. Uzark K, King E, Cripe L, et al. Health-Related Quality of Life in Children and Adolescents With Duchenne Muscular Dystrophy. *Pediatrics.* 2012;130(6):e1559-e1566.

105. Szende A, Janssen B. Self-Reported Population Health: An International Perspective based on EQ-5D. Chapter 3. Population Norms for the EQ-5D. 2014.

106. Silva TD, Massetti T, Monteiro CB, et al. Pain characterization in Duchenne muscular dystrophy. *Arq Neuropsiquiatr.* 2016;74(9):767-774.

107. Zebracki K, Drotar D. Pain and activity limitations in children with Duchenne or Becker muscular dystrophy. *Dev Med Child Neurol.* 2008;50(7):546-552.

108. Pangalila RF, van den Bos GA, Bartels B, Bergen M, Stam HJ, Roebroeck ME. Prevalence of fatigue, pain, and affective disorders in adults with duchenne muscular dystrophy and their associations with quality of life. *Archives of physical medicine and rehabilitation.* 2015;96(7):1242-1247.

109. Williams K, Buesch K, Acaster S. Symptoms and impacts of nonsense mutation Duchenne muscular dystrophy at different stages of ambulation. *Future Neurology.* 2022:FNL55.

110. Hendriksen JG, Vles JS. Neuropsychiatric disorders in males with Duchenne muscular dystrophy: Frequency rate of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and obsessive-compulsive disorder. *Journal of child neurology.* 2008;23(5):477-481.

111. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol.* 2016;58(5):508-515.

112. de Moura MC, Wutzki HC, Voos MC, Resende MB, Reed UC, Hasue RH. Is functional dependence of Duchenne muscular dystrophy patients determinant of the quality of life and burden of their caregivers? *Arq Neuropsiquiatr.* 2015;73(1):52-57.

113. Bray P, Bundy AC, Ryan MM, North KN, Burns J. Health status of boys with Duchenne muscular dystrophy : A parent ' s perspective. *Journal of Paediatric Child Health.* 2011;47(8):557-562.

114. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol.* 2016b;58(5):508-515.

115. Landfeldt E, Lindgren P, Bell CF, et al. Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J Neurol.* 2016a;263(5):906-915.

116. Khan Ka, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. *PharmacoEconomics.* 2014;32(7):693-706.

117. Powell P, Carlton J, Woods H, Mazzone P. *Patient reported outcome measures of quality of life in Duchenne muscular dystrophy (DMD): a systematic review of content and structural validity using COSMIN.* University of Sheffield;2019.

118. McDonald CM, McDonald D, Bagley A, Sienko-Thomas M. Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. 2010;25(9):1130-1144.

119. The University of Sheffield. CHU9D - Measuring health and calculating QALYs for children and adolescents. Accessed 14 December 2021; Available at: https://licensing.sheffield.ac.uk/product/CHU-9D.

120. Peay H, Tibben A, Fisher T, Brenna E, BB. B. Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. *Clin Trials.* 2014;11(1):77-85.

121. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *The Lancet Neurology.* 2018;17(5):445-455.

122. Biggar WD, Harris Va, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscular Disorders.* 2006;16(4):249-255.

123. Moxley RT, Pandya S, Ciafaloni E, Fox DJ, Campbell K. Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. *Journal of child neurology.* 2010;25(9):1116-1129.

124. Ricotti V, Ridout Da, Scott E, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *Journal of neurology, neurosurgery, and psychiatry.* 2013;84(6):698-705.

125. McDonald C, Henricson E, Abresch R, et al. The cooperative international neuromuscular research group duchenne natural history study-a longitudinal investigation in the era of glucocorticoid therapy: Design of protocol and the methods used. *Muscle and Nerve.* 2013;48(1):32-54.

126. National Institute for Health and Care Excellence. ddendum to Managed Access Agreement Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD) in patients aged between 2 years and 5 years. Available at: https://www.nice.org.uk/guidance/hst3/resources/addendum-to-managed-access-agreement-pdf-6779076589. Accessed 26 October 2021. 2019.

127. National Institute for Health and Care Excellence (NICE). *Addendum to Managed Access Agreement. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3). Available at: https://www.nice.org.uk/guidance/hst3/resources/addendum-to-managed-access-agreement-pdf-6779076589 (Accessed: 28 Apr 2021).* 2019.

128. Muntoni F, Buccella F, Desguerre I, et al. Poster EP.141: Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry. 26th International Annual

Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24 2021.

129. Michael E, Sofou K, Wahlgren L, Kroksmark AK, Tulinius M. Long term treatment with ataluren-the Swedish experience. *BMC Musculoskelet Disord.* 2021;22(1):837.

130. McDonald CM, Muntoni F, Penematsa V, et al. Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients. *J Comp Eff Res.* 2021.

131. Tian C KR, O'Mara E, Trifillis P, McIntosh J, Renfroe J. *Ataluren in patients aged ≥2 to <5 years with nonsense mutation Duchenne muscular dystrophy (nmDMD): 28-week results from a Phase 2 study.* Neuromuscular Diseases, Vienna, Austria 6-10 July 2018 2018.

132. Ebrahimi-Fakhari D, Dillmann U, Flotats-Bastardas M, et al. Off-Label Use of Ataluren in Four Non-ambulatory Patients With Nonsense Mutation Duchenne Muscular Dystrophy: Effects on Cardiac and Pulmonary Function and Muscle Strength. *Front Pediatr.* 2018;6:316.

133. Ruggiero L, Iodice R, Esposito M, et al. One-year follow up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: is earlier better? *Ther Adv Neurol Disord.* 2018;11:1756286418809588.

134. Bazancir Z, Aslan M, Güng R, Talu B. Ataluren and physiotherapy in a boy with nonsense mutation Duchenne muscular dystrophy: 2 years' follow up case report. *Acta Myologica.* 2018;37:342-348.

135. Blaschek A, Rodrigues M, Ille L, et al. Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy? *Neuropediatrics.* 2020;51(5):342-348.

136. NICE. NICE DSU TECHNICAL SUPPORT DOCUMENT 17:

THE USE OF OBSERVATIONAL DATA TO INFORM ESTIMATES OF

TREATMENT EFFECTIVENESS IN TECHNOLOGY APPRAISAL:

METHODS FOR COMPARATIVE INDIVIDUAL PATIENT DATA. 2015;Decision support unit.

137. The Cooperative International Neuromuscular Research Group (CINRG). www.cinrgresearch.org. Accessed: 24 August 2021.

138. McMurry TL, Hu Y, Blackstone EH, Kozower BD. Propensity scores: Methods, considerations, and applications in the Journal of Thoracic and Cardiovascular Surgery. *J Thorac Cardiovasc Surg.* 2015;150(1):14-19.

139. Goemans N, Signorovitch J, Sajeev G, et al. Suitability of external controls for drug evaluation in Duchenne muscular dystrophy. *Neurology.* 2020.

140. Angelini C, Peterle E. Old and new therapeutic developments in steroid treatment in Duchenne muscular dystrophy. *Acta Myol.* 2012;31(1):9-15.

141. Duboc D, Meune C, Pierre B, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J.* 2007;154(3):596-602.

142. Goemans N, Kirschner J, Mercuri E. New perspectives in the management of duchenne muscular dystrophy. *European Neurological Review.* 2014;9(1):78-82.

143. Mercuri E, R. Quinlivan, Tuffery-Giraud S. Early diagnosis and treatment – the use of ataluren in the effective management of Duchenne muscular dystrophy. *European Neurological Review.* 2018;13(1):31-37.

144. Ferizovic N, Summers J, Beitia I, Werner C, Jiang J. Disease Progression Indicators in Duchenne Muscular Dystrophy for Use in Matched Analyses Comparing Treatment Effects: A Targeted Literature Review. Abstract ID# 107126. ISPOR Europe 2020 14-16th November. 2020.

145. Inacio MC, Chen Y, Paxton EW, Namba RS, Kurtz SM, Cafri G. Statistics in Brief: An Introduction to the Use of Propensity Scores. *Clin Orthop Relat Res.* 2015;473(8):2722-2726.

146. PTC Clinical Study Report. PTC124-GD-020-DMD. A phase 3 efficacy and safety study of ataluren in patients with nonsense mutation dystrophinopathy. 2015.

147. Ptc. Data on file. Manuscript under review for publication under title: Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients. Submitted to Journal of Comparative Effectiveness Research in 2021. 2021.

148. PTC Therapeutics. *PTC124-GD025o-DMD Statistical Anlaysis Plan (31January 2021 Datacut): Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care.* 2021.

149. NorthStar Clinical Network & PTC Therapeutics. Statistical Analysis Plan, Version 4.2, Managed Access Agreement: Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)

2021.

150. PTC Clinical Study Report. *PTC124-GD-007. A Phase 2B efficacy and safety study of PTC124 in subjects with nonsense-mutation mediated Duchenne and Becker muscular dystrophy.* 2014.

151. PTC Clinical Study Report. *PTC124-GD-030-DMD. A phase 2 study of the safety, pharmacokinetics, and pharmacodynamics of ataluren (ptc124) in patients aged ≥2 to <5 years old with nonsense mutation dystrophinopathy*

2018.

152. Muntoni F, Tulinius M, Buccella F, et al. Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial. Presented at the 26th International Annual Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24, 2021 (Abstract #535). 2021.

153. PTC Clinical Study Report. PTC124-GD-025o-DMD. Long-term observational study of Translarna safety and effectiveness in usual care. Interim clinical study report. 04 February 2019.

154. PTC Clinical Study Report. *PTC124-GD-007-DMD. A phase 2b efficacy and safety study of PTC124 in subjects with nonsense-mutation-mediated Duchenne and Becker muscular dystrophy.* 14 November 2014.

155. PTC. *Ataluren 020e datacut.* 2016.

156. Mazzone ES, Coratti G, Sormani MP, et al. Timed rise from floor as a predictor of disease progression in Duchenne muscular dystrophy: An observational study. *PLOS ONE.* 2016;11(3):e0151445.

157. Ptc. *Data on file. CINRG patient disposition in the STRIDE/CINRG propoensity score matched analysis (January 2021 datacut).* 2021.

158. PTC Therapeutics. *Data on file: MAA analysis tables.* February 2022.

159. PTC Therapeutics. *NICE MAA Results Summary (North Star review).* February 2022.

160. European Medicines Agency. Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006. 2019. Available at: https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-p46-0025-epar-assessment-report_en.pdf. Accessed 21 November 2021.

161. Food and Drug Administration. Guidance for Industry: Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM450229.pdf. 2015; https://www.fda.gov/media/92233/download.

162. Gulati S, Saxena A, Kumar V, Kalra V. Duchenne muscular dystrophy: prevalence and patterns of cardiac involvement. *Indian journal of pediatrics.* 2005;72(5):389-393.

163. Finkel RS. Read-through strategies for suppression of nonsense mutations in Duchenne/ Becker muscular dystrophy: aminoglycosides and ataluren (PTC124). *J Child Neurol.* 2010;25(9):1158-1164.

164. Yiu EM, Kornberg AJ. Duchenne muscular dystrophy. *Journal of paediatrics and child health.* 2015;51(8):759-764.

165. Ward LM, Weber DR. Growth, pubertal development, and skeletal health in boys with Duchenne Muscular Dystrophy. *Curr Opin Endocrinol Diabetes Obes.* 2019;26(1):39-48.

166. Williams K, Buesch K, Piglowska N, Acaster S. Symptoms and Impacts of Nonsense Mutation Duchenne Muscular Dystrophy at Different Stages of Ambulation. Abstract accpeted for ISPOR Europe 16-19 November 2020. 2020.

167. Landfeldt E, Alfredsson L, Straub V, Lochmüller H, Bushby K, Lindgren P. Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. *Pharmacoeconomics.* 2017;35(2):249-258.

168. Powell PA, Carlton J, Woods HB, Mazzone P. Measuring quality of life in Duchenne muscular dystrophy: a systematic review of the content and structural validity of commonly used instruments. *Health Qual Life Outcomes.* 2020;18(1):263.

169. Landfeldt E, Lindberg C, Sejersen T. Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy. *Muscle Nerve.* 2020;61(3):363-368.

170. Landfeldt E, Zhang R, Childs AM, et al. Draft Manuscript: Assessment of face validity of a cost-effectiveness model of nonsense mutation Duchenne muscular dystrophy: a multi-national Delphi panel study. 2022.

171. Péntek M, Baji P, Pogány G, Brodszky V, Boncz I, Gulácsi L. Health Related Quality of Life of Patients and Their Caregivers In Rare Diseases Results of the Burqol-Rd Project In Hungary. *Value Health.* 2014;17(7):A538.

172. Péntek M, Herczegfalvi Á, Molnár MJ, et al. [DISEASE BURDEN OP DUCHENNE MUSCULAR DYSTROPHY PATIENTS AND THEIR CAREGIVERS]. *Ideggyogy Sz.* 2016;69(5-6):183-193.

173. Otto C, Steffensen BF, Højberg AL, et al. Predictors of Health-Related Quality of Life in boys with Duchenne muscular dystrophy from six European countries. *J Neurol.* 2017;264(4):709-723.

174. Otto C, Steffensen BF, Rahbek J, et al. Predictors of health-related quality of life in boys with Duchenne muscular dystrophy from six European countries. *Quality of Life Research.* 2016;25:101.

175. Audhya I RB, Szabo SM, Feeny D, Gooch KL. Health-related quality of life (HRQOL) associated with duchenne muscular dystrophy (DMD): A study using the health utilities index mark 3 (HUI3). . Paper presented at: MDA Conference 2021.

176. Crossnohere N, Fischer R, Bridges J. PRO86 HEALTH STATE UTILITY VALUES FOR STAGES OF FUNCTIONAL DECLINE IN DUCHENNE MUSCULAR DYSTROPHY: AN INTERNATIONAL STUDY. *Value in Health.* 2020;23:S344.

177. Crossnohere N, Fischer R, Peay H, Bridges JFP. PRO51 Responsiveness and acceptability of the EQ-5D to an International rare disease community. *Value in Health.* 2019;22:S344-S345.

178. Crossnohere NL, Fischer R, Lloyd A, Prosser LA, Bridges JFP. Assessing the Appropriateness of the EQ-5D for Duchenne Muscular Dystrophy: A Patient-Centered Study. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2021;41(2):209-221.

179. Gallop K FD, Lawrence C, Denjean E, Van Der Wild J, Acaster S. PMS61 Estimation of Health Utilities for NON-Ambulatory Duchenne Muscular Dystrophy (DMD) Patients and Their Caregivers. *Value in Health.* 2020;23.

180. Rowen D, Powell P, Mukuria C, Carlton J, Norman R, Brazier J. Deriving a Preference-Based Measure for People With Duchenne Muscular Dystrophy From the DMD-QoL. *Value Health.* 2021;24(10):1499-1510.

181. Szabo SM Al, Rogula B, Feeny D, Johnston K, Gooch KL. Health-related quality of life (HRQOL) associated with duchenne muscular dystrophy (DMD): A study using the health utilities index mark 3 (HUI3). Paper presented at: MDA Conference 2021.

182. Bhullar G, Wei Y, El Aloul B, Speechley K, Miller M, Campbell C. E-POSTERS - DMD - OUTCOME MEASURES: EP.81Quality of life and fatigue in Duchenne muscular dystrophy: perception of boys and their caregivers. *Neuromuscular Disorders.* 2019;29 (Supplement 1):S176.

183. Davidson ZE, Hughes I, Ryan MM, et al. Effect of a multicomponent nutritional supplement on functional outcomes for Duchenne muscular dystrophy: a randomized controlled trial. *Clinical nutrition (Edinburgh, Scotland).* 2021;40(7):4702-4711.

184. Jacques MF, Stockley RC, Onambele-Pearson GL, et al. Quality of life in adults with muscular dystrophy. *Health and Quality of Life Outcomes.* 2019;17(1).

185. Koken OY, Kucur O, Taskiran C, et al. Clinical features and quality of life in duchenne and becker muscular dystrophy patients from a tertiary center in Turkey. *Guncel Pediatri.* 2021;19(1):15-22.

186. Liang R, Chan SH, Ho FK, et al. Health-related quality of life in Chinese boys with Duchenne muscular dystrophy and their families. *Journal of child health care : for*

professionals working with children in the hospital and community. 2019;23(3):495-506.

187. Powell PA, Carlton J, Rowen D, Chandler F, Guglieri M, Brazier JE. Development of a New Quality of Life Measure for Duchenne Muscular Dystrophy Using Mixed Methods. *Neurology.* 2021;96(19):e2438.

188. Tapawan SJC, Wang FS, Lee MW, et al. Perspectives on Palliative Care Among Duchenne Muscular Dystrophy Patients and Their Families in Singapore. *Ann Acad Med Singapore.* 2020;49(2):72-77.

189. Campbell C, McColl E, McDermott Mp MWB, Guglieri M, Griggs RC, Nmd MSGT. Health related quality of life in young, steroid-naive boys with Duchenne muscular dystrophy. *Neuromuscular Disorders.* 2021;10:10.

190. Alemdaroglu-Gurbuz I, Bulut N, Bozgeyik S, et al. Reliability and validity of the turkish translation of pedsqlTM multidimensional fatigue scale in duchenne muscular dystrophy. *Neurosciences.* 2019;24(4):302-310.

191. Euctr DE. Clinical Trial to Evaluate the Efficacy, Safety, and Tolerability of RO7239361 (BMS-986089) in Ambulatory Boys With Duchenne Muscular Dystrophy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-001654-18-DE*. 2017.

192. Siegel BI, Cakmak A, Reinertsen E, et al. Use of a wearable device to assess sleep and motor function in Duchenne muscular dystrophy. *Muscle and Nerve.* 2020;61(2):198-204.

193. Carlton R RT, Narayanan S,. The economic impact of deflazacort for the treatment of duchenne muscular dystrophy. *Journal of Managed Care and Specialty Pharmacy.* 2018a;24:S90-S91.

194. Carlton R, Regan T, Narayanan S. PSY34 - The Budget Impact of Deflazacort for the Treatment of Duchenne Muscular Dystrophy (DMD). *Value in Health.* 2018b;21:S250.

195. Fabriani V, Marcellusi A, Mennini FS, Giannantoni P. Cost of Illness Analysis of Duchenne Muscular Dystrophy In Italy. *Value Health.* 2014;17(7):A528.

196. Magnetta DA KJ, Wearden PD, Smith KJ, Feingold B. Cost-effectiveness of ventricular assist device destination therapy for advanced heart failure in duchenne muscular dystrophy. *Acta Myologica* 2016;33(3):136-143.

197. Magnetta DA, Kang J, Wearden PD, Smith KJ, Feingold B. Cost-Effectiveness of Ventricular Assist Device Destination Therapy for Advanced Heart Failure in Duchenne Muscular Dystrophy. *Pediatr Cardiol.* 2018;39(6):1242-1248.

198. Agboola F, Lin GA, Fluetsch N, Walton SM, Rind DM, Pearson SD. The Effectiveness and Value of Deflazacort and Exon-Skipping Therapies for the Management of Duchenne Muscular Dystrophy. *J Manag Care Spec Pharm.* 2020;26(4):361-366.

199. Quach D, Boyer N, Samur S, et al. PMS57 IS DEFLAZACORT A COST-EFFECTIVE TREATMENT FOR DUCHENNE MUSCULAR DYSTROPHY? *Value in Health.* 2019;22:S704.

200. Nelson L, Curry A, Henry A, Horsburgh S, Filipovic Audhya I, Gooch K. PMS71 DELAYING THE PROGRESSION OF DUCHENNE MUSCULAR DYSTROPHY; IMPACT ON QUALITY OF LIFE AND WORK PRODUCTIVITY. *Value in Health.* 2020;23:S228.

201. Office for National Statistics. National Life Tables, 2017-2019. 2020.

202. Average weight of a man. 2022; https://www.onaverage.co.uk/body-averages/average-weight-of-a-man.

203. Formulary BN. Ataluren - Medicinal forms. 2022.

204. NICE. NICE health technology evaluations: the manual. *Process and methods [PMG36].* 2022.

205. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). *European journal of human genetics : EJHG.* 2013;21(10):1049-1053.

206. Office for National Statisitcs. Births in England and Wales 2020. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2020#:~:text=There%20were%20613%2C936%20live%20births,to%201.58%20children%20per%20woman. 2021.

207. Bladen CL, Salgado D, Monges S, et al. The TREAT-NMD DMD global database: Analysis of More than 7,000 Duchenne Muscular Dystrophy Mutations. *Human Mutation.* 2015;36(4):395-402.

208. Rodger S, Woods KL, Bladen CL, et al. Adult care for Duchenne muscular dystrophy in the UK. *Journal of Neurology.* 2015;262(3):629-641.

17 Appendices

All appendices are provided as separate documents.

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined

- copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- a PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up-to-date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology appraisal

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

Clarification questions

29th March 2022

File name	Version	Contains confidential information	Date
ID1642 ataluren nmDMD clarification letter to PM for company AIC - Company responses v2.0 (26APR2022)	**Version 1**	**Yes**	**30/03/2022**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Searches

A1. Company's submission (CS) Appendix 3 and Appendix 5. Please confirm the source of the filters used to identify evidence relevant to the reviews of economic analyses and health-related quality of life (HRQoL) studies, providing a citation to any published validation studies (where available).

Company response:

SLR searches were conducted for Medline and Embase using the Ovid interface and syntax.

When setting up the search strategies for the SLR, established study filters presented by SIGN (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) were used to identify QoL, cost-effectiveness and resource use data in the DMD population where possible/available.

Search terms for the economic reviews were adapted from the published SIGN economic filter (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). For the Medline economic search, adaptations included exploding the economics/ subject

heading, removing limits from the term “cost”, adding the term “resource” and not including “fiscal” or “funding” or “financial” or “finance” or “price$” or “pricing”.

Search terms for HRQoL were developed by the SLR project team (in the absence of a standard filter), using key subject headings for quality of life (such as “exp quality of life/”) and both broad (such as “quality of life.mp.”) and specific (such as “eq5d”) free text terms.

Clinical effectiveness evidence

A2. CS Section 9.5, page 85 and Appendix 17.1, Section 17.1.4; and Section 11.2.2, page 195 and Appendix 17.3, Section 17.3.4. Please confirm if data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review (original and updated) in the clinical and cost sections. If not, please justify.

Company response:

As stated in CS Appendix 17.1, Section 17.1.4 and Appendix 17.3, Section 17.3.4, the relevance of studies identified using the selection criteria was reviewed independently by two reviewers, with disagreements discussed and an additional review by a third independent reviewer if required. Similarly, data extraction and quality assessment were performed by two independent reviewers. The same procedure was undertaken for both the original and updated systematic literature review.

A3. CS Appendix 17.1, Section 17.1.4, Table 6, page 13. Please clarify why the company’s original 2016 clinical review included existing systematic reviews/meta-analyses (Table 7) but excluded these from the company’s updated clinical review (Table 10).

Company response:

The company understands that this question relates to the fact that the study by Campbell et al. (2020)[1] was mistakenly presented on the table of excluded papers in the company’s updated submission (17.1. Appendix 1: Search strategy for clinical evidence). The company would like to clarify that this study is included throughout the updated submission (as outlined below) and was only incorrectly presented in the excluded table in the appendix write-up.

The following sections in the updated submission present/discuss data from the study by Campbell et al. (2020)[1]:

- Impact of the new technology (page 14)
- 9.3.1.1 Ataluren clinical study overview (pages 57–58)
- 9.6.1.1 Summary of comparative efficacy data (page 96)
- 9.7.2.1 Overview of placebo-controlled clinical trial adverse reactions (page 138)
- 9.8.1.2 Post-hoc meta-analysis of studies 007 and 020 (pages 149–154)
- 9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology (page 157)

A4. CS, Section 9.3.1.2, page 58. Please comment on the concerns noted in the CHMP extension of indication variation (Procedure No. EMEA/H/C/002720/II/0037) evaluation on matching inconsistencies, robustness and effect size of the observed efficacy results in Study 030 and the external control CINRG data, including any influence caused by concomitant steroid use.

Company response:

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) extension of indication variation assessment report discusses possible limitations of the study 030/Cooperative International Neuromuscular Research Group (CINRG) analysis used to support the extension of indication to patients 2 years and older in Europe.[2]

The report comments that following matching between patients from Study 030 and the CINRG cohort, patients were well matched based on age, sex, height and BMI, but showed differences in weight and steroid use. Differences in weight may have contributed to different doses of corticosteroids received. Additionally, more patients in the Study 030 cohort received steroids (42.9%) compared to the matched CINRG cohort (29%).[2] PTC accept that imbalances in steroid use may influence disease progression, but higher rates of steroid use may also likely negatively contribute

towards the safety and tolerability profile of ataluren patients when comparing the two groups. Also, patients who started on steroids earlier within Study 030 cohort compared to the matched CIRNG patients may be those patients showing symptoms earlier, and could in fact be more severe based on earlier onset of symptoms.

It should also be noted that efficacy considerations were not the primary focus of the investigation. The primary outcomes from the Study 030 were focused on safety, pharmacokinetics, and pharmacodynamics of ataluren in participants aged 2 to 5 years of age.[3]

It is very difficult to demonstrate meaningful treatment benefit associated with ataluren in patients within this age subgroup over a follow up period of 60 weeks.

Children with DMD tend to improve overall mobility and muscular functionality up to the age of approximately 7 years due to the maturation process in young children, although the rate of improvement is hindered compared to healthy controls.[4] The influence of natural maturation, which may occur at different rates in different children, makes it difficult to isolate treatment effect when assessing mobility functionality such as with the 6 minute walk test. This is further impeded by the fact that it is not always possible to take robust measures of functionality using tests such as the 6 minute walk test or the NSAA in children so young, who may not be physically or cognitively capable of engaging fully in the functionality assessments.

When considering the gradual nature of disease progression at this age, a 60 week follow up period in patients is unlikely to be long enough to show a meaningful reduction in the rate of decline in physical function.

Despite these intrinsic challenges when attempting to assess comparative clinical efficacy for DMD within a clinical trial framework in patients so young, the results of the analyses did demonstrate a trend towards improved functionality in patients who received ataluren when compared to matched controls.[2]

Overall, the study was successful in providing sufficient evidence of the safety, tolerability, and treatment benefit associated with ataluren in this population to warrant an extension of the European licence to patients aged 2 and above.[2] Ataluren is the only approved causal treatment in nmDMD. It is the only treatment for nmDMD to date,

which has provided sufficient evidence to regulators to be recommended for clinical use, when other treatments have failed to achieve this. This further highlights the intrinsic challenges associated with successfully demonstrating meaningful treatment benefit and the importance of ataluren as an effective treatment option.

A5. CS, Section 9.3.1.5, page 59. The CS excludes three case series and one cohort study identified by the searches. These studies appear to have met the inclusion criteria for the systematic review (CS Appendix 17.1, section 17.1.4, Table 7). Please explain why these studies have been excluded.

Company response:

These studies were not included because they either evaluated a small number of patients (case studies) or assessed the effect of ataluren in a non-specific manner (cohort study), as summarised in Table 1. Although Ebrahimi et al., Ruggiero et al. and Bazancir et al. report pulmonary and performance test outcomes, these are case studies including a small number of patients and, as such, were considered to provide a low level of evidence and hence were not included in the submission. Ebrahimi et al also focusing on non-ambulatory patients so did not fit the population criterion. The study by Blaschek et al., (2020) is a cohort study which also only focused on a small number of ataluren treated patients. The primary focus of the study was the impact of many factors on exercise-induced fatigue, which was considered to be too unspecific and was therefore not included in the submission.

Table 1: Summary of excluded studies

Study reference	Title	Efficacy results	Safety results
Ebrahimi et al., 2018	Off-Label Use of Ataluren in Four Non-ambulatory Patients with Nonsense Mutation Duchenne Muscular Dystrophy: Effects on Cardiac and Pulmonary Function and Muscle Strength	Results (mean, standard deviation) are only presented for baseline to Time Period 2 Left ventricular fractional shortening (LVFS) (%): • Baseline: Mean 28.5 ± 2.6 • Time period 2: Mean change 0.5 ± 2.9	There were no adverse events. A possible side-effect was a reduction in body mass index

Study reference	Title	Efficacy results	Safety results
		Forced vital capacity (FVC) (%): • Baseline: Mean 39.6 ± 8.4 • Time period 2: Mean change 1.9 ± 9.7 FVC (L): • Baseline: Mean 1.29 ± 0.21 • Time period 2: Mean change 0.19 ± 0.33	
Ruggiero et al., 2018	One-year follow up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: is earlier better?	Case 1: • 6-minute walk distance (m): Baseline: 360; 3 months: 303; 6 months: 375; 9 months: 400;12 months: 370 • Timed 10m run/walk (s): Baseline: 10; 3 months: 6.5; 6 months: 7.5; 9 months: 6.7; 12 months: 7.5 • Timed four-stair ascend (s): Baseline: 7.0; 3 months: 7.2; 6 months: 7.5; 9 months: 8.3; 12 months: 7.6 • Timed four-stair descend (s): Baseline: 4.5; 3 months: 6.1; 6 months: 5.2; 9 months: 5.5; 12 months: 5.5 • Time stand from supine (s): Baseline: 35; 3 months: 26; 6 months: 25; 9 months: 16; 12 months: 44 Case 2: • 6-minute walk distance (m): Baseline: 64; 3 months: 100; 6 months: 101; 9	Ataluren was generally well tolerated, and no adverse events reported

Study reference	Title	Efficacy results	Safety results
		months: 119; 12 months: 118 • Timed 10m run/walk (s): Baseline: 30; 3 months: 19; 6 months: 22; 9 months: 16; 12 months: 17. The patient was unable to perform the remainder of the tests Case 3: • 6-minute walk distance (m): Baseline: 320; 3 months: 330; 6 months: 355; 9 months: 409; 12 months: 400; • Timed 10 run/walk (s): Baseline: 10; 3 months: 5.6; 6 months: 5.9; 9 months: 6.8; 12 months: 8.6; • Timed 4-stair ascend (s): Baseline: 14; 3 months: 10; 6 months: 11; 9 months: 15; 12 months: 14; • Timed 4-stair descend (s): Baseline: 9; 3 months: 9; 6 months: 10; 9 months: 9.7; 12 months: 10 • Timed stand from supine (s): Baseline: 4.5; 3 months: 5.6; 6 months: 4.2; 9 months: 5; 12 months: 7	
Bazancir et al., 2018	Ataluren and physiotherapy in a boy with nonsense mutation Duchenne muscular dystrophy:	After ataluren and physiotherapy, timed performance tests were shorter, North Star Ambulatory Assessment (NSAA) score rose from 22 to 28 and six-minute walk test (6MWT) distance increased	Not reported

Study reference	Title	Efficacy results	Safety results
	2 years' follow up case report	from 390 to 525. Timed up and go (TUG) test increased from 8.11 to 5.93 and 1 minute sit and stand test increased from 20 to 25. Thirty second calf raise test improved from 20 to 36. Visual analogue score (VAS) score was decreased from 3 to 0	
Blaschek et al., 2020	Is Exercise-Induced Fatigue a Problem in Children with Duchenne Muscular Dystrophy?	Nine patients received ataluren therapy (of a cohort of 55 Duchenne Muscular Dystrophy (DMD) patients) Ataluren therapy did not show an impact on fatigue in DMD patients, along with age, steroid therapy, overall disability or distance in the 6MWT	Not reported

A6. Priority. CS, Section 9.4.1.6, page 72. Please clarify how many patients in STRIDE initiated treatment with ataluren when they were less than 5 years of age. If available, please also provide a distribution of age at initiation of ataluren in STRIDE.

Company response:

As of January 2021, [redacted] patients in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) registry had initiated treatment when they were less than 5 years of age[5]. A full distribution of ages at ataluren initiation is presented in Table 2.

Table 2: Age at treatment initiation in the STRIDE registry

Statistic	Evaluable			Effectiveness (N=241)	Ambulatory (N=244)	Non-Ambulatory (N=66)
	Total (N=269)	≥2 to <5 Years (n=20)	≥5 Years (n=249)			
Age at treatment start date in the Registry (years)						

Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group at treatment start in the Registry, n (%)						
<5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5 to <7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥7 to <10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10 to <15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A7. CS, Section 9.4.1.6, page 72. Please clarify how many patients in STRIDE continued to receive ataluren treatment beyond loss of ambulation and for how long treatment continued beyond this timepoint. Please also comment on the extent to which the stopping criteria in STRIDE reflect the proposed stopping rule employed in the economic model.

Company response:

[redacted] participants reached the loss of ambulation milestone in the STRIDE registry as of January 2021. [redacted] treatment discontinuations/dose changes occurred during the study, of which [redacted] were due to loss of ambulation. The remaining [redacted] discontinuing/dose adjusted patients were not stratified by ambulatory status. Therefore, potentially up to [redacted] out of [redacted] ([redacted]%) non-ambulatory patients continued ataluren treatment beyond loss of ambulation, or at least did not explicitly discontinue due to loss of ambulation (LoA).

The stopping criteria agreed as part of the Managed Access Agreement (MAA), which stipulates that patients should discontinue ataluren by 6 months after LoA, was largely not adhered to in STRIDE as the majority of non-ambulatory participants continued ataluren treatment beyond loss of ambulation and the MAA was specific only to patients in England. The proposed stopping rule, which has been implemented in the economic model, allows patients to remain on treatment until they require night-time ventilation support, estimated by a predicted FVC (pFVC) < 50%. Within the STRIDE cohort, only [redacted] of [redacted] non-ambulatory patients reached the pFVC < 50% endpoint, and only [redacted] patient reached the pFVC < 30% endpoint (see response to question **B5**). By this measure, most patients remained on treatment beyond LoA, but very few patients remained on treatment beyond achieving a pFVC < 50% (because they have

not yet reached this endpoint, or a later endpoint). Therefore, a treatment stopping criteria of pFVC < 50% most closely aligns with the treatment patterns observed in the STRIDE registry, the clinical data used to inform the economic analysis.

A8. Priority. CS, Section 9.4.1.6, page 74 and Section 12.2.1, page 209. The CS states that [redacted] patients discontinued ataluren (within the STRIDE dataset). Please provide further details about why these registry participants discontinued treatment e.g., due to AEs, loss of ambulation (LoA), loss of other milestones or patient choice.

Company response:

Firstly for clarity, the stated value of [redacted] patients discontinuing ataluren during follow up within STIRDE is accurate as of the 2020 data cut. As of January 2021, [redacted] patients in the STRIDE registry had discontinued ataluren treatment or changed dose. The distribution of participants by reason for discontinuation is presented in Table 3.

Table 3: Cause of study and treatment discontinuation in the STRIDE study as of January 2021

Disposition	All (N=269) n (%)
Stop Translarna or changed dose:	[redacted]
Adverse events	[redacted]
Family/participant request	[redacted]
Non-response	[redacted]
Physician decision	[redacted]
Loss of ambulation	[redacted]
Other	[redacted]

A9. Priority. CS, Executive summary, page 11. Please clarify the evidence available to support the continued use of ataluren beyond the Managed Access Agreement (MAA) i.e., longer than LoA plus up to 6 months. Is this limited to the 13 patients in the Compassionate Use Programme and expert opinion?

Company response:

The extension of the stopping criteria beyond LoA was influenced by a number of factors, in addition to those stated in the question.

Primarily, it is suspected that genuine treatment benefit will continue to be experienced by patients who remain on treatment beyond LoA. Ataluren stimulates dystrophin production within all muscular systems, including upper limb muscles and the muscles

that support pulmonary and cardiac function. There is no clinical rationale to suggest that treatment with ataluren beyond LoA will not continue to reduce the rate of decline in the functionality of upper limb muscles and the muscles that support pulmonary and cardiac function. Moreover, UK clinicians were clear that they would encourage continued use of ataluren beyond LoA (see response to question **B19**).

Additionally, the primary clinical evidence base for ataluren within the company submission was sourced from patients within the STRIDE registry. STRIDE is a multicentre registry with patients from all across Europe and in Israel. As mentioned in response to question **A7**, of [redacted] ataluren patients who lost ambulation, only [redacted] discontinued treatment due to LoA. For this reason, the evidence from STRIDE used to inform the probability of reaching the non-ambulatory health states is primarily informed by patients who remained on ataluren. It is suspected that additional benefit may have been received in these patients contributing to further delays in reaching later health states.

At this moment PTC is unable to provide long-term data which demonstrates the magnitude of the benefit associated with continued treatment with ataluren beyond LoA. This is due to the limited number of patients who have reached later pulmonary function health states within the STRIDE dataset, and a very small number of patients who discontinued due to LoA (approximately [redacted] out of 241) for comparison. Adjusting the economic analysis to continue to apply treatment costs after LoA more closely aligns with what was experienced in the patients who inform the clinical parameters, and therefore avoids any potential bias of "free treatment benefit".

When considering supportive clinical opinion, real-world usage data, and ensuring the economic model avoids bias, it was decided a later stopping criteria until the need for night-time ventilation (proxy of pFVC < 30%) would be more appropriate than the stopping criteria specified within the MAA of within 6 months after LoA.

A10. Priority. CS, Executive summary, page 11. The current marketing authorisation for ataluren is in patients who are ambulatory. Please clarify if the proposed stopping rule would require an extension to the existing licence.

Company response:

The existing EMA licence would not require an extension to cover the proposed stopping rule. The current licensed indication specifies that "Translarna is a medicine that is used to treat patients aged 2 years and older with Duchenne muscular dystrophy who are able to walk.[6]" As discussed previously, Translarna is a dystrophin restoration therapy and as such restores dystrophin in all muscle types within the body. Long-term real-world data from STRIDE show that patients treated with Translarna preserve vital pulmonary function when compared to control patients within CINRG. In order to gain most benefit from treatment patients should commence therapy early (from 2 years) while ambulatory.

The current licence requires that treatment initiation occurs in ambulatory patients but does not specifically detail a stopping rule or prohibit patients continuing treatment beyond LoA. The EMA states "There were no apparent differences in either steady-state relative bioavailability or apparent clearance due to loss of ambulation. No dosing adjustment is needed for patients who are becoming non-ambulatory" and the indication was modified in July 2020 to remove the statement "Efficacy has not been demonstrated in non-ambulatory patients".[7,8]

In addition, as discussed in response to questions **A7** and **A9**, [redacted]% of patients from a number of European centres (including the UK, see **Error! Reference source not found.** 4) from within the STRIDE registry remained on ataluren despite LoA. This offers clear indication that European clinicians support the use of ataluren beyond LoA due to observed additional treatment benefit, and no other treatment options available.

The breakdown of the number of patients from each country within STRIDE is presented in Table 4**Error! Reference source not found.**.

Table 4: STRIDE enrolment by country

Country	All (N=269) n (%)
Austria	[redacted]
Czech Republic	[redacted]
France	[redacted]
Germany	[redacted]
Greece	[redacted]
Hungary	[redacted]

Israel	[redacted]
Italy	[redacted]
Latvia	[redacted]
Portugal	[redacted]
Romania	[redacted]
Sweden	[redacted]
United Kingdom	[redacted]

A11. CS, Section 9.4.1.6, page 72. Please provide further information on the completeness and accuracy of data in STRIDE. Please also comment on the frequency of protocol deviations, concomitant medication use and consistency of outcome definitions across sites.

Company response:

The STRIDE registry is the largest and most complete long-term real world evidence for patients receiving ataluren and is therefore the most appropriate dataset to inform the clinical parameters within the economic analysis.

When reviewing the completeness of the STRIDE dataset, consideration can be given to both the maturity of the data and the extent of missing data during follow up. Due to the timescale required to for a single patient to reach later disease milestones, only a small percentage of the STRIDE cohort reached these millstones. Please refer to Table 13 in response to question **B5** for the number of patients who reached each endpoint. This can partly be attributed to insufficient follow up duration as well as due to the delay in disease progression associated with successful treatment with ataluren. For this reason, it becomes challenging to assess the magnitude of treatment benefit caused by ataluren with regards to a delay in achieving pulmonary function disease milestones, as much of the treatment benefit is yet to be observed. PTC propose that the true delay in reaching more progressed disease milestones associated with successful ataluren treatment is longer than can be estimated using the most recent data from STRIDE. Therefore, the implementation within the economic analysis is a conservative estimate.

STRIDE is an ongoing study so data availability and maturity will increase overtime, which will provide more robust insights into the impact of ataluren treatment on disease progression.

When considering missing data, all observed data were used. Due to the nature of real world data collection, there were not pre-set, follow up points patients had to attend to provide assessments. When patients were assessed, the data was used to determine the age of a patient when/if they achieved the various disease milestones. Due to the gradual and progressive nature of DMD, sporadic follow up was sufficient to establish disease progression. Observations regarding time to LoA and decline in pulmonary function were recorded whenever clinical assessments took place. The time when a disease milestone was reached was recorded as the date of the first visit in which reaching this endpoint had been observed. For events that had not been observed by the end of the patients available follow up, the observed time was censored. The follow up approach does allow for a potential loss of accuracy as patients may have reached a disease milestone between two follow up points, and therefore the exact age of reaching that endpoint will not be recorded. Again, due to the gradual nature of disease progression, it is unlikely that any patients will have gaps between follow ups in which significant disease progression could take place unrecorded.

Deviations from informed consent procedures were recorded. None of the deviations were considered significant or presented a risk to patient safety.

[redacted] ([redacted]%) of the 266 evaluable patients received medication prior to ataluren initiation in the registry. [redacted] ([redacted]%) of the evaluable patients were reported to have at least one concomitant medication during follow up. The most commonly used concomitant medications were glucocorticoids, vitamin D and analogues, ACE inhibitors (plain), calcium, proton pump inhibitors, and laxatives. All other categories of concomitant medications were reported for <10% of patients overall. Among the patients with concomitant glucocorticoid use, deflazacort was the most common, followed by prednisolone and prednisone. As patients were well matched based on extent of corticosteroid use between the STRIDE and CINRG cohorts, it is assumed that concomitant medication use will not influence the treatment effectiveness comparisons between the matched cohorts.

When considering the consistency of outcome definitions across centres, efficacy measures including 6 minute walking distance, timed function tests, age at loss of ambulation, pulmonary function, and cardiac function were recorded as part of routine clinical practice. Evaluations were conducted as per usual care; there were no protocol-mandated procedures or diagnostic tests. However, in response to regulator feedback and with the goal of collecting a more robust set of efficacy data for this Registry, PTC undertook a multi-faceted approach to increasing consistency and completeness of efficacy data collection. In centres in which initiation occurred in 2017 or 2018 PTC required that sites commit to reporting a minimum set of efficacy assessments for each subject in the Registry, including 10-metre walk time, time to rise from floor, and pFVC, at the time of inclusion and at all follow-up visits. These assessments are validated, clinically relevant measures of disease outcomes in DMD that are widely used in clinical research to assess the effectiveness of interventional therapies. As a result of these initiatives, more complete reporting for efficacy measures was obtained.

A12. CS, Section 9.5.1, page 85. Please complete the ArRoWS critical appraisal tool for real world evidence (https://pubmed.ncbi.nlm.nih.gov/33011384/) for all registry sources discussed in the CS.

Company response:

Real world evidence discussed in the CS was obtained from the STRIDE, CINRG Duchenne Natural History Study (DNHS) and NorthStar registries. Critical appraisals of these studies using the Assessment of Real World Observational Studies (ArRoWS) critical appraisal tool are presented in

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
1. Is the research question or	Good - Three study objectives were provided: 1) obtain additional information	Good - The objectives of the study were to 1) study the relationship between impairment, activity	Good – The NorthStar registry was set up to agree protocols for assessment and best

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
objective(s) clear?	on all safety concerns being tracked in the risk management plan and long-term safety profile of Translarna; 2) Obtain additional information on the long-term effectiveness of Translarna; 3) Monitor the utilisation pattern of Translarna in usual care.	limitation, participation, and quality of life across a wide age range and spectrum of DMD disease severity using common clinical endpoints employed in clinical trials and novel outcome measures; 2) study the natural history of changes in measures of impairment, activity limitation, and quality of life over periods of 12 months to >5 years of follow-up; 3) examine the associations between both disease characteristics and the use of interventions and the onset of life altering clinical milestones that are due to the progression of disease; and 4) assess the incidence of secondary conditions of DMD and the relative risks of developing these conditions based on exposure to standard treatment (e.g., glucocorticoids) and preventive interventions recommended by the Centers for Disease Control and Prevention Care Considerations	practice treatment options for children with DMD. This included: • Assist clinicians working with muscle disease by developing a national clinical network and providing a discussion forum to promote best patient care. • Standardise and optimise steroid therapy in ambulant children with DMD throughout the UK. • Ensure a standard assessment protocol - for newly diagnosed children and those due to start corticosteroid treatment.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
2. Is the study sample representative of its target population?	Good - Patients with confirmed genetic diagnosis of nmDMD are eligible for inclusion if they are or will be receiving ataluren treatment. Patients receiving ataluren or placebo in an ongoing blinded or randomised clinical trial or any other clinical trial or access program that prevents participation in the study are excluded. Participants who meet the eligibility criteria and provide informed consent are invited through the prescriber's practice.	Good - Participants between 2 and 28 years of age were eligible for inclusion if they (or an older sibling for participants between the ages of 2 and 5 years) had a diagnosis of DMD supported by clinical evidence. Individuals with DMD were excluded from the study if they were glucocorticoid naïve and could ambulate without assistance beyond their 16th birthday or were currently on glucocorticoid therapy and could ambulate without assistance beyond their 16th birthday. The study aimed to recruit between 10 and 15 participants per year between 2 and 28 years of age.	Moderate - The registry population was representative of the UK clinical DMD population. 17 neuromuscular centres were sampled, and 513 ambulant patients were included in the analysis. Most patients had a genetic diagnosis of DMD. Inclusion and exclusion criteria were not described.
3. Has a sample size, power calculation or measure of uncertainty (e.gconfidence intervals, standard errors) been provided?	Yes - An initial enrolment target of 200 subjects was selected to allow statistically significant comparisons to be made while considering the small size of the nonsense-mutation DMD (nmDMD) population.	Yes - The sample size of the registry was 440 participants.	Yes - The sample size was 513 ambulant patients. 95% confidence intervals were also provided for age at LoA.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
	As of January 2021 the registry included 269 participants in the evaluable population. Continuous variables are summarised with standard deviation and confidence intervals.		
4. Are the exposure measures clearly defined and appropriate?	Good - Enrolled patients in STRIDE were/are or would/will be receiving ataluren at study start and treatment discontinuations had been/are captured across the study period.	Good - Historical and current glucocorticoid therapy was recorded at each assessment. As there was variation in glucocorticoid therapy, regimens were categorised into 3 exposure groups.	Good - All participants in the registry received daily or intermittent glucocorticoid therapy.
5. Is/are the outcome(s) clearly defined and appropriate?	Good - Three primary outcome measures are stated for the study: the percentage of participants with adverse events, the prescriber and participant compliance with prescribing information according to the approved labelling, and participant health	Good - The study outlined several physiological outcomes that were measured as well as patient reported HRQoL data.	Good - Disease progression outcomes were measured using the NSAA.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
	management measures. Efficacy outcomes were defined as the 6MWT, timed function tests, NSAA, and age at LoA, performance of upper limb, pulmonary function and cardiac function. These outcomes are relevant for clinical practice.		
6. Are confounders clearly defined and appropriate?	Good - Genotype, corticosteroid use, ambulatory status at baseline are important prognostic and potential treatment effect modifiers and were handled appropriately in the study protocol as per protocol, the efficacy of ataluren was assessed in study populations that accounted for important baseline and prognostic factors. The safety profile of ataluren was presented by corticoid use.	Good - Concomitant medications were recorded at each assessment.	Poor - The study did not report potential confounding variables,

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
7. Are the statistical analyses clearly defined and appropriate?	Good - Participants in the STRIDE registry were propensity-score matched against a sub-set of control participants in the CINRG DNHS registry on core prognostic indicators to allow for appropriate comparisons between ataluren and best standard care (BSC) treatment. Missing data were not included in the study report and observed data used for all analyses. Longitudinal efficacy analysis included only data for participants with at least 2 available assessments whose first and last assessments were than 40 or more weeks apart. Subgroup analysis was performed by age-group and ambulation status. Appropriate statistical	Moderate - Time to disease milestones was assessed using Kaplan-Meier analyses. Mortality odds-ratios were calculated for each corticosteroid treatment group. Loss to follow-up and missing data were not reported.	Good - Age at LoA was assessed using Kaplan-Meier analyses with 95% confidence interval (CI). NSAA scores were converted to linearised scores. For missing data, sensitivity analyses were performed with robust findings.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
	analyses are outlined in the study protocol for each objective. Participants lost to follow-up were discontinued from the registry.		
8. Are the limitations of the study defined and appropriate?	Good - It is recognised that as a real-world study, the registry is likely to include a more heterogenous population compared to a randomised clinical trial, and that this may affect the data collected.	Good - A number of limitations of the study were identified, including diagnosis imprecision and prediction of phenotype, biases resulting from the protocols used in clinical evaluations for safety and feasibility, and the representativity racial and geographic composition of the cohort.	Moderate - It was identified that the use of the NSAA as the primary study outcome is limited in a young cohort due to the fact that ambulatory ability increases in boys up to seven years of age, and that the NSAA is more appropriate as an outcome in randomized clinical trials rather than real world evidence studies. It was also recognised that the study lacks the longitudinal data to extrapolate conclusions regarding benefit of early glucocorticoid use to loss of ambulation. The registry did not record age at first symptoms, meaning this was potentially a flaw in the disease severity matching against ataluren treated patients in the MAA.
9. Have the authors drawn	Good - Appropriate conclusions have	Good - Conclusions regarding delay in disease	Good - Appropriate conclusions from the

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
appropriate conclusions from their results?	been made from the interim efficacy and safety results of the registry and comparison to CINRG DNHS for the target population of patients with nmDMD.	progression with corticosteroid use are limited to the target population.	NSAA scores were made and considered within the context of the study's limitations.
A1. Are the methods of follow up defined and appropriate? (Cohort studies)	Good - STRIDE is ongoing and expected to be completed in 2025, when patients would have been followed for at least 5 years. Throughout this period, patients are/will be followed-up during routine care visits at 3-to-6-month intervals. Participants lost to follow up were discontinued from the registry.	Good - Participants had follow-up assessments to assess measures of functional ability, health status, anthropometrics, timed motor performance, range of motion, skeletal muscle strength, pulmonary and cardiac function and HRQoL. Genotype/phenotype analysis of DNA samples was also performed.	Unclear - Follow-up methods and intervals were not reported for the UK cohort in the study.
A2. Is the length of follow up sufficient to ascertain outcomes? (Cohort studies)	Good - Participants are followed for at least 5 years, or until death or withdrawal of consent. This is an appropriate timeframe to observe the progress of nmDMD.	Good - Participants were assessed at baseline, 3, 6, 9 and 12 months (ambulatory) or 6 and 12 months (non-ambulatory). Long-term follow-ups were performed at 18 and 24 months and annually thereafter.	Unclear - Length of follow up was not reported in the study.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
A3. If the authors are measuring treatment effects, is the analysis appropriate (e.g. matching, propensity scoring, instrumental variables)? (Cohort studies)	Good - Treatment effect was compared against control patients receiving BSC treatment in the CINRG DNHS study. These patients were propensity score matched to control for core prognostic indicators.	Poor - Patients in each glucocorticoid treatment groups were not matched. This may have introduced bias due to confounding variables.	Unclear - It was not reported whether analysis between patients initiating glucocorticoid treatment before and after five years involved measures to control for other variables.
Overall Rating of Study	Good	Good	Moderate

.

Table 5: ArRoWS critical appraisal of STRIDE, CINRG DNHS and NorthStar registries

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
1. Is the research question or objective(s) clear?	Good - Three study objectives were provided: 1) obtain additional information on all safety concerns being tracked in the risk management plan and long-term safety profile of Translarna; 2) Obtain additional information on the long-term effectiveness of Translarna; 3) Monitor the utilisation pattern of Translarna in usual care.	Good - The objectives of the study were to 1) study the relationship between impairment, activity limitation, participation, and quality of life across a wide age range and spectrum of DMD disease severity using common clinical endpoints employed in clinical trials and novel outcome measures; 2) study the natural history of changes in measures of impairment, activity limitation, and quality of life over periods of 12 months to >5 years of follow-up; 3) examine the associations between both disease characteristics and the use of interventions and the onset of life altering clinical milestones that are due to the progression of disease; and 4) assess the incidence of secondary conditions of DMD	Good – The NorthStar registry was set up to agree protocols for assessment and best practice treatment options for children with DMD. This included: • Assist clinicians working with muscle disease by developing a national clinical network and providing a discussion forum to promote best patient care. • Standardise and optimise steroid therapy in ambulant children with DMD throughout the UK. • Ensure a standard assessment protocol - for newly diagnosed children and those due to start corticosteroid treatment.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
		and the relative risks of developing these conditions based on exposure to standard treatment (e.g., glucocorticoids) and preventive interventions recommended by the Centers for Disease Control and Prevention Care Considerations	
2. Is the study sample representative of its target population?	Good - Patients with confirmed genetic diagnosis of nmDMD are eligible for inclusion if they are or will be receiving ataluren treatment. Patients receiving ataluren or placebo in an ongoing blinded or randomised clinical trial or any other clinical trial or access program that prevents participation in the study are excluded. Participants who meet the eligibility criteria and provide informed consent are invited through the prescriber's practice.	Good - Participants between 2 and 28 years of age were eligible for inclusion if they (or an older sibling for participants between the ages of 2 and 5 years) had a diagnosis of DMD supported by clinical evidence. Individuals with DMD were excluded from the study if they were glucocorticoid naïve and could ambulate without assistance beyond their 16th birthday or were currently on glucocorticoid therapy and could ambulate without assistance beyond their 16th birthday. The study aimed to recruit between 10 and 15 participants per year between 2 and 28 years of age.	Moderate - The registry population was representative of the UK clinical DMD population. 17 neuromuscular centres were sampled, and 513 ambulant patients were included in the analysis. Most patients had a genetic diagnosis of DMD. Inclusion and exclusion criteria were not described.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
3. Has a sample size, power calculation or measure of uncertainty (e.gconfidence intervals, standard errors) been provided?	Yes - An initial enrolment target of 200 subjects was selected to allow statistically significant comparisons to be made while considering the small size of the nonsense-mutation DMD (nmDMD) population. As of January 2021 the registry included 269 participants in the evaluable population. Continuous variables are summarised with standard deviation and confidence intervals.	Yes - The sample size of the registry was 440 participants.	Yes - The sample size was 513 ambulant patients. 95% confidence intervals were also provided for age at LoA.
4. Are the exposure measures clearly defined and appropriate?	Good - Enrolled patients in STRIDE were/are or would/will be receiving ataluren at study start and treatment discontinuations had been/are captured across the study period.	Good - Historical and current glucocorticoid therapy was recorded at each assessment. As there was variation in glucocorticoid therapy, regimens were categorised into 3 exposure groups.	Good - All participants in the registry received daily or intermittent glucocorticoid therapy.
5. Is/are the outcome(s) clearly defined and appropriate?	Good - Three primary outcome measures are stated for the study: the percentage of participants with adverse events, the prescriber and participant compliance with	Good - The study outlined several physiological outcomes that were measured as well as patient reported HRQoL data.	Good - Disease progression outcomes were measured using the NSAA.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
	prescribing information according to the approved labelling, and participant health management measures. Efficacy outcomes were defined as the 6MWT, timed function tests, NSAA, and age at LoA, performance of upper limb, pulmonary function and cardiac function. These outcomes are relevant for clinical practice.		
6. Are confounders clearly defined and appropriate?	Good - Genotype, corticosteroid use, ambulatory status at baseline are important prognostic and potential treatment effect modifiers and were handled appropriately in the study protocol as per protocol, the efficacy of ataluren was assessed in study populations that accounted for important baseline and prognostic factors. The safety profile of ataluren was presented by corticoid use.	Good - Concomitant medications were recorded at each assessment.	Poor - The study did not report potential confounding variables,

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
7. Are the statistical analyses clearly defined and appropriate?	Good - Participants in the STRIDE registry were propensity-score matched against a sub-set of control participants in the CINRG DNHS registry on core prognostic indicators to allow for appropriate comparisons between ataluren and best standard care (BSC) treatment. Missing data were not included in the study report and observed data used for all analyses. Longitudinal efficacy analysis included only data for participants with at least 2 available assessments whose first and last assessments were than 40 or more weeks apart. Subgroup analysis was performed by age-group and ambulation status. Appropriate statistical analyses are outlined in the study protocol for each objective. Participants lost to follow-up were discontinued from the registry.	Moderate - Time to disease milestones was assessed using Kaplan-Meier analyses. Mortality odds-ratios were calculated for each corticosteroid treatment group. Loss to follow-up and missing data were not reported.	Good - Age at LoA was assessed using Kaplan-Meier analyses with 95% confidence interval (CI). NSAA scores were converted to linearised scores. For missing data, sensitivity analyses were performed with robust findings.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
8. Are the limitations of the study defined and appropriate?	Good - It is recognised that as a real-world study, the registry is likely to include a more heterogenous population compared to a randomised clinical trial, and that this may affect the data collected.	Good - A number of limitations of the study were identified, including diagnosis imprecision and prediction of phenotype, biases resulting from the protocols used in clinical evaluations for safety and feasibility, and the representativity racial and geographic composition of the cohort.	Moderate - It was identified that the use of the NSAA as the primary study outcome is limited in a young cohort due to the fact that ambulatory ability increases in boys up to seven years of age, and that the NSAA is more appropriate as an outcome in randomized clinical trials rather than real world evidence studies. It was also recognised that the study lacks the longitudinal data to extrapolate conclusions regarding benefit of early glucocorticoid use to loss of ambulation. The registry did not record age at first symptoms, meaning this was potentially a flaw in the disease severity matching against ataluren treated patients in the MAA.
9. Have the authors drawn appropriate conclusions from their results?	Good - Appropriate conclusions have been made from the interim efficacy and safety results of the registry and comparison to CINRG DNHS for the	Good - Conclusions regarding delay in disease progression with corticosteroid use are limited to the target population.	Good - Appropriate conclusions from the NSAA scores were made and considered within the context of the study's limitations.

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
	target population of patients with nmDMD.		
A1. Are the methods of follow up defined and appropriate? (Cohort studies)	Good - STRIDE is ongoing and expected to be completed in 2025, when patients would have been followed for at least 5 years. Throughout this period, patients are/will be followed-up during routine care visits at 3-to-6-month intervals. Participants lost to follow up were discontinued from the registry.	Good - Participants had follow-up assessments to assess measures of functional ability, health status, anthropometrics, timed motor performance, range of motion, skeletal muscle strength, pulmonary and cardiac function and HRQoL. Genotype/phenotype analysis of DNA samples was also performed.	Unclear - Follow-up methods and intervals were not reported for the UK cohort in the study.
A2. Is the length of follow up sufficient to ascertain outcomes? (Cohort studies)	Good - Participants are followed for at least 5 years, or until death or withdrawal of consent. This is an appropriate timeframe to observe the progress of nmDMD.	Good - Participants were assessed at baseline, 3, 6, 9 and 12 months (ambulatory) or 6 and 12 months (non-ambulatory). Long-term follow-ups were performed at 18 and 24 months and annually thereafter.	Unclear - Length of follow up was not reported in the study.
A3. If the authors are measuring treatment effects, is the analysis appropriate (e.g. matching, propensity	Good - Treatment effect was compared against control patients receiving BSC treatment in the CINRG DNHS study. These patients	Poor - Patients in each glucocorticoid treatment groups were not matched. This may have introduced bias due to confounding variables.	Unclear - It was not reported whether analysis between patients initiating glucocorticoid treatment before and after

Criteria	STRIDE[5]	CINRG DNHS[9,10]	NorthStar[11]
scoring, instrumental variables)? (Cohort studies)	were propensity score matched to control for core prognostic indicators.		five years involved measures to control for other variables.
Overall Rating of Study	Good	Good	Moderate

A13. CS Appendix 17.2, Section 17.1.4, page 28. Please clarify if other sources of evidence were searched for adverse events (AEs) e.g. the MHRA Yellow Card Scheme, EudraVigilance database?

Company response:

The specified databases were not included in the searches conducted. Nevertheless, PTC can confirm that post-marketing safety data collected via pharmacovigilance platforms including Eudravigilance and MHRA are consistent with the clinical trial and real-world evidence presented in the submission. All adverse events reported through these platforms is received by PTC Pharmacovigilance for case processing, signal detection analysis and inclusion in periodic safety reports. The EudraVigilance data analysis system (EVDAS) is also reviewed on a monthly basis by PTC Pharmacovigilance for signal detection purposes. There has been no updates to the Summary of Product Characteristics (SmPC) as a result of new safety information received or change to the benefit risk profile for ataluren. The overall benefit-risk balance for ataluren continues to be positive.

Real world usage of ataluren within 266 patients in the ≥5 years subgroup from the STRIDE registry demonstrated no additional safety concerns associated with long-term treatment. Among the 266 subjects in the ≥5 years subgroup, 110 (41.4%) subjects experienced a total of 313 treatment emergent adverse events (TEAEs). All bar 14 of these 110 subjects used corticosteroids. Based on Common Terminology Criteria for Adverse Events for reporting severity of AEs, most TEAEs were mild or moderate in severity. Thirteen (4.9%) subjects had Grade 3 (severe) TEAEs, none of which were considered related to Translarna. There were no Grade 4 (life-threatening) TEAEs, and no deaths were reported. Serious TEAEs occurred in 21 (7.9%) subjects, none of which were reported as related to Translarna.[5] Please refer to **Error! Reference source not found.** for more details.

No additional safety concerns were observed in the ≥2 to <5 years subgroup. [redacted] of the [redacted] subjects in the ≥2 to <5 years subgroup, all with corticosteroid use, had [redacted] TEAEs. Events in [redacted] subjects were reported as serious adverse events (SAEs). Maximum TEAE severity was mild for [redacted] subjects, moderate for [redacted] subject, and

severe for [redacted] subject. None of the events were considered related to treatment (Table 7)[5].

Table 6: Overview of Adverse Events (As-Treated Population ≥5 Years Subgroup)

	Corticosteroid Use		[redacted]
	[redacted]	[redacted]	
Number of TEAEs	[redacted]	[redacted]	[redacted]
Subjects with 1 or more (n, %):			
TEAE	[redacted]	[redacted]	[redacted]
TEAE related to Translarna	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
TEAE with a maximum severity[a]			
Not reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Life-threatening	[redacted]	[redacted]	[redacted]

Table 7: Overview of Adverse Events (As-Treated Population ≥2 to <5 Years Subgroup)

	Corticosteroid Use		
	[redacted]	[redacted]	[redacted]
Number of TEAEs	[redacted]	[redacted]	[redacted]
Subjects with 1 or more (n, %):			
TEAE	[redacted]	[redacted]	[redacted]
TEAE related to Translarna	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
TEAE with a maximum severity[a]			
Not reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Life-threatening	[redacted]	[redacted]	[redacted]

A14. Priority. CS, Section C (general). Please clarify if there is any comparative evidence from any clinical trial/registry comparison which supports the hypothesis that ataluren confers a survival benefit over BSC.

Company response:

Due to the timeframe in which Duchenne muscular dystrophy (DMD) patients are expected to survive, the age at which patients begin treatment with ataluren, and the expected extension of patient's survival due to successful treatment with ataluren, there is no comparative evidence to support the hypothesis. Long term survival trials have not been conducted, nor are there any registries that have been in place long enough to compare the survival benefit of ataluren vs BSC.

The assessment of treatment affects in DMD clinical trials is intrinsically associated with significant challenges. Long-term outcome data in the real-world setting are required to truly understand the clinical benefits of a therapy in terms of loss of ambulation and decline in pulmonary function. However, given that the course of DMD is irreversible, randomising patients to placebo for years, while they deteriorate and permanently lose meaningful function, is not ethically tenable.[84,98] These challenges are highlighted by the fact that it has taken more than a decade to demonstrate the long-term benefit of corticosteroids in the symptomatic treatment of DMD.[97]

In order to estimate the magnitude of the survival benefit associated with successful ataluren treatment in the cost effectiveness analysis, PTC utilised known links between decline in pulmonary function, and overall survival.

Since respiratory failure is the most common cause of death in patients with DMD, pulmonary function endpoints are critical outcomes and are considered to be prognostic of mortality. More specifically, forced vital capacity (FVC) below a threshold of 1 litre (approximately equivalent to a pFVC < 30%) is strongly predictive of mortality within 3 years and associated with a 4-fold increased risk of death.[20,21]

Treatment with ataluren has shown to delay the loss of ambulation compared with BSC, as well as demonstrating a delay in reaching declining pFVC milestones. Age of loss of ambulation is believed to be predictive of time to pulmonary failure and in turn, time to death in patients with DMD.[12–14] Hence any delay in LoA would be expected to

translate into a delay in reduced pulmonary function and therefore a survival benefit. This hypothesis is supported by a UK clinician (see response to question **B18**).

As such, comparative efficacy data explicitly demonstrating the survival benefit of ataluren over BSC does not exist.

Indirect comparisons and propensity score matching

A15. Priority. CS, Section 9.6.1.6, Tables C-28 and C-29, pages 115 to 117. Table C-29 provides a comparison of baseline characteristics for STRIDE versus the post-matched CINRG, but only for the 4 covariates included in the matching process. Please provide a more complete comparison of STRIDE versus the post-matched CINRG dataset, including all covariates detailed in Table C-28. Please also comment on the generalisability of the post-matched CINRG dataset to the target NHS population for ataluren.

Company response:

Baseline characteristics for matched STRIDE and CINRG patients are presented in Table 8. As presented in response to question **A16** all key prognostic variables used as matching covariates are well balanced between the two cohorts after matching. Additionally, Table 8 shows that baseline characteristics not included within the matching analysis are also similar between the cohorts after matching, including weight, height and BMI. On average, CINRG patients began follow up at an older age, although the efficacy outcome measures used within the analysis are "age when reaching disease milestones" and patients where matched on the "age of first symptom", so the difference in age of first assessment does not influence the overall efficacy analysis.

Table 8: Baseline characteristics for the matched STRIDE and CINRG patients

Assessment	STRIDE (N=241)	CINRG DNHS (N=241)
Mean age at first symptom, years (s.d.)	[redacted]	[redacted]
Mean age at first assessment, years (s.d.)	[redacted]	[redacted]
Mean age at last assessment, years (s.d.)	[redacted]	[redacted]

Any steroid duration, n (%):		
<1 month	[redacted]	[redacted]
≥1 month to <12 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]
Lifetime steroid use, n (%):		
<1 month	[redacted]	[redacted]
≥1 month to <12 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]
Mean weight, kg (s.d.)	[redacted]	[redacted]
Mean height, cm (s.d.)	[redacted]	[redacted]
Mean BMI kg/m^2 (s.d.)	[redacted]	[redacted]

BMI, body mass index; s.d., standard deviation

Given the similarity of the post-matched CINRG cohort to the ataluren cohort in key prognostic and potential treatment effect modifiers, the matching exercise was deemed to be successful, and therefore the matched CINRG cohort is considered to be a reliable source of comparative evidence.

Disease progression and therapy options are expected to be very similar across countries, specifically between Europe and the US. This is because there are very few effective treatment options available to treat nmDMD, exclusively corticosteroid use and ataluren. Patients within the CINRG cohort were selected specifically because they have not received ataluren and have been successfully matched based on corticosteroid usage.

Population demographic parameters such as ethnicity have not been demonstrated to be significant prognostic indicators, so there is no reason to assume there will be significant variation in disease progression due to international differences in patient demographics.[15] This is supportive evidence that the CINRG cohort is representative of UK based DMD patients.

A study investigating the suitability of real-world external controls in DMD concluded that the difference in 6 minute walking distance was consistent between placebo arms and real-world data and no evidence for systematic bias was detected, and therefore external controls can be suitable for drug evaluations in DMD. The 6 minute walking

distance was also consistent among different real-world evidence sources investigated. This is further supportive evidence that the CINRG cohort is representative of UK based DMD patients.

A16. Priority. CS, Section 9.6.1.6, Tables C-28 and C-29, pages 115 to 117. The CS provides limited diagnostic information around how well the propensity matching has worked:

(a) Please provide summaries of the standardised differences of means/proportions on all matching covariates and prognostic score, between the STRIDE and CINRG cohorts both before and after matching.

(b) Please include the variance ratio between the matched cohorts as a further diagnostic of balance.

(c) Please include Love plots/ alternative visual representations of covariate balance along with comparison plots of distributions on matching variables.

Company response:

Table 9 below presents the summary statistics used to assess balance of the key covariates for patients within STRIDE and CINRG registries, both before and after matching. This includes means, standard deviations, 95% confidence intervals, p-values, standardised differences, and variance ratios.

The balance assessments indicate all of the covariates are well balanced following matching. The standardised differences are all within the accepted threshold of 0.1 which demonstrates all key covariates are well balanced.[16] Additionally, a variance ratio of 1 indicates good matching, with a variance ratio less than 2 generally accepted.[17] All of the variance ratios are below 2 and within [redacted] of 1, further indicating that the covariates are well balanced after matching.

Table 9: Assessment of balance pre and post matching summary statistics

	Unmatched Population		Propensity-Matched Population	
	STRIDE (N=241)	CINRG (N=398)	STRIDE (N=241)	CINRG (N=241)
Age at first symptom, years[a]				
n	241	398	241	241
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
SEM	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
p value	[redacted]		[redacted]	
Standardised differences	[redacted]		[redacted]	
Variance ratio	[redacted]		[redacted]	
Age at steroid initiation, years[b]				
n	212	315	212	212
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
SEM	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
p value	[redacted]		[redacted]	
Standardised differences	[redacted]		[redacted]	
Variance ratio	[redacted]		[redacted]	
Deflazacort duration, n (%)				
<1 month	[redacted]	[redacted]	[redacted]	[redacted]
≥1 to <12 months	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]
p value	[redacted]		[redacted]	
Standardised differences (<1 month)	[redacted]		[redacted]	
Standardised differences (≥1 to <12 months)	[redacted]		[redacted]	
Standardised differences (≥12 months)	[redacted]		[redacted]	
Variance ratio (<1 month)	[redacted]		[redacted]	
Other steroid duration, n (%)				
<1 month	[redacted]	[redacted]	[redacted]	[redacted]
≥1 to <12 months	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]
p value	[redacted]		[redacted]	
Standardised differences (<1 month)	[redacted]		[redacted]	
Standardised differences (≥1 to <12 months)	[redacted]		[redacted]	
Standardised differences (≥12 months)	[redacted]		[redacted]	
Variance ratio	[redacted]		[redacted]	

PTC are unable to provide love plots or alternative visual representations of balance without the need for additional analyses that are unable to be completed within the timeframe of this response.

A17. Priority. CS, Section 9.6.1.6, Table C-28, page 115. The propensity matching between CINRG and STRIDE includes four variables. Please explain why type of corticosteroid use (intermittent versus daily) was not included as a covariate. If possible, please repeat the matching analysis including this covariate.

Company response:

At the time of submission, no consensus had been reached on whether corticosteroid regimen has a significant influence on disease progression. As such, it was not deemed necessary to include as a matched covariate.

Additionally, it is not feasible to match steroid regimen for the STRIDE/CINRG cohorts as in clinical practice there is wide variation between different daily and intermittent treatment regimens between patients, resulting in a large number of categorical variables which would be challenging to match. Many patients also change between dosing regimens over the course of their treatment, so it is not possible to assign individual patients to a particular regimen for matching.

Although it is not feasible to match based on corticosteroid regimen between cohorts, other factors related to corticosteroid usage have already been controlled for where possible. The propensity score matching included duration of deflazacort treatment, duration of other steroid treatment, and age at initial steroid treatment, and age at initial corticosteroid use. The cohorts were well balanced for these variables after matching. Covariates related to corticosteroid usage in the STRIDE and CINRG DNHS propensity score matched populations are presented in Table 10.

Table 10: Corticosteroid related variables in the STRIDE and CINRG DNHS propensity-matched populations

	Propensity-Matched Population	
	STRIDE (N=241)	CINRG (N=241)

Mean total corticosteroid exposure (days(SD))[18]	[redacted]	[redacted]
Mean age at first corticosteroid use (excluding corticosteroid-naïve patients) (years(SD))[18]	[redacted]	[redacted]
Deflazacort duration (n(%))[18]		
<1 month or corticosteroid naïve	[redacted]	[redacted]
≥1 to 12 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]
Other corticosteroid duration (n(%))[18]		
<1 month or corticosteroid naïve	[redacted]	[redacted]
≥1 to 12 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]

A18. Priority. CS, Section 9.4.1.6, page 115 and CS, Section 9.4.1.7, page 76. Please clarify why a different matching procedure was used for the comparison of STRIDE versus CINRG controls (CS, Section 9.4.1.6) than that used for the MAA analysis (CS, Section 9.4.1.7). Specifically, why have baseline North Star Ambulatory Assessment (NSAA) scores and floor rise time (or alternative measures of symptom severity) not been matched on for the STRIDE analysis? Similarly, why has regularity of steroid use not been matched on? Please include balance diagnostics on these measures.

Company response:

The NorthStar registry is a UK-based database, whereas the STRIDE registry includes centres from all across Europe and Israel, and the CINRG registry includes centres from all over the world, primarily based in the US.[5, 9, 11,18] Different data collection was experienced between registries and geographical locations. Specifically, due to the nature of real-world data collection and the time required to assess functionality scores such as NSAA and time to rise from supine, these measures were not recorded consistently for all visits at all centres within STRIDE and CINRG.

In STRIDE, ([redacted]/241) patients had measurements of NSAA and ([redacted]/241) had measurements for time to rise from floor. Fewer patients in the CINRG cohort had NSAA measurements ([redacted]/241 or [redacted]%), however most patients had measurements for time to rise from floor ([redacted]/241 or 98.8%). Fewer CINRG patients had both NSAA and time to rise from floor measurements ([redacted]/241 or [redacted]%). It was therefore not possible to include the baseline NSAA or time to rise from floor as a matching covariate because there was significant missing data across the cohorts. Consequently, age at first symptom was used as an indirect measure of disease severity based on literature and experts' recommendation.

The requirements of the MAA were stipulated by NICE and agreed by all parties as part of the ongoing assessment of Translarna in England. The NSAA score was chosen as an efficacy comparator because all centres in the UK record NSAA for all DMD patients as part of their ongoing assessments. In order to try and best match ataluren patients with control patients within the NorthStar Registry at baseline, the SAP was revised and although age at first symptom data was not available, time to rise from floor data was and this was used as a proxy for age at first symptom.

As discussed in response to question **A17**, it was not possible to match based on steroid dosing regimen as there are many different dosing regimens used, which would create a challenge requiring the introduction of a number of indicator variables. Additionally, many patients varied steroid regimen during follow up, meaning that it is not possible to assign a specific regimen indicator variable for each patient that is consistent across all time points.

Again, based on the inconsistency of data collection between the cohorts it means it is not possible to provide an assessment of balance between these variables.

A19. Please provide comparisons of those used for matching and those excluded from matching:

(a) In STRIDE versus CINRG 241 of 269 patients were matched on (CS, Section 9.4.5.5, page 84, and CS, Section 9.6.1.6, pages 116 to 117).

(b) In Study 019 only 60 of 94 patients were matched on (CS, Section 9.6.1.4, page 108).

(c) Please justify why complete case analysis was used and comment on whether any other missing data approaches were considered.

Company response:

The reason some registry participants were not included in the matching analysis was that some patients were ineligible due to any number of different factors. These are discussed in more detail below. A direct comparison in terms of key covariate values between the matched and excluded patients from STRIDE and Study 019 is either not possible due to values not being recorded (hence exclusion) or will not provide any additional clarity because these patients did not meet the minimum requirements to be included in the analysis.

As of January 2021, 288 patients signed informed consent to participate in the STRIDE study. The evaluable population was 269 patients. Patients were not included in the evaluable population for any of the following reasons: no signed informed consent, not treated, female patients, screen failures, frameshift mutations, missing mutation data, other outstanding critical queries.

The effectiveness population used for matching included 241 patients. Patients were not included in the effectiveness population if they discontinued registry participation, had new-born screening/prenatal diagnosis as the first symptom, missing data of age at first symptoms, data for steroid use but without steroid initiation date, missing data for age at loss of ambulation.

A full breakdown of effectiveness population is presented in Table 11:

Table 11: Breakdown of the effectiveness population

Analysis Population, n (%)	All	≥2 to <5 Years	≥5 Years
Screened	[redacted]	[redacted]	[redacted]

As-treated[a]	[redacted]	[redacted]	[redacted]
Evaluable[b]:	[redacted]	[redacted]	[redacted]
Ambulatory[c]	[redacted]	[redacted]	[redacted]
Non-ambulatory[d]:	[redacted]	[redacted]	[redacted]
Prior to study entry	[redacted]	[redacted]	[redacted]
During study	[redacted]	[redacted]	[redacted]
Effectiveness[e]:	[redacted]	[redacted]	[redacted]
Ambulatory[c]	[redacted]	[redacted]	[redacted]
Non-ambulatory[d]:	[redacted]	[redacted]	[redacted]
Prior to study entry	[redacted]	[redacted]	[redacted]
During study	[redacted]	[redacted]	[redacted]

Abbreviations: EAP, early access programme; NBS, newborn screening; PND, prenatal diagnosis Note: One screened subject who was not treated is excluded from the summary by age group.
Subjects may be ambulatory at treatment start and become non-ambulatory during study. Such subjects are counted under both Ambulatory and Non-Ambulatory Populations.
Subjects may have been in more than one category.
[a] As-Treated Population consists of all screened subjects who receive Translarna.
[b] Subjects are excluded from the Evaluable Population for the following reasons: no signed inform consent, not treated, female patients, screen failures, frameshift mutations, missing mutation data, other outstanding critical queries.
[c] Ambulatory Population is defined as the subset of the Evaluable or Effectiveness Population who were not full-time wheelchair bound or bedridden prior to the date of first recorded commercial or EAP Translarna use, or those who were not in the transition phase defined as greater than or equal to 30 seconds for their first 10-metre run/walk test on or after the date of first recorded commercial or EAP Translarna use.
[d] Non-Ambulatory Population is defined as the subset of the Evaluable or Effectiveness Population who were full-time wheelchair bound or bedridden on or before first recorded commercial or EAP Translarna use or anytime during the study.
[e] Subjects are excluded from the Effectiveness Population (a subset of the Evaluable Population) for the following reasons: no signed inform consent, not treated, female patients, screen failures, frameshift mutations, missing mutation data, other outstanding critical queries, NBS/PND as the first symptom, missing data of age at first symptoms, with steroid use but without steroid initiation date, missing data of age at loss of ambulation.

Similarly, for study 019, 94 patients enrolled in the study. 60 of these patients were included in the propensity score matching based on either receiving ataluren 40mg/kg/day (+SoC) in Study 19 and previous trials (n=27) or receiving ataluren 40mg/kg/day (+SoC) in Study 19 and 80mg/kg/day (+SoC) in prior ataluren trials (n=33).[19]

Complete case analysis was the most appropriate approach towards missing data when considering matching covariates because all of the matching covariates were deemed to be significant prognostic indicators. It was therefore necessary that only

patients with data for each variable were included within the matching analysis to ensure the covariates were well balanced between the populations.

Observations regarding time to LoA and decline in pulmonary function were recorded whenever clinical assessments took place. The time when a disease milestone was reached was recorded at the date of the first visit in which reaching this endpoint had been observed. For events that had not been observed by the end of the patients available follow up, the observed time was censored.

The longitudinal efficacy analysis includes data only for those subjects with at least 2 assessments during the defined treatment period (i.e., 30 days prior to the treatment start date to 30 days after the treatment end date) that are at least 40 weeks apart. Subjects with fewer than 2 available assessments or those whose first and last assessments were less than 40 weeks apart are excluded from the efficacy summaries of longitudinal data.

A20. CS, Section 9.6.1.7, pages 124 to 128. The CS includes some analyses of data collected as part of the MAA:

(a) Please clarify why the analysis of the matched MAA data does not include formal time-to-event comparisons similar to those presented for the comparison of STRIDE versus CINRG.

(b) Please comment on why the number of patients with a NSAA drops sharply over time in the matched groups (CS, Figure C-31, page 128).

(c) Please further justify why the MAA data have not been used to inform the economic analysis (including as sensitivity analyses).

Company submission:

The matched MAA patients were all observed within the NorthStar registry. The primary outcome measure of disease progression within the NorthStar registry is the change in NSAA score from baseline. It is only possible to evaluate the NSAA whilst a patient remains ambulatory. After a patient becomes non-ambulatory, they discontinue ataluren as per the UK commissioning policy, and are no longer followed up as part of the MAA.

Age at LoA was not recorded as a formal outcome measure and therefore no analysis was conducted. The analysis focused on the change in NSAA over time as stipulated in the MAA agreed with NICE following the original submission.[20] Additionally, patients were no longer followed as part of the MAA after loss of ambulation and discontinuing ataluren, and pulmonary function was not assessed. For these reasons it was not possible to use the MAA/NorthStar data to estimate the time to achieve the declining pulmonary function health states as evaluated using the STRIDE/CINRG data.

There were several reasons as to why the number of available observations from the MAA reduced at later endpoints. This included evaluator error, patient error, temporary reasons such as a broken leg, loss of ambulation, and unknown reasons. Table 12 and Table 13 below present the breakdown of the reasons for missing data for both treated patients and controls year by year.

Table 12: Reasons for missing data (untreated controls)

FUP	Number of Controls	Valid NSAA at visit	Missing NSAA at visit	Reason for missing NSAA total
Baseline	[redacted]	[redacted]	[redacted]	
1 year	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] evaluator error
2 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant
3 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] patient error, [redacted] missing
4 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant
5 years	[redacted]	[redacted]	[redacted]	[redacted] non-ambulant, [redacted] temporary reason

Table 13: Reasons for missing data (treated patients)

Number of visits	Number of Cases	Valid NSAA at visit	Missing NSAA at visit	Reason for missing NSAA total
Baseline	[redacted]	[redacted]	[redacted]	
1 year	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] temporary reason, [redacted] patient error
2 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] patient error

3 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] evaluator error, [redacted] patient error, [redacted] missing
4 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant, [redacted] temporary reason, [redacted] patient error*
5 years	[redacted]	[redacted]	[redacted]	[redacted] non ambulant*

*Please note that the number of non-ambulant patients appears to be larger in the ataluren patients compared to the untreated controls, however these values should be treated with caution as far more patients were followed up to later time points for ataluren compared to BSC, so the ambulatory status of the unobserved BSC patients is not known.

The structure of the economic model adopts a partitioned survival approach, whereby health state transition is informed by survival models based on the age of reaching progressive disease milestones. This model structure was agreed by a number of experts and key opinion leaders (KOLs) (including health technology assessment (HTA), patient group and clinician representatives) as part of project HERCULES as the most representative of the course of disease and to account for the cost and quality of life (QoL) implications.[21] As discussed above, it was not possible to generate time to event analyses investigating the age of reaching the specified disease milestones using the MAA/NorthStar data. It is therefore not possible to utilise the results of the MAA to inform the clinical efficacy within the economic analysis.

A21. CS, Section 9.4.1.1, page 62. Was exploration of genetic modifiers in the matched CINRG cohort conducted to ensure/evaluate whether bias was introduced?

Company response:

It is acknowledged that there is some evidence to suggest that specific genetic modifiers may play a non-trivial role in the overall progression of the disease, it is also acknowledged that more research is required in order to quantify the impact.[15]

Unfortunately, it was not possible to include any genetic modifiers as a matching covariate as specific genotypic information was not uniformly recorded within the STRIDE and CINRG datasets.[19,22]

Section B: Clarification on cost-effectiveness data

Survival modelling and relative treatment benefits

B1. Priority. CS, Section 12.2.2, page 210. The general approach used to model the benefit of ataluren involves shifting the survival functions to the right (by some time interval "X"). This implicitly assumes that events of interest are delayed by exactly X years for all patients. Please explain why this approach was used in preference to other more conventional statistical approaches for modelling relative benefits between groups (e.g., using hazard ratios or acceleration factors).

Company response:

The choice of methodology was selected based on the nature of the input from the clinicians.

Due to limited available data around rates of progression to later disease milestones for ataluren patients, as very few patients reached these stages of disease progression, expert opinion was required to ascertain credible estimates. In order to get reliable expert input, it was important to stay close to the expert's frame of reference. With the experts being a panel of clinicians, not statisticians or data analysts, we assessed that a specific number of years shift in survival would be close to what they experience and observe in daily clinical practice, and therefore the best metric to get reliable input. It would have been more difficult, and potentially less reliable to generate an estimate for a hazard ratio (HR) or an acceleration factor from clinicians' experience of treatment benefit.

The nature of the assumptions that drive the shifts in survival functions are of the form "early treatment will contribute to a delay in reaching different disease milestones by X years", "a delay in reaching pFVC < 30% for patients receiving ataluren compared to BSC patients is X years", "the delay in dying after reaching pFVC < 30% is 3 years". The most appropriate implementation to account for estimated delays of X years is to effectively shift the survival functions X years into the future by subtracting X years from the argument of the survival function i.e. (S(t-X)).

Had the assumptions been of the form “early treatment will reduce the **time** of transitioning to the next health state by X%” then an acceleration factor may be more appropriate, of the form of S(t*X%). Similarly, if the assumption was of the form of “early treatment will reduce the **rate** of transitioning to the next health state by a multiplying factor of X” then it would be more appropriate to apply a hazard ratio to the respective hazard functions.

B2. Priority. CS, Section 12.2.2, page 210. For each time-to-event endpoint used in the economic model informed by data (time to loss of ambulation, time to FVC<50% and time to FVC<30%) and for each treatment group, please provide a plot of the empirical/unsmoothed and smoothed hazard function for the data used in the analysis. Please also plot the hazard function of the selected parametric model used in the economic model on top of the empirical and smoothed hazard.

Company response:

The fitted hazard functions for each of the health state transitions are presented in Figure 1, Figure 2 and Figure 3 below. The black dotted line represents the observed data, and then the hazard function for each of the parametric survival models is overlayed.

The time to loss of ambulation figures show that both the empirical hazard functions for ataluren patients and natural history patients increase in instantaneous risk, followed by a reduced rate of increase. The selected survival model for both treatment arms was the log-logistic. The hazard function for the log-logistic model closely aligns with the empirical hazard plot for the natural history patients which has a more complete dataset. For the ataluren patients perhaps a log-normal or Weibull appear to more closely align with empirical hazard function. Functionality to explore alternative survival models such as the log-normal, or the Weibull is included within the economic model and results in minor changes to the incremental cost effectiveness ratio (ICER).

Figure 1: Hazard functions for time to loss of ambulation

[left] matched STRIDE patients, [right] matched CINRG patient

The empirical hazard functions for time to recorded pFVC < 50% presented in Figure 2 show a more monotonically increasing hazard function for both treatment arms. The selected survival model again was the log-logistic for both treatment arms. Due to the immaturity of the STRIDE data, it may be limited in accuracy of assessing the nature of the hazard function at later time points and whether the log-logistic model is the most appropriate. There are arguments to suggest either the Weibull or the Gompertz hazard functions more closely align with observed data for both treatment arms. Again, selecting these models in the cost-effectiveness analysis has only a small impact on the ICER.

Figure 2: Hazard functions for time to pFVC < 50%

[left] matched STRIDE patients, [right] matched CINRG patient

Figure 3 shows only the hazard functions for time to pFVC < 30% for matched natural history from the CINRG cohort. This is because there were too few patients in the STRIDE dataset who have reached this stage of disease progression in order to fit a survival model. The economic analysis applies the rate of transition observed in the natural history patients to the ataluren arm, shifted by an estimated delay induced by successful treatment.

The empirical hazard function appears to show an increasing instantaneous risk at constant rate. None of the proposed survival models appear to closely align with the observed data. The selected model used in the base case analysis was the log-normal model, based on goodness of fit measures and visual inspection of the survival function. For this situation, perhaps the survival function is more prominent when assessing the accuracy of the fitted model selection. Again, adjustment to a Generalised Gamma or Gompertz model has very little impact on the ICER.

Figure 3: Hazard functions for time to pFVC < 30%

Matched CINRG patient

Adjusting the economic model to implement the log-normal curve for time to LoA for ataluren patients and then Gompertz and Weibull curves for time to pFVC < 50% for ataluren and natural history patients respectively, results in an ICER of £[redacted]. This highlights the lack of sensitivity the model has to variation in the selected survival functions. It is important to reiterate that survival model selection should not

exclusively consider hazard functions and that the role of the survival function is also very important.

B3. Priority. CS, Section 12.2.2, page 210. For each time-to-event endpoint estimated from the STRIDE and CINRG datasets, please comment on how composite/competing risks are handled in the survival analysis. For example, in the analysis of time to FVC<50%, are LoA and death counted as events or are they censored?

Company response:

It is assumed events happen sequentially, i.e. a patient is expected to become non-ambulatory before recording a pFVC < 50%. At the point at which patients become non-ambulatory, they are assumed to have a pFVC ≥ 50%. This is supported by a consensus of the global Delphi panel where all of the [redacted] clinicians agreed that a patient would have an pFVC ≥ 50% at the point at which they lose ambulation (more details presented in response to question **B17)**.[23] In addition, all health states based on pFVC also occur sequentially based on declining percentages of pFVC, i.e. it is not possible to have a pFVC < 30% before recording a pFVC < 50%. Therefore, there was no need to account for competing risks within the survival analyses.

In addition, no patients within STRIDE had died by the 31st of January 2021 (data cut used in the submission)[5], and so there was also no need to account for premature patient deaths as part of the survival analysis.

A similar approach was applied to the CINRG cohort, whereby patients are assumed to lose ambulation before reaching a pFVC <50% and any patients who died before reaching an pFVC <30% were censored at the age of death (when considering any unachieved pFVC milestones) but were considered as events for the overall survival analysis.

B4. Priority. CS, Section 12.2.2, page 210. The re-based survival models apply different cut-points for each endpoint in the STRIDE dataset and the propensity-matched CINRG DNHS datasets.

(a) Please explain how the cut-points of 3.5 and 5 years used in the model were identified.

(b) Please clarify whether different cut-points were explored.

(c) Please justify the use of different cut-points between the ataluren and BSC groups.

(d) Please explain whether flexible parametric models (e.g. restricted cubic splines) were considered.

Company response:

The key source of challenge when fitting standard parametric models was determined to be the plateau at the start of the data, a result of the analyses starting from age 0 and events not being expected to occur for a number of years. It was therefore determined that the most effective and pragmatic method of correction for this observation was to re-base the data such that standard parametric fitting was applied from a point at which events could plausibly occur, and apply a 0% probability of events occurring before this data.

Within the re-based survival analysis, the cut off of 3.5 years and 5 years for BSC and ataluren patients were selected based on the earliest age at which any event occurred in each treatment arm respectively. DMD is a condition in which a number of years are expected to pass before the first milestone of disease progression (LoA) is reached. For this reason, the fit of the survival models is improved by re-basing the analysis to fit the survival models during the relevant period of follow up when the events took place.

The first event observed in the matched CINRG patients was at [redacted] years of age. The earliest event observed in the matched STRIDE patients was at [redacted] years, five years was selected as an appropriate value to represent the time period in which no events were expected to take place in ataluren patients based on this value.

The cut points were selected differently for the two treatment arms based on the difference between when the first events were observed, and because the survival

models were fit independently for each treatment arm, so there was no requirement to ensure the survival methodologies align between the treatment arms. The goal was to achieve the best fit for each treatment arm independently, based on the data observed.

Applying a cut point at 3.5 years for both treatment arms was explored to assess the sensitivity/robustness of the base case analysis. The results are generally consistent irrespective of the re-base timepoint chosen with only slight differences in the orderings of the AIC/BIC. There is very limited variation in these survival models from the base case re-based analysis in terms of estimated survival functions for each health state.

The economic analysis contains the functionality to explore using survival models that have not been re-based to inform the health state transitions. The impact of adjusting the model to use non-rebased survival models for all health state transitions increases the base case ICER very slightly to £[redacted].

More complex models such as splines could be used to achieve the same result, but this was not deemed to provide sufficient advantage over a simple method to warrant the additional complexity. Additionally, low sample sizes towards the end of the follow up period hinder the ability accurately fit more complex models such as cubic splines to later time points.

B5. Priority. CS, Section 12.1.1, pages 201 to 202. The text states that *"241 patients in the STRIDE effectiveness population have been matched using propensity scoring to CINRG DNHS patients."* However, the subsequent sentence states that a lower number of patients contributed data to the analysis of time to FVC<50% and time to FVC<1 litre (N=182 and N=173, respectively). Please clarify if these patient numbers relate specifically to the propensity-matched CINRG cohort or the STRIDE dataset as well, and explain why fewer patients were included in these analyses.

Company response:

The numbers of patients presented on pages 201 and 202 of the company submission refer to the number of available patients' data from the STRIDE registry to inform the time to reach each disease milestones.

The number of patients stated for each disease milestone represent the number of patients who were assessed for the relevant clinical measure in order to establish if that disease milestone has been achieved. Please refer to Table 14 below.

Additional explanation for the differences in numbers of patients assessed for each endpoint is as follows. Firstly, not all of the 241 patients in each registry were assessed for pFVC percentage. This is why approximately 50 patients from STRIDE were not assessed for a pFVC < 30%. Secondly, if a patient enters the registry with a baseline pFVC less than one of the thresholds, this patient is "left censored" as it is not known when this milestone was reached, hence they are not assessed for this endpoint, or any of the earlier endpoints. An example would be if a patient entered the registry with a baseline pFVC = 45%, then they would not be assessed for pFVC < 60% or < 50% as these endpoints have already been achieved, however they would be assessed for a pFVC < 30% as this event had not yet been achieved. This accounts for the differences between the number of patients assessed for each endpoint.

Table 14: Pulmonary function assessments for propensity score matched STRIDE and CINRG patients

Parameter	STRIDE (N=241)	CINRG (N=241)
% Predicted FVC below 60%		
Subjects assessed, n	[redacted]	[redacted]
Subjects with events[a], n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Median age (95% CI) at event (years)	[redacted]	[redacted]
p value[c]	[redacted]	
Hazard ratio (95% CI)[d]	[redacted]	
% Predicted FVC below 50%		
Subjects assessed, n	[redacted]	[redacted]
Subjects with events[a], n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Median age (95% CI) at event (years)	[redacted]	[redacted]
p value[c]	[redacted]	
Hazard ratio (95% CI)[d]	[redacted]	
% Predicted FVC below 30%		
Subjects assessed, n	[redacted]	[redacted]
Subjects with events[a], n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Median age (95% CI) at event (years)	[redacted]	[redacted]
p value[c]	[redacted]	
Hazard ratio (95% CI)[d]	[redacted]	
FVC <1 litre		
Subjects assessed, n	[redacted]	[redacted]
Subjects with events[a], n (%)	[redacted]	[redacted]

Subjects censored, n (%)	[redacted]	[redacted]
Median age (95% CI) at event (years)	[redacted]	[redacted]
p value[c]	[redacted]	
Hazard ratio (95% CI)[d]	[redacted]	

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
[a] Event = % predicted forced vital capacity (FVC) below 60%, 50%, 30%, or FVC <1 litre
[b] '+' indicates censored observation
[c] Log-rank test stratified by deflazacort and other steroid usage durations
[d] Stratified (by durations of deflazacort and other steroid use) Cox regression with covariate age at the first symptoms. Hazard ratio is Registry over CINRG
Note: Propensity score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort.
Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.

B6. Priority. CS, Section 12.2.1, page 209. The model includes an assumption that patients have a constant risk of discontinuation of [redacted] per 3-month cycle over the entire time horizon.

(a) Please provide a Kaplan-Meier plot showing observed time to treatment discontinuation in the STRIDE dataset.

(b) The CS (page 15) states that ataluren is well tolerated. Please comment on the plausibility of assuming a constant risk of discontinuation given that nmDMD is a very rare disease in which no alternative effective treatments exist.

(c) The constraints applied in the economic model (worksheet "Ataluren and BSC", columns AB:AD) override the discontinuation probability estimate from STRIDE. The ERG is unclear about what these calculations are intended to do. Please clarify what is being assumed about discontinuation in the model and provide an explanation about how these calculations work. A worked example may be helpful.

Company response:

As discussed in response to question **A8** of January 2021, [redacted] out of 269 patients within STRIDE discontinued ataluren or changed dose as of January 2021. A Kaplan Meier graph for the time on treatment is presented in Figure 4.

As shown in Figure 4 and discussed in response to questions **A7** and **A8**, patients discontinued for a number of reasons, including, adverse events, family/participant request, perceived lack of response, clinician's decision, LoA or unknown reasons. The STRIDE registry follows real-world usage of ataluren, therefore the rates of discontinuation observed is representative of UK clinical practice. PTC agree that due to the unavailability of alternative treatment options, for a chronic disease such as

DMD, treatment discontinuation is not advised. However, PTC are also willing to accept that a very low rate of natural discontinuation, as observed in the STRIDE patients, is very feasible over a lifetime treatment horizon. The proposed rate of discontinuation was supported by a UK clinician during an advisory meeting (see response to question **B18**).

Figure 4: Kaplan Meier graph for time on ataluren in STRIDE

Below is an explanation of the functionality of treatment discontinuation within the ataluren +BSC trace:

Discontinuation is separated for ambulatory/non-ambulatory. The stopping rule assumes all alive ambulatory patients remain on treatment.

- Column P represents the time to treatment discontinuation curve without application of stopping rules.
- Column AA represents the proportion of new patients to become non-ambulatory each cycle, accounting for expected mortality, i.e. those patients who die whilst ambulatory.
- Column AC – represents the number of non-ambulatory patients who remain on treatment. It does this by implementing a “CHOOSE” function which takes

into consideration the selection of the stopping criteria by the user. The formula also considers the impact of background discontinuation and mortality:

- If the stopping rule is set to discontinuation upon LoA, no patients are assumed to be on treatment after LoA.
- If the stopping rule is set to discontinuation at "6-months after LoA", this function estimates the number of patients becoming non-ambulatory over the past 2 cycles AND not dying AND then further caps this such that the total on treatment cannot exceed the number on treatment estimated from the continuous [redacted]% discontinuation rate (by applying a proportional split who would be expected to be on treatment).
- If the stopping rule is set to discontinuation at any of the pFVC health states:
  - If the total number of ambulatory patients + number of non-ambulatory patients (before selected stopping milestone) is greater than the number of patients who remain on treatment despite per cycle discontinuation, then it calculates what ratio of the continuing patients are non-ambulatory. If not, then it simply calculates the total number of patients who are non-ambulatory before reaching the selected treatment stopping milestone.

- Column AB represents the number of ambulatory patients who remain on treatment. This takes into consideration the number of patients who have discontinued treatment naturally per cycle by accounting for those non-ambulatory patients who remain on treatment calculated in AC, and ensures that the number of ambulatory patients who remain on treatment is never larger than:

  1. The number of ambulatory patients who remain on treatment from the previous cycle,
  2. The total number of patients on treatment from the previous cycle,

3. The number of patients who have continued despite per cycle discontinuation for that cycle.

4. The number of patients alive.

- Column AD then provides the resulting total number of patients on treatment

The general essence of what is happening – the columns account for the per cycle discontinuation, the impact of the stopping criteria and the impact of mortality. Overall, it calculates how many patients remain on treatment per cycle, split by ambulatory status. Please refer to Figure 5 for a graphical representation of the proportion of patients who remain on treatment over time for the base case stopping criteria of "discontinuation at pFVC<50%".

Figure 5: Base case health state transition curves and time on treatment curve for ataluren

Modelling health-related quality of life

B7. Priority. CS, Section 10.1.9, page 171. The approach used to estimate caregiver quality-adjusted life years (QALYs) within the model implicitly assumes that caregivers either die or survive with zero utility after the patient with nmDMD dies. Please clarify if this assumption is intentional and explain why the more commonly

used caregiver disutility approach (which was used in HST3) has not been applied in the current model.

Company response:

The interpretation is not that caregivers die or survive with 0 utility after the patient dies. The model aims to evaluate the total impact on costs and QoL associated with the life of the patient, as opposed to the caregivers, i.e. caregiver QALYs stop being accrued after a patient dies. This creates a situation in which there is a net benefit on caregiver QoL during the time in which the patient is alive, and overall caregiver QoL is not increased due to a patient dying.

There is an unavoidable limitation of the more commonly used "caregiver disutility implementation" in that it creates a situation in which patients dying earlier benefits caregivers. This is because the disutility is only applied during the timeframe in which the patient is still alive. Therefore, patients living longer contribute greater overall caregiver utility loss. Although there is a defendable argument to suggest daily burden imposed on caregivers is relieved after a patient dies, it would be difficult to defend that caregivers would have an overall improvement in QoL if their child/loved one died.

In a disease such as DMD there is a significant, progressively increasing, caregiver burden for the vast majority of the patient's lifetime. Ataluren is estimated to contribute a significant overall survival benefit compared to BSC, which under the "caregiver disutility implementation" would reduce the overall QoL of the carers for a longer time horizon.

In addition to this, the health state utility values for the patients, particularly in the non-ambulatory health states, are very low. Subtracting the significant caregiver disutilities for two full-time carers could easily result in a net QALY loss during the time patients spend in these health states. From a pragmatic point of view this seems counterintuitive, under the assumption that caregivers, healthcare systems and society in general would prefer for the patient to be alive, despite the significant caregiver burden.

A modelling implementation which avoids this scenario is to assume that caregivers gain positive QALYs over the course of the patient's lifetime, accounting for the increasing levels of caregiver burden through progressively reduced caregiver utility

values. This also augments the survival benefit associated with ataluren in that caregivers gain more QALYs overall due to the patient being alive for longer.

A 2019 paper by the University of Sheffield investigated the implementation of caregiver HRQoL within highly specialised technology appraisals to NICE.[24] The paper discusses the alternative options of implementing either a traditional caregiver disutility approach or the positive utility approach as implemented within this submission. The investigation discussed how a positive caregiver utility implementation avoids the issues of modelling a carer disutility linked to patient health status while alive assumes that there is no negative impact on carer HRQL when the patient dies. There is no clear consensus on the preferred implementation approach, although continued accrual of caregiver QoL beyond the death of the patient is not recommended.

B8. CS, Section 10.1.9, page 171. Given that carers are assumed to die or survive with zero utility after the patient with nmDMD dies, please clarify who the bereavement-related QALY loss is assumed to apply to.

Company response:

In a very similar argument as per the response to question **B7**, the model aims to generate the net positive impact on caregivers whilst a patient is alive, and then to consider that the impact of a patient's premature death would contribute to an overall net reduction in caregiver QoL after a patient has died. Again, the model aims to evaluate the impact of the patient's life on their caregivers, this includes the negative impact of a premature death.

Caregivers are assumed to no longer accrue positive utility during the timeframe after a patient has died. Moreover, they are assumed to have a net QoL loss following the death of a child/loved one due to bereavement. The method of bereavement implementation was sourced from the Strimvelis submission (HST7) in which caregiver's lose 9% of the discounted QALYs for the number of years earlier the patient died than the life expectancy for a healthy control.[25]

The functionality within the model allows for the bereavement disutility to be excluded from the QALY calculations. The net result is a small increase in the ICER from base case to £[redacted] per QALY gained.

B9. CS, Section 12.2.6, Table D.6, page 213. The number of caregivers was taken from a qualitative study, but no reference is given in the table. Please provide further details of this study, including a reference.

Company response:

The appropriate number of full-time caregivers required to support a patient from DMD was sourced from the global Delphi panel which included input from [redacted] expert clinicians with over [redacted] patients-years collective experience[23]. More details can be found in response to question **B17**.

B10. CS, Section 10.1.9, page 171. Please clarify why health state utility values have not been age-adjusted.

Company response:

Applying age-adjustments to utilities for children was not considered appropriate. Notably the Ara and Brazier 2010 equation for age-adjustment is derived from QoL data with a sample ranging from age 16-98.[26] Application of this equation to patients under the age of 16 would therefore be inappropriate.

While age-adjustment to the health state utility values could theoretically be applied to patients over the age of 16, given the severity of the disease, the considerable negative implications on patients QoL, and very low utility values assigned to more progressed health states, it is argued that the gradual decline in average QoL associated with aging is overshadowed by the symptoms of the condition. Median survival for ataluren patients is [redacted] years of age in the base case. QoL decline associated with aging is assumed to have a negligible impact on overall patient QoL over the course of their lifetime and was therefore not included in the submission.

PTC maintain that it would be inappropriate to account for age adjusted patient utility values within the model, however, the model functionality has been updated to explore what impact this analysis would have on the results. Age adjustment was applied to patients aged 16 and over, calculated as a percentage decrease from the utility value for a healthy 16 year old, using the Ara Brazier equations.[26] The results of this scenario are presented in Table 15.

Table 15: Scenario results for age adjusted patient utility values

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren + BSC							

*Total incremental QALYS are weighted using the HST decision modifier[204]
ICER: Incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

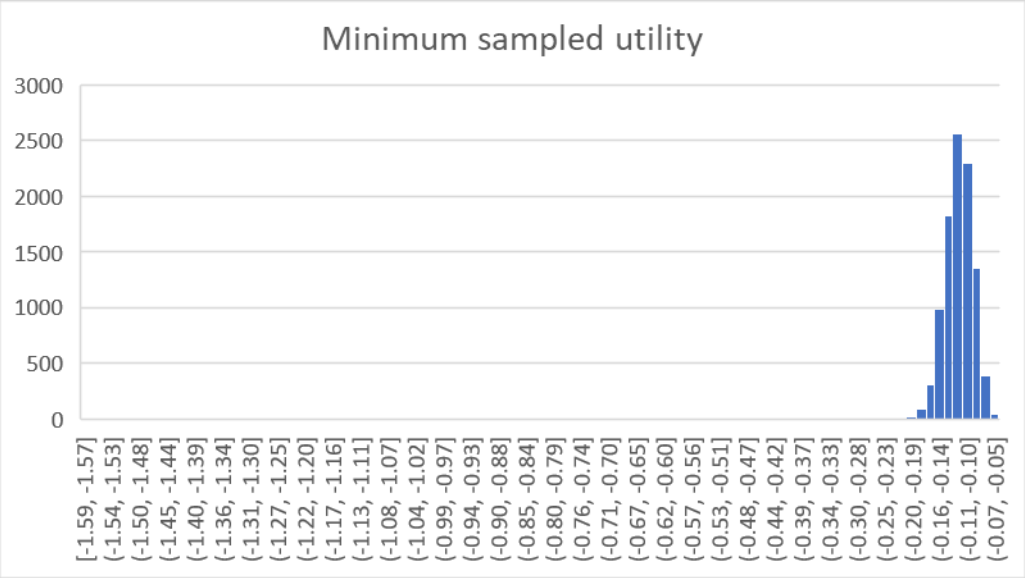
B11. CS, Section 12.4.2, page 221. Uncertainty around utility values have been modelled using shifted negative gamma distributions which range from minus infinity to 1.0. In principle, this approach can allow for sampling of values which are lower than the lower bound of the EQ-5D. Please clarify why this approach has been used.

Company response:

A shifted negative gamma distribution was selected to reflect the theoretical distribution of utilities, bounded between negative infinity and 1. The use of this distribution allows for sampling within the range without the need to force arbitrary limits (a requirement when sampling with beta or normal distributions). While it is common to apply a distribution bounded between 0 and 1, such as beta, in these circumstances utilities <0 are possible in the advanced states of the disease, and therefore applying such a distribution would result in bias. While it is acknowledged that there is an observed lower limit of the EQ-5D-5L with UK tariffs applied, the probability of values less than this being sampled is effectively zero.

To demonstrate, a test was conducted with 10,000 samples and the minimum sampled utility across all health states was recorded, only 0.4% of samples returning a minimum of less than -0.5, and only 0.07% of samples returning a minimum of less than -1. A histogram of the test is presented below in Figure 6.

Figure 6: Histogram of minimum samples from the shifted negative gamma distributions



Costs

B12. Priority. CS, Section 12.1.5, Table D.4, page 205. The model assumes that: (a) patient weight never increases as the cohort gets older and (b) the same number of sachets of ataluren are required for all ambulant/non-ambulant patients (ignoring the distribution of weight across the target population at individual ages). Please provide justification for these simplifying assumptions and comment on why more realistic assumptions of increasing weight with age which varies across the cohort were not applied in the model. Please consider revising this aspect of the model.

Company response:

The base case analysis assumes all patients, regardless of ambulatory status, weigh equal to that of average UK ataluren patients from the STRIDE registry. Ambulatory status was not available for three of the patients within the weight calculations so the average weight for all patients was applied to all patients to allow for all the available data to be used.

As the average weight is calculated using those patients who receive ataluren in clinical practice in the UK, the patient weight assumed in the economic analysis is representative of the indicated population considered in the appraisal. As treatment dosing, and consequently treatment cost, is dependent on weight, applying an average may underestimate the costs for older patients, but also overestimates the treatment

costs for younger patients considered at the beginning of the time horizon, where the influence of the annual discount rate is reduced.

The functionality to consider age based weight gain throughout the time-horizon is included within the model by adjusting the "Model Settings - weight based source" switch to "RCPCH". This assumes that patients gain weight as they age based on the median value presented in the child growth charts from the Royal College of Paediatrics and Child Health (RCPCH), reduced by [redacted]%, which is the average reduction from median weight based on age observed in the UK STRIDE patients. When implementing this scenario, the ICER increases to £[redacted] per QALY gained.

B13. CS, Section 12.2.6, Table D.6, page 211. The table refers to a model parameter labelled "Weight variation compared to healthy children." However, this parameter does not affect the incremental cost-effectiveness ratio (ICER) - this can be seen in the results of the deterministic sensitivity analyses in Tables D18 and D19 of the CS, or by applying alternative values in the executable model. Is this omission intentional?

Company response:

The parameters denoted as "weight variation compared to healthy children" only impact the analysis if the "Model Settings - weight based source" is switched to "RCPCH", which is not selected in the base case analysis. As described in response to question **B13**, the parameter represents the percentage reduction from median child weight based on age, which is applied to the estimated weight of the patients within the cost calculations. The value of [redacted]% presented in the model was calculated as the average percentage reduction in median weight for UK STRIDE patients compared to healthy child growth charts of the same age.

B14. Priority. CS, Section 12.3.6, Table D.5, page 217. The model assumes a treatment adherence level for ataluren of 95% for ambulant patients and 85% for non-ambulant patients. Please clarify the source of these estimates and, if available, provide empirical estimates of treatment adherence from the clinical studies of ataluren, including STRIDE. Ideally, these estimates should be split by ambulatory status.

Company response:

Adherence/compliance data for the use of ataluren was not recorded consistently as part of the real-world data collection from either the STRIDE registry or the NorthStar registry. Within STRIDE, measurements of treatment compliance decisions were made by the treating physicians according to their usual practice, in accordance with local regulations. As such, formal assessments of treatment compliance were not conducted in this non-interventional study. However, most subjects were characterised as highly compliant with treatment.[5]

In the absence of real world evidence, expert opinion was sought as a reliable estimation approach. The global Delphi panel[23] (described in more detail in response to question **B17**) asked clinicians to estimate the level of compliance for ataluren for each of four health states, defined as:

(1) Ambulatory;

(2) Non-ambulatory, not yet requiring ventilation support (pFVC: ≥ 50%);

(3) Non-ambulatory, requiring night-time ventilation support (pFVC: 30%-50%); and

(4) Non-ambulatory, requiring full-time ventilation support (pFVC: < 30%; or FVC <1 litre).

The panel of [redacted] specialist clinicians with a combined clinical experience of over [redacted] patients years reached a consensus that the estimated compliance for ataluren for each health state is as follows:

The average expected compliance to treatment with ataluren in disease stages (1), (2), (3), and (4) was estimated at [redacted]%, [redacted]%, [redacted]%, and [redacted]%, respectively.

The company submission applied a conservative approach which assumed a 95% compliance rate for all ambulatory patients, and then an 85% compliance rate was applied to all non-ambulatory patients who remain on treatment, regardless of pulmonary function status.

B15. CS, Section 12.3.6, page 216. The text states that *"The cost of BSC was not included in the analysis, as the cost of BSC is the same whether is it [sic] treated in*

combination with ataluren, or alone" However, the model suggests that ataluren plus BSC confers a survival benefit over BSC alone; hence, net BSC costs would be expected to be higher for the ataluren group. Please comment on this and, if appropriate, amend the model to include relevant BSC costs which are not already captured in the health state costs from Landfeldt *et al.*, 2017.

Company response:

The health state costs applied to those patients in each health state per cycle, sourced from Landfeldt 2017[27], were originally presented in a cost of illness study published in 2014, which was also authored by Erik Landfeldt[28]. Within the cost of illness analysis, patient medication was included as a cost contributor to the overall costs associated with treating DMD. The paper is not explicit as to exactly which medications were included, but it is assumed this covers all the proposed BSC costs relevant to UK clinical practice.

For this reason, it is the company's position that BSC medication costs accrued by both ataluren and BSC patients over the course of their lifetime are accounted for within the health state cost calculations sourced from Landfeldt 2014[28]. Explicitly modelling BSC costs would therefore be double counting, and over-estimate the total cost in both arms of the model.

B16. CS, Section 12.3.8, page 219. The text states that the costs associated with AEs are not included in the model. However, the model suggests that ataluren confers a survival benefit versus BSC alone, which may result in greater net costs associated with AEs for ataluren. Please comment on this and, if appropriate, amend the model to include relevant AE costs.

Company response:

PTC accept that there are established safety and tolerability issues associated with long-term corticosteroid usage. As the question implies, it is assumed the costs and QoL implications of adverse events associated with BSC will be similar between the treatment arms during the time patients are alive, therefore it is not necessary to model these explicitly.

As discussed in response to question **A13** the adverse event rates for patients receiving ataluren + BSC are negligible (<5% grade 3 or greater in the ataluren + BSC arm). The general approach taken towards economic modelling is to aim to consider only those adverse events that will results in a significant reduction in patient QoL or accrue genuine costs to the healthcare system. The rule PTC elected to apply is that AEs will be included if any specific adverse event occurs in greater than 5% of treated patients, at a grade 3 or higher. This aims to identify those adverse events that are actually correlated with treatment and are of a sufficient level of severity to reduce QoL and incur costs.

As presented in Table 6 and Table 7 in response to **A13**, no more than 5% of treated patients experienced any adverse events of grade 3 or greater. This implies that no individual AE occurred in greater than 5% of treated patients at grade 3 of above. For this reason, the decision was made that there is no significant influence on the cost-effectiveness analysis to include the impact of adverse events to either treatment arm, regardless of different lengths of survival.

Model validation

B17. Priority. CS, Section 12.1.5, Table D4 (all references to the global Delphi panel), page 205. The first row of Table D4 includes estimates of additional benefit for ataluren in delaying the time of loss of milestones. Several other assumptions in this table are also reported to have been derived from this Delphi panel. However, the description of this Delphi panel in Section 10.1.10 only appears to refer to the elicitation of health utility values and Section 12.3.2 refers to two published economic

studies by Landfeldt *et al.* Please provide further detail regarding the design and implementation of the global Delphi exercise, including:

(a) The questions asked to inform/support assumptions of benefit with early treatment with ataluren and other structural assumptions detailed in Table D4.

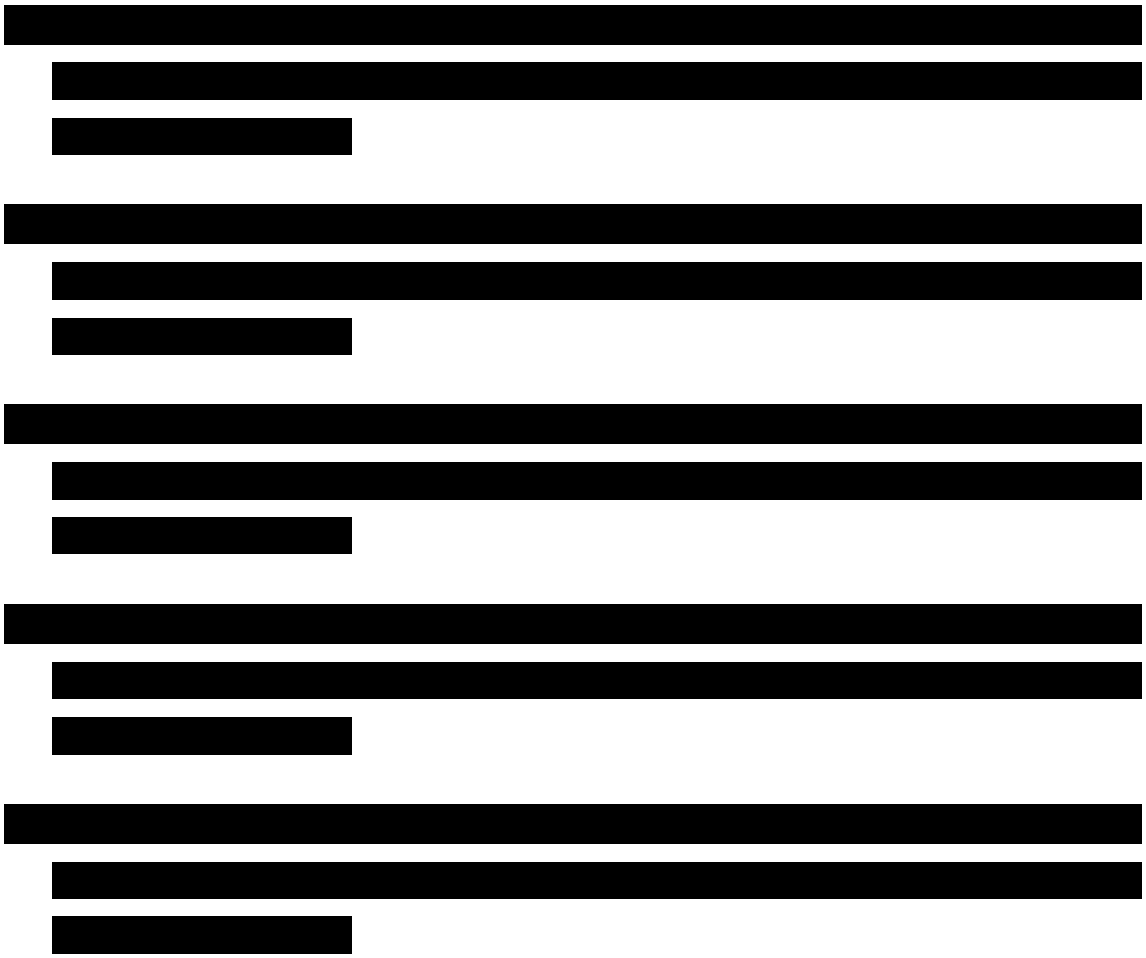
(b) The minutes of the meeting, if available.

(c) How disagreements between participants were resolved during the Delphi exercise, including how/whether feedback was given to participants to allow them to reassess their initial judgements.

(d) Whether subsequent input obtained from UK clinical experts fully agreed with the consensus values obtained from the Delphi exercise (and if not, how disagreements were resolved).

Company response:

The following questions were asked as part of the global Delphi panel questionnaire to inform assumptions listed in Table D4 of the CS:



[redacted]

Each iteration of the questionnaire provided feedback from the previous iteration to allow and encourage the panellists to re-assess their initial judgements. The panellists were asked to re-assess only questions for which consensus had not been reached based on summary feedback of the most common answers from the previous iteration. In this panel, consensus for each nominal/ordinal question was pre-specified to have been achieved when at least [redacted]% of the participating experts (rounded to nearest integer) agreed of the appropriate response level/category. Consensus for continuous outcomes was pre-specified to have been achieved when all ratings fell within a range

of ±[redacted]%, or when at least [redacted]% of the participating experts (rounded to nearest integer) agreed to an exact value.

Full details of the Delphi panel process and results can be found in the report that has been uploaded as part of the response[23].

The assumptions of delay in pulmonary disease milestones, number of caregivers and compliance made based on the global Delphi panel were supported by input from UK clinical experts. Minutes from these UK clinical expert discussions are provided in Appendix 1 and are discussed in response to question **B18**.

B18. Priority. CS, Section 12.2.5, page 211. The text states that *"Further validation with UK clinicians was conducted to validate key model assumptions."* Please clarify who determined the values prior to validation by external experts. If available, please provide minutes of these meetings.

Company response:

The assumptions validated by UK clinicians were either originally proposed by PTC in an attempt to most accurately model the impact on costs and QoL of DMD on patients, were initially based on the values obtained in the global Delphi panel or validated the generalisability of the STRIDE data to the UK population.

The assumptions which were validated by UK clinicians regarding inputs sourced from the Delphi panel were as follows:

- Improved quality of life in patients receiving ataluren plus BSC, versus BSC alone.
- Average number of caregivers per patient.
- Compliance for ambulatory and non-ambulatory patients receiving ataluren.

The following assumptions validated by UK clinicians were made based on data observed in the STRIDE registry:

- Extending the treatment stopping rule with ataluren beyond LoA.

- Delay in time to pFVC < 30% based on experiencing a delay in reaching earlier disease milestones.

- Weight variation in nmDMD patients.

Minutes from the interview with UK clinical expert Dr [redacted] and [redacted] are presented in Appendix 1.

It is worth commenting that there are a number of points the UK clinicians raised which did not perfectly align with the methods implemented within the economic analysis. Notably, comments regarding the stopping rule, the appropriateness of different health state utility values for each treatment arm and the number of full-time carers required within the ambulatory health state.

With regards to extending the stopping rule, comments from clinicians were taken into consideration that it would be more appropriate for patients to remain on treatment beyond LoA, however a more pragmatic approach was adopted which considered the cost-benefit relationship of keeping patients on treatment when their QoL is very poor and unlikely to improve. Therefore, the stopping criteria was amended to when night-time ventilation is required (proxy pFVC < 50%), which was deemed the most appropriate. This also more closely aligns with the treatment patterns observed within the STRIDE cohort as described in response to question A7.

For both the appropriateness of different health state utility values for each treatment arm, and the number of full-time caregivers required, the UK clinicians did not offer the same opinion. The original source for these assumptions was the global Delphi panel which provided the consensus of [redacted] clinicians over three rounds of the Delphi process[23]. The decision was made that, when there was differing opinions between UK clinicians, reverting back to the opinion of the Delphi panel was the most robust approach based on the number of clinicians who contributed to the Delphi panel, and the attempt to reach a consensus as part of the Delphi process. Additionally, utility values elicited from the Delphi panel were derived the health utility index (HDI) which contained questions related to specific aspects of QoL (emotion, pain, discomfort, mobility, etc.), whereas the questions proposed to clinicians as part of the local validation process were singular questions, seeking qualitative responses.

B19. Priority. CS, Section 12.2.2, page 210. The text states that parametric survival model selection included *"Visual inspection of curve fit to trial period and expected extrapolated period."*

(a) Please clarify how considerations of clinical plausibility were used to inform parametric model selection.

(b) If the parametric survival models were presented to clinical experts for the purposes of validation, please clarify if these were the unadjusted survival models, or the adjusted model predictions which include other constraints applied in the executable model.

Company response:

Clinical plausibility of the extrapolation was considered in a number of different contexts.

Firstly, distributions such as the "exponential" distribution, which obviously failed to capture the nature of observed data, were dismissed upon initial inspection.

The vast majority of the standard parametric models generated visually similar fits to the observed data, for all of the health state transitions, for both treatment arms.

At this stage our selection approach evaluated which survival models generated the best goodness of fit statistics and assessed whether the period of extrapolation beyond the observed period seemed clinically plausible. An example of a survival function not providing a clinically plausible extrapolation may be that the survival functions produces a "plateau" towards the end of the follow up period, in which the risk of observing the event has significantly reduced as time goes on. From a clinical perspective, it is very unlikely any patients will survive for a large number of years before experiencing disease progression when most patients have already reached this disease milestone at an earlier age. This is somewhat based on the inevitability of disease progression within DMD, an assumption that may not hold for oncology models, for example.

The selected survival models both optimised the goodness of fit statistics (indicating a good representation of the data over the observed period) and were deemed to provide clinically plausible extrapolation estimates, and were therefore accepted as optimal models to inform the economic analysis.

As mentioned in response to question **B2**, selecting alternative plausible survival curves to inform health state transitions in the economic analysis has a minor impact on the final ICER. This relates back to how similar each of the fitted survival models are with regards to the modelled survival functions.

B20. Priority. CS, Section 12.1.5, Table D.4, page 205. Incremental survival gains for ataluren are driven almost entirely by assumptions. Please provide a graphical comparison of model-predicted overall survival for the ataluren and BSC groups versus observed data from STRIDE and the propensity-matched CINRG dataset.

Company response:

Comparison between the STRIDE and propensity-matched CINRG DNHS datasets and the model-predicted overall survival is not possible because, as of the January 2021 cut-off, no participants have died in the STRIDE registry, despite patients being observed for up to 7 years. Therefore, there is no real-world data to compare mortality between patients receiving ataluren and BSC vs BSC alone. Because of this, it is necessary to make assumptions in the model to predict mortality in patients receiving ataluren. For this reason, delays in disease progression for earlier milestones have been used in the model to estimate delays in mortality.

Although 45 deaths were reported in the CINRG DNHS study[6], it was not reported how many of these occurred within the propensity score matched CINRG DNHS population, and as no patients died during follow up in STRIDE, it is not possible at this time to provide a graphical comparison between observed mortality and model predicted mortality.

Published literature supports that delays in pulmonary function such as a pFVC <1L (approximately equivalent to a pFVC < 30%) is strongly predictive of mortality within 3 years and associated with a 4-fold increased risk of death.[20,21] This assumption is supported by UK clinical expert validated evidence from the global Delphi panel. As pFVC < 30% was validated by the global Delphi panel as a prognostic indicator of a life expectancy of 3 years, the overall survival of patients receiving ataluren in the model relies on the assumption that a delay in the pFVC < 30% milestone is indicative of a delay in mortality. Please refer to the response to question **A14** for more details on the rationale behind the implemented assumptions.

The model mortality implementation also assumes that disease related deaths occur 3 years after a patients has reached a pFVC<30%. In practice it is possible patients die due to disease related causes earlier than this point. For this reason, the model mortality assumptions likely underestimate the mortality rate for patients receiving BSC as it assumes no patients die due to disease related causes before 3 years after reaching pFVC <30%, which is unlikely to be the case in practice.

The model also assumes an early treatment benefit associated with starting ataluren at 2 years of age rather than 5 years of age. This is applied to all health states, including reaching pFVC <30% which in turn delays mortality. This assumption was again supported by input from clinicians as part of the global Delphi panel, in the absence of long-term follow data to be able to inform this.

Model results

B21. CS, Section 12.5.11, pages 237 to 246. All deterministic sensitivity analysis and scenarios presented in this section apply the same severity weighting based on the undiscounted QALY gain estimate from the base case analysis. However, the value of this severity modifier may differ in deterministic sensitivity/scenario analyses which impact on incremental QALY gains. Please present the results of all sensitivity analyses excluding the severity modifier. If possible, for all analyses, provide the estimate of life years gained (LYGs) separately.

Company response:

As discussed in the correspondence, there is no longer the requirement to address this question.

The ERG did request that an explanation is provided as to how the model can be adjusted to present the results of a scenario in which Kaplan Meier data is used over the observed period for health state transitions. This can be achieved by setting cells D29, D30, D42, D43 and D54 to “Yes” in the “Model Settings” sheet.

Executable model

B22. Section 12.2.6, Table D.6, page 212. The text refers to assumptions applied in the “broad indication.” The ERG understands that this relates to the use of ataluren

in children from 2 years of age. Please clarify how to deselect this option in the executable model - i.e., can this be switched off using in-built model settings?

Company response:

The broad indication can be de-selected by changing the baseline age to 5, then removing all of the "early treatment benefit". All of the inputs required can be found on the "Model settings" sheet.

Formally, this involves editing cell D7 to "5 years old" and then cells D35, D48, and D60 to "0".

B23. CS, Section 12.1.7, Table D.5, page 208. The model employs a 3-month cycle duration. Please clarify why this cycle length was chosen.

Company response:

A 3-month cycle length was chosen as it would offer sufficient granularity and allows for a timeframe in which meaningful disease progression may be observed, without over-complicating the analyses. The model considers a lifetime time horizon from the age of 2, favouring long cycle lengths are important for the efficiency of the model. In addition, most routine visits occur at a 3- to 6- month interval, so a three-month cycle length was assessed to be sufficiently short, to not have two "events" occurring in the same cycle.

Secondly, a 3-month cycle length was proposed within the model developed as part of project HERCULES, providing a "transfer state" (i.e. a state between ambulatory and non-ambulatory), which was not included (which was not possible within this analysis due to data limitations).[21] The main focus of project HERCULES was to allow patients, clinicians, pharmaceutical company representatives, and HTA body representatives a platform to work collaboratively to develop an economic model which most accurately represents the costs and QoL implications of DMD.

B24. Model, life year gained (LYG) calculations in worksheet "Ataluren and BSC" cells AQ12:AZ12 and worksheet "BSC" cells AI12:AR12, The LYG calculations omit the first row of the half-cycle corrected model trace (i.e., the contribution to LYGs in the interval between cycle 0 and cycle 1 are ignored). This issue propagates through

the QALY and cost calculations. Please confirm that this is an error and correct the model.

Company response:

PTC agree that the calculations in the trace should be edited to include the first cycle of health state transitions. The economic model has been updated to reflect this change and the updated base case results are presented in Table 16Table 16 below.

Table 16: Updated base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren + BSC							

*Total incremental QALYS are weighted using the HST decision modifier[204]
ICER: Incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

References:

1. Campbell C, Barohn R, Bertini E, *et al.* Meta-analyses of ataluren randomized controlled trials in nonsense mutation Duchenne muscular dystrophy. *J Comp Eff Res* 2020. 9: 973–984.
2. translarna-h-c-2720-ii-0037-epar-assessment-report-variation_en.pdf. at <https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-ii-0037-epar-assessment-report-variation_en.pdf>
3. PTC Therapeutics. *A Phase 2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Ataluren (PTC124®) in Patients Aged ≥2 to <5 Years Old With Nonsense Mutation Dystrophinopathy*. (clinicaltrials.gov, 2020). at <https://clinicaltrials.gov/ct2/show/NCT02819557>
4. Henricson E, Abresch R, Han JJ, *et al.* Percent-Predicted 6-Minute Walk Distance in Duchenne Muscular Dystrophy to Account for Maturational Influences. *PLoS Curr* 2012. 4: RRN1297.
5. PTC Therapeutics Clinical Study Report. *(Fifth Interim Report) PTCT124-GD-0250-DMD. Long-term observational study of Tranlsarna safety and effectivenees in usual care*. (2021).
6. EMA. Translarna. *European Medicines Agency* 2018. at <https://www.ema.europa.eu/en/medicines/human/EPAR/translarna>
7. translarna-epar-product-information_en.pdf. at <https://www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information_en.pdf>
8. translarna-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. at <https://www.ema.europa.eu/en/documents/procedural-

steps-after/translarna-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

9. McDonald CM, Henricson EK, Abresch RT, *et al.* Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet Lond Engl* 2018. 391: 451–461.
10. McDonald C, Henricson E, Abresch R, *et al.* The cooperative international neuromuscular research group duchenne natural history study-a longitudinal investigation in the era of glucocorticoid therapy: Design of protocol and the methods used. *Muscle Nerve* 2013. 48: 32–54.
11. Ricotti V, Ridout D a, Pane M, *et al.* The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. *J Neurol Neurosurg Psychiatry* 2016. 87: 149–155.
12. Humbertclaude V, Hamroun D, Bezzou K, *et al.* Motor and respiratory heterogeneity in Duchenne patients: Implication for clinical trials. *Eur J Paediatr Neurol* 2012. 16: 149–160.
13. Rall S & Grimm T. Survival in Duchenne muscular dystrophy. *Acta Myol Myopathies Cardiomyopathies Off J Mediterr Soc Myol* 2012. 31: 117–120.
14. Essen AJV, Verheij JBGM, Reefhuis J, *et al.* The natural history of Duchenne muscular dystrophy . Analysis of data from a Dutch survey and review of age related events. *PhD Thesis* 1997.
15. Ferizovic N, Summers J, Zárate IBO de, *et al.* Prognostic indicators of disease progression in Duchenne muscular dystrophy: A literature review and evidence synthesis. *PLOS ONE* 2022. 17: e0265879.

16. Stuart EA, Lee BK & Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. *J Clin Epidemiol* 2013. 66: S84-S90.e1.

17. Zhang Z, Kim HJ, Lonjon G, *et al.* Balance diagnostics after propensity score matching. *Ann Transl Med* 2019. 7: 16.

18. Mercuri E, Muntoni F, Osorio AN, *et al.* Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *J Comp Eff Res* 2020. 9: 341–360.

19. McDonald CM, Muntoni F, Penematsa V, *et al.* Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients. *J Comp Eff Res* 2022. 11: 139–155.

20. Ribeiro D & Meadowcroft R. NICE Managed Access Agreement - Ataluren. 15.

21. Project Hercules – A Duchenne UK Global Collaboration. at <https://hercules.duchenneuk.org/>

22. Mercuri E, Muntoni F, Osorio AN, *et al.* Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *J Comp Eff Res* 9: 341–360.

23. Landfeldt E, Zhang R, Childs AM, *et al.* Draft Manuscript: Assessment of face validity of a cost-effectiveness model of nonsense mutation Duchenne muscular dystrophy: a multi-national Delphi panel study. 2022.

24. NICE DSU - Modelling carer health-related quality of life. at <https://nicedsu.sites.sheffield.ac.uk/methods-development/modelling-carer-health-related-quality-of-life>

25. NICE HST7 Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency [ID926].pdf.

26. Ara R & Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2010. 13: 509–518.

27. Landfeldt E, Alfredsson L, Straub V, *et al.* Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. *PharmacoEconomics* 2017. 35: 249–258.

28. Landfeldt E, Lindgren P, Bell CF, *et al.* The burden of Duchenne muscular dystrophy: An international, cross-sectional study. *Neurology* 2014. 83: 529–536.

Appendix 1.

Meeting minutes from discussions with UK clinicians.

Minutes from the interview with UK clinical expert Dr [redacted] are presented below:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Minutes from the interview with UK clinical expert Dr [redacted] are presented below:

[redacted]

[redacted]

NICE National Institute for Health and Care Excellence

Highly Specialised Technologies (HST)

Guidance review following a period of managed access - Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted] and [redacted]
2. Name of organisation	Muscular Dystrophy UK and Action Duchenne
3. Job title or position	[redacted] and [redacted]
4a. Provide a brief description of the organisation. How many members does it have?	Muscular Dystrophy UK is the charity bringing individuals, families, and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences Clinical Reference Group. Action Duchenne was the first national charity dedicated to supporting those living with Duchenne muscular dystrophy, affecting 2.500 young people, adults and their families in the United Kingdom. Action Duchenne has a very clear vision: a world where lives are no longer limited by Duchenne muscular dystrophy. We brought together scientists who developed the 'exon skipping' drugs that offer hope for some living with Duchenne. Our research funding has given more than 130 people the chance to take part in a clinical trial and we fund gene therapy clinical trials so even more families can be offered the opportunity. We build community through uniting and supporting families, educating about Duchenne and raising the profile of the condition to a wider audience. Our support officers provide a vital lifeline to over 2,000 families living with Duchenne every year. We are committed to strive for a more inclusive society promoting the importance of human equality, day to day acceptance of disability and accessibility. We are a member of World Duchenne Organisation and Genetic Alliance UK.

	This submission was written in collaboration with Action Duchenne. Both MDUK and Action Duchenne are members of the Translarna Managed Access Oversight Group.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	DATE AMOUNT DESCRIPTION 27-Jan-21 £10,103.00 MDUK/NorthStar funding - JAN, FEB , MAR 12-Mar-21 £6,000.00 SILVER SPONSORSHIP UCL TRANSLATIONAL CONFERENCE 06-Apr-21 £10,103.00 MDUK/NorthStar funding - APR, MAY , JUN 25-Jun-21 £18,000.00 SEMINAR MUSCLES MATTER SERIES 09-Jul-21 £10,103.00 MDUK/NorthStar funding - JUL, AUG, SEP 11-Oct-21 £10,103.00 MDUK/NorthStar funding - OCT,NOV,DEC £64,412.00 In 2021, Action Duchenne have received £60k grant from PTC: - £35k for the 2021 International Conference - £25k for the jointly Newly Diagnosed Families and Science Education Project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered by the following means: - Results from a national survey run by MDUK and Action Duchenne to gain insight into the physical and mental health impact experienced by people with Duchenne muscular dystrophy whilst taking Translarna. This included insight into the impact on ambulation, other healthcare aspects such as respiratory and cardiac function, quality of life, and the wider impact on their family and friends. From the approximately 60 people with Duchenne muscular dystrophy on the managed access scheme, we received 26 responses of which 4% were a person with DMD, 81% were parents of a child with DMD, and 15% were either a carer or a sibling/wider family member.

	- Feedback received during an online webinar held by MDUK and Action Duchenne where we heard from Duchenne families on the impact of Translarna. - The ongoing dialogue that both MDUK and Action Duchenne have with the Duchenne community. - Previous appraisal responses and surveys on the impact on Translarna from the original MAA scoping.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Duchenne muscular dystrophy (DMD) affects one in 5,000 live male births in the UK and a very small number of females. The average age at diagnosis is around five years, but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier. This delay in diagnosis can have a devastating impact on families who may have two or more children diagnosed with DMD by the time of diagnosis of the oldest child. There is often very little psychological support for a patient and their family when a DMD diagnosis is confirmed to help them come to terms with the diagnosis. Caregivers often suffer with depression and anxiety after diagnosis and have prolonged absences from work. Because of the progressive nature of the disease, the depression and anxiety continue at the loss of each milestone - both for patients and their caregivers. Children with DMD lose the ability to walk independently and most become reliant on wheelchairs for mobility between the ages of 8 and 13. Some children with DMD never walk. Many may initially retain the ability to weight bear and support transfers, for example from wheelchair to toilet or car, before losing the ability to stand. As DMD progresses patients will lose strength and mobility in their arms. They will lose the ability to feed themselves, brush their teeth or undertake any self-care activities. Patients are likely to retain some function in the hands and fingers into adult life. The impact of DMD on a child's mobility and ambulation leads to a requirement for a significantly adapted environment in order to accommodate mobility aids such as powerchairs and assistive mobility equipment

	such as ceiling hoists. This requires major and costly adaptations to an individual's home and finding a fully accessible educational environment can be a significant challenge. As DMD progresses, children with the condition may become more constrained in terms of the activities they can undertake compared to their peer group, which can place a strain on friendships as well as having a further psychological impact on the individual. In addition to ambulation, most individuals with DMD experience serious respiratory (such as chest infections), orthopaedic (weaker bones), and cardiac complications (weaker heart muscles). By the age of 18, most patients require ventilation support at night. There have been a range of estimates of life expectancy, with the most recent study by *Broomfield et al.* (2021), which involved undertaking a systematic review of available publications to better understand life expectancy, estimating a median life expectancy of 22 years rising to 28.1 years for patients born after 1990[1]. Life expectancy has increased through improvements in the standards of care, but it is worth noting many patients still die before they reach their twenties. Dystrophin is also present in the brain and many people with DMD may have learning disabilities or neurological disorders such as autism or learning disabilities. These usually remain static and do not worsen as DMD progresses.
7. What do carers experience when caring for someone with the condition?	DMD can have an acute impact on family and friends. Many parents have told us about the devastating psychological impact of hearing a confirmed diagnosis; of watching their children struggling to walk; and of them becoming non-ambulant. This impact becomes even more profound as children start developing respiratory and heart complications. We frequently hear that carers are worried how long their child will live and what quality of life they will experience. For example, seeing them unable to participate in activities with other children such as going to the park, playing sports, and going to friends' houses. One parent told us that they don't get the opportunity to enjoy being a parent as being a carer comes first. Many families also need to take time off work (or to stop working altogether) to take care of their child by attending appointments, helping with their treatments (such as physiotherapy), and their day-to-day

[1] Broomfield et al, Life Expectancy in Duchenne Muscular Dystrophy, October 2021: https://n.neurology.org/content/97/23/e2304

	activities. This can place a financial strain on the family but cannot be avoided to ensure their child gets the care they need.
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Treatment and care for DMD has improved over the years which has resulted in improvements in life expectancy. Standard medical management of DMD requires attention to the use of corticosteroids as well as respiratory, cardiac, orthopaedic, and rehabilitative interventions. However, these treatments focus on symptom management and are associated with a heavy burden of care. For example, corticosteroids slow the progression of muscle weakness and delays some of the complications of the disease, but they do not treat or correct the underlying causes of DMD. Additionally, they have severe and very detrimental side effects that hugely impact on quality of life. These include serious effects on bone health leading to excess fractures, extreme weight gain, stunted growth which causes psychological distress and physical pain, and can cause adrenal insufficiency and crisis if not administered correctly, can delay puberty and the associated psychological challenges of that, and can cause behavioural problems. Due to the progressive nature of the condition and that current treatments and care available on the NHS do not prevent that, patients can become disengaged from their care particularly as they enter adolescence, and the progression becomes more severe despite the strain and disruption of appointments with multiple specialists and health professionals. Translarna is the first treatment to tackle the underlying root cause of DMD.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	Yes, Translarna is the first treatment to tackle the underlying root cause of DMD.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA review patient submission guide	Overall, 100% of respondents to the MDUK and Action Duchenne survey stated they had a very positive experience in accessing and having Translarna. A strong theme was the ease at which Translarna could be administered as it is a powdered sachet. This made it easy to incorporate into their daily lives without placing an additional burden of treatment on them.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA review patient submission guide	<u>Ambulation</u> Feedback on the main advantage of the treatment is centred around improvements to ambulation, with 100% of respondents noticing this improvement. All respondents provided examples of how the person with DMD is now able to walk better, has experienced a significant reduction in trips and falls, and has stronger muscle strength. One respondent told us: *"Very positive experience, our son saw an improvement in his ability to walk within a couple of weeks, he's still walking well for a good distance, we also noticed a significant reduction in trips and falls. We also noticed that his concentration levels improved (school also noticed this)."* Similarly, another respondent told us: *"My son started taking Translarna when he was two. Before he started taking Translarna he couldn't crawl or walk. Within a week or two he was crawling then pulling himself up to stand and cruising along furniture. Within months he was finally walking, and we know this has a lot to do with Translarna."* These vast improvements were a dominating theme in our findings, with another respondent telling us: *"It has made our life to be honest. Seeing our child go from non-ambulant to ambulant when we thought he might never walk. It's just amazing and makes us so happy to watch him running around and having so much energy."*

	Heart and Respiratory 75% respondents fed back that heart and respiratory function remained stable due to Translarna. This in turn has had a positive impact on their overall health and wellbeing, with one respondent telling us: *"Very positive, my son is 12 and can run, cycle and swim. He has good cardiac and lung health, good upper body strength and no issues with side effects. He also only takes steroids 10 days on 10 days off."* Similarly, we heard that some experienced less chest infections and saw improvement to their breathing. For example, we heard: *"He used to suffer from recurring chest infections but since being on Translarna this has massively improved, and he hasn't had a chest infection."* Quality of Life 88% of respondents stated that being on Translarna had improved the individuals' overall quality of life. These patients were able to participate more in activities, found attending school much easier and were able to follow the workload (due to improvements in fatigue). Several respondents also noted the improvement in their child's behaviour as Translarna would lessen the number of emotional outbursts. One respondent told us: *"He has more energy he's literally never tired. He can play for longer periods with his friends and join in without any problems. He has less falls, can walk long distances without getting tired. He can do lots of fun things that he enjoys doing which greatly improve the quality of his life."* Another respondent told us: *"My son's behaviour improved almost immediately after taking Translarna and this made a fantastic difference to the whole family in terms of what we were able to do. He is not able to tolerate a full steroid dose but with Translarna there was an increase in ability as much as when he started taking steroids."* Mental Health 72% of respondents said that being on Translarna had a positive impact on their mental health. A leading theme in our survey results was on the potential of a treatment slowing the effects of DMD and there now being 'hope for a future'. Others focused on how much joy they got at being able to do everyday activities.

	For example, we heard from one respondent saying: *"As our son has gotten older, the fact that he is on something that could even potentially be slowing the effects of the DMD has a huge impact on his mental health"* Similarly, we heard from another respondent: *"A huge positive impact; being able to be mobile, to do more every day activities have given him so much happiness and enjoyment of life, and also hope for the future has increased with taking Translarna"* <u>Family and friends</u> Our results found that 100% of respondents mentioned that having access to a treatment gave them hope and reduced their anxiety when thinking about their child's future. Many highlighted that previously they would never think about the future whereas Translarna has given them the opportunity to start making plans and thinking about what their child could do such as in their career, starting a family, etc. For example, one respondent told us: *"It has given us hope, it allowed us to live a full life as he's able to play with his sister and friends, he's still walking really well…in fact asking to go for walks which gives us as family so much joy. It offers us a level of comfort, knowing that a treatment is available to our boy."* Similarly, we have heard what a relief it has been given how devastating the diagnosis was when there was no cure. For example, we heard: *"It has been very positive, as the prognosis at birth for our young person/family member was very bleak; we were told they wouldn't be ambulant by the age of twelve and would need assistance to breathe. We all think it's amazing that Translarna has helped to transform this diagnosis into a more hopeful outcome."*
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA review patient submission guide	We are not aware of any disadvantages relating to the taking of the technology, its impact on others, its financial impact on the patient and families or any associated side effects. Currently, ataluren has only been tested on ambulant and outcome measures have been focused on walking ability.

	Whilst ataluren's mechanics of action suggest it could improve other aspects of physical function, not solely related to walking, there have been no clinical trials as of yet to confirm this. There is no indication that the drug would have adverse effects on other aspects of the condition.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Translarna has had a clear impact on not just ambulation, but on the overall physical health for people with DMD which reduces their need to have as many face-to-face appointments and provides an opportunity for care to focus on prevention rather than reactive treatment as and when symptoms arise. The clear benefits experienced by patients receiving the treatment make it essential that it becomes a standard component of the treatment and care of DMD caused by nonsense mutations. Additionally, it is clear from our findings the wider positive impact that Translarna has had on mental health and quality of life for not just the individual but also on family and friends. Ensuring continued access to Translarna will in the long-term reduce the complexity of their care by decreasing the number of appointments they may need such as seeing a neuromuscular consultant and predominantly be seen by a physiotherapist or nurse. This will mean the consultants have more time for other patients with a neuromuscular condition. Additionally, given the impact the pandemic has had on mental health and the lack of support in place, having improved mental health will also reduce the pressure on mental health services.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the**	Although we are unable to comment on measuring the clinical effectiveness of the treatment, as with all tests and measurements in Duchenne it is important to remember what you are comparing results to. As Duchenne is a muscle-wasting condition, there will be a baseline level of decline in all patients. Some patients will experience decline more quickly, some will experience decline at a slower rate. When measuring the effectiveness of this treatment, and the impact it has on families and their lives, it is important to also consider how more advanced the decline may have been without access to the treatment. For many people living with Duchenne and their families, even the smallest increment of

effectiveness of the treatment?	reduction in decline due to access to a treatment, can be the difference between walking 2 steps and not walking at all, or getting in the bath themselves, versus needing a hoist to get them in the bath.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Due to the nature of Duchenne muscular dystrophy, fatigue, tightness of muscles and joints can occur at different levels on different days for each individual. It is also important to consider behavioural challenges and differences in North Star Assessment protocols when surveying the evidence to make sure it is balanced and takes all aspects into consideration. Although the standardised tests and assessments are industry standard, they may not always give an accurate result due to external, not recorded, factors, such as steroid regime on that day, did the child have PE or a late night etc.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	Overall, most patients felt the tests and assessments captured their experiences adequately. However, one respondent did raise a concern regarding how any fluctuation in results would be considered. They specifically mentioned: *"We feel Translarna has benefited our son, and it is a big concern to think about him not being able to continue taking it. If the data being used is taken from his physio appointments, he has had a few bad appointments which probably do not give the best results on the specific day. He struggles with the big appointment days and does not always do his best in the physio examination."* An addition underlying concern from parents has been on the completion rate of the data captured given some had to travel long distances to attend appointments and weren't always able to do so during the pandemic. MDUK's Shine a Light report (2021), which looked at the impact of COVID-19 on people with a muscle-wasting condition and their access to specialist services, found that many clinical trial appointments were cancelled or postponed. Parents were therefore concerned that there may be gaps in the data[2].

[2] Muscular Dystrophy UK, The impact of COVID-19 and the future of care for people with a muscle-wasting condition, July 2021: https://www.musculardystrophyuk.org/static/s3fs-public/2021-07/POL14%20-%20Impact%20of%20COVID%20report.v4.pdf?VersionId=apq4P8Je32l.hgaQFd0h8HyzX_DMxWw9

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	The MAA primarily focused on ambulation and quality of life. However, our findings have shown a myriad of wider benefits such as improved upper body strength, reduction in chest infections and less complications with the lungs and heart.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	As part of the MAA, there has been a clearly defined group eligible to receive treatment; those with a nonsense genetic mutation who are aged 2 and over who are able to walk. We urge NICE to broaden access to Translarna to everyone with a nonsense mutation who could benefit from the treatment. For example, we believe the scope should be widened to those who are non-ambulant as feedback has shown the wider benefits of Translarna beyond lower body mobility.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	We haven't heard from anyone who decided not to start the treatment when eligible.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

It is important to ensure that no patient has to travel excessive distances to receive the treatment given the level of disability that many face.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

No other issues to raise.

22. What do patients or carers think about the current treatment stopping rules in the managed access agreement?

The main stopping criteria is when a person is no longer ambulant. However given the wider benefits of the treatment, we strongly believe this stopping criteria should be reviewed.

23. What do patients or carers think about the removal of the following wording from section 4.1 of the Summary of Product Characteristics (SmPC) for ataluren: "Efficacy has not been demonstrated in non-ambulatory patients"

Patents and carers were pleased to hear this wording was removed. The DMD community have expressed concerns of excluding non-ambulatory patients given the other myriad of improvements they had experienced (such as heart, respiratory and upper body muscle strength). For example, one respondent told us their son stopped walking two years ago but that many other aspects of his health have improved thanks to Translarna.

24. What do patients or carers feel are the benefits and disadvantages of the potential continuation of treatment in people who have lost the ability to walk?

Patient and carers feedback on the advantages of Translarna for people who have lost the ability to walk has been very positive. These patients still feel the wider aspects of their Duchenne symptoms have improved such as stronger upper body muscles, as well improvements to their lungs and heart. This has a significant impact on their overall quality of life as they can still do their daily activities independently such as brushing their teeth, eating their own food, the stronger upper body means they can also hoist themselves out of their wheelchairs which gives them additional independence. Additionally, being able to keep this independence for longer also has a significant positive impact on their mental health.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- All respondents experienced significant improvements to their ambulation, with examples showing how the person with DMD is now able to walk better, they've noticed significant reduction in trips and falls, and stronger muscle strength.
- 75% of respondents fed back that there was a significant wider impact as well, mostly around improved upper body muscle strength, stronger heart and lungs, which in turn has had a positive impact on their overall health and well-being. This includes improvements to concentration and less fatigue which has enabled improvements at school.
- Overall, this has led to improved quality of life as people with DMD are able to stay independent for longer and able to undertake their daily activities and socialise more. As a wider result, families have expressed reduction in anxiety and burden of care with many stating they feel more 'like a family' rather than a carer.
- 72% of respondents said being on Translarna had a positive impact on their mental health. A leading theme in our survey results was on the potential of a treatment slowing the effects of DMD and there now being 'hope for a future' (for both the individual and their parents).

- The myriad of advantages from taking Translarna are clear and it is imperative that every person with DMD due to a nonsense mutation benefits, regardless of ambulation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Review following a period of managed access

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**NHS ENGLAND**
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for this condition or this treatment
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a nationally commissioned highly specialised service (HSS) for the treatment of Duchenne muscular dystrophy but it is one of the neurological conditions covered by the paediatric neurosciences (neurology) service specification. This service is commissioned from a number of expert centres.
8. What impact would the technology have on the current pathway of care?	If the technology were approved it would not change the pathway of care or where patients are treated.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This therapy is not commissioned for routine use by NHS England.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for this patient cohort.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be used in the existing specialised centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Starting the treatment would require a confirmed genetic diagnosis but this is already part of the care pathway.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Katherine Wedell**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ **x** a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Action Duchenne
4. Did your nominating organisation submit a submission?	☐ **x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ **x** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Firstly, devastation at our son [redacted]'s diagnosis (he was 4 years old); profound grief, depression, and anxiety in the years following diagnosis. Also a very steep learning curve at that time as we navigated the 19 or so specialists involved in our son's care. Major research/negotiations to find a wheelchair accessible school with an inclusive ethos. I had to give up my work and career, to deal with the impact of DMD, cope with the number and frequency of appointments, and get my head around the complexity of DMD. Because it's progressive, you always have to keep ahead of it, anticipate what's coming and what can be done to mitigate the effects. [redacted] is cognitively as well as physically affected by DMD and transferred aged 8 from mainstream to special education – so we are not dealing just with mobility impairment but also with significant learning disabilities.

	[redacted] has been on Ataluren since January 2014, when he had just turned [redacted]. In late 2017, just before his [redacted] birthday, he lost ambulation, not solely due to loss of muscle strength but due to tripping up and sustaining a spinal compression fracture. He has continued to have good upper body strength and respiratory function compared to his peers with DMD who are not on Translarna. Managing the side effects of steroids is a major issue - I would say that half of managing DMD is just managing the side effects of steroids, such as vulnerability to fractures, delayed puberty, behavioural challenges, and managing hunger/potential weight gain. Weight management is very challenging, especially for a teen when chocolate/burgers/chips are everywhere. Loss of ambulation has had a very significant impact on [redacted] and our family. We had to adapt our house, which cost £80k in total. The local authority provided equipment including a bed, shower chair, hoist, sling, wheelchair, and manual chair. In addition to medical appointments, we have appointments for regular servicing of equipment. [redacted] can't access friends'/relatives' houses and so is vulnerable to social isolation. We are not able to access informal care/respite networks such as sleepovers. You can't leave your child with untrained carers. This means that as parents we are also quite isolated, unable to go out unless we have carers. This is true for as long as [redacted] lives at home – and he's now [redacted]. Care work is utterly relentless. Due to the problems in social care we can't find enough carers to fill the slots we need, so Stuart ([redacted]'s Dad) and I fill in the gaps. It's exhausting. You need time, energy, and patience for care work – after the loss of ambulation, transfers can take 15 minutes rather than 2 minutes. We have a lot less time to be parents and partners and it impacts on our relationship with each other and with [redacted]. We are vulnerable to physical impacts, for example I have had three hernia operations and Stuart has back problems. Physiotherapy is more demanding and costly for non-ambulant people, for example travelling to use a pool with a hoist, accessing hydrotherapy. Travel is hugely more difficult – we have to have an adapted wheelchair accessible vehicle, [redacted] can't just get a lift somewhere with a friend. If we travel by train or plane everything has to be planned in advance, with very significant anxiety if plans fail – eg how are you going to get off the train.

	Going on holiday, either as a family or [redacted] accessing eg a summer school with his peers, is a major challenge and expense – we have to ensure that the accommodation is wheelchair accessible, pay for an extra room for a PA, pay for hiring a bed, a mattress, a hoist, and a shower chair, and either have enough direct payment hours from the local authority to pay for PA time, or pay for it ourselves.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Apart from Ataluren, no current treatments address the underlying cause of DMD. Steroids help to prolong muscle strength, but they have severe side effects – such as increased vulnerability to bone fractures, delayed puberty, behavioural challenges, and managing hunger/weight gain. All these side effects need to be proactively managed, and carers need time and mental space to support their children/young people to manage the impacts. Physiotherapy, ventilation, and heart medication have limited effectiveness because they don't tackle the underlying cause of the condition.
10. Is there an unmet need for patients with this condition?	Ataluren is the first and currently the only treatment for DMD which addresses the underlying cause of the condition. Ataluren should be made available to all with a nonsense mutation – our son [redacted] continued to take Ataluren after losing ambulation, on compassionate grounds because he took part in the clinical trial. In our experience it has significantly preserved his upper body strength and respiratory function. I can't imagine the anguish of parents whose children stop taking Ataluren when they lose ambulation.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Firstly, a delay in loss of ambulation. [redacted] was on the clinical trial and taking the active drug (as we found out afterwards). Before the trial, [redacted] was losing his walking ability and significantly lacked stamina compared to his peers without DMD. On the trial, [redacted]'s time on the 6 minute walk test was stable for almost a year. It then began to decline, but at a significantly slower rate than before the trial. Delaying the loss of ambulation has advantages that are numerous and hugely significant. It means for example being able to go to friends' houses, being able to get down to the water's edge and paddle in a stream - so many things that add quality to life. It means transfers take 2 minutes rather than 15 minutes, massively reducing the impact of care work on the family. It means you can go on holiday/travel without prohibitive cost and barriers to access. On Ataluren, compared to before the trial, [redacted] showed a significant increase in stamina and energy,

	for example, in a typical week managing a week at school, an after-school club, and going swimming. Before the trial, he had had one day off school per week to pace his energy and manage fatigue. Increased stamina means being able to being able to take advantage of opportunities to get out and about, having an active social life, and living life to the full. Respiratory function: [redacted] has never had a chest infection and at [redacted] does not need ventilation either day or night. Upper body strength: [redacted] loves cooking – preserving upper body strength for longer means being able for example independently to stir, pour, move pots and pans, and reach kitchen equipment. It means being able to access training courses in catering, which will lead to a variety of later employment opportunities in the food industry. Increased upper body strength, stamina, respiratory function, and the relatively late loss of ambulation all contribute to a longer life expectancy for [redacted] – years of adult life when [redacted] can use his talents and make his contributions to society. This makes a huge difference both to [redacted]'s and to our mental health and ability to cope psychologically with DMD.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	[redacted] and we as parents/carers have not seen any disadvantages or adverse effects of the technology.
Patient population	
13. Are there any groups of patients who might benefit more or less from the	Our experience suggests that all patients with nonsense mutation DMD benefit from Ataluren, both those who are ambulant and those who have lost ambulation.

technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • DMD is a devastating and complex condition which impacts on the whole family, emotionally, financially, and in terms of mental health and the burden of care work.	

- Ataluren is currently the only treatment which addresses the underlying cause of nonsense-mutation Duchenne muscular dystrophy.
- Ataluren stabilised [redacted]'s walking for almost a year, then significantly reduced the speed of decline, and has had an ongoing and significant positive impact on his stamina, energy, upper body strength, and respiratory function.
- Ataluren's ability to slow the effects of DMD increases [redacted]'s opportunities to pursue his interests and ambitions and enables him to look ahead to a longer life expectancy, which in turn impacts positively on his, and our, mental health.
- Ataluren should be made available to all who have DMD caused by a nonsense mutation, including those who have lost ambulation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Mark Silverman**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ **X** a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ **X** other (please specify): **Trustee, Action Duchenne**
3. Name of your nominating organisation	**Action Duchenne**
4. Did your nominating organisation submit a submission?	☐ **X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ **X** I have personal experience of the technology being appraised ☐ **X** I have other relevant personal experience. Please specify what other experience: Previously submitted (written) evidence to the NICE evaluation consulation document for Ataluren/Translarna in 2015 and (oral) evidence to the FDA Advisory Committee in 2017 for Ataluren/Translarna. ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Our son, [redacted], who is now [redacted], tells us how demoralising and debilitating it is living with a progressive condition. He is extremely frustrated that he needs help with so many day to day tasks, such getting out of bed, getting himself dressed, getting into the shower or getting to school. He feels guilty and knows that he can do fewer things independently than when he was younger. He knows that his reduced social circle is down to having Duchenne Muscular Dystrophy; although he attended mainstream school until he was 16, many of his peers are simply too independent for [redacted] to be able to keep up with, both physically and emotionally ([redacted] is also on the autistic spectrum). As parents and carers, we have seen [redacted]' world become smaller and smaller, as his level of social isolation has increased, unable to return to the post-Covid lockdown norm that his peers have been able to. The progression of his condition was exacerbated by Covid due to the cancellation of physiotherapy, hydrotherapy/swimming

	and other in-person medical appointments, as well as the reduced motivation to keep up with his peers in school, where prior to lockdown he was regularly walking in school between lessons. These were likely to have been factors in [redacted] finally losing ambulation last year, just before his [redacted] birthday. The impact on my wife and I from caring for [redacted], who was diagnosed when he was two years old, has been profound. It has severely impacted on our own relationship, mental health, careers, aspirations as a family and an ability to maintain any kind of normal social life with our own peers. We are frequently exhausted from caring for [redacted], both physically and emotionally, in the knowledge that our son has a life-limiting condition. Although we were able to move to a bungalow, this has required further adaptations and the installation of specialist equipment, some of which is not funded by the local authority or NHS. For example, a profiling bed which can turn [redacted] at night, cost us in excess of £12,000 and we have had to pay for standard features on his powerchair, such a riser, to enable him to raise his position to eye level with other people. As a chartered town planner with over 25 years experience, I have put any further career progression on hold as I am unable to commit to more senior roles which my employer has offered me; I am likely to have to reduce my hours and my wife is considering stopping work altogether, given the increasing carer responsibilities which we face. It has taken almost a year and a half to find a suitable support worker who can provide us with some respite and provide [redacted] with a little independence; however, we only have funding for 11 hours per week which we know is inadequate. We are tired before we have even started work. Everything takes much longer to do, given that [redacted] needs so much help to get ready or go out. Typically it can take two hours in the morning to get out bed, take his medication, physio, get washed and dressed and into the wheelchair accessible car, before school. We have to drive him to and from school because the local authority has not provided accessible transport for him.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Aside from Translarna, there are no treatments available on the NHS. The use of steroids, which are regarded by clinicians as the gold standard of care for treating Duchenne, have a range of life-altering side-effects and were never intended for or trialled in Duchenne. As a result of taking daily steroids for many years, [redacted] has stunted growth, cushingoid appearance, compression spinal fractures, delayed puberty and the onset of cataracts; these side-effects require multiple other interventions to try and manage their impact such a bisphosphonate infusions. He also has to take other medication, such as cardiac drugs, but these do not address the underlying cause of Duchenne.
10. Is there an unmet need for patients with this condition?	Yes. There is no cure or approved treatments for Duchenne, other than Ataluren, which remains a life-limiting condition and the most common fatal genetic disorder diagnosed in childhood.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	We know that from both [redacted]' personal experience and the wider 'real-world' data – where data from Ataluren-treated patients has been compared with a long-term natural history study – that Ataluren delivers clear benefits. [redacted] has been receiving Ataluren since 2015, when he was 10 years old and continued walking until just before turning 17. This exceeded ours (and his) expectations given the typical Duchenne prognosis in terms of loss of ambulation. In addition to the benefits of continued ambulation – which for [redacted] meant be able to walk around at home and in school as well as participating with his peers in his favourite sports (football and cricket) – the psychological benefits were significant. It is only as a result of Covid and the continued periods of lockdown and shielding, including 12 months of not attending school in person, that his self-confidence and optimism have been affected him to the extent that he has started taking anti-depressants. The published real-world data which has demonstrated the efficacy of Ataluren reflects our own experience. By way of example, [redacted] participated in the Phase 3 (020) trial and we were informed afterwards that [redacted] was on the placebo arm of the trial; he was then able to access the drug itself. In the months after the end of the 48 week trial period, we observed that he was much more active,

	including more regularly wanting to play football in the garden, compared to the previous summer when he had not been receiving the drug. We observed this without knowing at the time that he had been on the placebo arm of the trial 12 months previously. Maintaining ambulation is extremely important for those living with Duchenne but maintaining upper body strength is equally important in maintaining quality of life; [redacted] accesses the drug now on compassionate grounds and continues to benefit from the drug. He is still able to handwrite, collect items from cupboards and shelves, feed himself, play games on his playstation and participate in modified versions of some outdoor sports. He is still able to hit a six in the back garden in the same way that he could when playing cricket with me prior to losing ambulation; he does this while sitting in his powerchair but like anyone playing the game, he gets considerable enjoyment from being able to do so. His respiratory function remain good and he enjoys nothing more than belting out songs at full volume. The quality of life benefits are apparent to us but when considering the subgroup within the Duchenne population who are able to access Ataluren, there are also cost savings over time. This includes psychosocial improvements (psychotherapist/CAMHS interventions) and reduced support costs in school. In the longer term and through the long term use of Ataluren, there is also the increased likelihood that more young adults living with Duchenne will be able to work and pay taxes.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	We do not consider there to be any disadvantages associated with Ataluren. The drug is simple, safe and quick to prepare and administer on a daily basis. By comparison, the daily use of steroids in the Duchenne population has resulted in numerous, significant side-effects.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Both the published real-world data and our own experience show that that Ataluren will benefit all Duchenne patients with a nonsense mutation, both ambulant and non-ambulant.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People living with Duchenne Muscular Dystrophy have a disability, a protected characteristic. Ensuring that a population cohort can access the only available drug which addresses the underlying cause of their disability is of paramount importance.
Other issues	
15. Are there any other issues that you would like the committee to consider?	I would emphasise the importance of ensuring that both ambulant and non-ambulant patients are able to access the drug. Duchenne causes muscle weakness throughout the body and is not limited to leg muscles; it would be inappropriate and unfair to withdraw the drug from those who lose ambulation, given the importance of maintaining upper body strength.

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • Duchenne remains a severe, progressive and life-limiting condition for which there is still no cure; receiving this diagnosis was and remains completely shattering for my family. • [redacted]' own experience of taking Ataluren for almost seven years has demonstrated to us the efficacy of the drug, walking for longer than we ever expected and continuing to demonstrate remarkable upper body strength for someone of his age living with Duchenne. • Receiving a drug which we know benefits [redacted] has greatly enhanced his quality of life giving him the ability and self-belief to continue so many everyday activities and start planning for his post-school future • There are no other approved treatments addressing the underlying cause of Duchenne and [redacted], like others living with Duchenne, need to have continued access this medication. • It is not just the experience of families such as my own who can testify as to the benefits of Ataluren. Published real-world data has demonstrated the efficacy of the drug.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

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

External Assessment Group report

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Thomas Bayley, Statistician, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	15th June 2022 (version includes amendments following factual accuracy check)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR130835.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

The EAG's clinical advisors stated the following conflicts: Dr Michela Guglieri has received research funding from PTC Therapeutics (through the TREAT-NMD Enterprise). Dr Imelda Hughes is the UK Chief Investigator for the STRIDE study, which is sponsored by PTC Therapeutics.

Acknowledgements

We would like to thank Dr Imelda Hughes and Dr Michela Guglieri for providing clinical advice relating to this appraisal. We would also like to thank Kate Ennis, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tappenden P, Pandor A, Bayley T and Clowes M. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3). External Assessment Group Report. School of Health and Related Research (ScHARR), 2022.

Contributions of authors

Mark Clowes critiqued the company's searches. Abdullah Pandor summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Thomas Bayley critiqued the company's indirect treatment comparisons. Paul Tappenden critiqued the company's health economic analysis. All authors were involved in drafting and commenting on the final report.

CONTENTS

List of tables

List of figures

List of boxes

Abbreviations

6MWD	6-minute walk distance
ADHD	Attention-deficit hyperactivity disorder
ADL	Activities of daily living
AE	Adverse event
AIC	Akaike Information Criterion
ArRoWS	Assessment of Real World Observational Studies
ASA	Additional sensitivity analysis
ATT	Average treatment effect on the treated
BIC	Bayesian Information Criterion
BMI	Body mass index
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHU-9D	Child Health Utility 9-Dimensions
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
cITT	Corrected intention-to-treat
CPI	Consumer Price Index
CRD	Centre for Reviews and Dissemination
CS	Company's submission
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DNHS	Disease Natural History Study
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
EQ-5D-3L	Euroqol 5-Dimensions 3-Level
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
HTA	Health technology assessment
HUI3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
Kg	Kilogram
L	Litre
LoA	Loss of ambulation
LS	Least-squares
LYG	Life year gained
MAA	Managed Access Agreement
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEP	Maximal expiratory pressure
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency

MIP	Maximal inspiratory pressure
MMRM	Mixed model for repeated measures
mRNA	Messenger ribonucleic acid
N	Number
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
nmDMD	Nonsense mutation Duchenne muscular dystrophy
NR	Not reported
NSAA	NorthStar Ambulatory Assessment
OCD	Obsessive–compulsive disorder
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PEF	Peak expiratory flow
PODCI	Paediatric Outcomes Data Collection Instrument
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QuEENS	Quality of Effectiveness Estimates from Non-randomised Studies
RCPCH	Royal College of Paediatrics and Child Health
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RR	Relative ratio
RWE	Real world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-12	Short-Form 12
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
STRIDE	Strategic Targeting of Registries and International Database of Excellence
TEAE	Treatment-emergent adverse event
TFT	Timed function test
TID	*ter in die* (three times a day)
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
VAS	Visual analogue scale
ZBI	Zerit Caregiver Burden Interview

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and sensitivity analyses around key areas of uncertainty, together with the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 summarise the evidence presented in the company's submission (CS) and explain the key issues in more detail. The results of the EAG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology, evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The CS includes a systematic literature review (SLR) of studies of ataluren and three indirect treatment comparisons (ITCs) comparing ataluren plus best supportive care (BSC) versus BSC alone. The company's economic model assesses the cost-effectiveness of ataluren plus BSC versus BSC alone for the treatment of patients with Duchenne muscular dystrophy with a nonsense mutation (nmDMD).

The key issues identified by the EAG are summarised in Table 1.

Table 1: Overview of the EAG's key issues

ID1642	Summary of issue	EAG report sections
Issue 1	Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population	4.3 and 5.3.5 (critical appraisal points 3 and 5)
Issue 2	Inappropriate approach used to estimate incremental caregiver QALYs	5.3.5 (critical appraisal point 6c)
Issue 3	Limitations surrounding the company's survival modelling	5.3.5 (critical appraisal point 4)
Issue 4	Uncertainty surrounding the appropriateness of treatment-dependent patient utility values	5.3.5 (critical appraisal point 6a)
Issue 5	Uncertainty surrounding modelled acquisition costs of ataluren by age	5.3.5 (critical appraisal point 7a)
Issue 6	Uncertainty surrounding the discontinuation rate in patients with FVC>50%	5.3.5 (critical appraisal point 7b)
Issue 7	Uncertainty surrounding the most appropriate treatment discontinuation rule	5.3.5 (critical appraisal point 7b)
Issue 8	Weak characterisation of uncertainty	5.3.5 (critical appraisal point 8)

QALY - quality-adjusted life year; FVC - forced vital capacity

The key differences between the company's base case model and the EAG's preferred model relate to:

(i) The approach used to estimate health impacts on caregivers of patients with nmDMD. The company's model estimates absolute QALYs accrued by caregivers whilst the DMD patient is alive, whereas the EAG's preferred model applies caregiver disutilities to estimate QALY losses. Both the company's model and the EAG's preferred model also include separate bereavement-related QALY losses.

(ii) Whether utility values are adjusted for increasing age. The EAG's preferred model includes these adjustments, whereas the company's base case model excludes them.

(iii) The source of evidence used to estimate patient weight, which subsequently impacts on the acquisition costs of ataluren. The company's base case model uses fixed estimates of the mean weight of ambulatory and non-ambulatory patients from the 2021 data-cut of the Strategic Targeting of Registries and International Database of Excellence (STRIDE) registry in every model cycle. The EAG's preferred model applies age-specific weight estimates from the Royal College of Paediatrics and Child Health (RCPCH) together with a relative reduction in weight in DMD patients from STRIDE.

The EAG notes that several aspects of the company's model are heavily reliant on assumptions, which are necessary because of the limitations in the available evidence on the effectiveness of ataluren in the target population. In particular, key clinical uncertainties include: the expected clinical benefits of starting treatment with ataluren in younger patients (from age 2 years); the overall survival (OS) gain associated with ataluren; the most appropriate treatment discontinuation rule, and whether patients receiving ataluren experience an improved level of health-related quality of life (HRQoL) compared with those receiving BSC in the same state. The company's assumptions around these factors have not been amended in the EAG's preferred model, but instead their impact is explored in additional sensitivity analyses. As such, the EAG's preferred model should not be interpreted as a revised base case analysis, but rather as a more appropriate starting point for considering the impact of uncertainties in the clinical evidence on the cost-effectiveness of ataluren.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Ataluren is assumed to affect QALYs by:

- Delaying the age at which patients: (a) lose ambulation; (b) reach thresholds of lung function deterioration (specified as forced vital capacity [FVC] levels of <50% and <30%) after losing ambulation, and (c) die.

- Improving patient HRQoL in each state compared with patients receiving BSC alone.
- Impacting on health gains accrued by caregivers. The company's model predicts a large incremental QALY gain for caregivers of ataluren-treated patients. In contrast, the EAG's preferred model suggests that ataluren will lead to a small incremental caregiver QALY loss.

Overall, ataluren is assumed to affect costs by:

- Increasing total costs as a consequence of the acquisition cost of ataluren.
- Increasing disease management costs as a consequence of extending OS.

The modelling assumptions that have the greatest effect on the ICER are:

- The approach used to value caregiver QALY gains/losses. The choice of approach also impacts on the number of additional undiscounted QALYs accrued for ataluren, thereby influencing the decision modifier.
- The inclusion of treatment-dependent patient utility values in all health states.
- The approach used to estimate the costs of ataluren conditional on the patient's weight.
- The rate at which patients discontinue treatment with ataluren.
- The DMD milestone-dependent treatment stopping rule.

Whilst highly uncertain, the assumptions regarding additional OS gains and the benefits of early treatment with ataluren do not appear to substantially impact on the ICER.

1.3 The decision problem: Summary of the EAG's key issues

The EAG considers the company's description of the underlying health problem and its impact on patients and their caregivers to be appropriate. The decision problem addressed in the CS is generally in line with the final NICE scope. The population addressed in the CS is people with nmDMD; this is consistent with the population defined in the NICE scope. The company's model evaluates the cost-effectiveness of ataluren plus BSC in a population of nmDMD patients who begin treatment at age 2 years; this is not consistent with the evidence used to support the clinical effectiveness of ataluren in the CS. Uncertainty surrounding the clinical effectiveness of ataluren within the target population is described in Section 1.5 (Issue 1).

1.4 The clinical evidence: Summary of EAG's key issues

The company's current submission is a re-evaluation of ataluren for treating nmDMD (a review of NICE Highly Specialised Technology Appraisal Guidance Number 3 [HST3]). Existing clinical evidence from two key 48-week clinical trials of ataluren (Study 007 and Study 020) was originally

reviewed by NICE and guidance was issued in 2016. New additional key clinical evidence, subsequent to HST3, supporting the efficacy and safety of ataluren presented in the current CS includes a long-term (up to 336 weeks) open-label extension study (Study 019), support of the licence extension to patients aged ≥2 to <5 years (Study 030) and ongoing real-world safety and effectiveness evidence (the STRIDE registry [Study 025o] and the Managed Access Agreement [MAA]). Owing to the lack of additional comparative evidence, the company performed three ITCs based on propensity score matching to compare ataluren plus BSC versus BSC alone. The company selected the Cooperative International Neuromuscular Research Group (CINRG) Disease Natural History Study (DNHS) (an international registry of patients with DMD, aged 2 to 28 years) and the NorthStar registry (a UK registry of patients with DMD) datasets as indirect comparative evidence for BSC. The results of the three ITCs are summarised below.

A principal comparison was conducted between patients from the STRIDE cohort receiving ataluren plus BSC (n=241) and a matched population receiving BSC alone from the CINRG DNHS cohort (n=241). The results of this comparison suggest that:

- Patients receiving ataluren may experience a delay to loss of ambulation (defined as full-time wheelchair use) of 5.4 years compared with patients receiving BSC (median 17.9 vs. 12.5 years, respectively; hazard ratio [HR]: 0.374; p<0.0001). [redacted] There is also limited evidence to support an impact on pulmonary outcomes, particularly those experienced further on in disease progression. This was in part due to limited data availability in the STRIDE cohort, [redacted] which limits any examination of the average age at which these milestones are reached.

A second propensity score matched ITC was undertaken between patients signed up to the current ataluren MAA in England (n=59) and matched controls from the NorthStar registry (n=59). In the MAA/NorthStar analysis there was a significant decline in the availability of valid NorthStar Ambulatory Assessment (NSAA) score measures in both the ataluren patients and the matched NorthStar patients during the study period. Despite the limitations of this comparison, the results suggest that:

- There is some evidence to suggest that fewer ataluren patients experienced a decline across most function areas ([redacted] out of 17 function areas) over 36 months. In addition, the company

claims that the comparisons of transformed time to rise from floor (due to non-normality of the data) indicate that ataluren [redacted] disease progression compared to BSC. However, the company struggled to demonstrate a meaningful treatment effect due to limitations in the available data. Overall, the EAG believes that this ITC provides less compelling evidence for the benefit of ataluren compared with the STRIDE/CINRG comparison.

Whilst the main aim of Study 019 was to assess the long-term safety of ataluren, the company also performed an ITC with a matched cohort from the CINRG DNHS. The results suggest that:

- Ataluren treatment (n=60) delayed the loss of ambulation by 2.2 years (p=0.0006) compared with patients receiving BSC (n=60; median 15.5 vs. 13.3 years, respectively). There is some evidence that ataluren also results in delays in endpoints associated with pulmonary decline (FVC<60% [assessed only in non-ambulatory patients, each n=45]; p=0.004). It is unclear from the data whether this is due to a carry-over of the delay to loss of ambulation, or an additional effect of ataluren on pulmonary decline. Evidence presented in the CS in support of an additional treatment effect for ataluren in delaying decline to pulmonary endpoints is limited.

There were no additional safety concerns associated with ataluren in Study 030 (n=14, aged ≥2 and <5 years), in longer-term studies (e.g. Study 019 [n=94, as-treated population] and the STRIDE registry [n=286, as-treated population]) and AEs were in line with those known for patients aged 2 years and above or common childhood illnesses.

The uncertainties in the available clinical evidence also impact on the cost-effectiveness of ataluren. As such, all key issues are described in Section 1.5.

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company submitted a *de novo* economic model which assesses the cost-effectiveness of ataluren plus BSC versus BSC alone for the treatment of patients with nmDMD. The model adopts a partitioned survival approach including five health states: (i) ambulatory; (ii) non-ambulatory, FVC≥50%; (iii) non-ambulatory, FVC<50% (and ≥30%); (iv) non-ambulatory, FVC<30% and (v) dead. The intervention assessed within the model is ataluren given in conjunction with BSC from the age of 2 years, including a stopping rule when patients reach FVC<50%. The analysis adopts an NHS and Personal Social Services (PSS) perspective, including QALYs accrued by nmDMD patients and their caregivers (two per patient). Health outcomes for the BSC group are modelled using time-to-event data from the propensity score matched CINRG DNHS, whilst outcomes for the ataluren group are modelled using data from STRIDE plus additional assumptions relating to the benefits of early treatment with ataluren.

The model includes the existing Patient Access Scheme (PAS) for ataluren, which takes the form of a simple price discount of [redacted].

The company's base case model predicts that patients receiving ataluren will experience a delay in the mean age at loss of ambulation of [redacted] years, a delay in the mean age at FVC<50% of [redacted] years and delays in the mean ages at FVC<30% and death of approximately [redacted] years. The probabilistic version of the company's model suggests that the ICER for ataluren plus BSC versus BSC alone is [redacted] per QALY gained. The deterministic ICER is lower, at [redacted] per QALY gained. Both versions of the company's model suggest that ataluren leads to more than [redacted] additional undiscounted QALYs compared with BSC alone, thereby suggesting a decision modifier of [redacted].

A brief description of the key issues identified by the EAG is provided below.

Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population

Report section	4.3 and 5.3.5 (critical appraisal points 3 and 5)
Description of issue and why the EAG has identified it as important	The company's model predicts the age at which patients lose ambulation, reach FVC milestones and die using the STRIDE/CINRG ITC. Modelled treatment benefits in reaching FVC<30% and OS are reliant on clinical assumptions. Additional benefits associated with early initiation of ataluren for patients at age 2 years are also reliant on clinical assumptions. Each of these assumptions involve shifting fitted parametric survival curves applied in the ataluren group to the right by a specified number of years (loss of ambulation = STRIDE curve shifted by [redacted] years; FVC<50% = STRIDE curve shifted by [redacted] years; FVC<30% = CINRG curve shifted by [redacted] years). The company's modelled estimates of the relative effectiveness of ataluren versus BSC are subject to a number of uncertainties: • *Uncertainty surrounding the results of the company's ITC of STRIDE versus CINRG.* The results of this ITC are uncertain due to limitations in the data available for respiratory endpoints occurring at the later stages of disease progression, the unanchored nature of the ITC and the potential for imbalances in unmeasured confounders not included in the matching process. • *Exclusion of the MAA analysis from the model.* As noted in Section 1.4, the company's analysis of the MAA *"struggled to demonstrate meaningful treatment effect."* This ITC has not been used to inform the economic model. • *No evidence of OS benefit.* No data are available to demonstrate an OS gain for ataluren from any clinical study. The company's modelled mean OS gain for ataluren versus BSC is entirely dependent on assumptions. • *Uncertainty surrounding early treatment benefits.* Very few patients in STRIDE ([redacted] of 269 [redacted] patients included in the evaluable population) started ataluren treatment before the age of 5 years. However, the company's model assumes that all patients will start treatment at age 2 years. Additional delays associated with early treatment initiation are informed by clinical assumptions. • *Uncertainty surrounding the impact of the proposed discontinuation rule.* The company has proposed that treatment with ataluren should be continued until the patient reaches FVC<50%. The extent to which this stopping rule is reflected in the outcomes data from STRIDE, or in the estimates of treatment benefit elicited from the clinical experts consulted by the company, is unclear.

	• *Concerns regarding the approach used to shift survival curves.* The company's approach of shifting survival curves to the right assumes that competing risks (e.g., death due to DMD) would not impact on the shape of the survival curve and that all patients experience the same magnitude of delay. Neither of these assumptions is likely to hold. • *Concerns regarding plausibility of model predictions:* The EAG's clinical advisors commented that the mean delays in reaching DMD milestones predicted by the company's economic model appear to be optimistic.
What alternative approach has the EAG suggested?	The EAG has undertaken sensitivity analyses to explore the impact of modifying assumptions regarding early treatment benefits and additional OS gains for ataluren.
What is the expected effect on the cost-effectiveness estimates?	The deterministic ICER for ataluren versus BSC generated by the EAG's preferred model is estimated to be [redacted] per QALY gained. Removing the assumptions regarding early treatment benefit increases the ICER to [redacted] per QALY gained. In contrast, removing the OS gain for ataluren reduces the ICER to [redacted] per QALY gained. The impact of applying alternative discontinuation rules is considered under Issue 7.
What additional evidence or analyses might help to resolve this key issue?	Further input from clinical experts may help the Appraisal Committee determine a plausible set of assumptions regarding the expected effectiveness of ataluren in the target population. However, the EAG's additional sensitivity analyses indicate that the model is not particularly sensitive to these assumptions.

Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs

Report section	5.3.5 (critical appraisal point 6c)
Description of issue and why the EAG has identified it as important	The company's model includes health gains accrued both by nmDMD patients and their caregivers. Health gains accrued by caregivers are modelled using an "absolute" caregiver QALY approach. This approach stops counting caregiver QALYs after the nmDMD patient has died. As such, the company's model implicitly makes one of three assumptions: (i) when the DMD patient dies, their caregivers also die; (ii) when the patient dies, their caregivers survive with zero utility, or (iii) QALY gains accrued by caregivers of surviving patients are valuable to society and relevant for inclusion in an economic analysis, but QALY gains accrued by bereaved caregivers are not. The EAG does not consider any of these assumptions to be reasonable. The EAG believes that the company's approach to estimating caregiver QALYs produces a substantial bias in favour of ataluren and increases the predicted number of incremental QALYs gained for ataluren, which in turn, inappropriately inflates that magnitude of the decision modifier.
What alternative approach has the EAG suggested?	The EAG prefers the use of a caregiver disutility approach, whereby disutility values for caregivers are assigned to each patient health state, together with some consideration of the impact of bereavement (this latter effect is already included elsewhere in the model). The EAG's preferred approach is consistent with the majority of previous HSTs which have included health impacts on caregivers.
What is the expected effect on the cost-effectiveness estimates?	Based on the absolute caregiver QALY approach, the EAG-corrected version of the company's base case model produces a deterministic ICER for ataluren plus BSC versus BSC alone of [redacted] per QALY gained. This version of the company's model suggests that ataluren will generate an additional [redacted] discounted QALYs for patients and their caregivers (decision modifier = [redacted]). The application of caregiver disutilities within the EAG-corrected version of the model increases the ICER to [redacted] per QALY gained. The EAG's preferred model suggests that ataluren will generate an additional [redacted] undiscounted QALYs for

	patients and their caregivers (decision modifier = [redacted]). All of the EAG's additional sensitivity analyses also suggest a decision modifier of [redacted].
What additional evidence or analyses might help to resolve this key issue?	None. The EAG believes that a caregiver disutility approach should be used.

Issue 3: Limitations surrounding the company's survival modelling

Report section	5.3.5 (critical appraisal point 4)
Description of issue and why the EAG has identified it as important	The company fitted parametric survival models to estimate the age at which patients (i) lose ambulation; (ii) reach FVC<50%; and (iii) reach FVC<30%. The company's survival modelling is subject to several limitations: • No data are available on age at FVC<30% in STRIDE. • The analysis of available data was limited to consideration of standard parametric survivals (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions). • The models selected by the company do not appear to provide a good representation of the data for age at loss of ambulation from STRIDE, or age at FVC<50% in either the STRIDE or propensity score matched CINRG DNHS datasets. • With the exception of age at loss of ambulation in the CINRG DNHS, the selected models for all other endpoints in both treatment groups do not appear to reflect the empirical hazards. • For each endpoint, the company selected the model which provided the best relative statistical fit to the data. [redacted] The CS and the company's clarification response do not provide any further detail on how clinical input was used to inform model selection.
What alternative approach has the EAG suggested?	Consideration of a broader range of models, including flexible parametric survival distributions (e.g., restricted cubic splines), may have provided a better representation of the available time-to-event data. Further consideration of the plausibility of candidate survival models is required.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's preferred model, the use of Weibull distributions for all time-to-event endpoints reduces the ICER to [redacted] per QALY gained. The use of other models (e.g., the log-normal distribution) may substantially increase the ICER, but there is little justification for their use. The impact of using alternative parametric model types, which might better represent the observed data, is unknown.
What additional evidence or analyses might help to resolve this key issue?	Flexible parametric models may provide a better representation of the available time-to-event data. Additional clinical input is required to inform model selection.

Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values

Report section	5.3.5 (critical appraisal point 6a)
Description of issue and why the EAG has identified it as important	The company's model includes treatment-dependent utility values for the ataluren and BSC groups based on estimates obtained from a Delphi panel exercise in which six Swedish neuromuscular experts completed the Health Utilities Index Mark 3 (HUI3) for ambulatory and non-ambulatory DMD states (Landfeldt *et al.*, 2020). The patient utility values used in the model assume a substantial improvement for ataluren (ataluren versus BSC utility: ambulatory state 0.93 vs. 0.62; non-ambulatory state 0.32 vs. 0.16). The CS does not present any empirical evidence of HRQoL measured in nmDMD patients to support the assumption of treatment-dependent patient utility values. In addition, the treatment-dependent utility values within the model are applied indefinitely, irrespective of whether the patient is still receiving ataluren. These assumptions are likely to be highly optimistic. The EAG's clinical experts expressed uncertainty around whether it is reasonable to assume that patient utility values are treatment-dependent, particularly with respect to patients who are still ambulant. [redacted]
What alternative approach has the EAG suggested?	Three separate sensitivity analyses have been undertaken to explore uncertainty around the patient utility values applied in the model. • The first sensitivity analysis applies the same patient utility value to the ambulant state in both treatment groups (based on the value for BSC). • The second sensitivity analysis assumes that health utility values for patients who discontinue ataluren revert to those for the BSC group. • The third sensitivity analysis applies treatment-independent patient EQ-5D-3L values reported by Crossnohere *et al.* (2021).
What is the expected effect on the cost-effectiveness estimates?	All three sensitivity analyses around patient utility values increase the ICER generated from the EAG's preferred model: • Applying the BSC utility value for the ambulant state in both treatment groups increases the ICER from [redacted] to [redacted] per QALY gained. • Applying BSC utility values to patients who have discontinued ataluren increases the ICER from [redacted] to [redacted] per QALY gained. • The inclusion of treatment-independent utility values reported by Crossnohere *et al.* increases the ICER from [redacted] to [redacted] per QALY gained. These analyses highlight that this aspect of the model is a key driver of the ICER for ataluren.
What additional evidence or analyses might help to resolve this key issue?	Judgements are required by the Appraisal Committee regarding: (i) whether there is sufficient evidence to assume treatment-dependent utility values in the model; (ii) whether this assumption should apply to all or some model health states, and (iii) whether such benefits persist beyond treatment discontinuation.

Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age

Report section	5.3.5 (critical appraisal point 7a)
Description of issue and why the EAG has	Ataluren dosing is dependent on the patient's weight. The company's model applies fixed acquisition costs for ambulatory/non-ambulatory patients remaining on treatment in every model cycle, based on the mean weight of patients in the

identified it as important	2021 data-cut of STRIDE. This approach is subject to three problems: (i) It ignores variability in the distribution of patient weight. (ii) It assumes that as patients get older, the mean weight in the population remaining on treatment will remain constant. This is likely to underestimate costs. (iii) It overestimates the costs of ataluren at earlier ages where the discount rate multiplier is higher.
What alternative approach has the EAG suggested?	The company's model includes additional functionality which allows for the use of estimates of patient weight according to age based on child growth data from the RCPCH, together with an estimate of the relative reduction in weight for nmDMD patients (versus healthy patients) from STRIDE. The EAG prefers this approach over that used in the company's base case model.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred model, which includes patient weight data from the RCPCH and STRIDE, suggests an ICER of [redacted] per QALY gained. The equivalent analysis based on the mean weight in STRIDE results in an ICER of [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that the use of data from the RCPCH and the relative weight reduction estimate from STRIDE is reasonable.

Issue 6: Uncertainty surrounding the discontinuation rate in patients with FVC>50%

Report section	5.3.5 (critical appraisal point 7b)
Description of issue and why the EAG has identified it as important	The company's model applies a discontinuation rule whereby all patients discontinue treatment with ataluren when they reach FVC<50%. In addition, a constant probability of "natural discontinuation" is applied to patients with FVC>50% in every cycle, which is informed by data on patients discontinuing ataluren in STRIDE. Reasons for discontinuation in STRIDE included: AEs; family/participant request; perceived lack of response; clinician's decision; loss of ambulation and unknown reasons. The EAG's clinical advisors commented that the modelled rate of discontinuation appears implausibly high, and that given the severity of the disease and the lack of alternative effective therapies, patients with nmDMD generally wish to remain on treatment for as long as possible. The EAG has concerns that the company's estimated probability of natural discontinuation may be double-counting events which are already captured in the discontinuation rule. It is also unclear whether it is reasonable to apply a constant probability in every model cycle, or to assume that the discontinuation rate observed in STRIDE would also apply to a younger population of patients who start treatment at age 2 years.
What alternative approach has the EAG suggested?	The EAG has undertaken a sensitivity analysis which arbitrarily reduces the estimated discontinuation rate by 50%.
What is the expected effect on the cost-effectiveness estimates?	The EAG's sensitivity analysis increases the EAG's preferred ICER from [redacted] to [redacted] per QALY gained.
What additional	The EAG's sensitivity analysis indicates that the ICER for ataluren is sensitive to

evidence or analyses might help to resolve this key issue?	the discontinuation rate. Further exploration of the STRIDE discontinuation data may help to clarify the extent to which discontinuation events are being double-counted. Parametric survival modelling of the time to treatment discontinuation data and clinical judgement could be used to support or refute the company's assumption that the discontinuation rate is constant over time.

Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule

Report section	5.3.5 (critical appraisal point 7b)
Description of issue and why the EAG has identified it as important	The company's model applies a treatment discontinuation rule for all patients reaching FVC<50%. The current MAA for ataluren in England requires patients to discontinue ataluren within 6 months after loss of ambulation. The company has stated that the current licence for ataluren *"does not specifically detail a stopping rule or prohibit patients continuing treatment beyond loss of ambulation."* The EAG notes the following issues regarding the company's proposed extension to the current MAA discontinuation rule: • The EAG's clinical advisors commented that they would wish to use ataluren beyond the loss of ambulation. • The company's clarification response suggests that up to [redacted] of patients in STRIDE who lost ambulation continued to receive ataluren. However, the extent to which this continued exposure to treatment is consistent with the proposed FVC<50% discontinuation rule applied in the model is unclear. • There are no long-term data which demonstrate the magnitude of clinical benefit on pulmonary endpoints associated with continued ataluren treatment beyond loss of ambulation. • It is unclear whether the elicited estimates around early treatment benefit for the age at which patients reach FVC<30% specifically took account of the company's proposed FVC<50% discontinuation rule. • The company's economic model adopts a partitioned survival approach whereby clinical outcomes are not structurally dependent on whether the patient is still receiving treatment. The ability of the company's model to explore the costs and clinical consequences of alternative discontinuation rules is therefore limited.
What alternative approach has the EAG suggested?	Both the company and the EAG have conducted sensitivity analyses which apply treatment discontinuation rules at 6 months after loss of ambulation and at FVC<30%. The relevance of the results of these analyses is limited due to the concerns detailed above.
What is the expected effect on the cost-effectiveness estimates?	Sensitivity analyses undertaken using the EAG's preferred model suggest that the ICER for ataluren is sensitive to the assumed discontinuation rule: • Discontinue 6 months after loss of ambulation - ICER=[redacted]/QALY gained • Discontinue at FVC<50% - ICER=[redacted]/QALY gained • Discontinue at FVC<30% - ICER=[redacted]/QALY gained
What additional evidence or analyses might help to resolve this key issue?	The EAG's sensitivity analyses around ataluren discontinuation are limited by the lack of evidence for long-term outcomes for the continued use of ataluren in non-ambulatory patients and the structural limitations of the model. A different model structure would be required to estimate the impact of treatment discontinuation on outcomes associated with subsequent disease milestones. However, this would not resolve problems relating to the lack of clinical evidence.

Issue 8: Weak characterisation of uncertainty

Report section	5.3.5 (critical appraisal point 8)
Description of issue and why the EAG has	The CS reports the results of analyses using both the probabilistic and deterministic versions of the model. The EAG believes that the company's uncertainty analyses are subject to several limitations:

identified it as important	• For the majority of the parameters included in the company's probabilistic sensitivity analysis (PSA), standard errors (SEs) have been arbitrarily assumed to be 20% of the mean value, including where these are reported in the original evidence sources. • The company has used shifted gamma distributions which results in impossible utility values in a small number of cases. • No scenario analyses are presented for several key parameters/assumptions, including those relating to: (i) early treatment benefits; (ii) treatment-independent utility values; (iii) alternative parametric survival distributions or (iv) the rate of ataluren discontinuation. Overall, the EAG believes that the company's analyses do not fully reflect the uncertainty surrounding the cost-effectiveness of ataluren.
What alternative approach has the EAG suggested?	The EAG has conducted sensitivity analyses to explore the potential impact of alternative assumptions surrounding key uncertain model parameters (see Section 1.6, Table 2). The EAG cannot fully resolve the problems in the company's PSA – whilst SEs from the published studies could be applied in the model, the probabilistic analysis would only be meaningful if the uncertainty around elicited estimates of early treatment benefit and/or relative effectiveness was also included.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analyses suggest that even under optimistic assumptions, the ICER for ataluren is likely to be considerably higher than the company's base case analysis. The probabilistic ICER, based on an appropriate representation of uncertainty surrounding all model parameters, is unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG has presented a number of sensitivity analyses around key uncertain aspects of the company's model. Further analyses will be required if the Appraisal Committee identifies a preferred scenario which combines multiple alternative assumptions explored in the EAG's analyses. Some aspects of the company's PSA could be resolved by applying SEs from the published papers used to inform costs and utility values. It is unclear if the company has elicited meaningful estimates of uncertainty around the treatment benefit assumptions which could be included in the PSA.

1.6 Summary of EAG's preferred model and sensitivity analysis results

The results of the EAG's preferred model and additional sensitivity analyses are summarised in Table 2. Exploratory analysis 1 (EA1) reflects the EAG-corrected deterministic version of the company's model. Exploratory analyses EA2-5 also include these corrections. All additional sensitivity analyses (ASAs 1a-6b) reflect amendments applied to the EAG's preferred model (EA5).

The EAG's preferred model suggests that the ICER for ataluren plus BSC versus BSC is [redacted] per QALY gained (decision modifier = [redacted]). The EAG believes that this version of the model should be used as the starting point for exploring the impact of key uncertainties around the clinical effectiveness evidence on the cost-effectiveness of ataluren. The EAG's additional sensitivity analyses indicate that the ICER for ataluren may be substantially higher than that generated using the EAG's preferred model.

Table 2: Summary of EAG preferred model and sensitivity analysis results

Scenario	Incremental QALYs gained (patients and carers)	Incremental cost	ICER*	DM
Company's base case analysis (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred model				
EA1: Correction of errors	[redacted]	[redacted]	[redacted]	[redacted]
EA2: Use of caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]
EA3: Inclusion of age-adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]
EA4: Use of age-specific weight data from RCPCH	[redacted]	[redacted]	[redacted]	[redacted]
EA5: EAG preferred model (EA1-4 combined)	[redacted]	[redacted]	[redacted]	[redacted]
Additional sensitivity analyses				
ASA1a: Use of treatment-independent patient utility value in ambulatory state	[redacted]	[redacted]	[redacted]	[redacted]
ASA1b: Assume BSC patient utility values after ataluren discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
ASA1c: Use of treatment-independent patient utility values (Crossnohere *et al.*)	[redacted]	[redacted]	[redacted]	[redacted]
ASA2a: Early treatment benefits halved	[redacted]	[redacted]	[redacted]	[redacted]
ASA2b: Early treatment benefits removed	[redacted]	[redacted]	[redacted]	[redacted]
ASA3a: OS gain assumed to be equal to gain in delay in loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]
ASA3b: OS benefit removed	[redacted]	[redacted]	[redacted]	[redacted]
ASA4: Use of Weibull model for all time-to-event endpoints	[redacted]	[redacted]	[redacted]	[redacted]
ASA5: Discontinuation rate reduced by 50%	[redacted]	[redacted]	[redacted]	[redacted]
ASA6a: Discontinuation at 6 months after loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]
ASA6b: Discontinuation at FVC<30%	[redacted]	[redacted]	[redacted]	[redacted]

EAG - External Assessment Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; ASA - additional sensitivity analysis; RCPCH - Royal College of Paediatrics and Child Health; BSC - best supportive care; OS - overall survival; FVC - forced vital capacity

**All ICERs reported by the EAG exclude QALY weighting*

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease and the current treatment pathway for Duchenne muscular dystrophy with a nonsense mutation (nmDMD) in England.

2.1 Critique of the company's description of the underlying health problem

The company's submission (CS)[1] contains a comprehensive description of Duchenne muscular dystrophy (DMD) and its impact on patients and their caregivers. This is summarised below based on information provided in the CS, literature and additional input provided by the EAG's clinical advisors.

DMD is a rare, inherited, severe and progressive muscle wasting disease. DMD is an X-linked recessive disorder which predominantly, but not exclusively, affects males. The disease is characterised by the slow progression of muscle wasting and weakness, and by degeneration of skeletal and cardiac muscle.[2] The onset of physical muscle weakness occurs in early childhood, which results in limb weakness affecting the legs initially and then the arms; subsequently there is impairment in respiratory function and cardiac failure, ultimately leading to premature death in early adulthood.

DMD is caused by mutations in the *DMD* gene which encodes for the protein dystrophin. Patients with nmDMD lack normal dystrophin. Dystrophin is needed to help protect muscles from injury as they contract and relax. A minority of patients with DMD have a nonsense mutation in the *DMD* gene.

A recent meta-analysis[3] which included 40 studies reported a pooled global DMD prevalence of 7.1 cases (95% confidence interval [CI]: 5.0-10.1 cases) per 100,000 males and 2.8 cases (95% CI: 1.6-4.6 cases) per 100,000 individuals, and a pooled global DMD birth prevalence of 19.8 (95% CI:16.6–23.6 cases) per 100,000 live male births. Patients with a nonsense mutation comprise around 10% of the overall DMD population.[4] Due to its mechanism of action, ataluren is only available for patients with DMD carrying a nonsense mutation. The CS[1] states that there are [redacted] (ambulatory) patients currently receiving treatment with ataluren under the Managed Access Agreement (MAA) in England. Based on an analysis of data from the Welsh newborn bloodspot screening programme, the incidence of DMD has been estimated to be 1 case per 5,136 males, although the authors note that this is likely an overestimate.[5] The company estimates that 6 new patients with nmDMD would be eligible for treatment with ataluren each year.

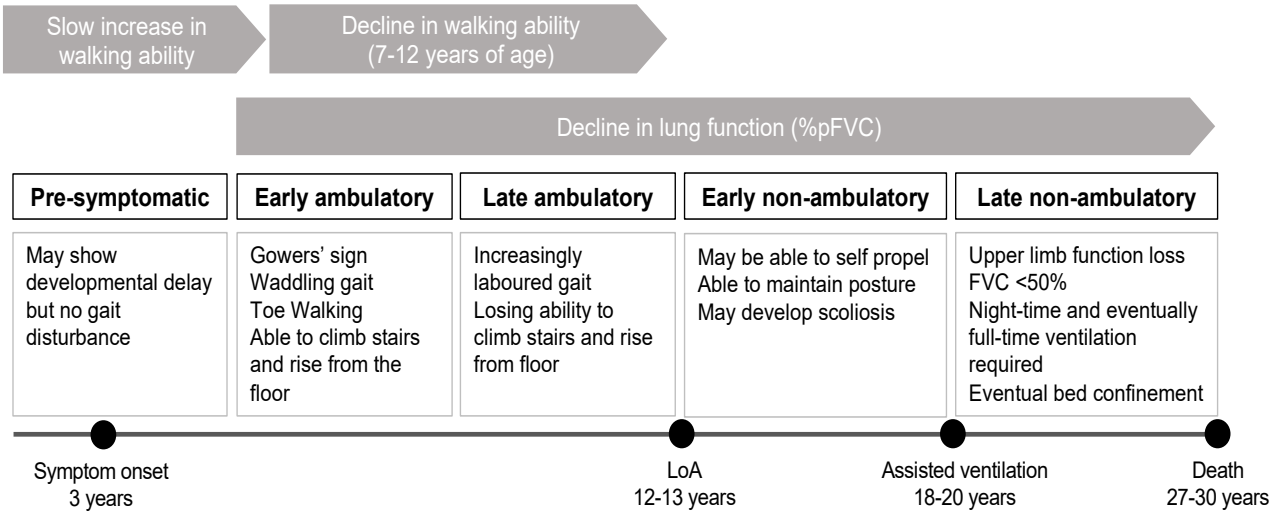
The broad stages of the natural history progression of DMD are illustrated in Figure 1. The disease follows a well-defined pattern from early childhood, with symptoms usually becoming apparent

between the ages of 1 and 3 years.[6] In younger children with DMD, early signs and symptoms of the disease typically manifest as delayed speech and/or walking compared to healthy children, and/or frequent falls. These symptoms can be subtle and often go unrecognised. Because of natural development, children with DMD may still continue to develop some motor function at this stage, albeit at a slower rate than healthy children, and with signs of functional impairment already being evident. At the early ambulatory stage of the disease, which typically occurs when the child reaches the age of around 5 years, classical symptoms of DMD become evident, including Gower's manoeuvre (the child supports themselves with hands on thighs when raising from floor), waddling-type of walking, toe-walking (the child walks on the balls of their feet with no contact between the heels and ground), and difficulties in running and climbing stairs by bringing the second foot up to join the first rather than going foot over foot.[7] At the late ambulatory stage, early symptoms worsen and walking becomes increasingly difficult, with children having increasing difficulty in getting up from the floor, climbing stairs and eventually losing the ability to walk. Care recommendations for DMD, including the use of corticosteroids from the age of 4-6 years, have been published in 2010 and updated in 2018.[8-10] The implementation of standards of care, including the use of corticosteroids, have changed the natural history of the disease, prolonging motor skills including the ability to walk, delaying DMD-associated cardiac and respiratory complications and ultimately prolonging survival. However, even with the use of corticosteroids, by around the age of 7 to 8 years, most children with DMD have difficulty arising from the floor and climbing stairs. Accidental falls whilst walking are also common and fractures experienced from falls can contribute to an accelerated decline towards permanent loss of ambulation.

Children typically lose the ability to walk and become fully wheelchair-bound at around 12 to 15 years of age if treated with corticosteroids,[11] although ambulation may be lost earlier in children who are steroid-naïve. Patients who have fully lost ambulation may still have some lower limb function, for example, the ability to transfer to and from a wheelchair or to turn over in bed for some period of time. Following loss of ambulation, upper limb function also steadily declines and simple activities such as personal grooming, toileting, bathing, dressing, sitting unsupported, and eating, become difficult or impossible to perform independently.[1] Deterioration of skeletal muscle may lead to contractures and scoliosis, which in turn, may further impair subsequent lung function. Once ambulation has been lost, respiratory function begins to steadily decline. Patients can experience respiratory symptoms such as poor cough, increased risk of chest infections and nocturnal hypoventilation (manifesting with morning headaches, fatigue and somnolence). By around 16 years of age, key pulmonary parameters (including forced vital capacity [FVC], peak expiratory flow [PEF], forced expiratory volume in the first second [FEV_1], maximal inspiratory pressure [MIP], and maximal expiratory pressure [MEP]) are less than 50% of predicted values for healthy children.[12, 13] As lung function further declines, patients may require

ventilation support, initially at night-time only, subsequently progressing to a requirement for both day-and-night-time ventilatory support with further worsening. This usually occurs before the patient reaches 23 years of age. The heart is also involved in DMD and manifests usually after the age of 10 years, with a progressive form of dilated cardiomyopathy. At the late non-ambulatory stage of the disease, the risks of respiratory and cardiac deterioration are high and patients often die from respiratory or cardiac failure in early adulthood, although cases of earlier death (in the late teens) are still reported.

Figure 1: Milestones and stages of DMD (reproduced from CS, Figure B-1)



DMD has a substantial negative impact on the health-related quality of life (HRQoL) of patients and their caregivers. The CS[1] highlights that children with DMD have a reduced capacity to engage in physical activity and cannot keep up with their peers. Patients are unable to participate in other activities normal for their age, for example, running around, and playing physical games with friends (e.g., football), or riding a bike. The loss of ambulation and the subsequent loss of upper limb function substantially affect the patient's ability to perform simple functional tasks, eventually resulting in a total loss of independence. The CS cites a UK qualitative study in which interviews were conducted with the parents of 10 individuals with nmDMD aged 4 to 19 years.[14] The study highlighted a number of key detrimental impacts of the disease which negatively affect HRQoL, including: muscle weakness; pain; fatigue and cognitive-behavioural symptoms; impacts on daily activities (e.g., limitations with self-care); social activities (e.g., difficulty keeping up with others) and emotional wellbeing (e.g., frustration). Further negative impacts include effects relating to the decline in lung function and the requirement for ventilation at the later stages of the disease, as well as the higher rates of neuropsychiatric disorders amongst DMD patients, including attention-deficit hyperactivity disorder (ADHD), learning difficulties, autism and obsessive–compulsive disorder (OCD). The CS states that HRQoL valuation studies in DMD consistently report a significantly lower level of HRQoL compared

to healthy children.[15, 16] A cross-sectional study of eight European countries (Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK) reported a mean EQ-5D index utility value for adult patients with DMD of 0.24, which is considerably lower than that for the age-matched general population.[17]

DMD also has a considerable detrimental impact on the HRQoL of caregivers, as a consequence of the ongoing and increasing caring burden as the patient's disease progresses and function is lost. The UK qualitative study[14] reported negative impacts relating to physical (e.g., lifting their child), emotional (e.g., anxiety/worry/stress) and time-related (e.g., administrative tasks) domains which were associated with impacts on work (e.g., time off work due to back pain), relationships (e.g., with partner) and social life. Behavioural problems may also be difficult to manage. The CS[1] highlights the considerable emotional burden of caring for children with DMD, including grief and sadness at the individual's condition, feeling hopeless, worry, anxiety, stress and loneliness.

2.2 Critique of the company's overview of current service provision

In 2016, the National Institute for Health and Care Excellence (NICE) issued a positive recommendation on the use of ataluren for the treatment of nmDMD following Highly Specialised Technology Appraisal Number 3 (HST3).[18] Ataluren is the only approved drug therapy in Europe which targets the underlying cause of DMD. Ataluren is available in England through an MAA.[19] The criteria for starting and stopping treatment with ataluren set out in the original MAA are summarised in Box 1. In 2019, an addendum was issued by NICE which provides access to ataluren treatment under the MAA for children aged 2 years or older.

Box 1: Ataluren MAA treatment starting and stopping criteria

Start criteria

- Patients must have a confirmed diagnosis of nmDMD, which is the identified presence of an in-frame nonsense mutation in the dystrophin gene as determined by genetic testing (full sequencing).
- Patients must be aged 5 years and older and able to walk 10 steps unaided.
- Patients should only start once a full set of standard baseline criteria has been obtained and once they have signed the Managed Access Patient Agreement.

Stop criteria

- The patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14 month period).
- If a patient has lost all ambulation (i.e. can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment.
    - In such cases as defined above, patients should stop treatment no later than 6 months after becoming fully non-ambulant.

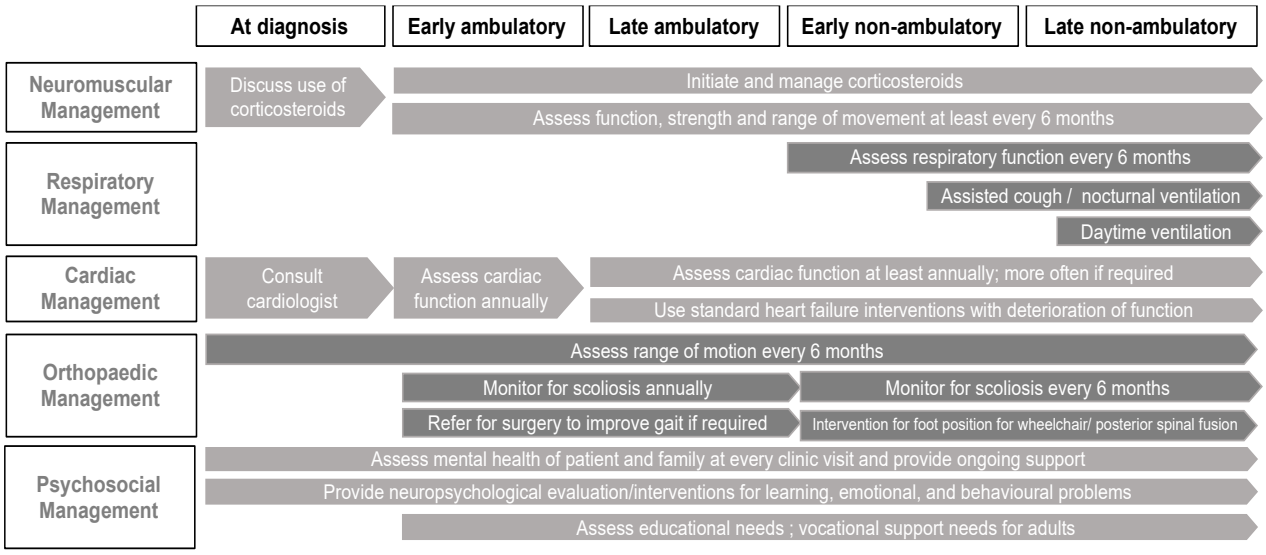
For patients who are not eligible for treatment with ataluren under the MAA in England, best supportive care (BSC) remains the only treatment option. In 2018, the DMD Care Considerations Working Group published updated care recommendations on the diagnosis and management of DMD. These care recommendations are published in three parts, focussing on: (i) diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management;[8] (ii) respiratory, cardiac, bone health, and orthopaedic management[9] and (iii) primary care, emergency management, psychosocial care, and transitions of care over the patient's lifetime.[10]

Care for patients with DMD requires a multidisciplinary approach, co-ordinated by a neuromuscular specialist. The CS[1] highlights that advances in multidisciplinary care, including corticosteroids and the more aggressive use of mechanical ventilation and early cardiac treatment, has led to improvements in the natural history and survival of patients with DMD. The CS includes a summary of the key aspects of multidisciplinary management, which is reproduced in Figure 2.

Corticosteroids have been shown to be effective in preserving motor function for a period of time and have additional benefits in terms of reduced (or postponed) risk of scoliosis, respiratory impairment and

cardiomyopathy, with evidence suggesting that daily use delays loss of ambulation compared with intermittent use.[11] However, there are safety concerns with the long-term use of steroids, and whilst muscle strength may be preserved for some time, patients will still eventually lose ambulation. Aside from corticosteroids and ataluren, there are limited pharmacological treatments for DMD. The extent of other treatment options is largely limited to supportive care interventions and symptom management.

Figure 2: Interdisciplinary management of DMD (reproduced from CS, Figure B.6)



3. CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[20] and addressed in the CS is presented in Table 3. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: Company's decision problem (reproduced from CS, Table A-1, with additional comments from the EAG)

	Final scope issued by NICE	Variation from scope	Rationale for variation from scope	EAG comments
Population	People aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk	None	**Note:** Whilst this aligns with the indication wording for ataluren, we would highlight that continued treatment with ataluren beyond loss of ambulation is expected to provide continued benefit by preserving remaining muscle function and vital functions such as pulmonary and cardiac function.	The modelled population is in line with the NICE scope. However, few patients in STRIDE[21] started treatment with ataluren before reaching the age of 5 years.
Intervention	Ataluren	None	Not applicable	Ataluren is assumed to be given in conjunction with BSC. The company's model assumes a stopping rule at FVC <50%. The extent to which this is reflected in STRIDE is unclear.
Comparator(s)	Established clinical management without ataluren	None	Not applicable	BSC is included as the sole comparator.
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 • HRQoL (for patients and carers).	Data on cardiac outcomes are not presented.	Whilst cardiac assessments are included in the patient registry (STRIDE) these data are immature and effect on cardiac function is unable to be presented in the submission.	The CS[1] presents comparative evidence for most of the outcomes listed in the NICE scope. However, data on cardiac function are not presented. Whilst the CS does not present any empirical evidence to demonstrate that ataluren improves survival, the economic model assumes that ataluren leads to a substantial survival gain.
Subgroups to be considered	None	None.	**Note:** Subgroup analysis relating to outcomes in patients based on baseline 6-minute walk distance (6MWD) will be included in the clinical evidence, however these do not reflect specific populations to be treated in practice and are not presented in the economic modelling.	The CS[1] does not contain any economic subgroup analyses.

	Final scope issued by NICE	Variation from scope	Rationale for variation from scope	EAG comments
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	None	Not applicable	The CS[1] includes a detailed description of the nature of the condition and its impact on patients with nmDMD and their caregivers.
Cost to the NHS and PSS, and Value for Money	• cost-effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used	None	Not applicable	The company's economic model is in line with the NICE scope.[1]
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise	None	Not applicable	The company's economic model includes impacts on patients with nmDMD and their caregivers. Following HST3,[18] ataluren has been available in England through an MAA since 2017;[19] hence, a positive recommendation is not expected to have implications for staffing or infrastructure. The CS[1] claims that ataluren is an innovative, first-in-class drug and is the first specific approved therapy for nmDMD that addresses the underlying cause of the disease. Cost impacts on other sectors are discussed.
Special considerations, including issues related to equality	None	None	Not applicable	None.

NICE - National Institute for Health and Care Excellence; STRIDE - Strategic Targeting of Registries and International Database of Excellence; CS - company's submission; HRQoL - health-related quality of life; 6MWD - 6 minute walk distance; FVC - forced vital capacity; HST - Highly Specialised Technology; NHS - National Health Service; PSS - Personal Social Services; BSC - best supportive care; nmDMD - nonsense mutation Duchenne muscular dystrophy

3.1 Population

The final NICE scope[20] specifies the relevant population as *"People aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk."*

The CS[1] presents evidence on the effectiveness and/or safety of ataluren from a number of studies, including randomised controlled trials (RCTs),[22, 23] single-arm studies[24-27] and analyses of observational and/or registry datasets.[19, 21, 28] The pivotal RCTs of ataluren, Study 007 and Study 020, which formed the basis of the original European Medicines Agency (EMA) conditional marketing authorisation issued in 2014, were undertaken in patients who were aged 5 years or older and between 7 to 14 years, respectively. The EMA and Medicines and Healthcare products Regulatory Agency (MHRA) conditional marketing authorisation for ataluren was extended July 2018 to include patients who are aged 2 years or older, based on additional evidence provided from Study 030[26] (a safety and pharmacokinetics study). None of these studies are used to inform the company's economic model (see Section 5.2). Data from the Strategic Targeting of Registries and International Database of Excellence (STRIDE) registry,[21] which is an ongoing non-imposed post-approval safety study designed to collect information on the safety and effectiveness of ataluren in the real-world setting as part of routine clinical practice, are used as the basis for the intervention group of the company's economic model. This study includes some younger patients including those aged between 2 and 5 years; at the January 2021 data-cut, [redacted] of 269 patients ([redacted]) in STRIDE had received treatment under the age of 5 years. The model includes additional assumptions which are intended to reflect the additional benefit associated with initiating ataluren at a younger age than that reflected in the overall STRIDE population.

The extended EMA/MHRA conditional marketing authorisation for ataluren is as follows: *"Translarna [ataluren] is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older."*[29] The Summary of Product Characteristics (SmPC) for ataluren states that patients must have a nonsense mutation in the dystrophin gene as part of their underlying disease state, as determined by genetic testing and that patients who do not have a nonsense mutation should not receive ataluren.

The EAG believes that the company's economic model is consistent with the final NICE scope[20] and this reflects the full population defined in the marketing authorisation for ataluren.[29]

3.2 Intervention

The intervention described in the CS[1] is ataluren (Translarna™), which is given in conjunction with BSC. Ataluren is indicated specifically in patients with nmDMD. A nonsense mutation in the

deoxyribonucleic acid (DNA) results in a premature stop codon within a messenger ribonucleic acid (mRNA) that prevents generation of a full-length protein. Ataluren enables ribosomal readthrough of mRNA containing a premature stop codon, resulting in production of full-length dystrophin proteins.[29] As noted in Section 3.1, the conditional marketing authorisation for ataluren was extended in July 2018 as the regulators recognised the potential benefit of beginning ataluren treatment earlier in a child's development, impeding the rate of irreversible functional decline during the patient's early life.[1]

Ataluren is available as granules which are taken orally. Ataluren is available in sachets at three different dosage strengths: 125mg, 250mg and 1,000mg. The SmPC[29] states that ataluren should be administered every day in three doses, with the first dose taken in the morning, the second taken at midday, and the third taken in the evening. The SmPC recommends dosing intervals of 6 hours between the morning and midday doses, 6 hours between the midday and evening doses, and 12 hours between the evening dose and the first dose on the following day. The recommended total daily dose is 40mg/kg body weight, with doses of 10mg/kg body weight in the morning, 10mg/kg body weight at midday, and 20mg/kg body weight in the evening. The dosing schedule recommended by the EMA/MHRA is shown in Table 4.

Table 4: Ataluren recommended dosing by body weight (reproduced from ataluren SmPC)

Body weight range (kg)		Morning			Midday			Evening		
		125mg sachets	250mg sachets	1,000mg sachets	125mg sachets	250mg sachets	1,000mg sachets	125mg sachets	250mg sachets	1,000mg sachets
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	0	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

mg – milligram; kg - kilogram; SmPC - Summary of Product Characteristics

Each pack of ataluren contains 30 sachets. The list price for ataluren is £2,532 for 30 x 125mg sachets, £5,064 for 30 x 250mg sachets and £20,256 for 30 x £1,000mg sachets.[30] As part of the commercial arrangement supporting the MAA,[19] a Patient Access Scheme (PAS) is available for ataluren, which takes the form of a simple price discount of [redacted] for all pack strengths. Including this discount, the price per pack of 125mg, 250mg and 1,000mg sachets is [redacted], [redacted] and [redacted], respectively.

The SmPC for ataluren[29] does not include a formal stopping rule. Following the HST3 appraisal in 2016,[18] ataluren has been available in the NHS in England through an MAA. The MAA requires that patients discontinue treatment with ataluren no later than 6 months after becoming fully non-ambulant (see Box 1). In contrast to the stopping criteria set out in the MAA, the company's economic model assumes that treatment is continued until patients reach FVC<50%.

3.3 Comparator

The final NICE scope[20] includes a single comparator: *"established clinical management without ataluren."* The CS[1] includes BSC as the sole comparator for ataluren. The EAG agrees that this is appropriate. The CS does not explicitly describe what BSC is comprised of in England. The company's economic model includes BSC-related health state costs which have been taken from a published modelling study reported by Landfeldt *et al.* (2019).[31] The BSC costs included in this model relate to: hospital admissions; emergency care; respite care; visits to physicians and other healthcare practitioners (nurses, general practitioners, specialist physicians, psychologists, therapists, physiotherapists, occupational therapists, care co-ordinators/care advisors, dentists, dietitians/nutritionists and speech/language/ swallowing therapists); tests and assessments; medications; medical aids devices and investments, community services (e.g., home help and personal assistants) and other informal care. The company's clarification response[32] (question B15) indicates that whilst not explicitly stated in the Landfeldt paper, the costing study used to inform the published model also includes the costs of drug treatments (e.g., corticosteroids).

3.4 Outcomes

The final NICE scope[20] lists a range of outcomes including those relating to: ambulation; muscle function and strength; ability to undertake activities of daily living (ADL); cardiac function; respiratory function; time to wheelchair use; falls; mortality; adverse events (AEs) and HRQoL.

The CS[1] includes comparative evidence relating to all of these outcomes except for mortality and cardiac function. Mortality data are not reported because no deaths were observed in Study 007, Study 020_[redacted] As noted in Table 3, the CS states that data on cardiac function from STRIDE are

immature and the company has been unable to present evidence for the effect of ataluren on cardiac outcomes.

The company's economic model is structured around the use of information from a propensity score matched indirect comparison of data from STRIDE[21] and the Cooperative International Neuromuscular Research Group (CINRG) Disease Natural History Study (DNHS),[28] including endpoints relating to the age at loss of ambulation (defined as full-time wheelchair use or bed-ridden) and the age at which different levels of lung function impairment are reached (defined in terms of FVC thresholds). Efficacy and safety data from the trials/MAA are not used to inform the company's model. Impacts on patient HRQoL are based on a Delphi panel consensus exercise including clinician assessments (as proxy),[33] whereas impacts on caregiver HRQoL are based on a survey of 770 individuals with DMD and their caregivers.[34] HRQoL data from the trials and/or the MAA are not used in the economic model. The economic model does not include the impact of AEs on HRQoL or costs. The company's economic analysis is described and critiqued in Chapter 5.

3.5 Other relevant factors

The CS[1] suggests that there are no special considerations relating to equity or equality.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for ataluren for the treatment of nmDMD. The CS contains a systematic literature review (SLR) of studies of ataluren and three indirect treatment comparisons (ITCs) comparing ataluren plus BSC versus BSC alone. Section 4.1 provides a critique of the company's SLR of clinical effectiveness and safety evidence. Section 4.2 provides a summary of the clinical effectiveness and safety results, together with a critique of the included studies. Section 4.3 provides a summary and critique of the company's ITCs. Section 4.4 presents the conclusions of the clinical effectiveness chapter and a discussion of the key uncertainties in the available evidence.

As the current submission is a re-evaluation of ataluren for treating nmDMD (i.e., a review of HST3[18]) this chapter focuses primarily on key additional evidence supporting the efficacy and safety of ataluren from a number of sources including long-term follow-up studies (Study 019[25]), support of the licence extension to patients aged ≥2 to <5 years (Study 030[35, 36]) and real-world observational evidence (the STRIDE registry [Study 025o],[21, 37-40] and the MAA[41]). For completeness, a summary of the main clinical evidence (Study 007[22] and Study 020,[23] including extension Study 020e[42]) included in the company's original submission for HST3 is also provided.

4.1 Critique of the methods of review(s)

The company undertook an SLR to identify all clinical evidence regarding the efficacy and safety of ataluren with BSC for the treatment of nmDMD. In summary, the current CS[1] updates the company's original systematic review for HST3.[18] The methods for the company's SLR of clinical evidence are detailed in the CS[1] and in CS Appendices 17.1 and 17.2.[43]

4.1.1 Searches

The company conducted searches on the 10th-11th June 2019 (updated on the 10th September 2021) and included the core databases required by NICE (MEDLINE, including In-Process and Epub Ahead of Print; EMBASE; the Cochrane Library; and the Centre for Reviews and Dissemination [CRD] database). All databases were searched from inception. Additional searches were undertaken of relevant congresses and trials registers in order to identify data from recent and ongoing trials. The EAG considers that the company's search strategies (reproduced in full in CS Appendix 17.1[43]) are well-designed, use appropriate subject headings and free text terms, and are likely to have retrieved all relevant studies. However, the EAG notes that it is unclear how the company identified and selected the CINRG DNHS as the best source of data for BSC, as the CS does not contain an SLR of BSC/natural history studies. This source is used in two of the company's three ITCs (see Section 4.3).

4.1.2 Inclusion criteria

The CS[1] describes an appropriate method of identifying and screening references for inclusion of clinical studies (RCTs, non-randomised controlled studies and uncontrolled studies) in the SLR of ataluren. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in the selection process were resolved through discussion between reviewers or consultation with a third reviewer, if required (see CS Appendix[43] 17.1.4, page 13). A summary of the inclusion and exclusion criteria, as reported in the CS, is presented in Table 5. In general, the specified inclusion and exclusion criteria were appropriate and generally reflect the decision problem set out in the final NICE scope.[20]

Table 5: Inclusion/exclusion criteria used to select studies of ataluren in the CS (reproduced with minor changes from CS, Table C-1)

Criteria	Inclusion criteria	Exclusion criteria
Population	People with nmDMD	People without nmDMD
Intervention	Ataluren (PTC-124)	Not ataluren
Comparators	No restriction; any comparator	
Outcomes	• All efficacy or effectiveness outcomes e.g., mortality, ambulation, loss of ambulation, time to wheelchair, number of falls, lung function, cardiac function, muscle function, muscle strength, mobility, quality of life, ability to undertake activities of daily living • All safety outcomes e.g., any grade of adverse events, discontinuation rate due to adverse events	Any outcomes other than efficacy, effectiveness or safety
Study design	• Only original papers of in-human studies	• Comment • Letter to editors • Editorial • Notes • Reviews • Animal studies
Geographical location	No restriction; any geographical location	
Language	No restriction; any language	
Publication date	No restriction; any study date	

nmDMD - nonsense mutation Duchenne muscular dystrophy

4.1.3 Critique of data extraction

The data extracted and presented in the CS[1] for the SLR of clinical evidence appear to be appropriate and comprehensive. As noted in the company's clarification response[32] (question A2), all relevant data were extracted by a single reviewer into a pre-defined data extraction table. All extractions were then checked for accuracy by a second independent reviewer. Any discrepancies were resolved through

discussion between the reviewers. Neither the EAG nor their clinical advisors are aware of any additional relevant completed studies within the scope of this appraisal.

4.1.4 Quality assessment

The company used various tools to assess the quality of each key source of evidence (CS,[1] Section 9.5). As noted in the company's clarification response[32] (question A2), assessment of the methodological quality of included studies was performed by one reviewer and checked by a second reviewer. In general, the EAG considers the quality assessment tools used by the company to be adequate.

The methodological quality of RCTs (Study 007[22] and Study 020[23]), was assessed using the minimum criteria for assessment of risk of bias and generalisability, as recommended in the current NICE user guide template for company evidence submissions.[44] For quantitative studies reporting correlations or associations (Study 030[35, 36] and Study 019[25]), the CS[1] used a quality appraisal checklist, as recommended in the previous NICE process and methods guidance for public health interventions.[45] Whilst the methods used in the CS were acceptable, the quality assessment of Study 019[25] would have benefited from the use of a complementary appraisal tool. As this study used propensity score matching to assess the long-term safety and tolerability of ataluren in patients with nmDMD who had received ataluren plus BSC in prior PTC Therapeutics-sponsored studies (Study 007 and Study 007e; Study 004 and 004e [at investigational sites outside the USA only]) compared with DMD patients treated with BSC alone in the CINRG DNHS, the use of the Quality of Effectiveness Estimates from Non-randomised Studies (QuEENS) checklist[46] would have helped to assess the strength and limitations of the ITC. A quality assessment of the company's ITC of STRIDE and the CINRG DNHS using the QuEENS checklist is presented in Section 4.3.1 (Table 16). This comparison uses the same ITC methodology as Study 019 (see Section 4.3.3).

The methodological quality of the STRIDE registry[21, 37-40] was assessed using the criteria recommended in the current NICE user guide template for company evidence submissions for non-randomised and non-controlled evidence.[44] However, the EAG believes that this tool is less appropriate for assessing the quality of real world evidence (RWE) studies. Following a request for clarification from the EAG (see clarification response,[32] question A12), the company critically appraised the observational RWE discussed in the CS[1] using the recently developed Assessment of Real World Observational Studies (ArRoWS) critical appraisal tool.[47] The company's response includes a critical appraisal of STRIDE,[21, 37-40] CINRG[25, 28, 38, 48] and the NorthStar registry[41] using this tool.

The EAG notes that the company did not quality assess all relevant studies included in the CS.[1] As noted in the CS, a Phase 2a proof-of-concept study (Study 004)[49] was part of the evidence base in HST3,[18] but this study was excluded from the current submission due to the company's decision to focus on newer clinical evidence. As this study was previously appraised in the original CS for HST3, the EAG is satisfied with its exclusion from the current CS.[1] More importantly, it is unclear why quality assessments were not provided by the company for the analysis of the MAA[41] (an observational RWE study reflecting treatment with ataluren in NHS patients in England [CS, Sections 9.3.1.4, 9.4.1.7 and 9.6.1.7]). Owing to time constraints, the EAG was unable to undertake any additional quality assessments.

4.1.5 Evidence synthesis

Section 9.8 of the CS[1] provides a brief summary of the methods and results of a published meta-analysis combining data from two RCTs of ataluren (Study 020 and Study 007).[50] Although specific methodological details were lacking in the CS,[1] further details of this analysis and critique are available in the original company's submission for HST3.[18] For the additional evidence supporting the efficacy and safety of ataluren, the company undertook a narrative synthesis of the evidence; however, no explicit details were provided on how this approach was undertaken. Ideally, a narrative synthesis approach should be pre-specified, justified, rigorous (i.e., describe results without being selective or emphasising some finding over others) and transparent to reduce potential bias.[51, 52] Despite the lack of transparency in the CS,[1] the EAG acknowledges that the narrative synthesis approach undertaken by the company was reasonable.

4.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

The key clinical studies from the company's clinical trial programme for ataluren (Study 007,[22] Study 020,[23] Study 019,[25] Study 030[35, 36]), along with global STRIDE registry,[21, 37-40] the MAA study[41] and the main studies used by the company to estimate outcomes for patients receiving BSC alone (CINRG[25, 28, 38, 48] and the NorthStar Registry[41]) are summarised in Table 6. It should be noted that Study 020[23] had an associated, open-label, single group, extension phase (Study 020e[42]) for patients who successfully completed the double-blind, placebo controlled study. As noted in the CS,[1] a Phase 2a proof-of-concept study (Study 004[49]) formed part of the evidence base for HST3,[18] but was excluded from the current submission due to the company's focus on newer clinical evidence.

Table 6: Summary of key studies (adapted from the CS, Tables C2, C3, C5, C6 to C11, and C34)

Study name	Design	Population	Sample size	Intervention	Comparator	Follow-up period	Primary outcome(s)
Ataluren studies							
Study 007[22]	• Phase 2b, randomised, double-blind, placebo-controlled • 37 sites, 11 countries, including UK	• Ambulatory males with nmDMD, • Aged ≥5 years (not required to be on corticosteroids at baseline)	174	• Ataluren 40mg/kg/day; TID (n=57) • Ataluren 80mg/kg/day; TID (n=60)	• Placebo, TID (n=57)	48 weeks	Change in 6MWD from baseline to week 48
Study 020[23]	• Phase 3, randomised, double-blind, placebo-controlled • 54 sites, 18 countries, including UK	• Ambulatory males with nmDMD, • Aged 7 to 16 years (on corticosteroid treatment)	230	• Ataluren 40mg/kg/day; TID (n=115)	• Placebo; TID (n= 115)	48 weeks	Change in 6MWD from baseline to week 48
Study 020e (NCT02090959)[42]	• Extension of Study 020 (open-label, single group)	• As above	218*	• Ataluren 40mg/kg/day; TID (n=218)	• N/A	up to 144 weeks	Safety (AEs, laboratory abnormalities)
Study 019[25]	• Long-term, open-label safety and efficacy study • 21 sites, 10 countries, including UK	• Ambulatory and non-ambulatory males with nmDMD who participated in prior PTC-sponsored Phase 2 ataluren studies, outside USA**	94	• Ataluren 40mg/kg/day; TID	• N/A	240 weeks (or up to 336 weeks in Canada)	Long-term safety and tolerability at 240 weeks
Study 030[35, 36]	• Phase 2, open-label safety and pharmacokinetic study • 6 sites, USA	• Males with nmDMD • Aged ≥2 to <5 years • Body weight ≥12kg	14	• Ataluren 40mg/kg/day; TID	• N/A	52 weeks (4 weeks PK portion and 48 weeks treatment extension)	Safety (abnormal laboratory values and/or AEs)

Study name	Design	Population	Sample size	Intervention	Comparator	Follow-up period	Primary outcome(s)
STRIDE Registry[21, 37-40]	• Patient registry • 64 sites, 13 countries, including UK (ongoing)	• Ambulatory and non-ambulatory patients with nmDMD • Aged ≥2 years	360 (estimated) (as of 31/01/2021, 286 patients received at least 1 dose ataluren; evaluable male population, n=269)	• Ataluren 40mg/kg/day; TID	• N/A	10 years (5 years target follow-up duration)	Outcomes included safety; efficacy evaluations conducted as per usual care: 6MWD, TFTs, LoA, NSAA, pulmonary and cardiac assessments
Managed Access Agreement[41, 53]	• Cohort study of English patients for conditional reimbursement (ongoing)	• Ambulatory patients with nmDMD, • Aged ≥2 years	60	• Ataluren 40mg/kg/day; TID	• N/A	6 years, approx. (March 2016 to January 2022)***	Outcomes included NSAA, patient quality of life (CHU-9D), caregiver quality of life (EQ-5D)
Natural history studies							
CINRG-DNHS Registry[25, 28, 38, 48]	• Natural history study • 20 sites, 9 countries	• Ambulatory and non-ambulatory patients with DMD • Aged 2 to 28 years	440	• N/A	• Standard care	10 years (>8 years target follow-up)	Outcomes included median survival, LoA, pulmonary function and TFTs
NorthStar Registry[41]	• Natural history study (UK)	• Patients with DMD	145	• N/A	• Standard care	2006 to present	Outcomes included NSAA, patient quality of life (CHU9D), caregiver quality of life (EQ-5D)

6MWD - 6-minute walk distance; TFT - timed function test, CHU9D - Child Health Utility Instrument (9 dimensions); EQ-5D - EuroQol-5 Dimensions; LoA - loss of ambulation; nmDMD - nonsense mutation Duchenne muscular dystrophy, N/A - not applicable; NSAA - NorthStar Ambulatory Assessment; TID - three times daily; AE - adverse event
** All participants who received at least 1 dose of study drug; ** Phase 2 studies included Study 007 and/or subsequent open label extension Study 007e (n=90) and Study 004 and/or subsequent open label extension Study 004e (n=3) and one patient did not have prior ataluren exposure but petitioned to be allowed into the study; ***Period extended to either publication of the updated NICE HST guidance or 20 January 2023, whichever occurs earliest*

4.2.1 Study 007 and Study 020 (including extension phase and meta-analysis)

Study 007[22] and Study 020[23] formed the main evidence base for HST3.[18] These pivotal RCTs are briefly summarised here, including additional data from an extension study (Study 020e),[42] a meta-analysis[50] and the NICE Appraisal Committee's conclusions regarding this evidence submitted to inform HST3.[18]

Study 007[22] was a Phase 2b, randomised, double-blind, placebo-controlled study conducted in 174 ambulatory males aged ≥5 years with nmDMD. Participants were recruited from 37 study sites in 11 countries including 7 patients from the UK. Stable use of concomitant corticosteroids was permitted. Patients with a screening 6-minute walk distance (6MWD) of ≥75 metres were randomised in a 1:1:1 ratio to either oral treatment with ataluren at a total daily dosage of 40mg/kg/day (the licensed dose) (n=57); 80mg/kg/day (n=60); or to placebo (n=57) for 48 weeks, and were stratified prospectively by age (<9 or ≥9 years), corticosteroid use (yes or no), and baseline 6MWD (<350 metres or ≥350 metres). All patients also received BSC. The primary endpoint was a change in the patient's ability to walk on a hard, flat surface measured using the 6MWD from baseline to Week 48 and analysed in the intention-to-treat (ITT) population, which included all randomised patients with a valid 6MWD available at baseline and at least one post-baseline visit.

At 48 weeks in a corrected ITT (cITT) analysis (data presented only for the ataluren licensed dose of 40mg/kg/day), the observed mean decline in 6MWD was 44.1 metres and 12.9 metres for placebo and ataluren, respectively. The difference of 31.3 metres was not statistically significant (p=0.056).[1] In a mixed model for repeated measures (MMRM) analysis, the estimated mean difference between ataluren 40mg/kg/day and placebo was 31.7 metres (95% confidence interval [CI] 5.1 to 58.3; p=0.0197).[18] A more pronounced effect was observed in the subgroup of patients in the decline phase of ambulation, defined *post hoc* as those aged 7 to 16 years treated with corticosteroids with baseline 6MWD of ≥150 metres and ≤80% predicted 6MWD. This *post hoc* subgroup cITT analysis (data not reported in CS[1] but described in the evidence submission for HST3[18]) showed that patients receiving ataluren (n=32) experienced a statistically significantly smaller reduction in 6MWD compared with patients receiving placebo (n=31) (difference in mean change in 6MWD: observed, 49.9 metres; MMRM analysis, 45.6 metres; p=0.0096).[18] As noted in the NICE Guidance for HST3, the decline phase was considered clinically important because patients younger than 7 years tend to increase their 6MWD over 48 weeks because of normal developmental improvements in walking. In a pre-specified subgroup of patients with a baseline 6MWD of <350 metres, the cITT analysis also found a statistically significantly smaller reduction in 6MWD with ataluren (n=25) compared with placebo (n=22) at 48 weeks (difference in mean change in 6MWD: observed, 68.2 metres;[1] MMRM analysis, 59.8 metres; p=0.0053).[18]

An analysis of secondary endpoints in the cITT population of Study 007[22] found statistically significant benefits for ataluren versus placebo only for the outcomes of time to climb 4 stairs (difference of 2.4 seconds; 95% CI: -4.8, 0.0; *p*=not reported [NR]) and frequency of accidental falls (relative ratio [RR] 0.38; 95% CI: 0.16, 0.94; *p*=NR). For all other outcomes (e.g., time to descend 4 stairs, run/walk 10 metres, and patient reported outcome measures), no statistically significant differences were reported (CS,[1] Section 9.6.1.2, pages 100 to 101).

Study 020[23] was a Phase 3, randomised, double-blind, placebo-controlled study conducted in 230 ambulatory males aged ≥7 to ≤16 years with nmDMD and on stable doses of corticosteroids. Participants were recruited from 54 study sites in 18 countries including the UK. Patients with a baseline 6MWD of ≥150 metres and ≤80% of the predicted normal value for age and height were randomised in a 1:1 ratio to receive ataluren at a total daily dosage of 40mg/kg/day (n=115) or to placebo (n=115) for 48 weeks. All patients also received BSC. Subsequently, patients were eligible to receive ataluren through an open-label extension study (Study 020e).[42] Randomisation was stratified by age (<9 years vs. ≥9 years), duration of previous corticosteroid use (6 months to <12 months vs. ≥12 months), and baseline 6MWD (<350 metres vs. ≥350 metres). The primary outcome was the change in 6MWD from baseline to Week 48, analysed in the ITT population (n=228), which included all randomised patients with a valid post-baseline 6MWD value. In the ITT population, a 15.4 metre difference was observed in 6MWD at 48 weeks favouring ataluren over placebo, which was not statistically significant. The least-squares (LS) mean change in 6MWD from baseline to 48 weeks was -47.7 metres for ataluren and -60.7 metres for placebo (difference 13.0 metres; *p*=0.213). A more pronounced effect was observed in a pre-specified subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres, with an observed difference of 47.2 metres in favour of ataluren versus placebo. The LS mean change in this subgroup was -27.0 metres for ataluren and -69.9 metres for placebo at week 48 (difference 42.9 metres; *p*=0.007).

An analysis of secondary endpoints in the ITT population of Study 020[23] showed that only time to descend 4 stairs (LS mean difference of -2.0 seconds; *p*=0.012) significantly favoured ataluren over placebo. For all other outcomes (e.g., run/walk 10 metres, 4 star climb, NorthStar Ambulatory Assessment [NSAA], and HRQoL using the Paediatric Outcomes Data Collection Instrument [PODCI]), no statistically significant differences were reported (CS,[1] Section 9.6.1.3, pages 101 to 106). In the subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres, ataluren showed significant benefits compared with placebo only in the 4 stair climb (LS mean difference, −3.5 seconds, *p*=0.003), 4 stair descend (LS mean difference −4.4 seconds, *p*<0.001) and the NSAA (*p*=0.041) (CS,[1] Section 9.6.1.3, page 104).

Patients who completed Study 020[23] were eligible to participate in an ongoing open-label, single group extension phase (Study 020e[42]). The primary objective of the extension study was to obtain long-term safety data for ataluren in male participants with nmDMD. Despite limited details of Study 020e being presented in the CS,[1] the company notes that of the 218 participants who received at least 1 dose of study drug, data were only available for a total of 68 patients who completed 144 weeks of treatment (CS, Table C-3 and CS, Section 9.7.2.2, page 142). As discussed in the EMA assessment report for ataluren,[54] the high rate of study non-completion, as indicated by the market authorisation holder, was due primarily to the commercial availability of ataluren (n=88).[42] The EMA questioned whether this was a valid justification for terminating the study, as DMD patients are screened regularly and data could have been collected. Nevertheless, due to ongoing trials addressing the efficacy and safety of ataluren, this issue was not pursued further by the EMA.[54] In general, the most frequently reported treatment-emergent adverse events (TEAEs) were: nasopharyngitis (26.1%); disease progression (25.7%); fall (22%); headache (19.3%) and vomiting (17.0%) (CS,[1] Section 9.7.2.2, page 142). The EMA assessment report[54] noted that *"No conclusions on efficacy in ambulatory and non-ambulatory patients can be drawn due to the design of the study, i.e. powered on safety and lack of a comparator arm."*

A pre-specified meta-analysis[50] using data from Study 020 (n=228) and Study 007 (patients who met Study 020 criteria; n=114) was conducted to assess total efficacy of ataluren (40mg/kg/day) compared with those receiving placebo. Fixed effect meta-analyses were conducted using ITT populations and two patient subgroups (baseline 6MWD ≥300 to <400 metres [Study 020, n=99; Study 007, n=44] or <400 metres [Study 020, n=144; Study 007, n=72]) from both trials. Meta-analysis of the ITT populations showed a statistically significant benefit for ataluren compared to placebo with an LS mean difference in 6MWD of 17.2 metres (p=0.0473). Meta-analyses for the subgroup of patients with a baseline 6MWD of ≥300 to <400 metres or <400 metres from Studies 007 and 020 also showed a more pronounced benefit with ataluren compared to placebo, with an LS mean difference of 43.9 metres (p=0.0008) and 27.7 metres (p=0.0109) in the 6MWD, respectively (CS,[1] Table C-46, page 153).

Additional analyses[50] of secondary outcomes from the two ITT populations showed statistically significant benefits in favour of ataluren over placebo in time to climb 4 stairs (p=0.0078) and descend 4 stairs (p=0.0055). However, there was no difference between treatments in time to run/walk 10 metres (p=0.0677). Compared with those receiving placebo, patients who received ataluren also had a significantly reduced risk of persistent 10% 6MWD worsening from baseline (p=0.0215). A more pronounced effect was observed in a subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres. The meta-analysis showed significant benefits with ataluren compared with placebo in

time to run/walk 10 metres (p=0.0149), climb 4 stairs (p=0.0004), and descend 4 stairs (p<0.0001). Similar significant findings were also observed in the <400 metres 6MWD subgroup.

The spectrum and severity of AEs were consistent across Study 020 and Study 007. As noted in the CS[1] (pages 138 to 139), the most common adverse reactions in the two placebo-controlled studies were: vomiting; diarrhoea; nausea; headache; upper abdominal pain, and flatulence. Each of these events occurred in ≥5% of ataluren-treated patients. No individuals discontinued because of AEs in Study 007; two patients discontinued due to AEs in Study 020 (ataluren, n=1 [constipation]; placebo, n=1 [disease progression]) and no deaths were reported in either trial.

As Study 007[22] and Study 020[23] formed the main clinical evidence for NICE HST3,[18] the Appraisal Committee's key conclusions on the clinical evidence presented in the appraisal are summarised below:

- The 6MWD was an appropriate primary outcome to assess the benefits of treatment with ataluren in the clinical trials.
- There was no meaningful improvement in the rate of decline in 6MWD with ataluren compared with BSC in the ITT populations of Study 007 and Study 020.
- In Study 007 and Study 020, there was no statistically significant difference in change in 6MWD between the ataluren and BSC groups in the ITT analyses.
- The Appraisal Committee noted the company's assertion that, in 48-week trials such as Study 007 and Study 020 that use change in 6MWD as a primary outcome, the optimum range in the 6MWD at baseline to detect a difference is 300 to 400 metres. The Appraisal Committee agreed to consider the 48-week clinical trial data from a subgroup of patients with a baseline 6MWD of 300 to 400 metres, but expressed concerns about the uncertainty and generalisability of the results to the broader ambulant population.
- The results of the primary and secondary clinical outcomes in Study 020 showed a benefit at 48 weeks for ataluren compared with BSC in patients with a baseline 6MWD of 300 to 400 metres. However, the Appraisal Committee also concluded that the size of this benefit in the overall ambulant population (in which the drug is intended to be used in clinical practice) remains highly uncertain.
- There were no specific safety concerns associated with ataluren.

4.2.2 Study 030

Following the original submission in HST3,[18] Study 030[35, 36] (a single-arm, open-label, Phase II study) was conducted to evaluate the safety, pharmacokinetics and efficacy of ataluren in 14 male patients aged ≥2 to <5 years with nmDMD and a body weight of ≥12 kg. Participants were recruited from 6

study sites in the USA and stable use of concomitant corticosteroids was permitted (42.9% of patients were on corticosteroids at baseline). Patients received ataluren at a total daily dosage of 40mg/kg/day for 4 weeks during the pharmacokinetic analysis phase, and for 48 weeks during the extension period. The primary outcomes focused on safety, including pharmacokinetics and pharmacodynamics. Secondary outcomes included assessment of the impact of ataluren therapy on proximal muscle function using timed function tests (TFTs; including time to climb 4 stairs, descend 4 stairs, run/walk 10 metres, and stand from a supine position) and change in motor function, assessed using the NSAA 16-Item Scale, and 2 revised subsets of 3 and 8 items. As noted in the CS[1] (page 114) and the EMA extension of indication variation assessment report (Procedure No. EMEA/H/C/002720/II/0037),[55] clinical experts agreed that the most relevant test for assessing motor function would be the revised 8-item NSAA, as it can be performed reliably by patients aged 4 years, which was the mean age of the patients in Study 030.

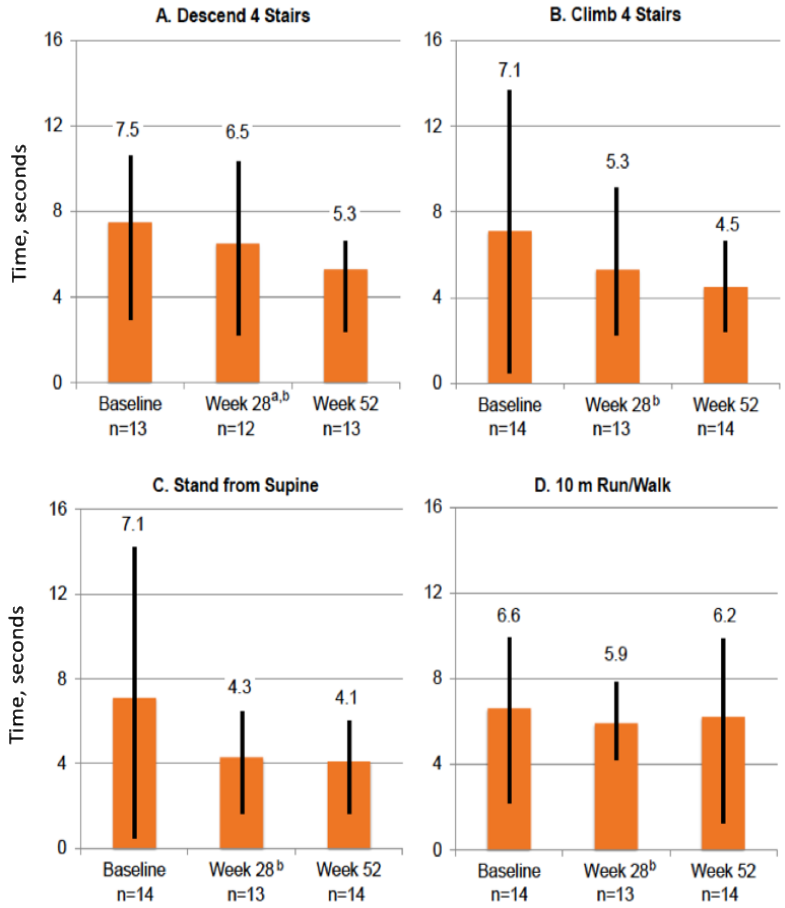
The CS[1] (page 144) provides only a very brief summary of the safety and tolerability data from Study 030 and there appear to be minor data discrepancies between evidence sources: the CS[1] and the EMA assessment reports (Procedure No. EMEA/H/C/002720/II/0037[55] and Procedure No. EMEA/H/C/002720/II/0049[56]). To allow for a comparison of safety in patients aged ≥5 years with those aged <5 years in the 28-day pharmacokinetic phase of Study 030, AE data from the first 28 days of treatment in Study 007 and 020 (patients with nmDMD aged ≥5 years) were pooled.[55] In general, the AE profile appeared to be similar in nmDMD patients aged ≥2 to <5 years compared with those aged ≥5 years in the pooled studies. During the first 28 days of exposure, the overall frequency of TEAEs in Study 030 was higher than in the pooled Studies 007 and 020 (71.4% [10 patients] versus 47.1% [81 patients]). The higher frequency appeared to be driven by a higher frequency of pyrexia (28.6%) and rash (21.4%), which may be considered as more frequent in younger children in general compared with those aged ≥5 years.[55]

Although not reported in the CS,[1] for the overall 52 week assessment, all 14 patients had experienced at least one TEAE; however, no patients experienced a serious adverse event (SAE) or prematurely discontinued the study drug due to a TEAE. The most common TEAE was pyrexia, which affected 6 patients (42.9%) at some point during the study. Other common TEAEs included: ear infection (35.7%); nasopharyngitis (28.6%); vomiting (28.6%); rash (21.4%) and cough (21.4%). The TEAEs classified as being possibly related to ataluren were: rash; flatulence; nausea and vomiting. All TEAEs possibly related to ataluren were classified as mild, except for 2 occurrences of vomiting which were classified as moderate. The EMA assessment report (Procedure No. EMEA/H/C/002720/II/0049[56]) concluded that

no unexpected safety issues were encountered and AEs were in line with the those known for patients aged ≥5 years or common childhood illnesses.

Whilst efficacy considerations were not a primary focus of Study 030,[35, 36] an analysis of secondary efficacy outcomes showed non-significant improvements in TFTs (CS,[1] Section 9.6.1.5, pages 112 to 115). As with the safety data discussed earlier, the EAG notes there are also minor data discrepancies between efficacy evidence sources: the CS[1] and the EMA assessment reports (Procedure No. EMEA/H/C/002720/II/0037[55] and Procedure No. EMEA/H/C/002720/II/0049[56]). As shown in Figure 3, the differences from baseline to Week 28 were 1 second, 1.8 seconds, 2.8 seconds and 0.7 seconds on time to descend 4 stairs, climb 4 stairs, to get up from the supine position and run/walk 10 metres, respectively. The differences from baseline to Week 52 were more pronounced for descending 4 stairs, climbing 4 stairs and standing from supine (2.2 seconds, 2.6 seconds, and 3 seconds, respectively).

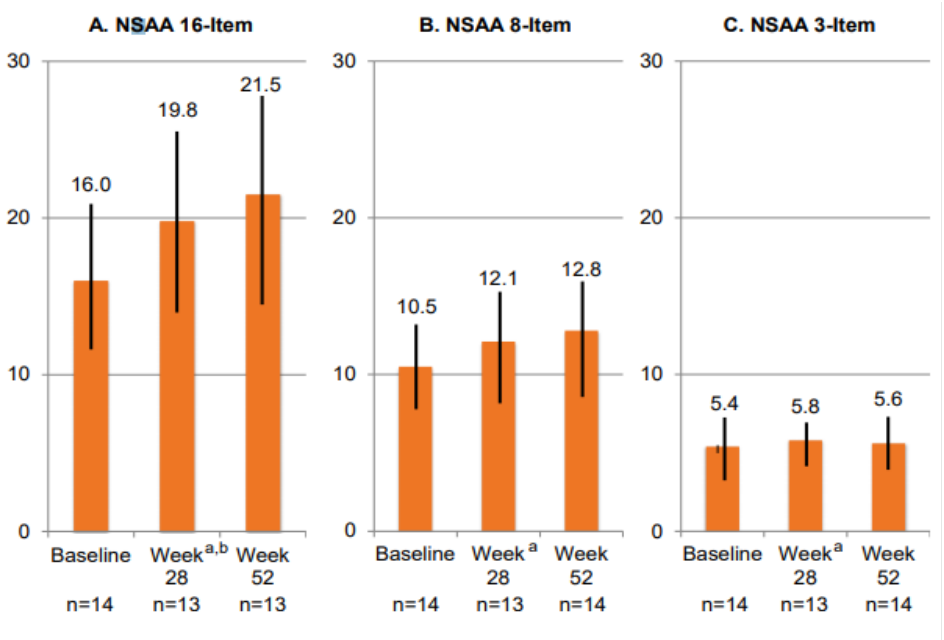
Figure 3: Timed function tests results (mean SD) at baseline, Week 28 and Week 52 in Study 030 (reproduced from CS, Figure C-20)



TFT - timed function test
[a] Baseline TFT measure for Week 28 timepoint was 7.1.
[b] After the original analysis, TFT results were re-examined with data from 1 subject removed as a result of the data being of questionable reliability due to poor listening

A similar trend was also observed for the NSAA and the revised NSAA results, both of which favoured ataluren-treated patients (see Figure 4). The differences observed for the NSAA score from baseline to Week 28 were 3.8 points, 1.6 points and 0.4 points on the 16-item, 8-item, 3-item scales, respectively. More pronounced differences in NSAA scores were observed from baseline to Week 52 on the 16-item scale and the 8-item scale (differences of 5.5 points and 2.3 points, respectively). The EMA assessment report (Procedure No. EMEA/H/C/002720/II/0049) states that "*On the data itself no conclusions can be drawn, as there is no comparator arm included. Generally, a slight improvement from baseline is observed for both TFT and NSAA, however, as these patients are developing, this could reflect the general development of the patient population*."

Figure 4: NSAA results (mean, SD) at baseline, Week 28 and Week 52 in Study 030 (reproduced from CS,[1] Figure C.21)



NSAA - NorthStar Ambulatory Assessment; SD - standard deviation
[a] After the original analysis, NSAA were re-examined with data from 1 subject removed as a result of the data being of questionable reliability due to poor listening.
[b] Mean baseline at Week 28 was 16.2.

Although not reported in the CS,[1] the EMA extension of indication variation assessment report (Procedure No. EMEA/H/C/002720/II/0037)[55] provides details of an indirect comparison of Study 030 and a matched historical data set from CINRG (n=31; 29% of whom were on steroid treatment) to provide a comparison of efficacy from baseline to Week 28. A summary of the results is provided in Table 7.

Table 7: Mean change in timed function tests and NSAA from baseline to Week 28 in Study 030 and CINRG natural history dataset (adapted from EMA assessment report)

Endpoint	Study 030		CINRG		Mean difference
	Baseline	Week 28	Baseline	Week 28	
Time to run/walk 10 metres, seconds					
n	12[a]	12[a]	31	31	
Outcome	6.7	6.1	7.32	7.0	
	Δ = -0.6 (8.9%[b])		Δ = -0.32 (4% [b])		-0.3
Time to climb 4 stairs, seconds					
n	12[a]	12[a]	28	28	
Outcome	7.4	5.3	7.3	6.0	
	Δ = -2.1 (28% [b])		Δ = -1.3 (18% [b])		-0.8
Time to stand from supine position, seconds					
n	12[a]	12[a]	25	25	
Outcome	7.6	4.3	5.68	5.03	
	Δ = -3.3 (43% [b])		Δ = -0.65 (11% [b])		-2.65
NSAA 8-item, points					
N	12[a]	12[a]	11	11	
Outcome	10.42	11.92	14.0	14.0	
	Δ = 1.5		Δ = 0.0		1.5
NSAA 3-item, points					
N	12[a]	12[a]	11	11	
Outcome	5.33	5.83	5.91	6	
	Δ = 0.5		Δ = 0.09		0.5
NSAA 16-item, points					
n	12[a]	12[a]	11	11	
Outcome	16.8	20.3	24.0	24.64	
	Δ = 3.4		Δ = 0.64		3

NSAA - NorthStar Ambulatory Assessment; CINRG - Cooperative International Neuromuscular Research Group
[a] One patient was excluded from this analysis due to a baseline assessment deemed invalid by the investigator, while a second patient did not have reported functional assessments at Week 28
[b] Percentage improvement from baseline

Despite a lack of detail on the statistical methods used for matching between patients from Study 030 and the CINRG cohort, the EMA report[55] and the company's clarification response[32] (question A4) state that patients were well-matched based on age, sex, height and body mass index (BMI), but showed differences in weight and steroid use. The company's clarification response states that differences in weight may have contributed to different doses of corticosteroids received, although one of the EAG's clinical advisors commented that this may not be relevant, as corticosteroid dose is calculated based on weight. Also, more patients in Study 030 received steroids (42.9%) compared to the matched CINRG cohort (29%). As such, imbalances in steroid use may influence disease progression (particularly in the first years of treatment). In addition, the lack of any improvement in the CINRG cohort (on the 8-item scale and the total NSAA) as compared to some improvement in Study 030 might also be due to the fact that the historical control group was not completely matched, as these were older boys able to perform more of the items on the NSAA, who were compared to younger boys still acquiring new skills and functions. Due to the inherent weaknesses of open-label designs, inconsistencies in the matching

of the historical controls, large variability, the presence of some baseline differences between the two groups (e.g., treatment with corticosteroids), and short study duration, the EMA assessment report[55] advises caution when interpreting the efficacy (positive trends but uncertain effect size and clinical relevance of observed results) and safety results. However, the EMA report acknowledges that a comprehensive assessment of efficacy in children aged ≥2 and <5 years is not feasible due to the rarity of diagnosed nmDMD patients aged <5 years. Overall, Study 030[35, 36] was successful in providing sufficient supporting evidence to justify a positive benefit/risk ratio conclusion associated with ataluren to warrant an extension of the European licence to patients aged 2 years and above. The EAG's clinical advisors commented that in clinical practice, they would initiate treatment with ataluren as early as possible in eligible patients aged ≥2 years with a confirmed diagnosis of nmDMD.

4.2.3 Study 019

Following HST3,[18] Study 019[25] (a long-term, open-label, uncontrolled, extension study) was conducted primarily to assess the safety and tolerability of ataluren in 94 male patients with nmDMD who had received ataluren in prior PTC Therapeutics-sponsored studies at investigational sites outside of the USA. Secondary objectives explored the long-term efficacy of ataluren and included measuring the ages at loss of ambulation and decline in respiratory function. The efficacy outcomes were compared to historical controls derived from the CINRG database[28] using a propensity score matching approach. This indirect comparison is described and critiqued in detail in Section 4.3.3. Participants were recruited from 21 study sites in 10 countries, of whom 90 had participated in both the Phase 2b pivotal study (Study 007) and the extension study (Study 007e), and three had participated in both the Phase 2a study (Study 004) and extension study (Study 004e). One patient did not have prior ataluren exposure and entered the study through a special exemption.

After completing the extension studies, patients (n=93) had a mean treatment gap of 2.9 (standard deviation [SD] ±0.5) years (ranging from 114 to 266 weeks) after which they enrolled in Study 019. Patients received ataluren at a total daily dosage of 40mg/kg/day for 240 weeks (or up to 336 weeks in Canada). The as-treated population included all patients who received at least one dose of ataluren. The mean age of enrolled patients at baseline was 12.8 (SD ±2.4) years, representing an older patient population with more advanced disease. In addition, 50 patients were ambulatory (i.e., those able to run/walk 10 metres in ≤30 seconds) and 44 patients were non-ambulatory (i.e., in those unable to run/walk 10 metres in ≤30 seconds). Patients who were non-ambulatory were heavier and had a higher BMI, likely due to decreased physical activity and caloric expenditure relative to ambulatory patients. Of the 50 ambulatory patients and 44 non-ambulatory patients, 47 (94%) and 37 (84%) were receiving corticosteroids, respectively. Of note, patients who were non-ambulatory at study entry had previously

received ataluren in a clinical trial during which they were ambulatory at baseline. Only 37 out of 94 enrolled patients (39.4%) completed the study and 57 (60.6%) discontinued (CS,[1] Table C-14, page 89). The primary reason for discontinuation was due to the commercial availability of ataluren. The EMA assessment report (Procedure No. EMEA/H/C/002720/II/0047)[57] states that it remains unexplained why subjects switching from the investigational product to the commercial product (n=40) could not have been followed-up for longer.

The safety profile of ataluren, observed up to 336 weeks, was consistent with other ataluren studies, and no new safety concerns were identified. A summary of the TEAEs experienced by patients in Study 019 is provided in Table 8. The majority of TEAEs were mild or moderate in severity (54/94 patients [57.4%]) and TEAEs that were considered drug-related were observed in 26/94 patients (27.7%). There were no life-threatening TEAEs. Thirty-one patients (33.0%) experienced SAEs: the SAEs in all but one of these patients were considered by the investigator to be unrelated to ataluren. Two patients experienced SAEs which led to death; neither of these events were considered by the investigator to be related to the study drug.

Table 8: TEAEs experienced by patients in the as-treated population of Study 019 (n=94) (reproduced with minor changes from CS, Table C-42)

TEAEs	**Corticosteroid use**		**Overall (n=94)**
	Yes (n=84)	**No (n=10)**	
Number of TEAEs[†]	1199	83	1282
Patients with at least one of the following			
TEAE	82 (97.6%)	9 (90.0%)	91 (96.8%)
TEAE related to ataluren	23 (27.4%)	3 (30.0%)	26 (27.7%)
TEAE leading to discontinuation of ataluren	2 (2.4%)	1 (10.0%)	3 (3.2%)
SAE	29 (34.5%)	2 (20.0%)	31 (33.0%)
TEAE with maximum severity[‡,§]			
Mild	21 (25.0%)	2 (20.0%)	23 (24.5%)
Moderate	26 (31.0%)	5 (50.0%)	31 (33.0%)
Severe	34 (40.5%)	1 (10.0%)	35 (37.2%)
Life-threatening	0	0	0
Fatal	1 (1.2%)	1 (10.0%)	2 (2.1%)
Patients with at least one of the following[‡,¶,#]			
Infections and infestations[‡]	63 (75.0%)	5 (50.0%)	68 (72.3%)
Gastrointestinal disorders[‡]	48 (57.1%)	6 (60.0%)	54 (57.4%)
Injury, poisoning and procedural complications[‡]	48 (57.1%)	3 (30.0%)	51 (54.3%)
General disorders and administration site conditions[‡]	46 (54.8%)	4 (40.0%)	50 (53.2%)
Musculoskeletal and connective tissues disorders[‡]	41 (48.8%)	7 (70.0%)	48 (51.1%)
Respiratory, thoracic and mediastinal disorders[‡]	31 (36.9%)	5 (50.0%)	36 (38.3%)
Nervous system disorders[‡]	32 (38.1%)	1 (10.0%)	33 (35.1%)
Investigations[‡]	17 (20.2%)	4 (40.0%)	21 (22.3%)
Cardiac disorders[‡]	16 (19.0%)	2 (20.0%)	18 (19.1%)
Skin and subcutaneous tissue disorders[‡]	17 (20.2%)	1 (10.0%)	18 (19.1%)
Metabolism and nutrition disorders[‡]	9 (10.7%)	2 (20.0%)	11 (11.7%)

TEAEs	Corticosteroid use		Overall (n=94)
	Yes (n=84)	No (n=10)	
Psychiatric disorders‡	10 (11.9%)	0	10 (10.6%)
Renal and urinary disorders‡	7 (8.3%)	0	7 (7.4%)
Surgical and medical procedures‡	6 (7.1%)	1 (10.0%)	7 (7.4%)
Eye disorders‡	6 (7.1%)	0	6 (6.4%)
Ear and labyrinth disorders‡	5 (6.0%)	0	5 (5.3%)
Vascular disorders‡	3 (3.6%)	0	3 (3.2%)
Endocrine disorders‡	2 (2.4%)	0	2 (2.1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)‡	1 (1.2%)	0	1 (1.1%)
Reproductive system and breast disorders‡	1 (1.2%)	0	1 (1.1%)

AE - adverse event; SAE - serious adverse event; TEAE - treatment-emergent adverse event
†TEAE is defined as any AE that occurred or worsened in the period extending from the day of a patient's first dose of ataluren to 6 weeks after the last dose of ataluren in this study
‡TEAE categories
§For patients with two or more AEs, the event with the maximum severity was reported. The order of severity is: 'Mild', 'Moderate', 'Severe', 'Life-threatening' and 'Fatal'.
¶AEs were coded using the Medical Dictionary for Regulatory Activities (version 20.1)
#A patient who reported two or more AEs with the same preferred term was counted only once for that term. A patient who reported two or more AEs with different preferred terms within the same organ class was counted only once in the system organ class.

As noted in the EMA assessment report (Procedure No. EMEA/H/C/002720/II/0047[57]), the overall mean duration of study drug treatment was 197.25 weeks (drug compliance 88.4%) and the most frequent TEAEs (occurring in ≥10% of patients) for the overall population during the treatment period were: nasopharyngitis (42.6%); headache (30.9%); vomiting (29.8%) and disease progression (28.7%). A summary of TEAEs occurring in ≥10% of patients is provided in Table 9. The EMA[57] concluded that the TEAEs in Study 019 remain within the known and predictable safety profile of ataluren and the reported AEs were similar and in line with the more severe stage of the condition in non-ambulatory patients compared to ambulatory patients for which ataluren is currently approved.

Table 9: TEAEs with a frequency of ≥10% in the as-treated (n=94) population of Study 019 (reproduced with minor changes, EMA Assessment report, Table 21)

Preferred term [1]	Ambulatory status		Overall (n=94)
	Yes (n=50)	No (n=44)	
Patients with at least one TEAE [2]	49 (98.0%)	42 (95.5%)	91 (96.8%)
Nasopharyngitis	20 (40.0%)	20 (45.5%)	40 (42.6%)
Headache	17 (34.0%)	12 (27.3%)	29 (30.9%)
Vomiting	16 (32.0%)	12 (27.3%)	28 (29.8%)
Disease progression	27 (54.0%)	0	27 (28.7%)
Fall	20 (40.0%)	2 (4.5%)	22 (23.4%)
Back Pain	12 (24.0%)	9 (20.5%)	21 (22.3%)
Gastroenteritis	10 (20.0%)	10 (22.7%)	20 (21.3%)
Pyrexia	9 (18.0%)	10 (22.7%)	19 (20.2%)
Upper respiratory tract disease	14 (28.0%)	5 (11.4%)	19 (20.2%)
Femur fracture	11 (22.0%)	6 (13.6%)	17 (18.1%)
Cough	5 (10.0%)	11 (25.0%)	16 (17.0%)
Abdominal pain Upper	9 (18.0%)	5 (11.4%)	14 (14.9%)

Preferred term [1]	Ambulatory status		Overall (n=94)
	Yes (n=50)	No (n=44)	
Oropharyngeal pain	8 (16.0%)	6 (13.6%)	14 (14.9%)
Diarrhoea	5 (10.0%)	8 (18.2%)	13 (13.8%)
Arthralgia	5 (10.0%)	4 (9.1%)	9 (9.6%)
Constipation	2 (4.0%)	7 (15.9%)	9 (9.6%)
Influenza	6 (12.0%)	3 (6.8%)	9 (9.6%)
Rhinitis	5 (10.0%)	4 (9.1%)	9 (9.6%)
Scoliosis	2 (4.0%)	7 (15.9%)	9 (9.6%)
Nausea	2 (4.0%)	5 (11.4%)	7 (7.4%)
Abdominal pain	1 (2.0%)	5 (11.4%)	6 (6.4%)
Joint injury	5 (10.0%)	0	5 (5.3%)
Ligament sprain	5 (10.0%)	0	5 (5.3%)

AE - adverse event; AT – as-treated; medDRA - medical dictionary for regulatory activities; SOC - system organ class; TEAE - treatment-emergent adverse event
[1] AEs were coded using MedDRA, Version 20.1
[2] TEAEs were defined as an AE that occurs or worsens in the period extending from the day of the patients first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more AEs with the same preferred term was counted only once for that term. A patient who reported 2 or more AEs with difference preferred terms within the same SOC was counted only once in the SOC.

A summary and critique of the indirect comparison of Study 019 vs. CINRG is provided in Section 4.3.3.

4.2.4 The STRIDE registry

The STRIDE registry[21, 37-40] is an ongoing post-approval safety and effectiveness study of ataluren use (40mg/kg/day; 10, 10 and 20mg/kg for morning, midday and evening doses, respectively) in patients with nmDMD in routine clinical practice, requested by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). STRIDE is underway in countries where ataluren is available commercially or through an early access program (if applicable). Patients will be followed up for ≥5 years, or until study withdrawal or death. Enrolment of patients in the STRIDE registry began in April 2015 and is expected to be completed by May 2025.[58] Originally, patients aged ≥5 years were enrolled; however, the eligibility criteria were expanded to include patients aged ≥2 years following the ataluren license extension in Europe (granted in 2018). As of the 31st January 2021, 286 patients with nmDMD who had received at least one dose of ataluren (the as-treated and safety populations) had been enrolled from 64 active study sites in 13 countries (including the UK). Within the CS,[1] 269 of these ambulatory and non-ambulatory male patients (including 58 patients from the UK) were investigated (described in the CS as the "evaluable population"). Patients were not included in the evaluable population for any of the following reasons: no signed informed consent; not treated; female; screening failures; frameshift mutations; missing mutation data or other outstanding critical queries (company's clarification response,[32] question A19).

Efficacy outcomes in STRIDE patients were compared to historical controls derived from the CINRG database[28] using a propensity score matching approach. This ITC is described and critiqued in detail in

Section 4.3.1. The STRIDE effectiveness population used to inform this ITC included 241 patients with confirmed nmDMD (217 patients were ambulatory at study entry, 20 were non-ambulatory at the start of study treatment and four were in the transition phase between being ambulatory and non-ambulatory [they completed the first 10-metre walk/run test in ≥30 seconds]). Patients were not included in the effectiveness population if they: discontinued registry participation; had newborn screening/prenatal diagnosis as the first symptom; had missing data on age at first symptoms; had data for steroid use but without steroid initiation date or had missing data for age at loss of ambulation (see company's clarification response,[32] question A19). The mean age of patients in the evaluable population at consent date was 9.9 years and 88.1% were receiving corticosteroids at any time during the study (CS,[1] Table C-28, pages 115 to 116). Data on these characteristics are not reported in CS[1] for the as-treated or efficacy populations. Most subjects had been on study treatment for at least [redacted] with a median of [redacted] days (range: [redacted]) (CS, Table C-10, page 74) and as noted in the company's clarification response (question A8),[32] [redacted] patients in STRIDE had discontinued ataluren treatment (physician decision, [redacted]; loss of ambulation, [redacted]; family/participant request, [redacted]; AEs, [redacted]; non response, [redacted], and other, [redacted]).

The most recent interim safety profile of ataluren, observed up to the 31st January 2021, is reported in the CS[1] (Section 9.7.2.5). This suggests that the results from the STRIDE registry continue to be consistent with other ataluren studies, and no new safety concerns have been identified. The company's clarification response (question B14)[32] states that "…*formal assessments of treatment compliance were not conducted in this non-interventional study. However, most subjects were characterised as highly compliant with treatment."* A summary of the TEAEs experienced by patients in the as-treated STRIDE population is provided in Table 10. Most were mild or moderate in severity (82/286 [28.7%]) and TEAEs that were considered drug-related were observed in 7/286 patients (2.4%). Thirteen patients (4.5%) experienced a TEAE that led to discontinuation of ataluren. There were no life-threatening TEAEs. Twenty-three patients (8.0%) experienced SAEs, all of which were considered by the investigator to be unrelated to ataluren and [redacted] deaths have been reported as of the data cut-off. In summary, CS[1] (Section 9.7.3, page 149) states that "*In the long-term observational study of ataluren in nmDMD (STRIDE), interim safety results continue to be consistent with the known safety profile of ataluren. With longer term routine clinical use, there was no cumulative toxicity or late occurring unexpected events with ataluren, and the AE profile tended to reflect the progression of the underlying DMD disease process.*"

Table 10: Overview of TEAs - as-treated population, 31 January 2021 data cut-off (adapted from CS, Tables C-43 to C-45)

	As-treated population ≥5 years subgroup			As-treated population ≥2 to <5 years subgroup			As-treated (All)		
	Corticosteroid use			Corticosteroid use			Corticosteroid use		
	Yes	No	All	Yes	No	All	Yes	No	All
	n=240	n=26	n=266	n=10	n=10	n=20	n=250	n=36	n=286
Number of TEAEs (n)									
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	278	41	319
Patients with 1 or more (n, %)									
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100 (40.0)	14 (38.9)	114 (39.9)
TEAE related to ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (2.4)	1 (2.8)	7 (2.4)
TEAE leading to discontinuation of ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (4.4)	2 (5.6)	13 (4.5)
SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19 (7.6)	4 (11.1)	23 (8.0)
TEAE with a maximum severity[a] (n, %)									
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10 (4.0)	0 (0.0)	10 (3.5)
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (2.4)	2 (5.6)	8 (2.8)
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39 (15.6)	4 (11.1)	43 (15.0)
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34 (13.6)	5 (13.9)	39 (13.6)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (4.4)	3 (8.3)	14 (4.9)
Life-threatening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs with a patient frequency ≥1% (n, %)									
System Organ Class/ Preferred Term[b]									
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Fall	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Off-label	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Femur fracture	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

	As-treated population ≥5 years subgroup			As-treated population ≥2 to <5 years subgroup			As-treated (All)		
	Corticosteroid use			Corticosteroid use			Corticosteroid use		
	Yes	No	All	Yes	No	All	Yes	No	All
	n=240	n=26	n=266	n=10	n=10	n=20	n=250	n=36	n=286
Ligament sprain	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Contusion	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Humerus fracture	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Laceration	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Subdural hematoma				-	-	-	-	-	-
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Gait inability	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pyrexia	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Infections and infestations	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Nasopharyngitis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Gastroenteritis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Bronchitis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Respiratory tract infection				-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Back pain	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Myalgia	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Arthralgia	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Abdominal pain	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Vomiting	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Constipation	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Diarrhoea	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Abdominal pain upper	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

	As-treated population ≥5 years subgroup			As-treated population ≥2 to <5 years subgroup			As-treated (All)		
	Corticosteroid use			Corticosteroid use			Corticosteroid use		
	Yes	No	All	Yes	No	All	Yes	No	All
	n=240	n=26	n=266	n=10	n=10	n=20	n=250	n=36	n=286
Nervous system disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Headache	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Idiopathic intracranial hypertension				-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Cough	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Myoglobinuria	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Eye disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Cataracts	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Vascular disorders	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Hypertension	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Patients with at least 1 of the following (n, %)									
Injury, poisoning and procedural complications	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Subdural hematoma	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Infections and infestations	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Upper respiratory tract infection	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Gastroenteritis	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Respiratory tract infection	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Nervous system disorders	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Idiopathic intracranial hypertension				[redacted]	[redacted]	[redacted]			

MedDRA - Medical Dictionary for Regulatory Activities; SAE - serious adverse event; TEAE - treatment-emergent adverse event

Note: TEAE is defined as any adverse event with an end date on or after the first ataluren use date. A subject who reported 2 or more occurrences with the same preferred term was counted only once for that term. Events with missing severity are considered Not reported.

[a] For subjects with 2 or more adverse events, the event with the maximum severity was reported in this summary. The order of the severity is 'Not Reported', 'Unknown', 'Mild', 'Moderate', 'Severe', and 'Life-threatening

[b] *Adverse events were coded using MedDRA, Version 20.1.*

4.2.5 Ataluren Managed Access Agreement (MAA)

As discussed in Section 2.2, in 2016, NICE issued guidance recommending ataluren under a conditional MAA as a treatment option for all ambulatory patients aged 5 years and older with nmDMD.[18] In 2019, the scope of the MAA was expanded to include all ambulatory patients aged between 2 and 5 years (in line with the extension of the licensed indication) with nmDMD.[59] Ataluren is added to existing standard treatment, including the use of corticosteroids.

The start criteria in the MAA[53] requires a confirmed diagnosis of DMD which is the identified presence of an in-frame nonsense mutation in the dystrophin gene, as determined by genetic testing (full sequencing). Patients must be aged 2 years and older and able to crawl, stand with support or walk and should only start once a full set of standard baseline specialist neuromuscular clinical and physiotherapy assessments (including an initial blood test) have been obtained. Patients/parents are required to sign up to the Managed Access Patient Agreement and are expected to attend their clinic two times a year for assessment within a 14-month period. The criteria for stopping treatment include non-compliance with assessments (defined as fewer than two attendances for assessment in any 14-month period) for continued therapy, and loss of all ambulation (i.e., can no longer stand even with support) and becoming fully dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an inter-current illness). In such cases, patients will stop treatment no later than 6 months after becoming fully non-ambulant. Patients who are taken off treatment will continue to be monitored and supported with normal best standard of care. These patients will continue to be assessed to allow gathering of important information regarding the natural history of non-ambulatory patients.

Data collection started in August 2016 and was planned to continue for up to 5 years (CS,[1] Table C-3, page 56). However, in July 2021, a contract variation was agreed, which extended the period of the MAA up to either publication of the updated NICE HST guidance or the 20th January 2023, whichever occurs earliest (CS,[1] page 59). The MAA primary efficacy measure is the change in the NSAA over the course of a 3 to 4-year period. As noted in the company's clarification response[32] (question A18), different data collection measures were recorded inconsistently between registries and geographical locations (e.g., the NorthStar, STRIDE and CINRG registries). The NSAA score was chosen as an efficacy outcome in the MAA because all centres in the UK record NSAA for all DMD patients as part of their ongoing assessments. HRQoL data were also collected both from patients and caregivers. Patient HRQoL was assessed using the Child Health Utility 9-Dimensions (CHU-9D) questionnaire, whereas caregivers were asked to complete the 5-level Euroqol 5-Dimensions (EQ-5D-5L) questionnaire. In order to assess efficacy outcomes, the company compared outcomes data for patients receiving ataluren in the MAA to a matched control group receiving BSC alone, using a propensity score matching approach. The matched control group were identified from patients included in the

NorthStar registry (owned and maintained by the NorthStar Clinical Network in the UK) and does not include any nmDMD patients (CS,[1] Section 9.4.1.7, page 76). A summary and critique of this indirect comparison is presented in Section 4.3.2.

4.3 Critique of ITCs included in the company submission

The CS[1] presents the methods and results of three ITCs which have been conducted to support the clinical effectiveness of ataluren. The principal comparison conducted is between patients from the STRIDE cohort[21] receiving ataluren plus BSC and a matched population receiving BSC alone from the CINRG DNHS.[28] This ITC is described and critiqued in Section 4.3.1. Additional comparisons have also been made between patients signed up to the current ataluren MAA in England[41] and matched controls from the NorthStar registry (Section 4.3.2) and between patients enrolled in Study 019[25] and the CINRG DNHS (Section 4.3.3). As the company's economic model is centred around the ITC of the STRIDE and propensity score matched CINRG datasets (plus additional assumptions regarding the benefit of early treatment with ataluren, described in Section 5.2), greater emphasis is placed on this comparison. However, the other two ITCs are also described as they provide supporting evidence for the relative efficacy of ataluren which has not been included in the economic analysis.

4.3.1 ITC 1: STRIDE versus CINRG DNHS - summary and critique

4.3.1.1 Summary of studies included in the ITC, STRIDE versus CINRG

Overview of STRIDE

STRIDE[21] is an ongoing international observational study of the safety and effectiveness of ataluren. Enrolment into STRIDE began in April 2015 and was designed to include patients receiving ataluren as part of their usual care at one of the participating centres and who consented to data collection. The study has an estimated enrolment of 360 participants with a current as-treated population (all screened participants receiving ataluren) of 286 patients. Within the CS,[1] 269 of these patients were investigated (described as the "evaluable population"; see patient inclusion criteria listed in Section 4.2.4). Participating centres are located primarily in Europe (67 of 71 centres); the remaining four centres are located in Brazil (1 centre) and Israel (3 centres). The study aims to follow up patients for a minimum of 5 years from their date of enrolment, unless the patient withdraws consent or dies before this timepoint. The study is expected to be completed in 2025. Originally, patients over the age of 5 years were enrolled; however, the eligibility criteria were expanded in 2018 to include patients over the age of 2 years in European centres, following the extension to the European license for ataluren. [redacted] patients within the evaluable population were between the age of 2 and 5 years. According to the CS,[1] data are collected in conjunction with routine care visits (estimated to occur at 3- to 6-month intervals).

Overview of CINRG DNHS

The CINRG DNHS[28] is a natural history study of 440 DMD patients aged 2 to 28 years who were receiving care at one of 20 participating centres. Ten of the 20 centres were located in the US; other sites were located in Canada, Puerto Rico, Australia, Argentina, India, Israel, Italy and Sweden. Enrolment began in 2006, after which patients were followed up for 10 years. The primary recruitment phase ran from May 2006 to July 2009 (340 patients), with an additional 100 patients aged between 4 and 8 years old being recruited between September 2012 to February 2016. The study was originally set up with the primary aim of examining DMD patients' physical abilities, the medical problems that they face, and the health care resources that they utilise. Additionally, genetic data were collected to analyse genetic variability in DMD outcomes and to make comparisons with healthy controls. Within the CINRG DNHS study, data were collected at yearly visits.

The CS[1] asserts that the CINRG cohort[28] provides a suitable population that can be used as a control population for ataluren studies that do not include a control arm. The company provides two main reasons for this. Firstly, they assert that both the STRIDE and CINRG populations are representative of the general DMD population due to the fact participants in the studies come from a wide range of countries, with varying ages, and ambulatory abilities. The second reason given is that CINRG "*includes patients receiving BSC who are experiencing the natural course of DMD progression"*(CS, Section 9.4.1.1, page 60). The CS notes that the study periods between STRIDE and CINRG do not overlap, but argues that with the exception of the conditional approval of ataluren by the European Commission in 2014, *"there have been no substantial changes in disease management and commercial availability of treatments that impact disease progression since 2006"* (CS, Section 9.4.1.1, page 61).

4.3.1.2 Summary of ITC methods and outcomes assessed, STRIDE versus CINRG

In order to assess the effectiveness of ataluren (plus BSC) using the data from STRIDE,[21] the company compared subjects in STRIDE against a propensity score matched cohort from the CINRG DNHS.[28] Specifically, propensity score matching was used to find a subpopulation of the CINRG patients with whom comparisons could be made. Further details on the matching procedure are presented in Section 4.3.1.4. In total, 241 patients from the broader STRIDE evaluable population, referred to as the "effectiveness population", were matched to participants in the CINRG cohort. Patients were not included in the effectiveness population if they: discontinued registry participation; had newborn screening/prenatal diagnosis as the first symptom; had missing data of age at first symptoms; had data for steroid use but without steroid initiation date, or had missing data for age at loss of ambulation (see clarification response,[32] question A19).

A summary of this ITC is shown in Table 11. Patients from STRIDE and CINRG were matched based on the following four characteristics:

- Age at first clinical symptoms
- Age at first corticosteroid use
- Duration of deflazacort use (<1 month, 1 to 12 months, 12 months or more)
- Duration of other corticosteroid use (< 1 month, 1 – 12 months, 12 months or more).

Age at first clinical symptoms was included as this is prognostic of disease severity, and variables covering steroid use were included as these factors also impact on disease progression. The frequency of corticosteroid use (i.e., intermittent versus daily use) was not included as a covariate in the matching process. Once a matched cohort from CINRG[28] had been selected, the efficacy of ataluren was assessed by analysing the time-to-event data for the following outcomes:

- Loss of ambulation (defined as full-time wheelchair use)
- TFTs (climbing stairs and standing from supine)
- Pulmonary function (measured by FVC).

Loss of ambulation was defined similarly in the STRIDE and CINRG studies,[21, 28] although there were some differences. In STRIDE, patients were considered non-ambulatory if they required a wheelchair full-time. In CINRG, loss of ambulation was defined as continuous wheelchair use, verified by the inability to walk 10 metres unassisted. One of the EAG's clinical advisors commented that this difference between the definitions might introduce bias towards earlier loss of ambulation in CINRG compared with STRIDE, but suggested that this may not be clinically important.

Each of the time-to-event endpoints were analysed using the median survival time (the age at which the probability of remaining event-free drops to 50% or below) based on Kaplan-Meier estimates. The survival curves were compared using a log-rank test, stratified by duration of deflazacort use and duration of other steroid use. The CS[1] does not describe under what conditions individuals were censored in the survival analysis; however, the EAG assumes that this is primarily due to patient follow-up finishing before the event was observed (administrative censoring). This is likely to affect STRIDE[21] more than CINRG.[28] The EAG also assumes that other reasons such as study withdrawal and loss to follow-up are handled via censoring. The hazard ratio (HR) describing the treatment effect for ataluren plus BSC versus BSC was then calculated using a stratified Cox proportional hazards (PH) model with study, age at first symptom and age at initial steroid usage as covariates.

The analysis of this ITC using an earlier data-cut of STRIDE[21] (9th July 2018) has been reported previously by Mercuri *et al.*[38] The ITC presented in the CS[1] uses an updated data cut-off for STRIDE

of the 31st January 2021. Data may not have been collected consistently across the study duration. The CS[1] notes that initially data in the registry were *"spontaneously reported during a clinical visit or derived during clinical visits or derived from hospital records, clinical records and evaluation checklists"* (CS, Section 9.4.1.6, Table C-10). Additionally, the company notes that there were *"no protocol-mandated procedures or diagnostic tests."* Initial data collection procedures were then updated using a "multi-faceted" approach (see CS, Section 9.4.1.6, Table C-10), although it is not clear what this new approach involved. In countries where initiation took place in 2017 or 2018, sites were required to adhere to minimum reporting standards; however, it is not clear what standards were required of sites whose initiation took place prior to 2017, or at what date they were required to meet the new data reporting standards. Loss of ambulation is always assessed and captured.

Table 11: Summary of STRIDE versus CINRG ITC

	Treated population: STRIDE	**Control population: CINRG DNHS**
Location:	Worldwide, predominantly Europe (multi-centre)	Worldwide (multi-centre)
Duration of study	>5 years target follow up	>8 years target follow-up
Patient population	nmDMD	DMD
Sample size	269 (241 used for matching)	440
Interventions	Ataluren + BSC	BSC
Matched sample size	241	241
Matching covariates	• Age at first clinical symptoms • Age at first corticosteroid use • Duration of deflazacort use (<1 month, 1 to 12 months, 12 months or more) • Duration of other corticosteroid use (< 1 month, 1 – 12 months, 12 months or more)	
Outcomes assessed	Median survival time (age at which survival probability drops to 50% or less) for time to event variables: • Loss of ambulation (defined as full-time wheelchair use) • Pulmonary function (Forced vital capacity) • Timed Function tests (climbing stairs and standing from supine)	

STRIDE - Strategic Targeting of Registries and International Database of Excellence; CINRG DNHS - Cooperative International Neuromuscular Research Group Disease Natural History Study; nmDMD - Nonsense mutation Duchenne muscular dystrophy; BSC - best supportive care

4.3.1.3 Patient eligibility criteria in STRIDE and CINRG DNHS

Table 12 lists key inclusion and exclusion criteria for participation in the STRIDE and CINRG studies.[21, 28] Given the different aims of the studies, there are naturally differences between their inclusion criteria. Patients enrolled into STRIDE will have a confirmed diagnosis of nmDMD and will be receiving ataluren as part of their usual care. Participants in the CINRG study are broader as they must have a diagnosis of DMD, not necessarily with a nonsense mutation.

The EAG notes that there also are some notable differences in the exclusion criteria in STRIDE and CINRG.[21, 28] Within CINRG, participants were excluded from the study if they were using glucocorticoid therapy and ambulated without assistance past their 16th birthday. This would imply that individuals in the CINRG cohort who have not had their DMD confirmed using the methods in the first bullet-point listed in Table 12, but who respond well to corticosteroids will have been excluded from the matched population. The EAG's clinical advisors commented that the use of this criterion in CINRG is appropriate and noted that whilst it is not also reflected in the STRIDE eligibility criteria, it would be unlikely to introduce bias.

Table 12: Key eligibility criteria in STRIDE and CINRG

	STRIDE	CINRG
Inclusion criteria	• Receiving or will be receiving usual care treatment with commercial supply of ataluren (or receiving care within a named patient early access program) • Willing to provide written informed consent to allow the study data collection procedures (either by the patient or through authorisation by a legal guardian)	• Participants aged 2-4 years with a diagnosis of DMD confirmed by dystrophin immunofluorescence or immunoblot, or both; an out-of-frame deletion; or complete dystrophin gene sequencing in the proband or sibling. • Participants aged 5–29 years with DMD meeting the criteria in (1) or documented clinical symptoms referable to DMD and direct support of the diagnosis by either a positive DNA analysis, a muscle biopsy showing abnormal dystrophin, or a combination of an increased creatine kinase (more than five times the upper limit of normal) in addition to an X-linked pedigree.
Exclusion criteria	• Patients who are receiving ataluren or placebo in a blinded, randomised clinical trial, or ataluren in any other ataluren clinical trial or cohort early access program that prevents participation in this study	• Naive to glucocorticoid treatment and ambulated without assistance past their 13th birthday; or use of glucocorticoid therapy and ambulated without assistance past their 16th birthday. • Patients younger than 16 years were enrolled irrespective of future ambulatory status.

DMD - Duchenne muscular dystrophy; DNA - deoxyribonucleic acid
Source: CS[J] Table C-5 and Table C-10

4.3.1.4 Propensity score matching approach, STRIDE versus CINRG

Propensity score matching was used to find a subpopulation of the CINRG DNHS cohort[28] that could be used for comparison against patients in STRIDE.[21] Within this approach, the company calculated a propensity score (the predicted probability of treatment) for each patient in the STRIDE and CINRG cohorts. This propensity score was calculated using a logistic regression model including the four matching variables listed in Table 11.

Once the propensity scores were calculated, a greedy algorithm using nearest neighbour matching without replacement was used to find a single match from the CINRG cohort[28] for each member of the STRIDE effectiveness population (n=241). The greedy algorithm matching procedure is described as a locally optimal matching algorithm, as it finds a match for each participant of the study cohort in turn, without considering the impact on any future matches.[60] Under this approach, the participants in the study cohort are randomly sorted. Then, for each member of this list in turn, a match is selected from the control cohort by choosing the participant whose propensity score is closest to the member of the study cohort. Within the procedure, matches are chosen irrespective of whether they may be a better match for a different patient later on in the list.[60] It has been suggested in the literature that this form of matching can create well-matched groups, whereas global matching also ensures that individual pairs are well-matched.[61] Within the nearest neighbour matching algorithm, closeness was defined using the absolute value difference between propensity scores. Specifically, for each STRIDE patient,[21] the member of the CINRG cohort[28] whose propensity score was closest in absolute value to the propensity score of the STRIDE patient was selected as the match. As matching was performed without replacement, this CINRG patient would then be unavailable for matching with STRIDE patients further down the list.

4.3.1.5 Selection of propensity score matching variables, STRIDE versus CINRG

In STRIDE,[21] patients were matched to controls from the CINRG DNHS[28] using: age at first clinical symptoms; age at first corticosteroid use, duration of deflazacort use (<1 month, ≥1 to <12 months, ≥12 months); and duration of other corticosteroid use (<1 month, ≥1 to <12 months, ≥12 months). The CS[1] states that age at first symptom is included as a marker of disease severity, since individuals who exhibit symptoms earlier are expected to experience worse disease progression. To support this, the company cites evidence that suggests that a one-year increase in age at onset of first symptoms is associated with a 10% reduction in annual risk for loss of ambulation.[62] Within their clarification response[32] (question A18), the company notes that age at onset of first symptoms is an indirect measure of disease severity. However, significant missing data in more direct measures of disease severity such as the NSAA and time to rise from floor meant that these measures were not used for matching. The EAG believes that this is a potentially important limitation which may affect the comparability of the matched groups.

Steroid use variables such as corticosteroid type, duration of use and age at first use were also included to control for differences in standard of care between STRIDE and CINRG patients.[21, 28] The CS[1] justifies the inclusion of these covariates through reference to analyses of data from CINRG that found that patients who had used steroids for more than a year lost ambulation on average 3 years later than those who had either never used steroids or used them for less than a year.[48] Deflazacort use was included due to evidence of its improved impact on loss of ambulation compared to prednisone. The CS also highlights analyses of data from CINRG which suggested that the median age at loss of

ambulation in patients who received daily deflazacort was approximately three years later than that for patients receiving daily prednisone.[48, 63]

Other prognostic indicators highlighted by the company were not included in the matching process. DMD genetic modifiers and mutation type were not included. The company justifies this by stating that *"patients with a nonsense mutation have a disease progression trajectory similar to other DMD subtypes"* (CS,[1] Section 9.4.1.1, page 62). The CS claims that the matching procedure will remove any potential bias associated with differences in DMD genotype between STRIDE and CINRG.[21, 28] Further to this, in the company's clarification response[32] (question A21) states that genetic modifiers were not recorded uniformly in STRIDE and CINRG, thereby precluding the use of these variables in the matching procedure.

The CS[1] (Section 9.4.1.1, page 62) notes that cardiac medication, orthoses, spinal surgery and ventilation support are also prognostic factors for DMD. These have not been matched on. However, the company claims that since the use of these interventions forms part of standard care in international guidelines, centres involved in the STRIDE[21] and CINRG[28] should provide similar levels of care on these factors. No analysis has been presented to demonstrate this, and so the lack of difference is assumed rather than empirically justified. It is unclear from the CS whether data on the use of these interventions were available from STRIDE and CINRG and whether they could have been included in the analysis.

The company's clarification response[32] (question A17) states that corticoid steroid regimen was not matched on as no consensus has been reached on whether it has a significant influence on disease progression. Additionally, it was suggested that differences between daily and intermittent treatment regimens that patients received would have resulted in practical challenges in creating a suitable matching procedure. In other words, not all patients receiving intermittent steroids would have been doing so in the same way, and similarly for those on daily regimens. Steroid regimens may have also changed over time, adding a further barrier to the use of this variable for matching.

4.3.1.6 Balance of covariates in the STRIDE and CINRG matched populations

The CS[1] presents a comparison of STRIDE[21] versus the pre- and post-matched cohorts from CINRG[28] for the variables included in the matching process; this comparison is reproduced in Table 13. Standardised mean differences (SMDs) were not provided in the CS, but were later provided as part of the company's clarification response[32] (question A16). Overall, these diagnostics suggest that the STRIDE cohort and matched CINRG cohort are well-balanced on the matching variables. All SMDs are less than 0.1 in absolute value and variance ratios are below 2.0, which indicates that the matches

for these variables are acceptable.[64] However, the CS does not provide a comparison of variables not included in the matching process.

Following a request for clarification from the EAG[32] (question A15), the company provided a further comparison of some baseline characteristics in the STRIDE population used for matching (n=241), and the matched CINRG cohort,[28] for variables not included in the matching. This additional information is presented in Table 14.

[redacted]

Table 13: Comparison of variables included in matching process, pre- and post-matched cohorts, STRIDE versus CINRG (adapted from CS, Table C-29; mean differences and variance ratios from company's clarification response)

	Unmatched		Post-matching		
	STRIDE	**CINRG**	**CINRG**	**SMD**	**Variance ratio**
Age at first symptoms, years					
N	241	398	241		
Mean (SD)	[redacted]				
Median					
Min, Max					
p-value (vs. STRIDE)					
Age at first corticosteroid use (excluding corticosteroid-naïve patients),[a] years					
N	212	315	212		
Mean (SD)	[redacted]				
Median					
Min, Max					
p-value (vs. STRIDE)					
Deflazacort duration,[b] n (%)					
<1 month	[redacted]				
≥1 to <12 months					
≥12 months					
p-value (vs. STRIDE)					
Other steroid duration,[b] n (%)					
<1 month	[redacted]				
≥1 to <12 months					
≥12 months					
p-value (vs. STRIDE)					

CINRG - Cooperative International Neuromuscular Research Group; Max - maximum; Min - minimum; N/a - not applicable; SD - standard deviation; STRIDE - Strategic Targeting of Registries and International Database of Excellence; SMD - standardised mean difference
[a] Treatment-naive patients were excluded to calculate the true age at first corticosteroid use.
[b] Corticosteroid duration is calculated from the date at which corticosteroid use was started and the loss of ambulation/censored

Table 14: Baseline characteristics for the matched STRIDE and CINRG patients (adapted from clarification response, question A15)

Assessment	STRIDE (N=241)	CINRG DNHS (N=241)	SMD
Mean age at first symptom, years (SD)	[redacted]	[redacted]	[redacted]
Mean age at first assessment, years (SD)	[redacted]	[redacted]	[redacted]
Mean age at last assessment, years (SD)	[redacted]	[redacted]	[redacted]
Any steroid duration, n (%):			
<1 month	[redacted]	[redacted]	[redacted]
≥1 month to <12 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]
Lifetime steroid use, n (%):			
<1 month	[redacted]	[redacted]	[redacted]
≥1 month to <12 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]
Mean weight, kg (SD)	[redacted]	[redacted]	[redacted]
Mean height, cm (SD)	[redacted]	[redacted]	[redacted]
Mean BMI kg/m^2 (SD)	[redacted]	[redacted]	[redacted]

STRIDE - Strategic Targeting of Registries and International Database of Excellence; CINRG - Cooperative International Neuromuscular Research Group; DNHS - disease natural history study; SMD - standardised mean different; BMI - body mass index; SD - standard deviation

4.3.1.7 Summary of ITC results, STRIDE versus CINRG

Table 15 provides a summary of the ambulatory and pulmonary outcomes in the STRIDE and propensity score matched CINRG cohorts.[21, 28] Kaplan-Meier plots for time to loss of ambulation and time to FVC<50%, both of which are used in the company's economic model (see Section 5.2), are presented in Figure 5 and Figure 6, respectively. Kaplan-Meier plots for the other endpoints included in the ITC can be found in Section 9.6.1.6 of the CS;[1] for brevity, these are not reproduced here.

Overall, the company's ITC suggest that compared with BSC alone, ataluren confers a statistically significant benefit to patients in terms of functional ability (delays in time to loss of ambulation and time to loss of ability to stand from supine ≥10 seconds) as well as time to respiratory function impairment (time to predicted FVC<60%, time to predicted FVC<30% and time to FVC<1 litre). As discussed in the CS,[1] the evidence supporting benefits in respiratory function are limited and subject to very high levels of censoring (particularly for STRIDE[21]) for endpoints relating to milestones which occur later on in the disease course. These outcomes are discussed in further detail below.

Table 15: STRIDE versus CINRG propensity score matched population – ambulatory and respiratory function (reproduced from CS, Table C-19)

Assessment	STRIDE (ataluren + BSC) N=241	CINRG (BSC alone) N=241
Loss of ambulation		
Median age at event, years (95% CI)	17.9 (14.4, NA)	12.5 (11.6, 13.5)
HR (95% CI)[b]	0.374 (0.273, 0.512)	
p-value[a]	<0.0001	
Loss of time to climb 4 Stairs ≥10 seconds		
Median age at event, years (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p-value	[redacted]	
Loss of stand from supine ≥10 seconds		
Median age at event, years (95% CI)	[redacted]	[redacted]
HR (95% CI)[b]	[redacted]	
p-value[a]	[redacted]	
Predicted FVC <60%		
Median age at event, years (95% CI)	17.6 (16.2, NA)	15.8 (15.1, 16.5)
HR (95% CI)[b]	0.544 (0.343, 0.863)	
p-value[a]	0.0051	
Predicted FVC below 50%		
Median age at event, years (95% CI)	[redacted]	[redacted]
HR (95% CI)[b]	[redacted]	
p-value[a]	[redacted]	
Predicted FVC <30%		
Median age at event, years (95% CI)	NA (NA, NA)	25.4 (20.6, 29.4)
HR (95% CI)[b]	0.107 (0.014, 0.813)	
p-value[a]	0.0085	
FVC <1 litre		
Median age at event, years (95% CI)	[redacted]	[redacted]
HR (95% CI)[b]	[redacted]	
p-value[a]	[redacted]	

STRIDE - Strategic Targeting of Registries and International Database of Excellence; CINRG - Cooperative International Neuromuscular Research Group; CI - confidence interval; HR - hazard ratio; FVC - forced vital capacity; NA - not applicable; BSC - best supportive care

[a] *p value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.*

[b] *HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE versus CINRG.*

Source: PTC Therapeutics Study 025o CSR 2021;[65] Tulinius et al. 2021;[40] Mercuri et al. 2021[37]

Figure 5: Time to loss of ambulation, STRIDE versus propensity score matched CINRG (reproduced from CS, Figure C.22)

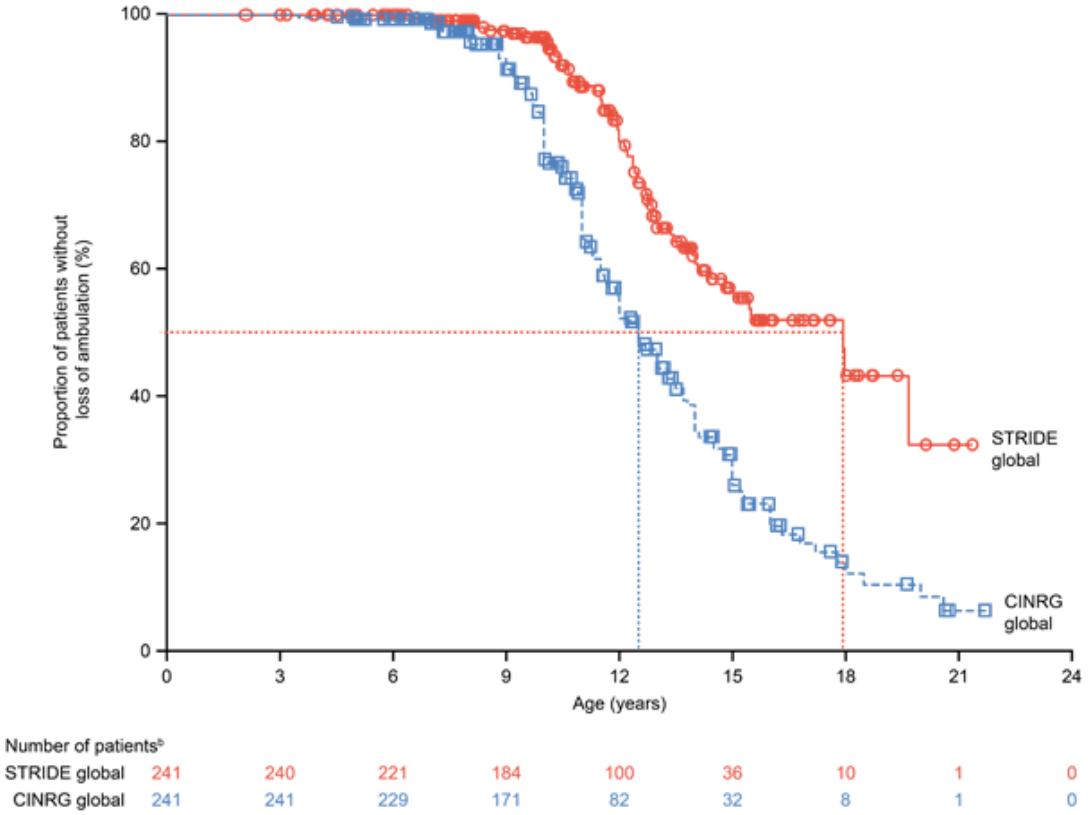


Figure 6: Time to FVC<50%, STRIDE versus propensity score matched CINRG (reproduced from CS, Figure C.26)

Loss of ambulation

On average, patients in the STRIDE cohort[21] were older when they lost ambulation than those in the matched CINRG cohort.[28] Specifically, the median age at loss of ambulation in STRIDE patients was 17.9 years compared to 12.5 years in the propensity score matched CINRG cohort. Additionally, fewer

patients in the STRIDE cohort lost ambulation overall during the study (60 of 241 patients [24.9%]) than did those in the matched CINRG cohort (127 of 241 patients [52.7%]).[1] The HR describing the difference between the groups for time to loss of ambulation was statistically significant (p<0.0001). The EAG notes that it is unclear whether the analysis considered the data to be paired or not. Some authors advise when matched samples have been used, a paired data analysis should be performed to take account of the lack of independence between the samples.[60, 66] There is some debate in the literature around whether this is necessary or not;[61] however, in the context of survival analysis there is evidence that stratifying the log-rank test over matched pairs gives improved accuracy in type I error rates.[67]

Timed function tests

[redacted] Specifically, the median age at which STRIDE patients began taking more than 10 seconds to climb four stairs was [redacted], whereas in the matched CINRG cohort this age was [redacted] The median age at which STRIDE patients began taking 10 seconds or more to stand from supine was [redacted], compared to [redacted] in the matched CINRG cohort. [redacted]

Pulmonary outcomes

[redacted][28] The median age at which STRIDE patients reached a predicted FVC<60% was at age 17.6 years, compared to 15.8 years in the CINRG cohort. The median age at which participants reached a predicted FVC <50% was [redacted] in the STRIDE cohort; in the CINRG cohort this was at age [redacted] Very few patients in the STRIDE cohort declined to a predicted FVC of <30%. One patient in STRIDE was assessed to have an FVC <30% [redacted]. In CINRG, 25 patients had predicted FVC <30% and [redacted]. Because of the limited number of events, it was not possible for the company to compare the median age at which participants reached these milestones, and the HRs for these endpoints should be considered to be highly uncertain.

4.3.1.8 EAG critique of company's ITC, STRIDE versus CINRG

The propensity score matching method used in this study relies on two main assumptions: (i) ignorability of treatment (conditional independence), and (ii) overlap. Conditional independence assumes that once an appropriate set of covariates has been adjusted for, potential outcomes are independent of treatment assignment. The overlap assumption means that for any combination of

covariates, there is always the chance of seeing individuals in both the treatment and control groups. This section presents the EAG's critique of these assumptions alongside other potential methodological issues in the comparison. Table 16 presents a critique of the ITC based on the QuEENS checklist from NICE Decision Support Unit (DSU) Technical Support Document (TSD) Number 17.[46]

Table 16: EAG critical appraisal of ITC comparing STRIDE versus CINRG - QuEENS checklist

Question	Response
1. Have different methods been compared within the study?	No. Alternative methods for calculating the treatment effect have not been presented.
2. Have results been compared to others in the literature?	No. Other studies presented in the CS[1] use similar methods, and results have generally not been compared across these studies. Some comparison is made between the STRIDE/CINRG comparison and the Study 019/CINRG comparison (CS, Section 9.9.1, pages 154-155).
3. Is there discussion of what treatment effect is identified?	No discussion is presented on what treatment effect is identified. The EAG believes that this reflects the ATT, although this is not specifically stated in the CS.
4. Were checks conducted on model specification?	No checks are reported. Analyses assessing the sensitivity of the results to the choice of matching algorithm were not presented.
5. Is the assumption of selection on observables assessed?	Yes, four variables associated with disease prognosis were used for matching members of the STRIDE cohort[21] to members of the CINRG cohort.[28] Other variables indicative of prognosis were argued to be balanced across the matched groups based on assumptions of similar care standards in STRIDE and CINRG, as well as through reference to literature suggesting that nmDMD disease progression is similar to that of non-nmDMD disease progression.
6. What checks were done to assess overlap	Yes, minimal checks were presented. Checks were conducted using the SMDs and variance ratios. However, these checks were univariate and so do not check multiple combinations of covariates. Distributions of propensity scores in the treatment and control group are not presented.
7. Has balancing of covariates been checked after matching?	Yes, minimal checks are presented. Checks were conducted using the SMDs and variance ratios. Distributions of propensity scores in the treatment and control group were not presented.
8. Is the propensity score function sufficiently flexible?	It appears that the propensity score was calculated using a linear combination of the matching variables, though this is not fully clear from the description in the CS. As such, no interactions or other functions of the covariates were included.
9. Are potential IVs excluded from the set of conditioning variables?	Instrumental variables are not discussed in CS. It is unclear whether these exist and/or whether they have been excluded from the matching process.
10. Data quality: are there data quality issues: a. comparable data and definitions for treated and control groups, b. treated and control groups come from same environment/area, c. rich set of variables used for matching, d. reasonable sample sizes	a. Definitions of loss of ambulation differed slightly between the STRIDE and CINRG cohorts b. Both populations come from worldwide multi-centre studies. However, approximately half of the centres in the CINRG study were in the US, with the remaining being in Canada, Australia, Argentina, India, Israel, Italy and Sweden. This differs from the STRIDE substantially, which has no participating centres in the US. In STRIDE, all but 4 of the 71 study centres are located in Europe. As such there may be differences in standard of care between the two groups. There were also differences in the exclusion criteria between the STRIDE and CINRG studies.

Question	Response
	c. The four variables used for matching are all suggested to be prognostic for nmDMD. The first is an indicator of disease onset, and the remaining three variables describe the use of steroids within the patient's care. Other prognostic factors and baseline characteristics were not matched on. d. The sample size (241 treated and 241 controls) is reasonable.
11. For nearest neighbour – has bias adjustment been conducted if more than one variable was included when matching on covariates?	No use of bias adjustment is described.
12. Is the choice of replacement (with/without) reasonable?	Matching without replacement is likely reasonable, and is in line with methods deemed appropriate in the literature.[68]
13. Is the choice of the calliper radius/ number of matches reasonable?	No calliper radius was set. 1-to-1 matching is likely reasonable, since using multiple matches for each STRIDE patient would have required members of the CINRG cohort to be included in the control cohort multiple times. There is also a risk of increased bias if additional matches after the first are poor. However, no evaluations of this are presented.

CS - company's submission; STRIDE - Strategic Targeting of Registries and International Database of Excellence; CINRG - Cooperative International Neuromuscular Research Group; EAG – External Assessment Group; ATT - average treatment effect on the treated; nmDMD - Nonsense mutation Duchenne muscular dystrophy; IV - instrumental variable

Overall, the EAG considers the specific matching methodology applied by the company to be reasonable. Specifically, the choices of matching with replacement and number of matches are likely reasonable and are in line with recommended approaches reported in the literature.[61, 68] Similarly, the use of a greedy algorithm is unlikely to have greatly influenced the results, as evidence suggests that this algorithm performs similarly to optimal matching.[68]

The credibility of both the key assumptions of ignorability and overlap has been assessed in the CS,[1] albeit minimally. To assess the assumptions of selection on observables, four covariates prognostic for DMD were matched on. These covariates appeared to be sufficiently balanced between the two groups. However, other prognostic variables were not matched on, and balance was justified in the CS only through reference to the literature. Additional information provided in the company's clarification response on other baseline characteristics not included in the matching process indicates some imbalances. Little consideration was given to the issue of overlap, with only minimal checks described in the CS. Whilst including every prognostic variable in the matching procedure is likely impractical, no quantitative exploration has been conducted to investigate potential imbalance between these additional covariates, though it is not clear if data were available to do this. A number of desirable features are also missing from the company's ITC. Specifically, the analysis does not include any investigation of the sensitivity to model structure and methodology, and no discussion of the treatment effect identified is presented.

Further to the above, data quality issues and methodological limitations may have impacted the results of the company's ITC. The patients included in STRIDE[21] have been treated primarily in Europe. Patients in CINRG[28] have been treated across a range of continents, with over half being treated in North America. Only three of the 20 participating centres preside in countries that were also analysed in STRIDE. It is unclear whether these geographical differences may have had an impact on the standard of care available, or the populations able to receive care in the two cohorts. This may impact on the assumption within propensity score matching that patients are drawn from the same underlying population. In effect, there may be unobserved confounding which could weaken the assumption of selection on observables.

In terms of methodological limitations, it is not clear from the CS[1] whether the tests of statistical significance employed to compare the STRIDE and matched CINRG cohorts[21, 28] have taken into account the paired nature of the data. Despite there being some debate on the necessity of paired analysis for propensity matched samples[61, 66, 69] in the context of survival analysis some simulation studies have found that paired analyses gives improved performance for tests of statistical significance.[70, 71] Since no mention of using paired analysis is made in the CS, the EAG assumes that a paired analysis has not

been performed. This means that the tests of statistical significance presented here rely on the assumption that the two samples are independent. However, as the data come from matched samples, this assumption might not hold. There is no discussion in the CS of these considerations or how they might impact the results of the study. As such, some caution should be applied when interpreting the statistical significance of HRs in the study.

4.3.1.9 Conclusions on the ITC, STRIDE versus CINRG

Overall, the comparison between the STRIDE and CINRG cohorts[21, 28] indicates that patients receiving ataluren may experience a delay in loss of ambulation compared with patients receiving BSC. [redacted]

There is limited evidence to support an impact on pulmonary outcomes, particularly those experienced further on in disease progression. This was in part due to limited data availability in the STRIDE cohort,[21]

[redacted] which limits any examination of the average age at which these milestones are reached. STRIDE is an ongoing study and so some patients will not have reached the later stages of disease progression before the end of follow-up. Additionally, benefits accrued from receiving ataluren during the ambulatory phase of disease may have also had a knock-on effect on the time to reach FVC milestones, reducing the number of events observed.

The EAG believes that the results of the company's ITC of STRIDE and CINRG[21, 28] should be interpreted with some degree of caution. Methodological limitations may have impacted the estimates of effectiveness presented in the CS.[1] Firstly, data quality issues may have impacted on the estimation of treatment effects. The participating centres for the STRIDE and CINRG studies have different geographical locations in which there are substantial differences in the availability of healthcare. This may therefore have had led to differences between the cohorts in the populations receiving treatment, and potentially in the standards of care received. Secondly, residual confounding may exist due to potential imbalances between prognostic factors not included in the matching procedure. Balance on prognostic factors excluded from the matching procedure was assumed using references to literature and guidelines; however, no direct empirical analysis was presented. Several potentially important prognostic factors were not included (e.g., baseline TFTs). Hence, this balance is subject to uncertainty and may have influenced the estimated relative treatment effects. Lastly, tests of statistical significance do not appear to have taken account of the paired nature of the data and the CS does not present any

discussion as to how the statistical analysis deals with these concerns. Overall, the above concerns highlight uncertainty in the estimated treatment effects for ataluren versus BSC.

4.3.2 ITC 2: MAA versus NorthStar registry - summary and critique

4.3.2.1 Summary of ITC, MAA versus NorthStar registry

In order to receive ataluren on the NHS, eligible patients with nmDMD in England were required to sign up to the MAA following the original NICE appraisal of ataluren in HST3.[18] Within the CS,[1] patients in the MAA have been compared to a matched control group receiving BSC alone in the NorthStar registry[41] (CS, Section 9.6.1.7). Patients within this control group do not exhibit the nonsense mutation and as such they suffer from different sub-types of DMD compared with those receiving ataluren. Within the propensity score matching procedure, patients were matched on the following characteristics:

- Age at baseline
- Age at initial use of steroid
- Deflazacort use duration (≤1 month, 1-12 months, ≥12 months) before baseline*
- Duration of other steroid use (≤1 month, 1-12 months, ≥12 months) before baseline*
- Steroid use regimen (daily/intermittent and other)
- Baseline NSAA total score
- Baseline time to rise from floor.

*Subjects who did not use any steroids were placed in the category of steroids (< 1 month) and initial age of steroid use was imputed to 30.

The primary analysis within the MAA compared the decline in NSAA score over time using both total score and NSAA linear score. These outcomes were analysed using an MMRM. In addition to this, HRQoL data were also collected from both patients and caregivers. Patient HRQoL was assessed using the CHU-9D questionnaire, whereas caregivers were asked to complete the EQ-5D-5L.

Table 17: Summary of MAA versus NorthStar registry ITC

Study Name:	Treated population: MAA patients	Control population: NorthStar cohort
Location:	United Kingdom	United Kingdom
Duration of study	March 2016 – January 2022	2006 - Present
Patient population	nmDMD	DMD (not nmDMD)
Sample size	60	145
Interventions	Ataluren + BSC	Standard care
Matched subsample size	59 (no match found for remaining patient)	59
Matching covariates	• Age at baseline • Age at initial use of steroid • Deflazacort use duration (≤1 month, 1-12 months, ≥12 months) before baseline* • Duration of other steroid use (≤1 month, 1-12 months, ≥12 months) before baseline* • Steroid use regimen (daily/intermittent and other) • Baseline NSAA total score • Baseline time to rise from floor.	
Outcomes assessed	• NSAA • Patient HRQoL – CHU-9D • Caregiver HRQoL – EQ-5D-5L	

MAA - Managed Access Agreement; nmDMD - nonsense mutation Duchenne muscular dystrophy; BSC - best supportive care; NSAA - NorthStar Ambulatory Assessment; HRQoL - health-related quality of life; CHU-9D - Child Health Utility instrument (9 Dimensions); EQ-5D-5L - Euroqol 5-Dimensions (5-Level)
**For boys not on steroids, age at starting steroids was set to 30 years*

4.3.2.2 Patient eligibility criteria in the MAA and NorthStar registry

All MAA data are collected within the NorthStar registry; hence, the main difference between the intervention and control group populations relates to the presence/absence of the nonsense mutation. The criteria for starting and stopping ataluren under the MAA have been described earlier in Section 2.2 (Box 1).

4.3.2.3 Propensity score matching approach, MAA versus NorthStar registry

Matching in the analysis of the MAA/NorthStar data was similar to the approach used for the ITC of STRIDE versus CINRG (see Section 4.3.1.4). Specifically, a greedy algorithm using both nearest neighbour and calliper approaches was used to find matches from the control group. Matches were made without replacement. However, in this analysis, closeness was assessed using the absolute value of the difference between the logit of the propensity scores. The addition of a calliper approach was used to ensure that a maximum tolerance for closeness could not be exceeded. This approach aims to prevent poor matches being made in situations where a close enough match does not exist.[68] The CS[1] does not state what calliper radius was used within the matching procedure.

4.3.2.4 Selection of propensity score matching variables, MAA versus NorthStar registry

The variables included in the matching procedure (listed in Section 4.3.2.1) were chosen based on a matching report produced by the NorthStar registry and interim data on patients who had lost

ambulation. Further details may be available from Version 4.2 of the MAA statistical analysis plan,[41] although some of this information is redacted in the online documentation. Similar to the analysis of STRIDE/CINRG,[21, 28] age at initial use of steroids, deflazacort use duration, and duration of other steroid use were included to ensure that matches were made on current care being received. Additionally, steroid use regimen has been matched on to provide further matching on the standard of care being received. Baseline NSAA score and time to rise from floor give an indication of disease severity at baseline. Age at baseline was matched on due to known differences in disease trajectory between different age groups.

4.3.2.5 Balance of covariates in the MAA and NorthStar registry cohorts

Baseline characteristics after matching are shown for matched variables in Table 18. [redacted]

The CS[1] also suggests that the control group suffered [redacted] on average than the ataluren group at baseline. To support this, the CS presents a comparison of the number of patients who had lost each of the 17 NSAA functions at baseline. In [redacted] function areas, more ataluren patients had lost function at baseline, in [redacted] function areas more control patients had lost function, and in [redacted] function areas equal numbers had lost function in the two groups (see Figure 7).

Table 18: Baseline characteristics after matching, MAA and control cohort (reproduced from CS, Table C-35)

Matching factor	Ataluren (N=59)	Controls (BSC) (N=59)	Standardised difference
Age at baseline (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
On steroids*	[redacted]	[redacted]	[redacted]
Age at starting steroids (years)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Duration of deflazacort prior to baseline[#] <1 month or 1–12 months	[redacted]	[redacted]	[redacted]

Matching factor	Ataluren (N=59)	Controls (BSC) (N=59)	Standardised difference
≥12 months			
Duration of other steroids prior to baseline[#] <1 month or 1–12 months ≥12 months	[redacted]	[redacted]	[redacted]
Steroid regime Daily Other None	[redacted]	[redacted]	[redacted]
NSAA Total score	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Can rise from floor (NSAA rise>0)	[redacted]	[redacted]	[redacted]
Baseline time to rise from supine, seconds	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

MAA - Managed Access Agreement; BSC - best supportive care; SD - standard deviation; NSAA - NorthStar Ambulatory Assessment
**For boys not on steroids, age at starting steroids set to 30 years.*
[#]Lower 2 categories combined for matching, so we consider <12 months and ≥12 months. This was done because of small frequencies in some cells and also the 3-level categorisation was felt to be too refined, based on the typical 6 monthly visiting schedule. This was agreed between NorthStar and PTC.
Source: PTC MAA data tables

Figure 7: Number of patients who lost functions at baseline (a score of 0) (reproduced from CS, Figure C.29)

[redacted]

4.3.2.6 Summary of ITC results, MAA versus NorthStar registry

There was a significant decline in the availability of NSAA scores in both the ataluren patients and the matched NorthStar registry patients during the study period. Due to this, the CS[1] only presents analyses from the first three years of data. The decline in mean NSAA score and mean linearised NSAA score was similar in the two groups. Despite this, there is some evidence that fewer ataluren patients experienced a decline across the specific function areas. In [redacted] out of 17 function areas, a greater number of patients in the BSC group lost function compared with patients in the ataluren group, whereas in only [redacted] function areas the reverse trend was observed (see Figure 8).

Figure 8: Number of patients who lost function over 36 months (reproduced from CS, Figure C.33)

The CS[1] also presents an analysis of participants with complete NSAA data from Month 0 through Month 36. The CS does not state how many patients are included in the analysis, although Figure C.31 of the CS suggests that there will be a maximum of 28 BSC patients and 24 ataluren patients in this sample. In this comparison, the mean decrease in NSAA score and linearised NSAA score was smaller in the ataluren group than the control group. However, it is unclear whether this difference was statistically significant, or whether covariates remained balanced across the two groups after cases with missing data were removed from each group.

An analysis of time to rise from floor was also presented in the CS.[1] The data were transformed using the reciprocal due to non-normality of the data, though the normality of the transformed data is not presented. The CS[1] claims that the comparisons of transformed time to rise from floor indicate that ataluren [redacted] disease progression (CS, Section 9.6.1.7, Figure C.35).

The CS[1] also presents a summary of HRQoL data from the MAA for the CHU-9D (for ataluren-treated patients) and EQ-5D-5L (for caregivers of ataluren-treated patients) by domain. Index utility values are not presented for the CHU-9D and no comparison of patient or caregiver utility is made against patients receiving BSC.

4.3.2.7 EAG critique of company's ITC, MAA versus NorthStar registry

Given the similarities between the methods used in the ITC comparing STRIDE versus CINRG and the MAA versus the NorthStar registry, much of the critique presented in Section 4.3.1.8 also applies here. The EAG believes that the matching methodology is reasonable and is unlikely to have strongly influenced the results. However, the choice of calliper radius used is not stated in the CS[1] and thus could not be critiqued. The assumptions of overlap and selection on observables have again been assessed by selecting matching variables that are prognostic for nmDMD and assessing balance using SMDs. Again, statistical analyses do not appear to have taken into account the matched nature of the samples.

4.3.2.8 Conclusions on the ITC, MAA versus NorthStar registry

The CS[1] states that the analysis of the MAA data *"struggled to demonstrate meaningful treatment effect due to a number of underlying limitations of the analysis"* (CS, Section 9.6.1.7, page 135). Three reasons are given for this. Firstly, the imbalance in baseline age is suggested to have resulted in improved outcomes for the control group, since more members of this cohort are under the age of 7 years and will experience improvements to their function. Secondly, the company suggests that the omission of age at first symptom from the matching procedure means that a key prognostic indicator was missing from the matching procedure. Thirdly, a decline in available data at later time points also affected the company's ability to analyse long-term trends. Overall, the company suggests that more emphasis should be given to the ITC of STRIDE versus CINRG.[21, 28] The EAG notes that the CS contains very limited information about why data were missing and what was done to explore the data more thoroughly. The company's clarification response[32] (question A20) states that missing data comes from a variety of sources including: loss of ambulation leading to the end of participation; evaluator error; patient error; temporary reasons such as a broken leg and unknown reasons. Overall, the EAG believes that this ITC provides less compelling evidence for the benefit of ataluren compared with the STRIDE/CINRG comparison.

4.3.3 ITC 3: Study 019 versus CINRG - summary and critique

4.3.3.1 Summary of ITC, Study 019 versus CINRG

Whilst the main aim of Study 019 was to assess the long-term safety of ataluren, the study design also included an ITC with a propensity score matched cohort from the CINRG study.[28] The CS presents this comparison as supplementary evidence on the efficacy of ataluren versus BSC. The results of this

efficacy study have previously been published by McDonald *et al.* (2021).[25] Participants in Study 019 were matched to patients from the CINRG cohorts using the following 4 covariates:

- Age at onset of first symptoms (using age at diagnosis as a proxy)
- Age at initiation of corticosteroid use
- Duration of deflazacort use
- Duration of use of other corticosteroids.

Since age at first symptoms was not available within Study 019, age at first diagnosis was used as a proxy. The CS[1] states that the company is *"confident that selection of age at diagnosis is a conservative proxy"* (CS, Section 9.6.1.4, page 108). One of the EAG's clinical advisors highlighted that data from the FOR-DMD study suggests a delay between the mean age at first parental concerns and mean age at genetic diagnosis of 25.9 months.[72]

Similar to the comparison between STRIDE and CINRG (see Section 4.3.1), Kaplan-Meier curves were used to estimate the distribution of the age at which patients reached the following disease milestones: (i) loss of ambulation; (ii) predicted FVC <60%; (iii) predicted FVC <50% and (iv) predicted FVC <1L. The survival curves were compared using a log-rank test, stratified by the duration of deflazacort and other corticosteroid use.

Within Study 019, outcomes were assessed every 48 weeks during the ataluren treatment period, except for weight, which was measured every 24 weeks. Loss of ambulation was defined as having two consecutive visits in which the patient took longer than 30 seconds to walk 10 metres or if a clinician defined them as non-ambulant. The age at the first of these visits was then taken as the age at loss of ambulation.[25] This is different to the definition of loss of ambulation in the CINRG study,[28] which defined loss of ambulation as continuous wheelchair use or the inability to walk 10 metres unaided.

Table 19: Summary of Study 019 versus CINRG ITC

	Treated population: Study 019	**Control population: CINRG**
Location:	Worldwide (multi-centre)	Worldwide (multi-centre)
Duration of study	240 weeks (336 weeks in Canada)	>8 years follow up
Patient population	nmDMD	DMD
Sample size	94	440
Interventions	Ataluren plus BSC	BSC
Matched sample size	60 (Assessment of loss of ambulation) 45 (Assessment of pulmonary outcomes)	60 (Assessment of loss of ambulation) 45 (Assessment of pulmonary outcomes)
Matching covariates	• Age at diagnosis • Age at first corticosteroid use • Duration of deflazacort use (<1 month, 1 to 12 months, 12 months or more) • Duration of other corticosteroid use (< 1 month, 1 – 12 months, 12 months or more)	
Outcomes assessed	• Ambulatory outcomes (including the age at loss of ambulation (defined as *"full-time wheelchair requirement"*) age at time to climb four stairs ≥10 seconds and age at time to stand from supine ≥10) • Pulmonary function outcomes - (age at predicted FVC <60%; - age at predicted FVC <50%; age at predicted FVC <30% and age at FVC <1L). • For ambulatory patients, the endpoints were change from baseline in 6MWD, TFTs, and NSAA. • Loss of ambulation was defined as a patient having two consecutive visits in which they took longer than 30s to walk 10m or if a clinician defined a patient as non-ambulant.	

CINRG - Cooperative International Neuromuscular Research Group; ITC - indirect treatment comparison; nmDMD - Nonsense mutation Duchenne muscular dystrophy; BSC - best supportive care; FVC - forced vital capacity; TFT - timed function test; NSAA - NorthStar Ambulatory Assessment; 6MWD - 6 minute walk distance

4.3.3.2 Patient eligibility criteria in Study 019 and CINRG DNHS

Table 20 summarises the key inclusion and exclusion criteria for Study 019 and CINRG.[25, 28] Given the different primary aims of the studies, there are considerable differences between the inclusion and exclusion criteria. The criteria for participation in Study 019 focus on including patients who are not taking other medications that could affect patient safety or the ability to estimate the safety of ataluren. In contrast, the criteria for CINRG focus on there being a confident diagnosis of DMD.

Table 20: Key eligibility criteria in Study 019 and CINRG

	Study 019	CINRG
Inclusion criteria	• Ability to give written, informed consent (by parents/guardian if applicable)/consent (if <18 years old) • Male gender • Patients with a nmDMD who in one or more clinical studies had previously used ataluren • Laboratory tests within normal values (hepatic, adrenal, renal, and serum electrolyte parameters) • In sexually active patients, willingness to refrain from sexual activity or to use contraception during the use of the study medication and the 6-week follow-up periods • Willingness and ability to comply with planned visits, drug administration plan, study procedures, laboratory testing, and study restrictions	• Participants aged 2–4 years with a diagnosis of DMD confirmed by dystrophin immunofluorescence or immunoblot, or both; an out-of-frame deletion; or complete dystrophin gene sequencing in the proband or sibling. • Participants aged 5–29 years with DMD meeting the criteria in (1) or documented clinical symptoms referable to DMD and direct support of the diagnosis by either a positive DNA analysis, a muscle biopsy showing abnormal dystrophin, or a combination of an increased creatine kinase (more than five times the upper limit of normal) in addition to an X-linked pedigree.
Exclusion criteria	• Use of any other experimental drug within 1 month of commencement of the study medication • Participation in another clinical trial with ataluren • Known hypersensitivity to any of the components or excipients of the study medication • Continued use of coumarin-based anticoagulants (eg, warfarin), phenytoin, tolbutamide, paclitaxel, or systemic aminoglycoside antibiotics • Medical/surgical condition, electrocardiogram findings, or laboratory abnormalities that, in the evaluator's judgement, could adversely affect patient safety or make it unlikely that the duration of treatment or follow-up studies would be completed	• Naive to glucocorticoid treatment and ambulated without assistance past their 13th birthday; or use of glucocorticoid therapy and ambulated without assistance past their 16th birthday. • Patients younger than 16 years were enrolled irrespective of future ambulatory status.

CINRG - Cooperative International Neuromuscular Research Group; nmDMD - Nonsense mutation Duchenne muscular dystrophy; DNA - deoxyribonucleic acid

4.3.3.3 Propensity score matching approach, Study 019 versus CINRG

The CS[1] does not provide a clear description of how the matching for Study 019 has been performed, beyond giving the matching covariates and stating that the matching was performed 1-to-1. As such, the EAG assumes that the process is the same as that described in the key publication associated with Study 019 provided in the CS (McDonald *et al*.[25]). Based on information given in this paper, propensity score matching was performed similarly to that in the ITC of STRIDE vs. CINRG (see Section 4.3.1). The propensity score was calculated using a logistic regression model with the following matching variables: age at first clinical symptoms (age at diagnosis used as a proxy); age at initiation of

corticosteroid use; duration of deflazacort use, and duration of corticosteroid use. Matching was not done based on mutation type as this would have substantially reduced the sample size available for analysis.

Matches were then selected from the CINRG cohort[28] using a greedy algorithm to find nearest neighbour matches without replacement. As with the STRIDE versus CINRG ITC, the nearest neighbour for a Study 19 patient was the CINRG patient whose propensity score (the predicted probability from the logistic regression model) was closest in absolute value to that of the Study 019 patient that had not already been used for matching.

Not all patients in Study 019 were eligible for matching. To be eligible for inclusion in the analysis of loss of ambulation, patients in Study 19 had to have data available for age at loss of ambulation and the four covariates used for matching. As such, 60 patients were used for matching in the loss of ambulation analysis and 34 patients were excluded. To be eligible for the propensity score matched analysis of age at decline of respiratory function, patients must have been non-ambulatory and had data for: age at loss of ambulation, the four matching covariates and four respiratory endpoints (FVC< 60%; FVC <50%; FVC <30% and FVC <1L). They must have also not declined below one of these FVC endpoints before entry to the study. Forty-five patients were eligible for matching in the analysis of pulmonary decline; 49 patients were excluded.

4.3.3.4 Balance of covariates in Study 019 and CINRG

The CS presents a comparison between the baseline characteristics for patients in Study 019[25] and CINRG[28] after matching for the covariates used for matching along with baseline TFTs (reproduced in Table 21). A more detailed summary of baseline characteristics for Study 019 participants can be found in McDonald *et al.* 2021;[25] however, these are not compared to the matched CINRG cohort in the paper. Tests for significance between the covariates were conducted using a two-sample t-test for continuous variables or a Chi-square for categorical variables. No recommended methods of analysis are presented in the CS[1] to assess balance of the covariates; only *p*-values associated with two sample t-tests and Chi-square difference tests are presented, which are not recommended in the literature.[64]

The EAG calculated SMDs using the data presented in the CS (shown in Table 21). These SMDs suggest that some imbalances exist between the two groups. Specifically, they suggest that in comparison to the matched controls, on average, patients within the Study 019 cohort: (i) are younger; (ii) are more likely to have used deflazacort for a longer time period and (iii) take less time to complete the TFTs. Overall. this may suggest that Study 019 patients were suffering from less severe disease at baseline than the matched CINRG controls and have received a different baseline level of care. One of the EAG's clinical advisors also commented that the mean age of initiation of steroids in both groups

(around age 10-11 years) appears to be very late, as patients usually start corticosteroids between the ages of 4 and 6 years. They also commented that the percentage of patients with a steroid duration of <1 month appears very high.

Table 21: Baseline demographics and characteristics for all patients in Study 019 and CINRG DNHS, after propensity score matching for loss of ambulation analysis (adapted from CS, Table C-26)

Assessment	Study 019 N = 60 (of 94)	CINRG N= 60 (of 418)	SMD
Age at first symptoms, years[†]			
Mean (SD)	NA	3.9 (1.7)	-0.162[‡]
Age at diagnosis, years			
Mean (SD)	3.6 (2.0)	4.9 (2.3)	
Age at corticosteroid initiation, years[§]			0.099
Mean (SD)	10.9 (8.1)	10.1 (8.1)	
Deflazacort duration, n (%)[¶]			
<1 month	24 (40.0)	27 (45.0)	-0.101
≥1 to <12 months	1 (1.7)	2 (3.3)	-0.102
≥12 months	35 (58.3)	31 (51.7)	0.132
Other corticosteroid duration, n (%)[¶]			
<1 month	37 (61.7)	37 (61.7)	0
≥1 to <12 months	4 (6.7)	2 (3.3)	0.156
≥12 months	19 (31.7)	21 (35.0)	-0.070
Time to climb four stairs at first assessment, seconds[#]			-0.258
n	60	31	
Mean (SD)	5.3 (5.9)	6.9 (6.5)	
Time to walk/run 10m at first assessment, seconds[#]			-0.368
n	60	33	
Mean (SD)	6.6 (4.2)	8.2 (4.5)	
Time to stand from supine at first assessment, seconds[#]			0.082
n	60	26	
Mean (SD)	7.8 (8.5)	7.2 (5.9)	

CINRG - Cooperative International Neuromuscular Research Group; SMD - standardised mean difference; SD - standard deviation; NA - not applicable
[†] The patients' age at first symptoms was not captured in patients in Study 019.
[‡] p-value is for the comparison between the age at diagnosis for Study 019 patients and age at first symptoms for CINRG DNHS patients.
[§] Age at initiation of corticosteroid use for steroid-naïve patients (patients who had never used steroids or used steroids after loss of ambulation) in Study 019 was set to 30 years.
[¶] Corticosteroid duration is calculated from starting use of corticosteroid to loss of ambulation/censored date.
[#] Time to climb four stairs, walk/run 10 m, and stand from supine at first assessment were determined using baseline values from the prior ataluren studies that the patients were enrolled in, i.e., Study 007/007e or Study 004/004e.
Source: McDonald et al. 2021[25]

4.3.3.5 Summary of ITC results, Study 019 versus CINRG

The results of the company's ITC comparing Study 019[25] versus CINRG[28] are summarised in Table 22. The CS[1] states that these analyses provide evidence of the impact of ataluren on pulmonary outcomes,

as indicated by a delay in the age at which FVC<60% is reached, and to some degree, the delay in reaching predicted FVC <50%.

Table 22: Study 019 versus CINRG propensity score matched population – ambulatory and pulmonary function outcomes (reproduced from CS, Table C-18)

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

CINRG - Cooperative International Neuromuscular Research Group; BSC - best supportive care; FVC - forced vital capacity; NR - not reported
Source: McDonald et al. 2021[25]

The results suggest that ataluren treatment results in a 2.2 year delay in the median age of loss of ambulation. The difference in estimated time-to-event as per the log-rank test was statistically significant at the 5% level (p=0.006).

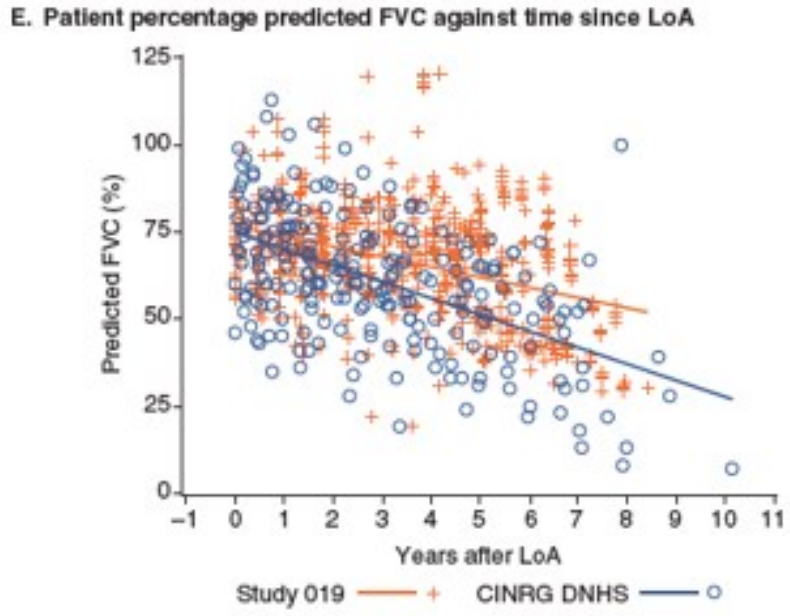
Similarly, ataluren treatment resulted in a 3 year delay in the age at which FVC<60% is reached. This difference was statistically significant at the 5% level as per the stratified log-rank test (p=0.0004). Study 019 participants were also older on average than matched CINRG controls when reaching predicted FVC<50%. This difference was not statistically significant (p>0.05).

In order to assess whether the delay in FVC was due to a carry-over from benefits to loss of ambulation, or an additional treatment effect in of itself, a comparison of the time from loss of ambulation until FVC<60% was made between non-ambulatory Study 019 patients and the matched CINRG cohort. Overall, the company suggests these data are indicative of a continued benefit over and above that given by delays to loss of ambulation; however, the evidence supporting this is limited. The median duration for patients to reach FVC <60% from loss of ambulation was 4.9 years in Study 019 patients, and 3.6 years in matched CINRG patients. This difference was not statistically significant (p=0.219).

Figure 9 presents a scatterplot of percentage predicted FVC over time to examine differences in the decline in FVC for ataluren versus BSC. The company suggests that this scatterplot demonstrates a

more gradual decline in progression to FVC <60% for ataluren patients compared with those receiving BSC alone. However, it is unclear how the lines of best fit have been calculated in the plot, and no additional statistical comparisons have been made. As such, the company's interpretation regarding the treatment benefit of ataluren appears to come from inspection of the plot only.

Figure 9: Patient percentage predicted FVC against time since loss of ambulation, Study 019 vs. CINRG (reproduced from CS, Figure C.19, Panel E)



4.3.3.6 EAG critique of company's ITC, Study 019 versus CINRG

The methodology used within this ITC appears to be very similar to that used for the comparison of STRIDE[21] versus CINRG;[28] hence, the issues raised in Section 4.3.1.8 also apply here. Overall, the methods used to generate matches are likely reasonable, although little was done to explore the impact of modelling choices, and the statistical analyses performed do not appear to have considered whether it is necessary to account for the matched structure of the data in statistical tests. The balance of covariates was assessed minimally, meaning that notable imbalances still existed between the cohorts.

Complete case analysis was used to ensure balance between Study 019 and matched CINRG patients on the prognostic variables used for matching. However, given that covariates still appear to be imbalanced, this benefit has not been realised. Less than two-thirds of the Study 019 participants were used for the analysis of loss of ambulation, and less than half of the participants were used in the analysis of respiratory outcomes. Complete case analysis only gives unbiased results when data are missing completely at random, and it is not clear what the suspected missing data mechanisms in the study were. Explanations of missing data are not presented by the company and so the potential for bias from this modelling decision is unclear.

4.3.3.7 Conclusions on the ITC, Study 019 versus CINRG

Similar to the results of the analysis of STRIDE versus CINRG (Section 4.3.1.7), the results of this ITC suggest that ataluren confers a benefit to patients in terms of loss of ambulation, such that patients receiving ataluren will, on average, lose ambulation later compared with patients receiving BSC. There is some evidence that ataluren also delays milestones associated with pulmonary decline; however, it is unclear from the data whether this is due to a carry-over of the delay to loss of ambulation, or an additional effect of ataluren on pulmonary decline. Evidence presented in the CS[1] in support of an additional treatment effect for ataluren in delaying decline to pulmonary endpoints is limited.

Additionally, notable imbalance exists between the Study 019 cohort and matched CINRG controls which may have confounded the estimated treatment effects. Specifically, matched CINRG controls are older and may be suffering from more severe disease at baseline, leading to poorer outcomes in the study. Furthermore, the analysis is hindered by methodological limitations that may impact on the estimation of treatment effects. Specifically, the analysis does not appear to have taken into consideration the paired structure of the matched data, and it is not clear whether alternative approaches to dealing with missing data would have been more appropriate than complete case analysis.

4.4 Conclusions of the clinical effectiveness section

4.4.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

Existing supporting evidence from two key 48-week clinical trials (Study 007[22] and Study 020[23]) was originally reviewed by NICE and guidance was issued in 2016.[18] The current submission is a re-evaluation of ataluren for treating nmDMD (a review of HST3[18]). New additional evidence presented for assessment included a long-term (up to 336 weeks) open-label extension study (Study 019[25]), support of the licence extension to patients aged ≥2 to <5 years (Study 030[35, 36]) and ongoing real-world safety and effectiveness evidence (STRIDE registry,[21, 37-40] and the MAA[41]). The company also selected the CINRG[28] and NorthStar[41] natural history datasets as indirect comparative evidence for BSC. Although the EAG and their clinical advisors are confident that no additional relevant studies (published or unpublished) have been missed, an SLR to identify BSC should nevertheless have been conducted by the company. However, the EAG's clinical advisors agreed that the CINRG DNHS represents the most relevant study for estimating outcomes for patients receiving BSC alone.

4.4.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator, and outcomes

Due to the lack of additional comparative studies of ataluren with BSC in nmDMD (i.e., new evidence subsequent to HST3),[18] three ITCs based on propensity score matching were performed using the

CINRG[28] or NorthStar[41] natural history datasets as comparator datasets. A principal comparison was conducted between patients from the STRIDE cohort[21] receiving ataluren plus BSC (n=241) and a propensity score matched population receiving BSC alone from the CINRG cohort (n=241).[28] The results suggest that:

- Patients receiving ataluren may experience a delay in loss of ambulation of 5.4 years compared with patients receiving BSC (HR=0.374; p<0.0001). [redacted] There is limited evidence to support an impact on pulmonary outcomes, particularly those experienced further on in disease progression. This was in part due to limited data availability in the STRIDE cohort,[21] [redacted] which limits any examination of the average age at which these milestones are reached.

A second propensity score matched ITC between UK patients signed up to the current ataluren MAA[41] (n=59) and matched controls from the NorthStar registry (n=59) was also made. In the MAA/NorthStar analysis there was a significant decline in the availability of valid NSAA score measures in both the ataluren patients and the matched NorthStar patients during the study period. Despite this and other limitations, the results suggest:

- There is some evidence to suggest that fewer ataluren patients experienced a decline across most function areas ([redacted] out of 17 function areas) over 36 months. In addition, the CS[1] claims that the comparisons of transformed time to rise from floor (due to non-normality of the data) indicate that ataluren [redacted] disease progression compared to BSC. However, the CS notes that the company struggled to demonstrate a meaningful treatment effect due to limitations in the available data. Overall, the EAG believes that this ITC provides less compelling evidence for the benefit of ataluren compared with the STRIDE/CINRG comparison.

Whilst the main aim of Study 019[41] was to assess the long-term safety of ataluren, the company also performed an ITC with a propensity score matched cohort from the CINRG study.[28] The results suggest that:

- Patients receiving ataluren (n=60) will, on average, lose ambulation later (p=0.0006; 2.2 year delay) compared with patients receiving BSC (n=60). There is some evidence that ataluren also results in delays to endpoints associated with pulmonary decline (FVC<60% [only assessed in

non-ambulatory patients, each n=45]; *p*=0.004); however, it is unclear from the data whether this is due to a carry-over of the delay to loss of ambulation, or an additional effect of ataluren on pulmonary decline. Evidence presented in the CS[1] in support of an additional treatment effect for ataluren in delaying decline to pulmonary endpoints is limited.

There were no additional safety concerns associated with ataluren in Study 030 (n=14, aged ≥2 and <5 years)[35, 36] or in longer-term studies (e.g. Study 019 [n=94, as-treated population][25] and the STRIDE registry [n=286, as-treated population][21]) and AEs were in line with the those known for patients aged 2 years and above or common childhood illnesses.

4.4.3 Uncertainties surrounding clinical effectiveness

The EAG identified several weaknesses and uncertainties relating to the evidence presented by the company to estimate the relative effectiveness of ataluren versus BSC based on the ITCs. While the EAG considers the propensity score matching approach applied by the company to be reasonable, data quality issues (e.g., missing data, variance in the quality of data and inconsistency of data collection between registries, population differences between studies, accuracy of reporting and differences in standards of care, including temporal between different countries/centres) and methodological limitations (e.g., inconsistencies in the matching of the controls, potential baseline differences between prognostic factors not included in the matching process and residual confounding and other statistical issues) may have impacted the estimates of effectiveness. As such, the magnitude of benefit in delaying the loss of ambulation, improvements in TFTs and pulmonary outcomes in the overall licensed population remains uncertain. In addition, there is no comparative efficacy data explicitly demonstrating the survival benefit of ataluren over BSC and no data are available on the effect of ataluren on cardiac outcomes.

As noted in the company's clarification response[32] (question A7 and A9), the stopping criteria agreed as part of the MAA, which stipulate that patients should discontinue ataluren by 6 months after loss of ambulation, were largely not adhered to in STRIDE (for centres outside of the UK) as the majority of non-ambulatory participants continued ataluren treatment beyond loss of ambulation. The company's clarification response (question A11)[32] states that: "*the current licence requires that treatment initiation occurs in ambulatory patients but does not specifically detail a stopping rule or prohibit patients continuing treatment beyond LoA. The EMA states "There were no apparent differences in either steady-state relative bioavailability or apparent clearance due to loss of ambulation. No dosing adjustment is needed for patients who are becoming non-ambulatory" and the indication was modified in July 2020 to remove the statement "Efficacy has not been demonstrated in non-ambulatory patients."* The EAG notes that the EMA (application number II/0058,[73] page 3) states that the removal of this

sentence from the indication does not lift the currently imposed restriction i.e., the benefit-risk balance of ataluren remains positive only in ambulatory nmDMD patients aged ≥2years. As acknowledged by the company (clarification response,[32] question A9), there are no long-term data which demonstrate the magnitude of the benefit associated with continued treatment with ataluren beyond loss of ambulation.

In addition, efficacy data in children aged ≥2 and <5 years are limited due to the rarity of diagnosed nmDMD patients <5 years of age.

5. VALUE FOR MONEY

This chapter provides a summary and critique of the company's economic analysis of ataluren, together with additional exploratory analyses undertaken by the EAG. Section 5.1 summarises and critiques the company's SLR of published economic analyses. Sections 5.2 and 5.3 present a detailed description and critique of the company's economic model of ataluren. Section 5.4 presents the EAG's exploratory analyses, including a preferred model and additional sensitivity analyses. Sections 5.5 and 5.6 summarise the company's budget impact analysis and wider costs and benefits associated with the use of ataluren. Section 5.7 presents overall conclusions and highlights key uncertainties.

5.1 Critique of company's review of existing economic analyses

5.1.1 Summary and critique of company's searches

Section 11 of the CS[1] reports details of the company's SLR of existing economic studies. The company's search strategies used for the SLR of economic studies are presented in CS Appendix 3, whilst those used to inform the SLR of resource use studies are presented in CS Appendix 4.[43] These were run in parallel with the searches for the clinical SLR in June 2019 and updated in September 2021. Searches were undertaken from database inception without date limits. The EAG considers that the company's searches were well-designed and documented, and covered all of the core databases recommended for reviews of economic evaluation studies (MEDLINE, Embase, Cochrane, CRD and EconLit). Supplementary searches were also undertaken to retrieve appropriate "grey literature" on DMD from conferences and international health technology assessment (HTA) reports. Further searches were also conducted to identify studies reporting HRQoL data for DMD; these are reported in CS Appendix 17.5.3.[43] As above, these were run in two phases (in 2019 and 2021, respectively).

During the clarification round, the EAG queried the source of the filters used to identify included study types (see clarification response,[32] question A1). The company's response states that the economic filter was based on those on the website of the Scottish Intercollegiate Guidelines Network (SIGN) and provided details of the modifications made to this. Quality of life terms were developed by the SLR team and include an extensive list of specific measures. Whilst the EAG always prefers to see the use of filters which have been formally validated (i.e., their sensitivity and specificity have been tested against a gold standard set of studies eligible for inclusion), it recognises that the evidence base on the retrieval of utility data is less well-developed than that for other study types. Moreover, the EAG acknowledges the SIGN website as a respected source and is broadly satisfied that the terms used are sufficient, meaning that it is unlikely that any relevant evidence has been missed.

5.1.2 Summary and critique of company's review of existing economic studies

The inclusion criteria for the SLR of economic studies are reported in Table D-1 of the CS.[1] Studies were eligible for inclusion in the review if the population related to people with DMD (any form) and

if they reported: life years gained (LYGs); quality-adjusted life years (QALYs) gained; cost-effectiveness or cost-utility estimates; costs (medical, non-medical and/or cost of illness); budget impact or healthcare resource utilisation. The eligibility criteria for the review were not restricted by intervention, study design or language.

The original search identified 66 citations (across 59 studies) which met the inclusion criteria. The update search identified a further 21 eligible citations (across 19 studies). Across both searches, nine citations related to health economic studies reporting on the costs and/or cost-effectiveness of interventions for DMD, including corticosteroids, exon-skipping therapies and ventricular assist device destination therapy for advanced heart failure in DMD. Across these studies, the model-based analyses included state transition and partitioned survival approaches (see CS,[1] Table D-2). None of the included studies evaluated ataluren and none were considered relevant to the decision problem addressed in the CS. Section 11.2.2 of the CS provides a quality assessment of one DMD economic modelling study reported by Landfeldt *et al.* (2017)[31] which is used to inform the health state costs used in the company's economic model (see Section 5.2.4). The CS does not report any overall conclusions regarding the quality of this study, but no major issues were noted. Given that this study is used as a source of costs of managing nmDMD in the company's economic model for this appraisal, the reason for assessing the quality of the economic models reported by Landfeldt *et al.* (2017), rather than the cross-sectional survey used to derive the cost estimates for that model (Landfeldt *et al.* (2014)[74]), is unclear.

The EAG agrees that none of the studies included in the company's review are directly relevant to the decision problem. The EAG notes that the company's economic model for this appraisal differs from that used to inform the original HST3 appraisal[18] and that the original model was not included in the company's review. The model used to inform HST3 adopted a semi-Markov approach, with health states defined by ambulation status, the need for ventilation assistance and scoliosis. Transition probabilities were informed by Study 007[22] and secondary sources.[11, 75] In contrast, the model developed to inform the current appraisal adopts a partitioned survival model approach based on comparisons of age at loss of ambulation and respiratory function-related milestones using data from STRIDE[21] and CINRG[28] (see Section 5.2). The EAG believes that it would have been useful for the company to have included the economic model used to inform HST3 (and potentially other models submitted to other HTA agencies for the reimbursement of ataluren) in their SLR.

5.2 Summary of the company's submitted economic evaluation

As part of their submission to NICE,[1] the company submitted a model-based economic analysis programmed in Microsoft Excel.® The structure of the model is based on patients' survival status, ambulation status and level of respiratory function. Loss of ambulation is defined in terms of when the patient becomes full-time wheelchair bound or bed-ridden. Respiratory function is defined in terms of

FVC percent predicted. The clinical outcomes predicted by the model are informed by a comparison of data from the STRIDE registry[21] for the ataluren group and the propensity score matched CINRG dataset[28] for the BSC group (see Section 4.3.1), together with additional assumptions sourced from clinical experts regarding the additional expected benefits associated with early treatment with ataluren. Data from the RCTs of ataluren and the MAA are not used to inform the model.

5.2.1 Scope of the company's economic analyses

The scope of the company's economic analysis is summarised in Table 23. The company's analysis assesses the cost-utility of ataluren (plus BSC) versus BSC alone for the treatment of ambulatory male patients with nmDMD in terms of the incremental cost per quality-adjusted life year (QALY) gained. The analysis adopts an NHS and Personal Social Services (PSS) perspective, including health outcomes accrued by patients and their caregivers and costs borne by the NHS and PSS. The model adopts a lifetime horizon. Health outcomes and costs are discounted at a rate of 3.5%. Costs are valued at 2021 prices, except for drug acquisition costs which reflect current prices.

Table 23: Summary of scope of company's economic analysis

Population	Male patients with nmDMD who are ambulatory (aged 2 years at treatment initiation)
Intervention	Ataluren plus BSC
Comparator	BSC
Type of analysis	Cost-utility analysis including health outcomes for patients and caregivers
Economic outcome measure	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime (70 years)
Discount rate	3.5% for health outcomes and costs
Price year	2021

nmDMD - nonsense mutation Duchenne muscular dystrophy; BSC - best supportive care; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

Population

The target population reflected in the model relates to individuals with nmDMD who are male. All patients are assumed to be 2 years of age at model entry (the time of initiating treatment with ataluren). All patients are assumed to be ambulant at model entry. Patient weight is assumed to reflect the average characteristics of patients in the 2021 data-cut of STRIDE.[21]

Intervention

The intervention evaluated within the company's economic analysis is ataluren, which is assumed to be given in addition to BSC. Ataluren is administered orally three times daily, with dosing (strength and number of sachets) based on the patient's weight (see Section 3.2, Table 4). The model assumes that ataluren is administered by the patient or by a caregiver in the home setting. A PAS discount of [redacted] is available for ataluren, which applies to all sachet sizes (125mg, 250mg and 1,000mg sachets). The

model assumes that ambulatory patients have a mean weight of [redacted] which corresponds to a cost of [redacted] per 3-month cycle, and non-ambulatory patients have a mean weight of [redacted] which corresponds to a cost of [redacted] per 3-month cycle. Patient weight is not updated with increasing age; hence, these costs are applied to all ambulant/non-ambulant patients who have not yet discontinued ataluren treatment in each model cycle.

The model includes a stopping rule whereby patients are assumed to discontinue ataluren at the point at which they reach FVC<50%. This stopping rule relates to a later timepoint in the disease course compared with that specified in the MAA, which states that patients should stop treatment with ataluren no later than 6 months after becoming fully non-ambulant.[19] The model also assumes that a proportion of patients will discontinue treatment for other reasons, for example, due to AEs or patient/family choice, prior to reaching FVC<50%.

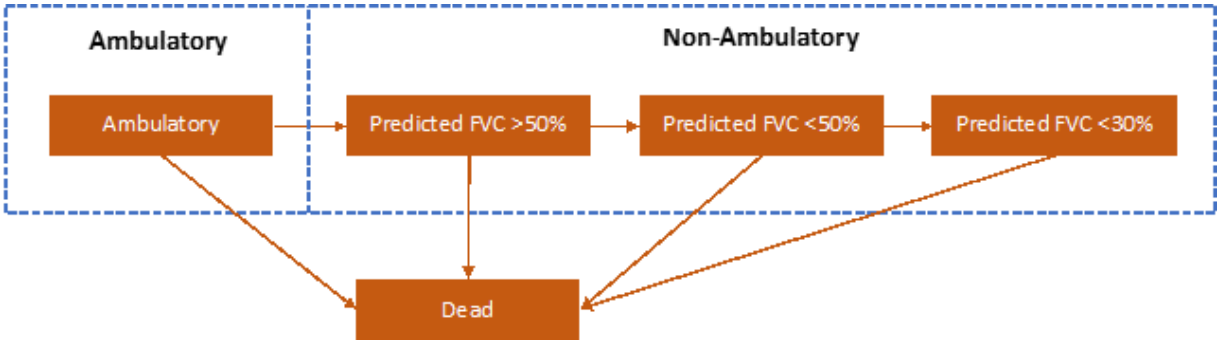
Comparators

The comparator included in the model is BSC. The interventions that comprise BSC are reflected in the costs assigned to each of the model health states and are based on values reported in a published economic modelling study reported by Landfeldt *et al.* (2017),[31] which in turn, were informed by a cross-sectional burden of illness study (also by Landfeldt *et al.* (2014)[74]). Landfeldt *et al.* (2017) reports direct costs relating to: hospital admissions; emergency care; respite care; visits to physicians and other healthcare practitioners (nurses, general practitioners, specialist physicians, psychologists, therapists, physiotherapists, occupational therapists, care co-ordinators/care advisors, dentists, dietitians/nutritionists and speech/language/ swallowing therapists); tests and assessments; medications; medical aids devices and investments, community services (e.g., home help and personal assistants) and other informal care.[31] Whilst it is unclear from the Landfeldt *et al.* (2017) paper, the company's clarification response[32] (question B15) suggests that the costs associated with pharmacological therapies (e.g., corticosteroids) are also included in the disease management cost estimates.

5.2.2 Model structure

The company's model adopts a partitioned survival approach including five health states: (i) ambulant; (ii) non-ambulant, FVC≥50% predicted; (iii) non-ambulant, FVC<50% (and ≥30%) predicted; (iv) non-ambulant, FVC<30% predicted and (v) dead (see Figure 10). The CS[1] states that the model structure was designed to align with the key milestones included in the natural history model developed as part of Project HERCULES.[76] The model adopts a 70-year time horizon with 3-monthly cycles.

Figure 10: Company's model structure (reproduced from CS, Figure D.3)



FVC - forced vital capacity

The model logic operates as follows. All patients enter the model in the ambulatory health state and receive either ataluren (plus BSC) or BSC alone. In the BSC group, the cumulative survival probabilities for time to loss of ambulation (at which point all patients are assumed to have FVC>50%), reaching FVC<50% and reaching FVC<30% are based on parametric survival models fitted to data from the propensity score matched CINRG dataset.[28] FVC<30% is assumed to be equivalent to FVC<1L. Each of these models have been fitted according to time defined by patient age, rather than time since study entry. Overall survival (OS) data were not available from CINRG; instead, the model assumes that patients will die 3 years after reaching the FVC<30% state, based on clinical opinion obtained by the company. This assumption is incorporated into the model by shifting the FVC<30% curve fitted to the propensity score matched CINRG dataset to the right by 3 years.

In the ataluren plus BSC group, the cumulative survival probabilities for the age at which patients reach each DMD milestone are based on parametric survival models fitted to the data from STRIDE[21] for two endpoints (age at loss of ambulation and age at FVC<50%), the same parametric model for age at FVC<30% as that applied in the BSC group, and the same assumption relating to the time from reaching FVC<30% to death as that applied in the BSC group. The model also includes additional assumptions regarding the benefits of early treatment with ataluren, which for each endpoint are assumed to shift the fitted parametric survival models fitted to the right by a specified number of years. Age at loss of ambulation is shifted by [redacted] years, age at FVC<50% is shifted by [redacted] years and age at FVC<30% is shifted by [redacted] years ([redacted] years of which are assumed to relate to the relative benefit of ataluren versus BSC and [redacted] years relate to the additional benefit of starting treatment at age 2 years).

In each treatment group, the probability of residing in each health state at each timepoint is calculated using a partitioned survival approach, based on the following calculations:

- The probability of remaining ambulant at any time *t* is informed directly by the cumulative survival probability for age at loss of ambulation
- The probability of being in the FVC>50% state at any time *t* is estimated as the difference between the cumulative probabilities for age at FVC<50% and age at loss of ambulation

- The probability of being in the FVC<50% state at any time *t* is estimated as the difference between the cumulative probabilities for age at FVC<50% and age at FVC<30%
- The probability of being dead at any time *t* is calculated by one minus the cumulative OS probability (which, in turn, is modelled as a function of age at FVC<30% plus an assumed survival duration of 3 years after reaching this milestone).

The model includes a series of constraints which ensure that the cumulative survival probability for reaching each milestone cannot be lower than that for the next least advanced milestone in the sequence (e.g., the survival curve for age at FVC<50% cannot be lower than that for age at loss of ambulation). The model also includes further adjustments which ensure that the risk of death in all modelled nmDMD health states is at least as high as the risk of death for the age- and sex-matched general population, based on life tables for England.[77]

The model includes health outcomes accrued by nmDMD patients and their caregivers, assuming that each patient has 2 caregivers. Utility values for patients and caregivers are assigned to each of the four alive model health states. For both patients and caregivers, QALYs are calculated by multiplying the time spent in each health state by the patient/caregiver utility for that state. This approach makes implicit assumptions regarding the impact of patient death on caregiver QALYs; these assumptions are discussed in further detail in Section 5.3.5. The model also includes further QALY losses associated with bereavement following the death of the patient. HRQoL impacts associated with AEs are not included in the model. Utility values are not adjusted for increasing age.

The model includes costs associated with: (i) drug acquisition and (ii) health state costs. Costs associated with managing AEs are not included. Ataluren acquisition costs are modelled as a function of the dosing schedule for the mean patient weight (split according to ambulatory status), the unit costs of packs of ataluren and the PAS discount.

The incremental cost-effectiveness of ataluren is calculated in a pairwise fashion, with total QALYs gained calculated as the sum of the QALYs accrued by patients and their caregivers.

5.2.3 Key structural assumptions

The model employs the following key assumptions:

- All patients start treatment with ataluren aged 2 years.
- nmDMD follows a progressive sequence in which patients first lose ambulation and subsequently suffer loss of respiratory function. Impacts of DMD on cardiac function and scoliosis are not explicitly captured in the model structure.
- The relative treatment effects of ataluren versus BSC on disease milestones are modelled through two mechanisms: (i) through differences in parametric survival models fitted to the

STRIDE dataset[21] and the propensity score matched CINRG DNHS dataset[28] and (ii) through additional assumed benefits associated with early treatment with ataluren, which shift the survival models applied in the ataluren group to the right by a specified number of years (loss of ambulation = STRIDE curve shifted by [redacted] years; FVC<50% = STRIDE curve shifted by [redacted] years; FVC<30% = CINRG curve shifted by [redacted] years ([redacted] years relate to the relative benefit of ataluren versus BSC and [redacted] years relate to early treatment benefit).

- Whilst a direct OS benefit of ataluren is not modelled, the combination of early treatment benefit assumptions described above means that the assumed shift applied to the age at FVC<30% curve corresponds approximately to the modelled incremental OS gain for ataluren versus BSC.
- The model includes constraints which: (a) force the cumulative survival probability for any state to be at least as high as that for the previous milestone in the sequence and (b) ensure that modelled mortality risks for patients with nmDMD are at least as high as those for the age- and sex-matched general population. Time to treatment discontinuation (TTD) is structurally independent of the parametric survival models relating to DMD milestones.
- Health utility values for patients applied in each health state are assumed to be treatment-dependent, with higher utility values for patients receiving ataluren compared with those receiving BSC. Utility values for caregivers are not treatment-dependent. In both treatment groups, higher patient and caregiver utility values are applied to the ambulant health state compared to the non-ambulant health states.
- Caregiver QALYs are calculated using an "absolute" caregiver QALY approach. This implicitly assumes that when the DMD patient dies, the caregivers also die or survive with zero utility, or that QALYs accrued by bereaved caregivers are not relevant for inclusion in the economic analysis. Each patient is assumed to have 2 caregivers.
- Caregivers incur an additional bereavement-related QALY loss, which is assumed to be 9% of the expected general population QALYs lost at the point of a patient's death.
- Patients reaching the FVC<50% state require night-time ventilation support. Patients reaching the FVC<30% state require full-time ventilation support. These assumptions are reflected in the selection of utility and cost estimates assigned to the model health states.
- All patients who are still receiving ataluren upon reaching FVC<50% discontinue at this point. Patients may also discontinue ataluren for other reasons before reaching this milestone.
- Patient weight remains constant in every model cycle, based on the average characteristics of patients in the 2021 data-cut of STRIDE.[21]

5.2.4 Evidence used to inform the model parameters

The evidence sources used to inform the model are summarised in Table 24. These are discussed in detail in the subsequent sections.

Table 24: Evidence sources used to inform the company's model

Model parameter/group	Evidence source
Patient characteristics	
Patient sex, age and weight	STRIDE[21]
Time-to-event parameters	
Age at loss of ambulation - BSC	Re-based log-logistic model fitted to propensity score matched data from CINRG DNHS[28] with cut-point at age 3.5 years.
Age at loss of ambulation - ataluren plus BSC group	Re-based log-logistic model fitted to data from STRIDE[21] with cut-point at age 5 years. Fitted survivor function shifted to the right by [redacted] years to reflect assumed benefit of early treatment with ataluren.
Age at FVC<50% - BSC group	Re-based log-logistic model fitted to propensity score matched data from CINRG DNHS[28] with cut-point at age 3.5 years.
Age at FVC<50% - ataluren plus BSC group	Re-based log-logistic model fitted to data from STRIDE[21] with cut-point at age 5 years. Fitted survivor function shifted to the right by [redacted] years to reflect assumed benefit of early treatment with ataluren.
Age at FVC<30% - BSC group	Re-based log-normal model fitted to propensity score matched data from CINRG DNHS[28] with cut-point at age 3.5 years.
Age at FVC<30% - ataluren plus BSC group	Same model as BSC model for age at FVC<30% shifted to the right by [redacted] years to reflect assumed benefit of treatment with ataluren ([redacted] years) and additional benefit of early treatment ([redacted] years).
Time to death after reaching FVC<30% - both groups	Assumption - age at FVC<30% curve for each group shifted to right by 3 years.
All-cause mortality	ONS life tables for England[77]
TTD - ataluren plus BSC group	Constant rate estimated using data on discontinuations in STRIDE.[21]
Health-related quality of life	
Patient utility values for model health states	Landfeldt *et al.* (2020)[33] - assumes higher utility values for ataluren-treated patients versus BSC-treated patients in same state.
Carer utility values for model health states	Landfeldt *et al.* (2017)[31] - assumes treatment group-independent utility values for caregivers.
Bereavement QALY loss	Quality adjusted life expectancy estimated using Ara and Brazier.[78] Percentage of total QALY loss applied based on NICE HST7.[79]
Number of carers per patient	Unpublished global Delphi panel with [redacted] clinicians[1]
Resource use and costs	
Ataluren list price	BNF[30]
Ataluren PAS	CS[1]
Mean patient weight	STRIDE[21]
Treatment adherence	Unpublished global Delphi panel with [redacted] clinicians[1]
Health state costs	Landfeldt *et al.* (2017)[31]

FVC - forced vital capacity; BSC - best supportive care; CINRG DNHS - Cooperative International Neuromuscular Research Group Duchenne Natural History Study; ONS - Office for National Statistics; STRIDE - Strategic Targeting of Registries and International Database of Excellence; QALY - quality-adjusted life year; PAS - Patient Access Scheme; BNF - British National Formulary; CS - company's submission; TTD - time to treatment discontinuation

Patient characteristics

The modelled population is assumed to be 2 years of age at model entry; this reflects the minimum age at which patients can begin treatment with ataluren, based on the extension to the marketing authorisation for ataluren.[29] All patients are assumed to be ambulatory and male. Mean weight for ambulatory and non-ambulatory patients is based on estimates from STRIDE.[21]

Time-to-event model parameters

The company fitted a series of standard parametric survival models to time-to-event data from the STRIDE and propensity score matched CINRG datasets.[21, 28] Models were fitted independently to data for each treatment group, excluding a treatment-indicating covariate. Models were fitted to data on three endpoints: (i) age at loss of ambulation; (ii) age at FVC<50% and (iii) age at FVC<30% (data on this endpoint were available from CINRG only). The numbers of patients contributing data to the analysis of each endpoint are summarised in Table 25. Six parametric models were fitted, including the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. More flexible parametric survival distributions, such as restricted cubic spline (RCS) models, were not considered. Piecewise hybrid models which use Kaplan-Meier estimates up to some timepoint and parametric survival functions thereafter were considered in sensitivity analysis (see Section 5.2.6). For each time-to-event endpoint, the survival models were "re-based" according to the earliest age at which it was assumed that events could occur: cut-points of 3.5 years and 5 years were assumed for the BSC and ataluren groups, respectively. Whilst this approach assumes that prior to the cut-point, no events are possible, the economic model includes an adjustment for deaths occurring in all model cycles based on life tables.[77]

The relative goodness-of-fit of the parametric survival models was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics. The CS[1] states that parametric models were selected for inclusion in the base case economic model based on goodness-of-fit statistics and the plausibility of the long-term extrapolations. However, no details are provided in the CS regarding how plausibility influenced model selection and the base case analysis uses the best-fitting models for all endpoints.

Table 25: Number of patients from STRIDE and CINRG contributing data to company's parametric survival models

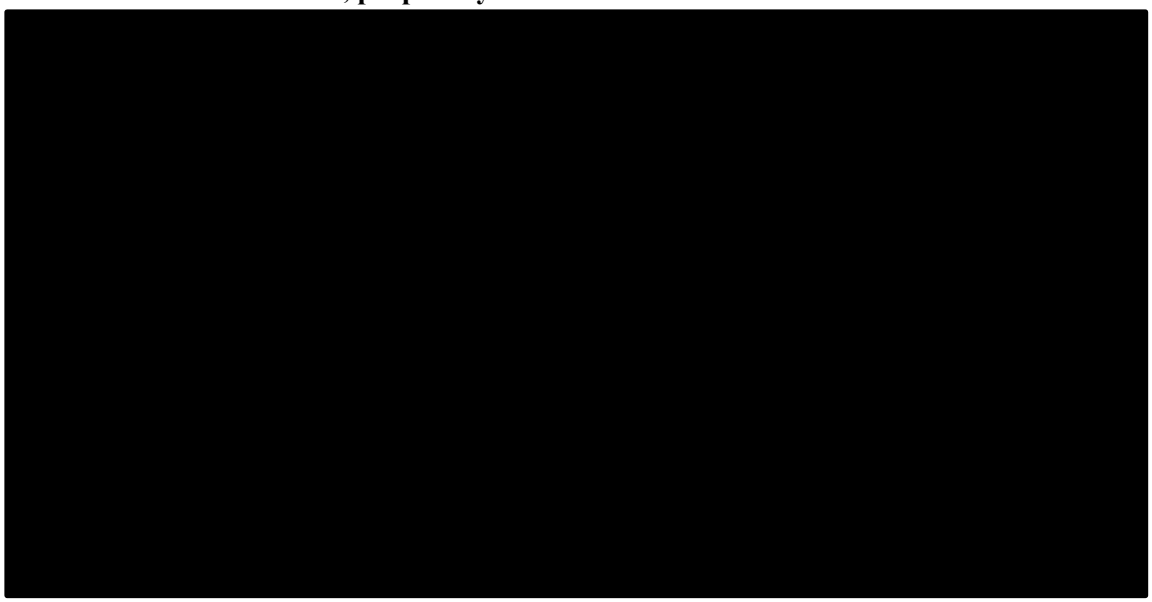
Model endpoint	Matched CINRG DNHS (cut-point = 3.5 years)	STRIDE (cut-point = 5 years)
Age at loss of ambulation	241*	241
Age at FVC<50%	182*	182†
Age at FVC<30%	173‡	Not applicable. Modelled outcomes based on CINRG survival model plus assumptions
Time to death after reaching FVC<30%	Not applicable. Based on assumption of death after 3 years	

CINRG DNHS - Cooperative International Neuromuscular Research Group Duchenne Natural History Study; STRIDE - Strategic Targeting of Registries and International Database of Excellence; FVC - forced vital capacity
**Determined by number of patients with available data in STRIDE*
†Excludes patients not assessed for FVC in STRIDE and those with FVC<50% at entry into the registry (see clarification response,[32] question B5)
‡Patients who died before reaching FVC<30% were censored at the time of death (see clarification response,[32] question B3)

Age at loss of ambulation

Comparisons of the Kaplan-Meier survivor functions and model-predicted age at loss of ambulation for the propensity score matched CINRG dataset[28] and the STRIDE dataset[21] are presented in Figure 11 and Figure 12, respectively. AIC and BIC statistics for the fitted parametric survival models are presented in Table 26. For both groups, the log-logistic distribution was the best fitting model: this model was selected for inclusion in the company's economic model.

Figure 11: Parametric survival models and Kaplan-Meier survivor function - age at loss of ambulation, propensity score matched CINRG DNHS



Notes: Plot excludes model constraints. The log-logistic model (red) was selected for inclusion in the base case analysis

Figure 12: Parametric survival models and Kaplan-Meier survivor function - age at loss of ambulation, STRIDE

Notes: Plot excludes model constraints. The log-logistic model (red) was selected for inclusion in the base case analysis

Table 26: AIC and BIC statistics - age at loss of ambulation (adapted from CS Appendix 6, Tables 41 and 42)

Distribution	BSC group (CINRG)	Ataluren group (STRIDE)

	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; BSC - best supportive care
Best-fitting model highlighted in bold

Figure 13 presents a comparison of model-predicted age at loss of ambulation applied in the ataluren and BSC groups of the company's economic model. As discussed in Section 5.2.3, the company's base case economic model applies an assumption that the early use of ataluren would result in the ataluren curve from STRIDE being shifted to the right by [redacted] years. (solid versus dashed blue lines).

Figure 13: Model-predicted age at loss of ambulation, both groups, with/without assumption of additional early treatment benefit for ataluren

[redacted]

BSC - best supportive care
Notes: The figure includes general population mortality risks. The dashed blue line reflects the model fitted to data from STRIDE without additional assumptions of early treatment benefit

Age at FVC<50%

Comparisons of the Kaplan-Meier survivor functions and model-predicted age at FVC<50% for the propensity score matched CINRG dataset[28] and the STRIDE dataset[21] are presented in Figure 14 and Figure 15, respectively. AIC and BIC statistics for these models are summarised in Table 27. For both groups, the log-logistic distribution was the best fitting model: this model was selected for inclusion in the company's base case model.

Figure 14: Parametric survival models and Kaplan-Meier survivor function - age at FVC<50%, propensity score matched CINRG DNHS

Notes: Plot excludes model constraints. The log-logistic model (red) was selected for inclusion in the base case analysis

Figure 15: Parametric survival models and Kaplan-Meier survivor function - age at FVC<50%, STRIDE

Notes: Plot excludes model constraints. The log-logistic model (red) was selected for inclusion in the base case analysis

Table 27: AIC and BIC statistics - age at FVC<50% (adapted from CS Appendix 6, Tables 43 and 44)

Distribution	BSC group (CINRG)		Ataluren group (STRIDE)	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; BSC - best supportive care
Best-fitting model highlighted in bold

Figure 16 presents a comparison of model-predicted age at FVC<50% applied in the ataluren and BSC groups of the company's economic model. As discussed in Section 5.2.3, the company's base case economic model includes an assumption that the early use of ataluren would result in the ataluren curve from STRIDE being shifted to the right by [redacted] years (solid versus dashed blue lines).

Figure 16: Model-predicted age at FVC<50%, both groups, including assumption of additional early treatment benefit for ataluren

[redacted]

BSC - best supportive care
Notes: The figure includes general population mortality risks. The dashed blue line reflects the model fitted to data from STRIDE without additional assumptions of early treatment benefit

Age at FVC<30%

A comparison of the Kaplan-Meier survivor function and model-predicted age at FVC<30% for the propensity score matched CINRG dataset[28] is presented in Figure 17. AIC and BIC statistics for these models are presented in Table 28. The log-normal distribution was the best fitting model: this model was selected for inclusion in the company's base case model. Data on age at FVC<30% were not available from STRIDE;[21] instead, outcomes for the ataluren group were modelled by applying

assumptions to the parametric model selected for the BSC group to reflect expected outcomes for patients receiving ataluren plus BSC.

Figure 17: Parametric survival models and Kaplan-Meier survivor function - age at FVC<30%, propensity score matched CINRG DNHS

Notes: Plot excludes model constraints. The log-normal model (purple) was selected for inclusion in the base case analysis

Table 28: AIC and BIC statistics - age at FVC<50% (adapted from CS Appendix 6, Table 45)

Distribution	BSC group (CINRG)		Ataluren group (STRIDE)
	AIC	BIC	Not applicable. Modelled outcomes for ataluren group based on CINRG DNHS plus assumptions
Exponential			
Weibull			
Gompertz			
Log-normal (base case)			
Log-logistic			
Generalised gamma			

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; BSC - best supportive care
Best-fitting model highlighted in bold

Figure 18 presents a comparison of predicted age at FVC<30% applied in the ataluren and BSC groups of the company's economic model. As discussed in Section 5.2.3, the company's base case model applies an assumption that the early use of ataluren would result in outcomes consistent with the BSC curve from CINRG[28] being shifted to the right by [redacted] years (solid versus dashed blue lines). Model-predicted OS is shown in Figure 19; these estimates are driven by the models for age at FVC<30% plus the assumption that all patients die within 3 years of reaching this milestone.

Figure 18: Model-predicted age at FVC<30%, both groups, including assumption of additional early treatment benefit for ataluren

BSC - best supportive care
Notes: The figure reflects adjusted models including all model constraints, including general population mortality risks. The dashed blue line reflects the model fitted to data from CINRG without additional assumptions of treatment benefit

Figure 19: Model-predicted OS, including assumption of additional early treatment benefit for ataluren

BSC - best supportive care
Notes: The figure reflects adjusted models including all model constraints, including general population mortality risks. The dashed blue line reflects the model fitted to data from CINRG without additional assumptions of treatment benefit

Health-related quality of life

Patient utility values

Patient utility values were taken from a Delphi panel study reported by Landfeldt *et al.* (2020).[33] The purpose of this study was to investigate clinical expert consensus on the health status and utility of patients with nmDMD treated with ataluren plus BSC care versus BSC in Sweden. Six clinical experts from two neuromuscular centres in Sweden participated in the study. All respondents were required to have experience with and/or substantial clinical knowledge of ataluren for the treatment of nmDMD.

Each respondent completed the Health Utilities Index Mark 3 (HUI3) questionnaire and a Visual Analogue Scale (VAS) for four health states which related to ambulatory and non-ambulatory nmDMD states in patients treated with ataluren plus BSC or BSC alone. Ataluren was assumed to be initiated at a mean patient age of 9 years and discontinued at the time of loss of independent ambulation, and patients were specified not to have scoliosis or require ventilatory support for survival. For the states valued in the Delphi exercise, ambulatory patients were assumed to have a mean age of 13 years with a 6MWD of 410 metres for those receiving ataluren plus BSC and a 6MWD of 316 metres for those receiving BSC alone. For the non-ambulatory states, patients were assumed to have a mean age of 17 years with no assumption made about functional ability. Consensus for each question on the HUI3 was considered to have been reached when at least 80% of the participating experts were in agreement on the appropriate level (for each intervention and health state, respectively). Three Delphi rounds were undertaken. Consensus was reached amongst all six experts for the ambulatory health states, but consensus was not reached for the domain relating to dexterity in non-ambulant patients. In order to reflect the participants' differing views on utility for non-ambulatory states, the study authors report two separate values which reflect the range of severities for non-ambulant patients.

The patient utility values used in the company's economic model are summarised in the upper section of Table 29. The values selected to represent patient utilities for the non-ambulant states in the company's model reflect the higher set of values reported by Landfeldt *et al.* (2020).[33]

Caregiver utility values

Caregiver utility values were taken from an economic modelling study reported by Landfeldt *et al.* (2017).[31] The utility values used in the published models were based on EQ-5D-3L values collected within a previously published cross-sectional HRQoL study assessing the burden of caregiving in DMD (Landfeldt *et al.*, 2016).[34] Within this study, caregivers of 770 patients completed the EQ-5D-3L, a VAS, the Short-Form 12 (SF-12) Health Survey and the Zerit Caregiver Burden Interview (ZBI). EQ-5D-3L utility values are reported for four states: (i) early ambulatory; (ii) late ambulatory; (iii) early non-ambulatory and (iv) late non-ambulatory.

The caregiver utility values used in the company's economic model are summarised in the lower section of Table 29.

Table 29: Patient and caregiver utility values applied in the company's model

Patient utility values (Landfeldt *et al.* (2020)[33])			
Model health state	**BSC**	**Ataluren+BSC**	**Health state valued**
Ambulant	0.62	0.93	Ambulatory stage
Non-ambulant, FVC>50%	0.16	0.32	Non-ambulatory stage (levels "b" and "c" on HUI III question on dexterity: "ability to use hands and fingers")
Non-ambulant, FVC<50%			
Non-ambulant, FVC<30%			

Caregiver utility values (Landfeldt *et al.* (2017)[31])			
Model health state	**BSC**	**Ataluren+BSC**	**Health state valued**
Ambulant	0.84		Model II "late ambulatory"
Non-ambulant, FVC>50%	0.84		Model III "no ventilation"
Non-ambulant, FVC<50%	0.78		Model III "night-time ventilation"
Non-ambulant, FVC<30%	0.77		Model III "day and night-time ventilation"

BSC - best supportive care; FVC - forced vital capacity; HUI - Health Utilities Index

Bereavement-related disutility

The model also includes QALY losses associated with caregiver bereavement. These are calculated by estimating the quality-adjusted life expectancy (QALE) lost for an individual in the general population dying at each age, based on utility values reported by Ara and Brazier.[78] The age-specific QALE lost is then discounted and multiplied by 9%; this proportion was based on an assumption previously used in NICE HST7,[79] which in turn, was drawn from an assumption applied in a previous modelling study of meningitis vaccination (Christensen *et al.*[80]). The company's model applies a single age-specific bereavement-related QALY loss at the time of the patient's death.

Resource costs

Drug acquisition costs

Drug acquisition costs for ataluren per day are calculated as a function of: (i) the price of ataluren sachets (including the PAS) and the number of sachets required to treat an ambulant/non-ambulant patient with nmDMD. In line with the SmPC for ataluren,[29] the number and strength of ataluren sachets required per day are dependent on the patient's weight (see Section 3.2, Table 4). Ambulatory patients are assumed to have a mean weight of [redacted]kg, and require [redacted] sachets per day. Non-ambulatory patients are assumed to have a mean weight of [redacted]kg, and require [redacted] sachets per day. The model assumes that treatment compliance is [redacted] and [redacted] for ambulant and non-ambulant patients, respectively; the company's clarification response[32] (question B14) states that these estimates were based on an unpublished global Delphi panel involving [redacted] clinical experts.[1] Based on the above dosing assumptions and the PAS prices listed in Table 30, the compliance-adjusted 3-monthly cost of ataluren is estimated to be [redacted] for ambulant patients and [redacted] for non-ambulant patients. These costs are applied to patients in the ambulant and non-ambulant states in each model cycle in which the patient has not yet discontinued.

Table 30: Ataluren acquisition costs

Ataluren sachet size	List price	PAS price	PAS discount
125mg	£84.40	[redacted]	[redacted]
250mg	£168.80	[redacted]	
1,000mg	£675.20	[redacted]	

PAS - Patient Access Scheme; mg - milligram

Time to treatment discontinuation

The model includes two types of discontinuation: (i) "natural" discontinuation and (ii) a stopping rule, whereby all patients are assumed to discontinue treatment upon reaching the non-ambulant FVC<50% state.

The natural discontinuation rate was based on data from STRIDE,[21] in which [redacted] patients out of a total of [redacted] patients discontinued ataluren over a period of [redacted] years, resulting in a 3-monthly discontinuation probability of [redacted]. The company's model assumes that this probability applies in every model cycle.

The stopping rule for ataluren is applied as part of the model structure. The base case model assumes that all patients remaining on treatment at the point of reaching the non-ambulant FVC<50% state will immediately discontinue treatment. The company's approach to modelling discontinuation has no impact on modelled health outcomes. The company's modelled estimates of time on treatment are shown in Figure 20 (solid blue line). As shown in the figure, the model applies the treatment discontinuation rate from STRIDE[21] until around [redacted] years after starting ataluren, which then increases sharply to mirror the rate at which patients leave the ambulant/non-ambulant FVC>50% states.

Figure 20: Modelled time on ataluren treatment

TTD - time to treatment; FVC - forced vital capacity

Health state costs

The costs of BSC were taken from the economic evaluation study Landfeldt *et al*. (2017),[31] which in turn, were based on the burden of illness study reported by Landfeldt *et al.* (2014).[74] Within this study, 770 patients with DMD from Germany, Italy, the UK and the US completed an online questionnaire with a caregiver. The questionnaire included questions relating to health care resource use, informal care, household expenses as well as patient and caregiver HRQoL. The cost components included in this study have been described previously in Section 5.2.1. Cost estimates were reported by Landfeldt

et al. (2017)[31] at 2015 prices and were uplifted to 2021 values by the company using the Office for National Statistics (ONS) Consumer Price Index (CPI). The health state costs per 3-month cycle applied in the company's model are summarised in Table 31. The company's base case economic model includes only direct medical and non-medical costs; indirect costs are considered in sensitivity analysis (see Section 5.2.6).

Table 31: 3-monthly health state costs applied in the company's model

Model health state	Cost per 3-month model cycle	Model/health state in Landfeldt *et al.* (2017)[31]
Ambulant	£6,450	Model II (late ambulatory)
Non-ambulant, FVC>50%	£6,897	Model III (no ventilation)
Non-ambulant, FVC<50%	£13,213	Model III (night-time ventilation)
Non-ambulant, FVC<30%	£14,802	Model III (day- and night-time ventilation)

FVC - forced vital capacity

5.2.5 Model evaluation methods

The CS[1] presents base case cost-effectiveness results for ataluren plus BSC versus BSC alone using the list price and the PAS price for ataluren. Results are presented using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are also presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). The distributions used in the company's PSA are summarised in Table 32.

The results of the deterministic sensitivity analyses (DSAs) are presented graphically using a tornado plot and in tabular form. The CS[1] also reports on a number of scenario analyses exploring alternative assumptions regarding: the types of costs included (indirect costs included); the use of child growth estimates data from the Royal College of Paediatrics and Child Health (RCPCH) to inform patient weight by age; discount rates; alternative sources of patient utility values; the exclusion of bereavement-related QALY losses; alternative stopping rules, and alternative approaches to survival modelling (hybrid Kaplan-Meier/parametric approaches and excluding cut-points in the survival models).

Table 32: Summary of distributions used in company's PSA with comments from the EAG

Parameter/ group	Distribution applied in PSA	EAG comments
Patient characteristics		
Mean patient weight	Log-normal	SEs arbitrarily assumed to be 20% of the mean. SE from STRIDE[21] not used.
Time-to-event model parameters		
Time-to-event models (age at loss of ambulation, FVC<50% and FVC<30%)	Multivariate normal	Appears to be appropriate.
Time from FVC<30% to death	Gamma	SEs arbitrarily assumed to be 20% of the mean. Expectation of samples does not match point estimates.
Early treatment benefits of ataluren assumptions	Gamma	
HRQoL parameters		
Patient utility values	Shifted negative gamma	SEs reported in Landfeldt *et al.* (2017)[31] not used in PSA. Instead, SEs arbitrarily assumed to be 20% of the mean. Approach permits sampled values which are below the lower bound of the HUI3 and the EQ-5D.
Caregiver utility values	Shifted negative gamma	
No. of caregivers	Gamma	SEs arbitrarily assumed to be 20% of the mean.
Caregiver bereavement QALY proportion	Beta	SEs arbitrarily assumed to be 20% of the mean.
Resource use and cost parameters		
Treatment adherence	Beta	Large SE used in PSA results in very wide sampled interval. Source/appropriateness of SE unclear.
Health state costs	Gamma	SEs reported in Landfeldt *et al.* (2017)[31] not used in PSA. SEs arbitrarily assumed to be 20% of the mean.

PSA - probabilistic sensitivity analysis; EAG – External Assessment Group; FVC - forced vital capacity; QALY - quality-adjusted life year; SE - standard error

5.2.6 Company's model results

This section presents the results from the company's model. All of the ICERs estimated from the sensitivity analyses and scenario analyses presented in the CS[1] include the decision modifier, based on the number of incremental undiscounted QALYs predicted in each analysis. This decision modifier is applied in the model by weighting the incremental QALY gains. For the sake of clarity, all results presented in this section exclude any QALY weighting.

Company's central estimates of cost-effectiveness

Table 33 presents the central estimates of cost-effectiveness generated using the company's original submitted model. When only patient health gains are included, the probabilistic version of the model suggests that ataluren plus BSC is expected to generate an additional [redacted] discounted QALYs at an additional cost of [redacted]; the corresponding ICER is [redacted] per QALY gained. The model also predicts that ataluren will lead to [redacted] additional discounted QALYs for caregivers of each nmDMD patient

treated. When both patient and caregiver health gains are included in the analysis, the ICER for ataluren plus BSC versus BSC is expected to be [redacted] per QALY gained. The deterministic version of the model generates ICERs which are broadly similar to the probabilistic version of the model.

The company's deterministic model suggests that ataluren will lead to [redacted] additional undiscounted QALYs compared to BSC ([redacted] additional undiscounted QALYs per nmDMD patient treated plus [redacted] additional undiscounted QALYs for their caregivers).

Table 33: Company's central estimates of cost-effectiveness

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)
Probabilistic model†							
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model							
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
**Undiscounted*
†Generated by the EAG by modifying the company's VBA sub-routine for running PSA

Table 34 summarises the model-predicted time to reach each milestone for each treatment group. The model predicts that ataluren will delay the loss of ambulation by [redacted] years and the age at FVC<50% by [redacted] years. Modelled delays in time to reach FVC<30% and death are very similar ([redacted] and [redacted] years, respectively.

Table 34: Mean time to reach modelled milestone (years)

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

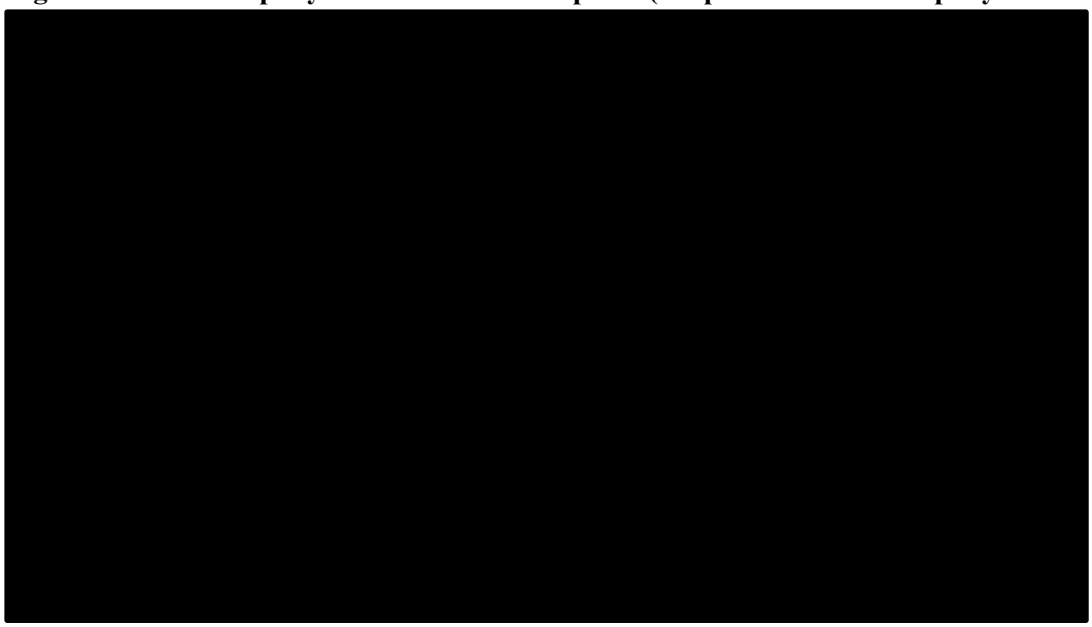
BSC - best supportive care; FVC - forced expiratory volume
**Calculated based on mean time to reach each milestone when all early/relative treatment benefits are set equal to zero*
†No data were available from STRIDE for these endpoints; hence. modelled delays in these endpoints are driven entirely by assumptions about (a) relative benefit for ataluren versus BSC and (b) early treatment benefit

Probabilistic sensitivity analysis results

The results of the company's PSA are presented as a cost-effectiveness plane and CEACs for ataluren plus BSC versus BSC alone (Figure 21 and Figure 22, respectively). Both plots include QALY gains accrued by patients and their caregivers. Assuming willingness-to-pay (WTP) thresholds of £100,000

per QALY gained and £300,000 per QALY gained, the probability that ataluren plus BSC generates more net benefit than BSC alone is estimated to be [redacted] and [redacted], respectively.

Figure 21: Company's cost-effectiveness plane (adapted from the company's model)



WTP - willingness-to-pay; QALY - quality-adjusted life year

Figure 22: Company's CEAC (adapted from the company's model)

WTP - willingness-to-pay; BSC - best supportive care

Company's DSA results

The results of the company's DSA are presented in the form of a tornado plot in Figure 23; this plot includes patient and caregiver QALY gains. The company's analyses indicate that the ICER is

particularly sensitive to the patient and caregiver utility values. The lowest ICER reported across all DSAs is estimated to be in excess of [redacted] per QALY gained.

Figure 23: Company's DSA tornado plot (reproduced from the company's model)

BSC - best supportive care; FVC - forced vital capacity

Company's scenario analysis results

The results of the company's deterministic scenario analyses are presented in Table 35.

Table 35: Company's scenario analysis results

Scenario	Inc. QALYs - patients	Inc. QALYs - carers	Inc. QALYs - patients + carers	Inc. costs	ICER - patients	ICER - patients + carers
Base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA1 Inclusion of indirect costs from Landfeldt *et al.* (2017)[31]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA2 Patient weight based on RCHCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA3 Discount rate QALYs = 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA4 Delphi panel utilities (international)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA5 Delphi panel/Landfeldt *et al.* (2019)[31] hybrid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA6 Exclude bereavement-related QALY loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA7 Stopping rule – within 6 months of loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Inc. QALYs - patients	Inc. QALYs - carers	Inc. QALYs - patients + carers	Inc. costs	ICER - patients	ICER - patients + carers
SA8 Stopping rule – FVC<30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA9 CINRG effectiveness population (not re-based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA10 Kaplan-Meier piecewise analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SA - sensitivity analysis; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; RCPCH - Royal College of Paediatrics and Child Health; CINRG - Cooperative International Neuromuscular Research Group
** The results presented in the CS for this scenario analysis erroneously uses patient utility values from Scenario SA5 (Delphi pane/Landfeldt (2017) hybrid). Results reported in the table have been corrected to use the values from Landfeldt et al. (2020)[33]*

5.3 Critical appraisal of the company's health economic analysis

5.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying health economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[81, 82]
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 Model verification by the EAG

The EAG double-programmed the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 36, the EAG's results are very similar to those generated using the company's submitted model. During the process of rebuilding the model, the EAG identified two minor errors (see Section 5.3.5, critical appraisal point [1]). These relate to an error in how the half-cycle corrected model trace is used and an error in the calculation of discounted disease management

costs. Overall, the EAG is confident that the company's model has been implemented without significant programming error.

Table 36: Comparison of company's submitted model and EAG's double-programmed model (deterministic)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)
EAG's double-programmed model							
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's model							
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EAG - External Assessment Group; BSC - best supportive care

5.3.3 Correspondence of the model inputs and the original sources of parameter values

Where possible, the EAG checked the model input values against their original sources. The EAG was able to identify all of the cost and utility values applied in the model from the original source papers.[31, 33] The majority of other model parameters are drawn from analyses of individual patient data (IPD) from STRIDE[21] or CINRG.[28] These IPD were not made available; hence, the EAG cannot verify that these analyses have been undertaken appropriately. Model parameter values based on assumptions reflect those described in the CS.[1]

5.3.4 Adherence to NICE Reference Case

The extent to which the company's economic model adheres to the NICE Reference Case[83] is summarised in Table 37. Overall, the company's model is in line with the Reference Case – the most pertinent issues relate to the approach used to estimate the relative benefits of ataluren versus BSC within the target population. These issues are discussed in detail in Section 5.3.5.

Table 37: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The model is in line with the final NICE scope.[20] The company's model estimates health outcomes and costs for patients with nmDMD who are 2 years of age at initiation of ataluren.
Comparator(s)	As listed in the scope developed by NICE	The model includes a single comparator – BSC. This is consistent with the comparator listed in the final NICE scope (*"Established clinical management without ataluren"*).[20]
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health outcomes accrued by patients and their caregivers.
Perspective on costs	NHS and PSS	
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 70-year time (lifetime) horizon. At the end of the time horizon, virtually all (>99.98%) patients in both treatment groups have died.
Synthesis of evidence on health effects	Based on systematic review	Relative treatment effects on clinical endpoints are estimated from a comparison of the STRIDE and propensity score matched CINRG datasets,[21, 28] plus additional assumptions regarding the benefits of early treatment.[1]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	The NICE Manual for Health Technology Evaluations[83] states that the EQ-5D is the preferred measure of HRQoL for adults, but does not stipulate a preferred HRQoL instrument for measuring health in children. Health state utility values for patients were taken from Landfeldt *et al.* (2020)[33] and are based on HUI3 utility values obtained from a Delphi panel involving clinical experts (as proxy). Health state utility values for caregivers are based on values reported by Landfeldt *et al.* (2017),[31] and reflect EQ-5D-3L estimates obtained from caregivers of DMD patients.[34] Bereavement-related QALY losses are based on EQ-5D-3L estimates reported by Ara and Brazier.[78]
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Base case results are presented with and without the decision modifier (calculated from the incremental undiscounted QALYs). All sensitivity analysis results presented in the CS[1] include the decision modifier. QALY weighting is not included in the results presented in this EAG report.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Health state costs are based on values reported in Landfeldt *et al.* (2017)[31] and have been uplifted to 2021 values. The cost of ataluren is based on its current list price.[30] Results in the CS are presented with and without the PAS for ataluren.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

HTA - health technology assessment; nmDMD - nonsense mutation Duchenne muscular dystrophy; NHS - National Health Service; PSS - Personal Social Services; BSC - best supportive care; STRIDE - Strategic Targeting of Registries and International Database of Excellence; CINRG - Cooperative International Neuromuscular Research Group; HRQoL - health-related quality of life; QALY - quality-adjusted life year; HUI3 - Health Utilities Index Mark 3; EQ-5D-3L - Euroqol 5-Dimensions (3-Level)

5.3.5 Main issues identified from the EAG's critical appraisal

Box 2 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 2: Main issues identified from the critical appraisal undertaken by the EAG

(1) Model errors
(2) Issues relating to company's model structure
(3) Uncertainty surrounding the effectiveness of ataluren in the target population
(4) Issues relating to company's survival analysis
(5) Concerns regarding plausibility of model predictions
(6) Issues relating to patient and caregiver utility values
(7) Issues relating to costs
(8) Weak characterisation of uncertainty

(1) Model errors

The EAG identified two errors in the company's executable model:

(i) *Exclusion of first row of half-cycle corrected trace from cost and QALY calculations*. The company's model includes calculations which apply a half-cycle correction to estimates of health state occupancy. Expected QALY gains and undiscounted costs are then estimated from this half-cycle corrected model trace. However, whilst the half-cycle correction calculations are applied correctly, the subsequent calculations of per-cycle QALY gains and costs exclude the first row of the corrected trace (i.e., the calculations begin in the second interval rather than the first). The company's clarification response[32] (question B24) confirms that this is an error.

(ii) Use of uncorrected trace for discounted costs. The model uses the half-cycle corrected model trace to calculate undiscounted health state costs, but erroneously uses the uncorrected trace to calculate discounted health state costs. This issue was identified by the EAG after the clarification letter was submitted, but the EAG considers this to be an unequivocal error.

Both of these issues are minor and have a small impact on the ICER for ataluren. These errors are corrected in the EAG's exploratory analyses (see Section 5.4).

As part of their clarification response,[32] the company submitted an updated version of the model which included additional functionality and some error corrections. The updated model addresses issue (i), but not issue (ii). In addition, the company's updated model introduced a further minor error whereby the discount rate multiplier, rounded down to the integer value for each year, was applied for one cycle too long (the first five 3-month cycles apply a multiplier of 1.0). For these reasons, this updated model is not discussed further here.

(2) Issues relating to company's model structure

The company's economic model is structured around clinical events relating to the loss of ambulation, the decline in respiratory function beyond specified FVC thresholds and survival, assuming a linear progressive sequence of loss of function and subsequent death (see Figure 10). The probability of reaching each successive milestone at each model timepoint is determined using a partitioned survival approach using the STRIDE and propensity score matched CINRG datasets,[21, 28] together with additional assumptions relating to the benefits of early treatment with ataluren.

The company's model submitted for this appraisal features several structural differences compared with the original model developed to inform HST3.[18] In the earlier NICE appraisal of ataluren for nmDMD, the company implemented a semi-Markov model which was structured around six health states relating to ambulatory status, the presence/absence of scoliosis, the need for ventilation assistance and death. Transition probabilities for the ataluren and BSC groups were estimated using data on 6MWD from Study 007,[22] other clinical studies[11, 75] and assumptions.

The CS[1] states that the partitioned survival model submitted for this appraisal aligns with the Project HERCULES natural history model,[76] enables the use of longer-term time-to-event data from STRIDE[21] and CINRG,[28] and avoids reliance on the 6MWD. The CS also argues the current model provides *"a stronger cost-utility analysis"* compared with the model submitted to inform HST3.[18]

The EAG's clinical advisors made the following comments regarding the company's model structure:

- The linear sequence of progressive loss of ambulation and respiratory function for all patients reflected in the model is appropriate and is consistent with the disease trajectory for people with nmDMD.
- The clinical advisors agreed that it is broadly reasonable to assume that FVC<1L is equivalent to FVC<30%.
- The clinical advisors agreed that aligning the economic model for ataluren with the Project HERCULES model[76] is appropriate. They commented that the Project HERCULES model includes explicit consideration of independent transfer, and stated that this has a substantial impact on patients' perceived independence and their HRQoL. The clinical advisors also noted that maintaining upper limb function is particularly important to people with nmDMD and that this has substantial implications for their HRQoL. The advisors stated that loss of upper limb function typically occurs between the time at which patients reach FVC50% and FVC30%. These factors are not explicitly included in the model structure.
- The clinical advisors agreed that the exclusion of distinct model health states relating to cardiac failure is reasonable, as patients may die from cardiac causes in any state. For many patients, this usually occurs after the age of 10 years and more frequently after the age of 15 years.

- The clinical advisors commented that the onset of scoliosis has important implications for costs and patient HRQoL, particularly for those who lose upper limb function following scoliosis surgery. This factor is not explicitly included in the model health states.
- The clinical advisors disagreed with the company's assumptions that all patients reaching FVC<50% will require night-time ventilation and that all patients reaching FVC<30% will require full-time ventilation. One of the advisors noted that whilst these assumptions are consistent with recommendations set out in the 2018 DMD Care Considerations Working Group guidance,[9] they do not reflect UK clinical practice, with many patients only requiring ventilation once their respiratory function has passed beyond these thresholds. [redacted]

Overall, the EAG considers the structure of the company's model to be generally appropriate, provided that the health utility values applied to the broad health states adequately reflect other factors which have not explicitly been included in those states, in particular, the impact of transfer, maintenance/loss of upper limb function and impacts of scoliosis and its treatment. It appears that the proxy utility values reported by Landfeldt *et al.* (2020)[33] do not fully reflect all of these factors, as the patients were specified not to have scoliosis or to require ventilatory support for survival. Whilst the company's base case analysis assumes treatment-dependent utility values for patients (see Table 29), [redacted] The EAG's clinical advisors also expressed uncertainty around the appropriateness of this assumption, noting that it might potentially be plausible in non-ambulatory patients but perhaps less so in those who are still ambulatory. This issue is discussed further as part of critical appraisal point [6].

With respect to the company's decision to use a partitioned survival approach rather than the semi-Markov approach used in HST3,[18] the EAG notes the following:

- The use of a partitioned survival model may be reasonable, provided that the data included in the survival modelling are sufficient to provide plausible long-term projections of the time to reach each disease milestone. The Kaplan-Meier plots shown in Figure 11, Figure 12, Figure 14, Figure 15 and Figure 17 indicate that the data from STRIDE[21] are subject to greater levels of censoring than CINRG,[28] insufficient data were available to model age at FVC<30% in patients receiving ataluren, [redacted]. As such,

modelled gains for ataluren in terms of age at FVC<30% and OS are entirely reliant on clinical assumptions rather than empirical evidence.

- It appears that the company had access to the IPD from both STRIDE[21] and CINRG,[28] as these were used in the propensity score matching used in the ITC (see Section 4.3). Therefore, it may have been possible to use a semi-Markov approach to estimate survival curves for each milestone, conditional on the time since reaching the previous milestone. This approach could have avoided the assumption that time to death is exactly 3 years after reaching FVC<30% for all patients and could have allowed for the incorporation of other external evidence beyond that available from STRIDE and CINRG. The impact of using an alternative structural approach and/or other external data on the cost-effectiveness of ataluren is unclear.

(3) Uncertainty surrounding the effectiveness of ataluren in the target population

The EAG believes that there is considerable uncertainty surrounding the effectiveness of ataluren for the treatment of nmDMD. Several factors contribute to this uncertainty, including: (a) limitations of the data and methods used in the company's ITCs; (b) the exclusion of data from the MAA from the economic analysis; (c) uncertainty surrounding the impact of the company's proposed stopping rule on health outcomes; (d) the absence of evidence to inform the magnitude of benefit associated with early treatment with ataluren, and (e) the strong assumptions which underpin the company's approach for modelling early treatment benefits. Each of these issues are discussed below.

(a) Uncertainty surrounding propensity score matched ITC of STRIDE versus CINRG

The company's propensity score matched ITC of STRIDE[21] and CINRG[28] suggests that ataluren may confer benefits in terms of delays to loss of ambulation and some later respiratory-related endpoints. As discussed in Section 4.3, the EAG considers the treatment effect estimates to be uncertain due to limitations in the data available for respiratory endpoints occurring at the later stages of disease progression, the unanchored nature of the ITC and the potential for imbalances in unmeasured confounders not included in the matching process. The uncertainty around the results of the company's ITC inevitably leads to uncertainty around the cost-effectiveness of ataluren.

(b) Data from the MAA do not inform the company's model

As described in Section 4.3.2, the company has used the data collected in the MAA to provide some, albeit limited, evidence in support of the clinical effectiveness of ataluren. However, these data have not been used to inform the company's economic model. Whilst the EAG considers the company's decision to use the comparison of STRIDE[21] and CINRG[28] in preference to the other ITCs discussed in Section 4.3 to be reasonable, it was likely that at the time of HST3,[18] the Appraisal Committee's intention was that the data collected in the MAA would inform the economic analysis within the re-

evaluation of ataluren in this appraisal. This has not happened. Given the company's difficulty in demonstrating treatment effects for ataluren from the MAA/NorthStar ITC, it is reasonable to speculate that including these data in an economic model would result in less favourable cost-effectiveness estimates for ataluren compared with those presented in the CS.[1] This would however have required a different model structure, based on the NSAA.

(c) Uncertainty around the impact of the company's stopping rule on health outcomes

The company's model includes a stopping rule which applies to all patients once they reach FVC<50%. The company's clarification response[32] (question A7) states that [redacted] patients lost ambulation in STRIDE[21] and that up to [redacted] ([redacted]) of these continued to receive ataluren for some period of time beyond this milestone. The company's response also states that of these [redacted] non-ambulant patients, only [redacted] reached FVC<50% and [redacted] reached FVC<30%. It is unclear how long these patients would (or did) continue to receive ataluren beyond the loss of ambulation, and as such, it is unclear whether the company's modelled health outcomes for ataluren (based on STRIDE[21] and additional early treatment benefit assumptions) reflect the level of benefit that would be observed if the company's proposed FVC<50% treatment stopping rule was applied to all patients in clinical practice.

(d) Additional assumptions regarding the benefits of early treatment with ataluren

The company's clarification response[32] (question A6) states that at the January 2021 data-cut, only [redacted] of 269 patients ([redacted]) in STRIDE[21] had received ataluren under the age of 5 years. In contrast, the company's model assumes that all patients will begin treatment at the age of 2 years. As described in Section 5.2.2, the company's model assumes that the earlier use of ataluren will shift the fitted parametric survival models for each milestone to the right. These assumptions of early treatment benefit appear to have been obtained from an unpublished global Delphi panel, with some further consideration by two UK clinical experts (see clarification response,[32] questions B17 and B18 and Appendix 1).

[redacted]

[redacted]

(e) Company's approach to modelling relative treatment benefit by shifting the survival curves

The EAG has further concerns regarding the company's approach used to model delays in reaching disease milestones. During the clarification process, the EAG asked the company to explain why they chose to model relative treatment benefits by shifting the survival curves to the right, rather than using other more conventional statistical metrics such as HRs or acceleration factors (see clarification response,[32] question B1). The company's response states that the choice of methodology was selected *"based on the nature of the input from the clinicians"* and that *"With the experts being a panel of clinicians, not statisticians or data analysts, we assessed that a specific number of years shift in survival would be close to what they experience and observe in daily clinical practice."* The EAG believes that the company's approach might be considered pragmatic, but unconventional. The EAG also notes that modelling treatment effects by shifting the whole survival curve relies on two strong assumptions: (i) that delaying events further along in the sequence of disease progression will not be impacted on by competing risks of other events (e.g., DMD-related death); (ii) that the assumed amount of benefit of early treatment will be accrued by every patient receiving ataluren. It is unlikely that either of these assumptions hold. The magnitude of any bias resulting from this approach is unclear.

(4) Issues relating to company's survival analysis

The EAG has several concerns regarding the parametric survival modelling presented in the CS.[1] These concerns are discussed below in terms of the general considerations around model fitting and selection set out in NICE DSU TSD 14.[84]

(a) Use of independent models fitted to data for each treatment group

The company's survival modelling involved fitting independent survival models to the time-to-event data from the STRIDE and the propensity score matched CINRG datasets.[21, 28] The EAG believes that this is reasonable, although no exploration of the appropriateness of the PH assumption is presented in the CS.[1]

(b) Range of models assessed

The company fitted six standard parametric models. Other more flexible survival distributions, e.g., RCS models, were not considered. All of the company's survival models adopt a piecewise approach whereby prior to some cut-point the risk of experiencing the event of interest is assumed to be zero (except for general population mortality risks), and the risk of the event of interest is subsequently modelled using the hazard predicted by the parametric survival model. Different cut-points are used in each group (at age 3.5 years in the BSC groups and 5 years in the ataluren group). The CS[1] does not

provide a clear justification for the choice of cut-points and no consideration is given to the use of alternative time-points at which these could be applied.

The company's clarification response[32] (question B4) states that an additional analysis was undertaken applying a cut-point of 3.5 years in both datasets. The company's response states that the results of this analysis were generally consistent with the base case analysis with only slight differences in the rank ordering of the AIC and BIC statistics. The results of these sensitivity analyses are not presented in the CS[1] or the clarification response. The company's response further comments that RCS models could have been used, but that the additional complexity and limited patient numbers at later follow-up timepoints did not warrant pursuing this approach. The EAG believes that it may have been valuable to present these analyses as they would provide greater flexibility in capturing the shape of the hazard function over time.

(c) Statistical and visual goodness-of-fit

The EAG notes the following observations regarding the fitted models for each time-to-event endpoint:

(i) *Age at loss of ambulation* (see Table 26, Figure 11 and Figure 12). The log-logistic model has the lowest AIC and BIC for both groups; the company selected this model for inclusion in the base case analysis. With respect to the CINRG data,[28] the Weibull model has similar AIC and BIC values. With respect to the STRIDE data,[21] the log-normal model has similar AIC and BIC values. The log-logistic model provides a reasonable visual fit to the CINRG data, but a comparatively worse visual fit to the STRIDE data (in particular, the risk of loss of ambulation may be under-predicted in the tail, although few events have been observed in patients aged >15 years).

(ii) *Age at FVC<50%* (see Table 27, Figure 14 and Figure 15). The log-logistic model has the lowest AIC and BIC values for both groups; the company selected this model for the base case analysis. With respect to the CINRG data,[28] none of the other models have similar AIC or BIC values. With respect to the STRIDE data,[21] the log-normal, Weibull and generalised gamma models have similar AIC values and the log-normal and Weibull models have similar BIC values. The models for both groups appear to over-predict age at FVC<50% in the tail of the distributions.

(iii) *Age at FVC<30%* (see Table 28 and Figure 17). The log-normal model has the lowest AIC and BIC values; the company selected this model for the base case analysis. The log-logistic and generalised gamma models have similar AIC values, and the log-logistic model has a similar BIC value. The log-normal model provides a reasonably good visual representation of the available data.

(d) Consideration of nature of hazards

The CS[1] does not present plots of the empirical and/or modelled hazard functions for any of the time-to-event endpoints; these plots can be useful for assessing whether the nature of the hazards for the selected models are consistent with the empirical hazards in the observed data.

As part of their clarification response[32] (question B2), the company provided hazard plots for all three endpoints included in the survival modelling (age at loss of ambulation, age at FVC<50% and age at FVC<30%). These plots are reproduced in Figure 24, Figure 25 and **Figure 26**, respectively.

Figure 24: Hazard functions - age at loss of ambulation (left panel - STRIDE; right panel - CINRG) (reproduced from clarification response, question B2)

Figure 25: Hazard functions - age at FVC<50% (left panel - STRIDE; right panel - CINRG) (reproduced from clarification response, question B2)

Figure 26: Hazard functions - age at FVC<30% (left panel - STRIDE; right panel - CINRG) (reproduced from clarification response, question B2)

With respect to these hazard plots, the EAG notes the following observations:

- *All endpoints.* It is unclear what method was used to generate the smoothed hazard functions, or what bandwidth has been used for smoothing. This may have masked potential turning points in the empirical hazards.
- *Age at loss of ambulation.* In both groups, the empirical hazard increases then decreases, which is consistent with the company's selected log-logistic model. The log-logistic model provides a good representation of the empirical hazard observed in the CINRG dataset.[28] Conversely, all of the candidate models appear to overestimate the hazard observed in STRIDE[21] after 9 months or earlier.
- *Age at FVC<50%.* In both groups, the empirical hazard increases over time. The company's selected log-logistic model is inconsistent with this pattern. None of the fitted parametric models in either group provide a good representation of the observed hazard functions, with all models underestimating the hazards observed in CINRG and STRIDE.[21, 28]
- *Age at FVC<30%.* The empirical hazard function appears to increase linearly after 4 months. None of the candidate models reflect this pattern.

As discussed above, more flexible parametric survival models may have provided a better representation of the underlying hazards in the data for each milestone.

(e) Consideration of long-term clinical plausibility

According to the CS,[1] the parametric survival models used in the base case analysis *"were selected based on both goodness of fit statistics and the plausibility of the long-term extrapolation"* (CS, Table

D-4). However, for all time-to-event endpoints, the company has selected the parametric models which have the lowest AIC and BIC values. The CS does not provide any further information regarding how judgements regarding clinical plausibility were used to inform model selection.

The company's clarification response[32] (question B19) suggests that considerations of clinical plausibility were limited to judgements made by the company, for example, the exclusion of the models which predicted a plateau towards the end of the observed follow-up period. The EAG notes that these types of considerations may be used to exclude implausible models, but they do not help to assess whether the selected model is clinically plausible. [redacted]

The clarification response does not provide any further information regarding how clinical input was used to inform model selection. The EAG's clinical advisors views regarding the plausibility of the model-predicted age at which each milestone is reached, including the additional assumptions regarding early treatment benefits, are described later under critical appraisal point [5].

(f) Sensitivity analysis

No sensitivity analysis is presented for any other parametric model using the selected cut-points, although as described above, one additional analysis using a cut-point of 3.5 years in both treatment groups is described in the company's clarification response[32] (question B4). The CS[1] does however report scenario analyses using models without cut-points and using a hybrid Kaplan-Meier parametric model approach; neither of these alternative models substantially impact on the estimated QALY gains for patients or the ICER (see Table 35).

EAG's conclusions

Overall, the EAG believes that the company's survival analysis is limited by the range of models assessed, the poor fit of some of the selected models (particularly for the ataluren group) and the absence of clinical input in the model selection process.

(5) Concerns regarding plausibility of model predictions

As discussed in Section 5.2, modelled predictions of delays to DMD milestones are a function of the fitted survival models, together with the assumptions regarding the benefits of early treatment with ataluren. The CS[1] provides very little discussion around the plausibility of the model-predicted probabilities of reaching each endpoint for each of the treatment groups (including OS). The EAG asked their clinical advisors for comments on these model predictions; their views are summarised below.

Age at loss of ambulation (propensity score matched CINRG versus STRIDE plus [redacted] year curve shift)
Both of the EAG's clinical advisors agreed that it was reasonable to assume that earlier treatment with ataluren would lead to better outcomes compared with later treatment. The first clinical advisor commented that the [redacted] year early treatment benefit assumption was *"reasonable"* and *"proportionate to what is seen in clinical practice."* They did however express some uncertainty around the magnitude of this additional benefit and suggested that a plausible range might be at least [redacted] and possibly less than [redacted]. However, they were surprised by the magnitude of the difference in the model-predicted median delay in loss of ambulation between the ataluren and BSC groups ([redacted] years) and commented that this seemed *"too optimistic*", even with earlier treatment initiation. The second clinical advisor commented that the tail of model-predicted age at loss of ambulation curve from CINRG[28] (see Figure 13, solid red line) was likely to drop off more rapidly, as not many 20-30 year olds with nmDMD are still ambulant. They also commented that the difference between the ataluren and BSC groups, excluding the early benefit assumptions, seemed to be more than what is seen in clinical practice. They also commented that there is a lack of evidence to support the [redacted] year additional early benefit assumption, but noted that earlier treatment may make a difference to outcomes as it would allow for some dystrophin to be restored before the muscle has become too fibrotic. Despite this uncertainty, they stated that the assumed value of [redacted] years *"may be reasonable."*

Age at FVC<50% (propensity score matched CINRG versus STRIDE plus [redacted] year curve shift)
The first clinical advisor commented that it is appropriate to assume that delaying the age at loss of ambulation would also lead to a further delay in loss of respiratory function. They agreed that, in principle, some additional delay in the loss of respiratory function might be plausible, for example, delaying the loss of ambulation will reduce the potential risk of scoliosis which may preserve respiratory function for longer. Again, they expressed uncertainty around this value and suggested potentially plausible values of between [redacted] and [redacted] years. They commented that the modelled delay in the age at FVC<50% for ataluren versus BSC of [redacted] years (Table 34) appeared *"optimistic."* The second clinical advisor commented that the assumed [redacted] year additional benefit appears to be *"optimistic"* and *"potentially excessive."* They stated that they *"would like to hope it might be reasonable"* but noted that there was no evidence to substantiate it.

Age at FVC<30% and OS (propensity score matched CINRG versus same model with [redacted] year curve shift, and assumption that time to death from FVC<30% is 3 years in both groups)
The first clinical advisor stated that it is plausible that there would be an OS gain for ataluren over BSC, but that there is no evidence to support this. They also commented that BSC has improved over time,[2, 85] which may affect the reliability of any cross-study comparison. They did not believe that the company's assumed [redacted] year gain in OS was plausible and instead suggested that the OS gain might

plausibly reflect only the delays in reaching earlier milestones. The second clinical advisor commented that the [redacted] year assumed gain is more than might be expected and *"perhaps a bit optimistic."* They also commented that survival is longer than 3 years once patients reach FVC<30% if they have been established on non-invasive ventilation (NIV).

The company's clarification response[32] (question B20) highlights that [redacted] and no other data on OS are presented in the CS.[1] Given the absence of evidence, and the EAG's clinical advisors' concerns detailed above, the EAG believes that the company's assumptions, including the assumed OS gain for ataluren, should be considered highly uncertain and potentially optimistic.

(6) Issues relating to patient and caregiver utility values

The EAG has concerns regarding the utility values used in the economic model as well as the approach used to estimate incremental QALY gains accrued by caregivers.

(a) Assumption of treatment-specific utility values

The company's model applies treatment-specific patient utility values from a Delphi study of clinical experts acting as proxy for patients with DMD (Landfeldt *et al.* (2020)[33]). This paper suggests that for patients in each same health state, those receiving ataluren will experience a higher level of HRQoL compared to those receiving BSC (utility for ambulant state: ataluren = 0.93, BSC = 0.62; utility for non-ambulant states: ataluren = 0.32, BSC = 0.16). The company's scenario analyses using alternative sources of health utility values (see Table 35) also make this same assumption of improved HRQoL for ataluren in each state. Each of these analyses also assume that treatment-dependent patient utility values persist even after the patient has discontinued ataluren. The EAG considers that these assumptions are likely to be optimistic. The EAG also notes that in HST3, the Appraisal Committee was not convinced that different utility values for ataluren and BSC should be applied after loss of walking.[18]

The EAG's clinical experts expressed uncertainty around whether patient utility values for each health state would be treatment-dependent, particularly for patients who are still ambulant. [redacted] As such, the EAG considers that whilst it is plausible that patients receiving ataluren could experience improved HRQoL compared to BSC, at least in some of the model health

states, this aspect of the analysis should be considered highly uncertain. The CS[1] does not present any empirical evidence of HRQoL measured in DMD patients with/without ataluren to support the assumption of treatment-dependent utility values.

The EAG also notes that the company's review of HRQoL studies (described in CS,[1] Section 10 and CS Appendix 5[43]) contains very little discussion around why other studies reporting patient utility estimates from the literature have not been considered in the economic model. Whilst several utility studies were identified, only one of these was available in full text form in English and reported health utility values from patients with valued states which broadly correspond to the health states included in the economic model (Crossnohere *et al.*[86]). This study reports utility values for early and late ambulatory and early and late non-ambulatory DMD states based on an international cross-sectional sample of adults with DMD and caregivers' reported patient health status using self- or proxy-reported EQ-5D-3L (n=263). The values reported in the paper do not differentiate between patients who had received ataluren (if any did) or BSC; hence, the values presented are not treatment-dependent. The EAG believes that this study should at least have been considered in the company's scenario analyses.

(b) Age-adjustment of utility values

The company's model does not include the adjustment of utility values for increasing patient age. In response to a request for clarification from the EAG (see clarification response,[32] question B10) the company stated that *"applying age-adjustments to utilities for children was not considered appropriate."* The company's response also argues that *"the gradual decline in average QoL associated with aging is overshadowed by the symptoms of the condition."* The EAG disagrees with the company's view, as the model predicts that the majority of patients survive into adulthood (see Figure 19) and that it would be appropriate to age-adjust utilities during this phase of the modelled time horizon.

(c) Use of absolute caregiver QALY approach

The company's model includes QALYs accrued by both patients and their caregivers. QALY gains for each caregiver are estimated using an "absolute" caregiver QALY approach, which involves multiplying the probability that a patient resides in each health state in each cycle by the caregiver utility value associated with the nmDMD patient being in that state. This approach therefore links the QALYs accrued by caregivers to the patient's survival status and stops counting caregiver QALYs when the patient dies. As such, the company's approach implicitly makes one of three assumptions: (i) when the patient dies, their caregivers also die; (ii) when the patient dies, their caregivers survive but with zero utility, or (iii) QALY gains accrued by caregivers of surviving DMD patients are valuable to society and relevant for inclusion in the economic analysis, but QALY gains accrued by bereaved caregivers are not. The CS[1] does not discuss any of these assumptions. Irrespective of which interpretation is intended by the company, the EAG does not consider that any of these assumptions are appropriate. Given the inclusion of these assumptions, it is further unclear to whom the caregiver bereavement-

related QALY losses are intended to apply (because caregivers might be implicitly assumed to have also died). The approach used to capture HRQoL effects on caregivers in the company's model has important implications for the cost-effectiveness of ataluren and the decision modifier (as this is calculated from the undiscounted QALYs gained by both patients and caregivers).

The EAG notes that with one exception, all previous HSTs which have included caregiver QALYs, including the previous model of ataluren used to inform HST3,[18] have adopted a "caregiver disutility" approach (see Table 38). This alternative approach involves assigning disutilities for caregivers to each patient health state. The one exception is HST7, which included a caregiver bereavement-related QALY loss.[79] The caregiver disutility approach is also subject to some problematic assumptions, for example, it typically assumes that caregiver HRQoL rebounds to the level of the general population after the patient dies. This unlikely to be reasonable, as it can lead to situations which imply that the premature death of the patient is preferable to extending patient survival in a state associated with poor HRQoL. This problem can be addressed to some degree by the inclusion of some assumption regarding the impact of bereavement on caregiver HRQoL. These issues were discussed in detail during the Appraisal Committee meetings for NICE Technology Appraisal 755 (TA755; risdiplam for treating spinal muscular atrophy [SMA]) and the absolute caregiver QALY approach was not accepted by the Appraisal Committee.[87]

Table 38: Approach used to estimate caregiver QALYs in all completed NICE HST appraisals

Appraisal	Title	Approach used to estimate caregiver QALY impacts
HST1	Eculizumab for treating atypical haemolytic uraemic syndrome	None included
HST2	Elosulfase alfa for treating mucopolysaccharidosis type IVa	Caregiver disutility approach
HST3	Ataluren for treating nmDMD	Caregiver disutility approach
HST4	Migalastat for treating Fabry disease	None included
HST5	Eliglustat for treating type 1 Gaucher disease	None included
HST6	Asfotase alfa for treating paediatric-onset hypophosphatasia	None included
HST7	Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency	Lump-sum QALY loss associated with carer bereavement for premature death of child (scenario analysis only)
HST8	Burosumab for treating X-linked hypophosphataemia in children and young people	Caregiver disutility approach
HST9	Inotersen for treating hereditary transthyretinrelated amyloidosis	Caregiver disutility approach
HST10	Patisiran for treating hereditary transthyretin amyloidosis	Caregiver disutility approach

Appraisal	Title	Approach used to estimate caregiver QALY impacts
HST11	Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations	Caregiver disutility approach
HST12	Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2	Caregiver and sibling disutility approach
HST13	Volanesorsen for treating familial chylomicronaemia syndrome	Caregiver disutility approach
HST14	Metreleptin for treating lipodystrophy	Caregiver disutility approach
HST15	Onasemnogene abeparvovec for treating spinal muscular atrophy	Caregiver disutility approach (sensitivity analysis only)
HST16	Givosiran for treating acute hepatic porphyria	Caregiver disutility approach
HST17	Odevixibat for treating progressive familial intrahepatic cholestasis	Caregiver disutility approach
HST18	Atidarsagene autotemcel for treating metachromatic leukodystrophy	Caregiver disutility approach

HST - Highly Specialised Technology; QALY - quality-adjusted life year

As part of the clarification process, the EAG asked the company to clarify whether they had intended to assume that caregivers die or survive with zero utility when the patient with nmDMD dies, and to explain why the caregiver disutility approach had not been used in the model (see clarification response,[32] question B7). The company's response states that "*The interpretation is not that caregivers die or survive with 0 utility after the patient dies. The model aims to evaluate the total impact on costs and QoL associated with the life of the patient, as opposed to the caregivers, i.e. caregiver QALYs stop being accrued after a patient dies. This creates a situation in which there is a net benefit on caregiver QoL during the time in which the patient is alive, and overall caregiver QoL is not increased due to a patient dying."* The company's response also discusses the problems with the caregiver disutility approach described above.

The EAG believes that the company has misunderstood the assumptions underpinning the absolute caregiver QALY approach applied in their model and that despite its problems, the caregiver disutility approach, with some consideration of the impact of caregiver bereavement, is more appropriate for informing decision-making.

(7) Issues relating to costs

The EAG believes that the modelled drug acquisition costs are subject to two problems: (a) the application of a fixed drug cost based on a constant dose in every cycle and (b) limitations in the data and assumptions used to model TTD.

(a) Application of fixed dosing costs

The company's model applies the cost of [redacted] sachets of 125mg ataluren to ambulatory patients and [redacted] sachets of 125mg ataluren to non-ambulatory patients in every cycle, based on the mean weight of the population of STRIDE at the 2021 data-cut.[21] This approach is problematic for three reasons. Firstly, it ignores the distribution of patient weight across the ataluren-treated population. Patients who weigh less than the mean value may require fewer sachets, whilst those who weigh more than the mean may require more sachets (see ataluren dosing schedule in Table 4). Ignoring variability in patient weight at any given age across the target population may bias the costs in either direction. Secondly, applying the costs associated with the mean weight of the ambulatory/non-ambulatory STRIDE cohort will lead to biased estimates of cost if the distribution of weight changes as the surviving treated target population gets older. The use of a constant mean weight will produce a bias in favour of ataluren if, as the model suggests, treatment extends OS, as there will be an increase in older adult survivors who would likely weigh more than younger children. Thirdly, as discussed in the company's clarification response[32] (question B12), applying the mean patient weight in every cycle will overestimate the costs of ataluren at earlier ages where the discount rate multiplier is higher.

Owing to these problems, the EAG prefers the approach applied in the company's scenario analysis (see Table 35, Scenario SA2), whereby patient weight at each age is instead based on median weight estimates from the RCPCH, together with an estimate of the relative difference in median weight in DMD patients (from STRIDE[21]) compared to that in healthy children (relative reduction=[redacted]). However, this is still not ideal, as variability in weight across patients at each age is not reflected in the calculations.

(b) Approach to modelling time to discontinuation (TTD)

The company's model applies an estimate of the per-cycle treatment discontinuation rate from STRIDE[21] (probability=[redacted]). The same probability is applied in every cycle until the time on treatment function coincides with age at FVC<50% function (shown by the solid and dashed blue lines in Figure 20). The EAG notes the following issues with this approach:

(i) It is unclear from the CS[1] whether this discontinuation probability reflects "natural" discontinuation, or whether some patients discontinued because they lost ambulation or reached some other respiratory function-related milestone. If competing risks are not properly accounted for in the analysis, the risk of discontinuation may be overestimated.

(ii) The EAG's clinical advisors commented that the modelled discontinuation rate appears implausibly high and noted that whilst AEs can occur at any time, patients generally wish to remain on treatment for as long as possible.

(iii) It is unclear whether it is reasonable to apply a constant rate in every model cycle. The CS[1] does not present a Kaplan-Meier plot, a hazard function or any clinical input to support the assumption that TTD follows an exponential distribution.

(iv) The use of a partitioned survival model necessarily means that predicted health outcomes are not structurally dependent on whether the patient is still receiving treatment. As such, any assumptions about discontinuation have no effect on model-predicted QALY gains. This is illustrated in Table 39. The EAG would have preferred that the company implement a model structure which explicitly links the probability of being on treatment to the benefits derived from that treatment. This might have been possible using a state transition approach.

Table 39: QALY gains under alternative assumptions regarding time on treatment

Ataluren time on treatment scenario	Ataluren discounted QALYs (patients)	Ataluren discounted costs
Company's base case (discontinuation probability=)		
Base case value doubled (discontinuation probability=)		
All patients discontinue after first cycle		

QALY - quality-adjusted life year

During the clarification round, the EAG asked the company to provide a Kaplan-Meier plot for TTD from STRIDE[21] and to comment on the plausibility of applying a constant risk of discontinuation in each cycle (see clarification response,[32] question B6). The Kaplan-Meier plot provided by the company is reproduced in

Figure 27. The company's response states that the discontinuations in STRIDE included a number of reasons, including: AEs; family/participant request; perceived lack of response; clinician's decision; loss of ambulation and unknown reasons. In contrast to the views of the EAG's clinical advisors, the company believes that the discontinuation rate applied in the model is low.

Figure 27: Kaplan-Meier plot for time to treatment discontinuation in STRIDE (reproduced from clarification response, question B6)

The EAG notes the following concerns:

- Discontinuation events in STRIDE[21] included milestone-related events (loss of ambulation, "perceived lack of response" and potentially other reasons listed above); hence, there is some potential for double-counting, as discontinuations for these reasons are reflected in the modelled stopping rule.
- No information is provided regarding the empirical hazard over time and parametric survival models have not been fitted to the data. Therefore, the justification for assuming constant discontinuation rate remains unclear.
- It is unclear whether the pattern of discontinuation observed in STRIDE would be observed in a cohort of patients who start treatment with ataluren at the age of 2 years.

(8) Weak characterisation of uncertainty

The EAG has several concerns regarding the company's uncertainty analysis:

- For most of the parameters included in the company's PSA, standard errors (SEs) have been arbitrarily assumed to be 20% of the mean value. For several parameters, SEs are reported in the publications used as evidence sources, but these have not been used.
- The shifted gamma distributions assigned to patient and caregiver utility values permit samples which are substantially lower than the lower bound of the HUI3 and the EQ-5D. For example, the distribution applied for patient utility in the ambulatory state includes samples which are as low as -1.97, whereas the distribution applied for caregiver utility in the ambulatory state includes samples which are as low as -0.85. The company's clarification response[32] (question B11) comments that these implausible samples are rare.

- The company's scenario analyses (shown in Table 35) are limited. No scenario analyses are presented for several key parameters/assumptions, including those relating to: (i) early treatment benefits; (ii) treatment-independent utility values; (iii) alternative parametric survival distributions or (iv) the rate of ataluren discontinuation.

Overall, the EAG believes that the company's analyses inadequately reflect the uncertainty surrounding the cost-effectiveness of ataluren.

5.4 Exploratory analyses undertaken by the EAG

5.4.1 EAG exploratory analysis - methods

EAG preferred model

The EAG's preferred version of the model is comprised of four sets of amendments to the company's base case analysis; these are detailed below. All exploratory analyses (EAs) were undertaken using the deterministic version of the model. All analyses were implemented by one modeller and checked by a second modeller.

EA1: Correction of errors

The EAG applied two corrections to the company's model:

- EA1a: The QALY and cost calculations were amended to include the first half-cycle corrected interval of the model trace.
- EA1b: The formulae used to calculate discounted disease management costs were amended to reflect the half-cycle corrected model trace.

All subsequent exploratory analyses undertaken by the EAG were applied using the corrected version of the model.

EA2: Use of caregiver disutility approach

In line with the majority of previous NICE HSTs, the model was amended to adopt a caregiver disutility approach. This was based on the following assumptions and data sources:

- Patients have two caregivers (one female and one male)
- Caregivers are assumed to be 29 years old at the time of childbirth; hence, they enter the model at age 31 (patient age = 2 years)
- In line with the company's model, caregiver utility values were based on Landfeldt *et al.* (2017)[31]
- EQ-5D-3L values for the UK general population were taken from Hernandez Alava *et al.*[88]
- The same caregiver disutility values are applied to each treatment group.

The resulting estimated disutility values applied in the model are summarised in Table 40.

Table 40: Disutility values applied in EAG's exploratory analyses

Model health state	Caregiver utility values (Landfeldt *et al.*[33])	Caregiver disutility values
General population*	0.91	-
Ambulant	0.84	-0.07
Non-ambulant, FVC>50%	0.84	-0.08
Non-ambulant, FVC<50%	0.78	-0.14
Non-ambulant, FVC<30%	0.77	-0.14

BSC - best supportive care; FVC - forced expiratory volume
** Estimated from Hernandez Alava et al.[88]*

The bereavement-related QALY loss was retained in the model, but the age-specific EQ-5D-3L utility estimates from Ara and Brazier[78] used to calculate it were replaced with those reported by Hernandez Alava *et al.*[88]

EA3: Inclusion of age-adjusted utility values

The model was amended to include age-adjusted utility values. This was implemented by calculating adjustment weights which were applied to the patient and caregiver QALY gains in each model cycle. The weights were calculated using a multiplicative approach based on values reported by Hernandez Alava *et al.*[88] For nmDMD patients, no weighting was applied until they reach 16 years of age. For caregivers, weights were estimated based on their age at entry into the model (initial age = 31 years).

EA4: Use of age-specific patient weight estimates to calculate ataluren acquisition costs

The model was amended to use estimates of median patient weight by age from the RCPCH,[89] together with an estimate of the relative reduction in weight in nmDMD patients using data from STRIDE.[21] This analysis was implemented using pre-existing settings in the company's model (Scenario SA2 in Table 35).

EA5: EAG-preferred model

The EAG's preferred model includes EA1-4. This analysis should not be interpreted as the EAG's revised base case analysis, but rather as a more appropriate starting point for considering the impact of uncertainties in the clinical evidence on the cost-effectiveness of ataluren.

Additional sensitivity analyses

As detailed in Section 5.3.5, the EAG believes that there is considerable uncertainty surrounding several aspects of the company's model, including: the use of treatment-specific utility values; the magnitude of benefit associated with early treatment with ataluren; the assumed OS gain for ataluren; the preferred parametric models applied to each health state; the most appropriate discontinuation rule and the rate

of ataluren discontinuation. The EAG undertook six additional sets of sensitivity analyses (ASAs) using the EAG-preferred version of the company's model; these are described below.

ASA1: Alternative patient utility values

Three sensitivity analyses were undertaken to explore uncertainty around patient utility values.

ASA1a: Use of treatment-independent patient utility value in ambulatory state

Within this analysis, the patient utility value for the ambulant state in the ataluren group was set equal to the value for the BSC group. This analysis retains the treatment-dependent utility values in the non-ambulant health states.

ASA1b: Assume BSC patient utility values after ataluren discontinuation

The model was amended to apply patient utility values for the BSC group to patients who have discontinued ataluren. This analysis therefore assumes that any additional HRQoL benefits are lost at the point of discontinuation. The company's model structure does not fully track how many patients in each of the health states are on/off treatment. For simplicity, the overall discontinuation probability was applied to all health states within this analysis.

ASA1c: Use of treatment-independent patient utility values

The model was amended to use treatment-independent patient utility values reported by Crossnohere *et al.;*[86] this study was identified by the company's SLR of HRQoL studies, but was not considered further in the CS.[1] The utility values reported in the study and their assumed correspondence to the model health states are summarised in Table 41.

Table 41: Patient utility values from Crossnohere et *al.* applied in EAG ASA1c

Patient utility values (Crossnohere *et al.*[86])			
Model health state	**BSC**	**Ataluren+BSC**	**Health state valued**
Ambulant	0.49		Late ambulatory
Non-ambulant, FVC>50%	0.31		Early non-ambulatory
Non-ambulant, FVC<50%	0.26		Late non-ambulatory
Non-ambulant, FVC<30%	0.26		Late non-ambulatory

BSC - best supportive care; FVC - forced expiratory volume

ASA2: Alternative assumptions regarding early treatment benefits

Two alternative scenarios were undertaken to explore uncertainty around the company's early treatment benefit assumptions. In the first analysis (ASA2a), the assumed magnitude of the additional benefits of early treatment were halved. For OS, only the [redacted] year early benefit assumption was halved, resulting in an incremental OS gain of [redacted] years. In the second analysis (ASA2b), all early treatment benefit assumptions were removed from the model (the company's assumed [redacted] year OS advantage was retained in the analysis).

ASA3: Alternative assumptions regarding survival

Two sensitivity analyses were undertaken around the company's assumed OS gains for ataluren. In the first analysis (ASA3a), the assumed survival gain for ataluren versus BSC was assumed to be equal to the mean delay in the age at loss of ambulation ([redacted] years). In the second analysis (ASA3b), the OS gain was removed from the model. In both analyses, all other early benefit assumptions were retained.

ASA4: Use of Weibull model for all time-to-event endpoints

In this analysis, the Weibull model was selected for all three time-to-event endpoints (age at loss of ambulation, FVC<50% and FVC<30%) as this model was considered to be potentially plausible by the company for some endpoints. The use of this model provides a generally less optimistic extrapolation in both treatment groups.

ASA5: Slower rate of discontinuation

In this analysis, the rate of discontinuation assumed in the company's base case was arbitrarily reduced by 50%.

ASA6: Alternative discontinuation rules

In this analysis, the model was amended to apply discontinuation rules for ataluren at: (a) 6 months after loss of ambulation and (b) progression to FVC<30%. The EAG notes that the results of this analysis should be interpreted with caution, as clinical outcomes are not structurally linked to discontinuation; the extent to which applying earlier or later discontinuation rules would impact on clinical outcomes is unclear.

5.4.2 EAG exploratory analysis - results

Table 42 presents the results of the EAG's preferred analysis. The correction of errors increases the company's deterministic ICER (including caregiver QALYs) for ataluren plus BSC versus BSC alone from [redacted] to [redacted] per QALY gained (EA1). The EAG's exploratory analysis which applies caregiver disutilities rather than absolute caregiver QALYs substantially increases the ICER to [redacted] per QALY gained (EA2). The other two exploratory analyses (the inclusion of age-adjusted utility values and use of RCPCH/STRIDE data to model patient weight – EA3 and EA4) also increase the ICER for ataluren as they reduce incremental QALY gains and increase drug costs. The EAG's preferred model, which combines all four amendments, results in a deterministic ICER for ataluren of [redacted] per QALY gained (EA5). This is substantially higher than the company's base case ICER.

The EAG's preferred model suggests that ataluren plus BSC generates an additional [redacted] undiscounted QALYs for patients and caregivers compared with BSC alone, which leads to a decision

modifier of [redacted]. This is markedly lower than the estimate generated by the company's base case model. This difference is attributable to the caregiver disutility approach.

Table 42: EAG preferred model results

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's base case model (deterministic)								
Ataluren+BSC								
BSC								
Incremental								
EA1: Correction of errors								
Ataluren+BSC								
BSC								
Incremental								
EA2: Use of caregiver disutilities								
Ataluren+BSC								
BSC								
Incremental								
EA3: Inclusion of age-adjusted utilities								
Ataluren+BSC								
BSC								
Incremental								
EA4: Use of age-specific weight data from RCPCH								
Ataluren+BSC								
BSC								
Incremental								
EA5: EAG preferred model								
Ataluren+BSC								
BSC								
Incremental								

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier (weighting); EA - exploratory analysis; BSC - best supportive care; RCPCH - Royal College of Paediatrics and Child Health
** Undiscounted*

Table 43 presents the results of the EAG's additional sensitivity analyses. These analyses indicate that the model is highly sensitive to the company's assumption of treatment-specific utility values. Removing the assumption of treatment-dependent patient utility values in the ambulatory health state increases the ICER to [redacted] per QALY gained (ASA1a). Applying BSC utilities to patients who have discontinued ataluren increases the ICER to [redacted] per QALY gained (ASA1b). Applying treatment-independent patient utility values from Crossnohere *et al.*[86] in both groups increases the ICER to in excess of [redacted] per QALY gained (ASA1c). The ICER is not particularly sensitive to the assumptions relating to early treatment benefits or OS gains (ASA2a/b and AS3a/b): the ICER remains below [redacted] per QALY gained across all scenarios explored. The use of the Weibull distribution to model all time-to-event endpoints reduces the ICER to [redacted] per QALY gained (ASA4). The assumptions which determine time on treatment have the propensity to either increase or reduce the ICER; lower discontinuation rates and/or treating until FVC<30% each increase the ICER, whereas applying a discontinuing rule in which patients discontinue treatment at 6 months after loss of ambulation decreases the ICER (ASA5 and ASA6a/b). The decision modifier remains [redacted] across all of the EAG's additional sensitivity analyses.

Table 43: EAG additional sensitivity analysis results

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
EA5: EAG preferred model								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA1a: Use of treatment-independent patient utility value in ambulatory state								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA1b: Assume BSC patient utility values after ataluren discontinuation								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA1c: Use of treatment-independent patient utility values								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA2a: Early treatment benefits halved								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA2b: Early treatment benefits removed								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA3a: Survival gain assumed to be equal to delay in loss of ambulation								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA3b: Survival gain removed								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA4: Use of Weibull model for all time-to-event endpoints								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA5: Discontinuation rate reduced by 50%								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA6a: Discontinuation at 6 months after loss of ambulation								
Ataluren+BSC	[redacted]							
BSC	[redacted]							
Incremental	[redacted]							
ASA6b: Discontinuation at FVC<30%								
Ataluren+BSC	[redacted]							
BSC	[redacted]							

Incremental		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier (weighting); EA - exploratory analysis; ASA – additional sensitivity analysis; BSC - best supportive care; * Undiscounted*

5.5 Costs to the NHS and PSS - eligible population and net budget impact

Section 13 of the CS[1] presents the results of a budget impact analysis for ataluren. The CS states that there are [redacted] patients with nmDMD currently receiving ataluren in England through the MAA. The company estimates that there will be 6 incident patients each year. Taking these figures into account, together with the company's proposed extended stopping rule (for patients reaching FVC<50%), DMD mortality rates and an assumed uptake of 100%, the company estimates that [redacted] patients in England will be eligible to receive ataluren in Year 1, increasing to [redacted] patients in Year 5. The company's budget impact analysis, which includes an assumption that treatment adherence is [redacted] for all patients, suggests an expected total cost for ataluren of [redacted] in Year 1, rising to [redacted] in Year 5.

Table 44: Company's estimates of budget impact over 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost (per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The CS[1] notes the following limitations associated with the budget impact analysis:

- The estimated incidence figure is based on Welsh bloodspot screening data[5] and may be an overestimate
- The estimated rates at which patients reach FVC<50% and death are based on the economic model; potential survival benefits which are included in the economic model have not been included in the budget impact analysis
- Treatment adherence is based on clinical judgement.

The company's executable budget impact model was not provided as part of the CS;[1] however, the EAG considers it unlikely that alternative incidence assumptions would substantially reduce the budget impact estimates reported in Table 44. The EAG also notes that it is unclear why the survival advantage included in the economic model has been excluded from the budget impact calculations.

5.6 Potential wider costs and benefits not included in the company's economic analysis

Section 14 of the CS[1] provides a detailed description of the costs associated with DMD which fall on patients and their caregivers. Many of these costs are a consequence of extensive caregiving needs resulting from the patient's loss of independence following the onset of severe physical disability. In particular, the CS highlights the following:

- Patients with DMD rarely succeed in participating in working life or contributing to society. The CS cites a CARE-NMD survey which compared the care experience of UK DMD patients to that in other European countries.[90] Of the 42 respondents from the UK who participated, all were non-ambulatory, none were in employment, and 25.6% were still in education (at a

secondary school, special needs school, in vocational training, or at university). Nearly 93% of the UK respondents were adults living at home.

- DMD results in substantial caregiving needs, with the patient's caregivers usually being their parents. The burden of illness study reported by Landfeldt *et al.* (2014)[74] suggested that in the UK, 55% of caregivers were employed, whilst 49% had reduced working hours or stopped working because of their relative's DMD. Landfeldt *et al.* (2018)[91] reported a mean estimate of 63 hours of informal care per week.
- Cavazza *et al.*[17] estimated the total annual cost of illness of DMD in the UK to be US$72,870 (£53,325) per patient. At least 46% of this cost was attributable to the costs of informal care and lost productivity. The CS also states that a large proportion of non-medical community care and home adaptations are paid for privately by families.

The CS[1] also discusses costs associated with DMD which fall on other sectors outside of the NHS and PSS, which may be reduced or postponed due to the availability of ataluren. These include impacts on:

- The education budget – e.g., due to the costs of classroom assistance and adaptation which may be reduced or postponed.
- The local government budgets – e.g., Disabled Facilities Grants, which may be reduced if fewer or less expensive adaptations are required.
- The Welfare budget – e.g., ataluren may increase a patient's level of independence and physical capability, which may reduce dependence on respite care, disability or other welfare payments.

The EAG and its clinical advisors agree that DMD is associated with a substantial emotional and financial burden on patients and their caregivers, and that relevant costs will fall on other sectors outside of the NHS and PSS. However, the CS[1] does not provide empirical evidence to quantify any cost savings associated with ataluren. The EAG also notes that many of the potential cost savings may only be postponed rather than avoided.

5.7 Conclusions

The company's SLR did not identify any published economic analyses of ataluren for the treatment of DMD.

The CS[1] presents the methods and results of a *de novo* economic model which assesses the cost-effectiveness of ataluren plus BSC versus BSC alone for the treatment of patients with nmDMD. The model adopts a partitioned survival approach, with health states defined according to survival status, ambulation status and level of respiratory function. The intervention assessed within the model is ataluren given in conjunction with BSC from the age of 2 years, with treatment permitted until the patient reaches FVC<50%. The analysis adopts an NHS and PSS perspective, including QALYs

accrued by nmDMD patients and their caregivers. Health outcomes for the BSC group are modelled using time-to-event outcomes from the propensity score matched CINRG DNHS dataset,[28] whilst outcomes for the ataluren group are modelled using data from STRIDE[21] plus additional assumptions relating to the benefits of early treatment with ataluren. The model includes the existing PAS for ataluren.

The company's model predicts that patients receiving ataluren will experience a delay in the age at loss of ambulation of [redacted] years, a delay in the age at FVC<50% of [redacted] years and delays in the ages at FVC<50% and death of approximately [redacted] years. The probabilistic version of the company's model suggests that the ICER for ataluren plus BSC versus BSC alone is [redacted] per QALY gained. The deterministic ICER is lower, at [redacted] per QALY gained. The deterministic version of the model suggests that ataluren will lead to [redacted] additional undiscounted QALYs compared to BSC, leading to a decision modifier of [redacted].

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's model. The EAG's critical appraisal identified several issues and uncertainties relating to the model itself and the evidence used to inform its parameters. The most important of these include: (i) the use of an absolute caregiver QALY approach, which stops counting caregiver QALYs when the DMD patient has died; (ii) uncertainty surrounding the relative effectiveness of ataluren in the target population; (iii) uncertainty surrounding the assumption of treatment-dependent patient utility values; (iv) uncertainty around the rate of discontinuation and its impact on subsequent health outcomes; (v) limitations in the company's survival analysis and (vi) the assumption that patient weight and associated drug costs will not increase as the surviving population gets older.

The EAG's preferred model includes: the correction of model errors; the application of a caregiver disutility approach; age-adjustment of all utility/disutility values and the use of data from the RCPCH[89] and STRIDE[21] to reflect the relationship between patient age and weight. The EAG's preferred model suggests that the deterministic ICER for ataluren versus BSC is [redacted] per QALY gained. This analysis suggests that ataluren is expected to generate [redacted] additional undiscounted QALYs (decision modifier = [redacted] The EAG's additional sensitivity analyses indicate that the ICER would be in excess of [redacted] if treatment-independent patient utility values are used for all health states. This is a key area of uncertainty, as the clinical experts consulted by the company and the EAG did not consistently agree that it is appropriate to apply treatment-dependent utility values to all/any states, and the CS does not present evidence to support this assumption based on HRQoL measured in children with nmDMD. The ICER is also somewhat sensitive to the rate of natural discontinuation and the stopping rule. The use of

alternative survival models and early treatment benefit assumptions appear to have a lesser impact on the ICER. All of the EAG's additional sensitivity analyses indicate a decision modifier of [redacted].

6. OVERALL CONCLUSIONS

6.1 Conclusions on clinical effectiveness

The new additional key clinical evidence, subsequent to HST3,[18] supporting the efficacy and safety of ataluren is based on a long-term (up to 336 weeks) open-label extension study (Study 019),[25] a license extension to expand the indication to include patients aged ≥2 to <5 years (Study 030)[35, 36] and ongoing real-world safety and effectiveness evidence (STRIDE registry,[21, 37-40] and the MAA).[41] Due to the lack of additional comparative evidence, the company performed three ITCs using propensity score matching to compare ataluren plus BSC versus BSC alone. The company selected the CINRG[28] and NorthStar[41] natural history datasets as indirect comparative evidence for BSC. Although the ITCs suggest favourable effects for ataluren in delaying the age of loss of ambulation and the majority of functional outcomes (e.g. TFTs and pulmonary outcomes), the EAG advises caution when interpreting the results. Whilst the EAG considers the propensity score matching approach applied by the company to be reasonable, data quality issues (e.g., missing data, variance in the quality of data and inconsistency of data collection between registries, population differences between studies, accuracy of reporting and differences in standards of care, including temporal between different countries/centres) and methodological limitations (e.g., inconsistencies in the matching of the controls, potential baseline differences between prognostic factors not included in the matching process and residual confounding and other statistical issues) may have impacted the estimates of effectiveness. As such, the magnitude of benefit in delaying the loss of ambulation, improvements in TFTs and pulmonary outcomes in the overall licensed population remains uncertain. In addition, there are no comparative efficacy data which demonstrate an OS advantage for ataluren over BSC; no data are available on the effect of ataluren on cardiac outcomes; no long-term data are available that demonstrate the magnitude of the benefit associated with continued treatment with ataluren beyond loss of ambulation, and efficacy data in children aged ≥2 and <5 years are limited due to the rarity of diagnosed nmDMD patients <5 years of age. There were no additional safety concerns and AEs appear to be consistent with the known safety profile of ataluren.

6.2 Conclusions on value for money

The probabilistic version of the company's model suggests that the ICER for ataluren plus BSC versus BSC alone is [redacted] per QALY gained (deterministic ICER=[redacted] per QALY gained). The deterministic version of this model suggests that ataluren will generate [redacted] additional undiscounted QALYs compared to BSC, leading to a decision modifier of [redacted]. The EAG's preferred model generates a deterministic ICER for ataluren plus BSC versus BSC alone of [redacted] per QALY gained. The EAG's preferred model suggests that ataluren will generate [redacted] additional undiscounted QALYs compared to BSC, leading to a decision modifier of [redacted]. The main driver of these differences is the approach used to quantify QALYs accrued by caregivers of DMD patients: the company's model

applies an absolute caregiver approach, whereas the EAG's preferred model applies a conventional caregiver disutility approach. The other amendments included in the EAG's preferred analyses result in higher drug acquisition costs as well as slightly lower incremental patient QALYs. The EAG's preferred model is not intended to be a revised base case, but instead the EAG considers that it should be used as the starting point for exploring the impact of other clinical uncertainties on the cost-effectiveness of ataluren.

The EAG's additional sensitivity analyses indicate that EAG-preferred model is highly sensitive to the use of treatment-dependent patient utility values; if treatment-independent utility values are used, the ICER for ataluren increases to more than [redacted] per QALY gained. This is important, as the evidence to support the use of treatment-dependent patient utility values is based on an expert Delphi panel, rather than empirical evidence of HRQoL measured in DMD patients, and clinical experts consulted by the EAG and the company expressed uncertainty about whether such additional benefits should apply to all or any of the modelled health states. Whilst the EAG considers the company's assumptions regarding the benefit of early treatment with ataluren and OS to be highly uncertain, the ICER does not appear to be particularly sensitive to these. The EAG believes that the probability of discontinuation is likely to have been overestimated in the company's model; applying a lower per-cycle probability of discontinuation increases the ICER for ataluren. The use of discontinuation rules at earlier milestones in the progression of the disease (e.g., within 6 months of loss of ambulation, as per the MAA) will reduce the ICER for ataluren, although the company's model structure cannot reflect the impact of stopping treatment on subsequent health outcomes. The decision modifier remains [redacted] across all of the EAG's sensitivity analyses.

7. REFERENCES

1. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's submission to NICE. PTC Therapeutics: Guildford, UK; 2022.
2. Passamano L, Taglia A, Palladino A, Viggiano E, D'Ambrosio P, Scutifero M*, et al.* Improvement of survival in Duchenne muscular dystrophy: retrospective analysis of 835 patients. *Acta Myologica* 2012;31:121-5.
3. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifirò G*, et al.* Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet Journal of Rare Diseases* 2020;15.
4. Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, Kosma K*, et al.* The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Human Mutations* 2015;36:395-402.
5. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). *European Journal of Human Genetics* 2013;21:1049-53.
6. van Ruiten HJ, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. *Archives of Disease in Childhood* 2014;99:1074-7.
7. Aartsma-Rus A, Hegde M, Ben-Omran T, Buccella F, Ferlini A, Gallano P*, et al.* Evidence-based consensus and systematic review on reducing the time to diagnosis of Duchenne muscular dystrophy. *Journal of Paediatrics* 2019;204:305-13.
8. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D*, et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurology* 2018;17:251-67.
9. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A*, et al.* Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurology* 2018;17:247-361.
10. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK*, et al.* Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurology* 2018;17:445-55.
11. Ricotti V, Ridout DA, Scott E, Quinlivan R, Robb SA, Manzur AY*, et al.* Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *Journal of Neurology, Neurosurgery and Psychiatry* 2013;84:698-705.
12. Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E*, et al.* The 6-minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: Longitudinal comparisons and clinically-meaningful changes over one year. *PLoS Currents* 2013;5.
13. Mayer O. Advances in pulmonary care in Duchenne muscular dystrophy. *US Neurology* 2017;13:35-41.
14. Williams K, Davidson I, Rance M, Boehnke A, Buesch K, Acaster S. Symptoms and impacts of ambulatory nonsense mutation Duchenne muscular dystrophy: a qualitative study and the development of a patient-centred conceptual model. *Journal of Patient Reported Outcomes* 2021;5.
15. Bendixen RM, Senesac C, Lott DJ, Vandenborne K. Participation and quality of life in children with Duchenne muscular dystrophy using the International Classification of Functioning, Disability, and Health. *Health And Quality Of Life Outcomes* 2012;10.

16. Wei Y, Speechley K, Campbell C. Health-related quality of life in children with Duchenne muscular dystrophy: A review. *Journal of Neuromuscular Diseases* 2015;2:313-24.
17. Cavazza M, Kodra Y, Armeni P, De Santis M, López-Bastida J, Linertová R*, et al.* Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. *European Journal of Health Economics* 2016;Suppl1:19-29.
18. National Institute for Health and Care Excellence. HST3 - NICE Guidance: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. NICE: London, UK; 2016.
19. National Institute for Health and Care Excellence. Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD). Managed Access Agreement. NICE: London, UK; 2016.
20. National Institute for Health and Care Excellence. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of Highly Specialised Technologies Guidance 3). Final scope. London, UK; 2022.
21. PTC Therapeutics Inc. Registry of Translarna (ataluren) in nonsense mutation Duchenne muscular dystrophy (nmDMD) (STRIDE); 2022.
22. Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP*, et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy (Study 007). *Muscle & Nerve* 2014;50:477-87.
23. McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N*, et al.* Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial (Study 020). *Lancet* 2017;390:1489-98.
24. McDonald CME, Muntoni F, Selby K, Jin F, Panaghie-Meltzer G, et al. Long-term pulmonary function outcomes in non-ambulatory patients with nonsense mutation duchenne muscular dystrophy treated with ataluren: 240-week data from an open-label extension study' (Study 004). Presented at the 15th International Child Neurology Congress 2018 2018.
25. McDonald CM, Muntoni F, Penematsa V, Jiang J, Kristensen A, Bibbiani F*, et al.* Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients (Study 019). *Journal of Comparative Effectiveness Research* 2022;11:139-55.
26. PTC Therapeutics Inc. Study of ataluren in ≥2 to <5 year-old male participants with Duchenne muscular dystrophy (Study 030). Clinicaltrials.gov trial record (available from https://clinicaltrials.gov/ct2/show/NCT02819557); 2020.
27. PTC Therapeutics Inc. An extension study of ataluren (PTC124) in participants with nonsense mutation dystrophinopathy (Study 020e). Clinicaltrials.gov record (available from https://clinicaltrials.gov/ct2/show/NCT02090959); 2020.
28. The Cooperative International Neuromuscular Research Group (CINRG). CINRG disease natural history dataset. 2022.
29. European Medicines Agency. Summary of product characteristics - Translarna (ataluren). EMA: London, UK; 2021.
30. Joint Formulary Committee. British National Formulary (online). BMJ Group and Pharmaceutical Press: London, UK; 2022.
31. Landfeldt E, Alfredsson L, Straub V, Lochmüller H, Bushby K, Lindgren P. Economic evaluation in Duchenne muscular dystrophy: Model frameworks for cost-effectiveness analysis. *PharmacoEconomics* 2017;35:249-58.
32. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's response to clarification questions from the EAG. PTC Therapeutics: Guildford, UK; 2022.

33. Landfeldt E, Lindberg C, Sejersen T. Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy. *Muscle & Nerve* 2020;61:363-8.
34. Landfeldt E, Lindgren P, Bell CF, Guglieri M, Straub V, Lochmüller H*, et al.* Quantifying the burden of caregiving in Duchenne muscular dystrophy. *Journal of Neurology* 2016;263:906-15.
35. Clinicaltrials.gov. NCT02819557. Study of ataluren in ≥2 to <5 year-old male participants with Duchenne muscular dystrophy.
36. Tian C KR, O'Mara E, Trifillis P, McIntosh J, Renfroe J. Ataluren in patients aged ≥2 to <5 years with nonsense mutation Duchenne muscular dystrophy (nmDMD): 28-week results from a Phase 2 study. Paper presented at: Neuromuscular Diseases; Vienna, Austria, 6-10 July 2018.
37. Mercuri E, Muntoni F, Buccella F, Desguerre I. Poster EP.142: Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Duchenne Natural History Study: a matched cohort analysis. 26th International Annual Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24.
38. Mercuri E, Muntoni F, Osorio AN, Tulinius M, Buccella F, Morgenroth LP*, et al.* Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *Journal of Comparative Effectiveness Research* 2020;9:341-60.
39. Muntoni F, Desguerre I, Guglieri M, Osorio AN, Kirschner J, Tulinius M*, et al.* Ataluren use in patients with nonsense mutation Duchenne muscular dystrophy: Patient demographics and characteristics from the STRIDE Registry. *Journal of Comparative Effectiveness Research* 2019;8:1187-200.
40. Tulinius M, Buccella F, Desguerre I, Kirschner J. Poster EP.144: Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Duchenne Natural History Study: a matched cohort analysis. 26th International Annual Congress of the World Muscle Society (WMS) Virtual Congress, September 20–24.
41. NorthStar Clinical Network; PTC Therapeutics. Statistical analysis plan, Version 4.2, Managed Access Agreement: Ataluren for treating nonsense mutation Duchenne muscular distrophy (nmDMD). 2021.
42. Clinicaltrials.gov. NCT02090959. An extension study of ataluren (PTC124) in participants with nonsense mutation dystrophinopathy https://clinicaltrials.gov/ct2/show/results/NCT02090959.
43. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's submission appendices. PTC Therapeutics: Guildford, UK; 2022.
44. National Institute for Health and Care Excellence (NICE). Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template - Process and methods [PMG24]. NICE: London, UK; 2022.
45. National Institute for Health and Care Excellence (NICE). Methods for the development of NICE public health guidance (third edition) - Process and methods [PMG4]. NICE: London, UK; 2012.
46. Faria R, Hernandez Alava M, Manca A, Wailoo AJ. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data. NICE Decision Support Unit; 2015.
47. Coles B, Tyrer F, Hussein H, Dhalwani N, Khunti K. Development, content validation, and reliability of the assessment of real-world observational studies (ArRoWS) critical appraisal tool. *Annals of Epidemiology* 2021;55:57-63.
48. Bello L, Gordish-Dressman H, Morgenroth LP, Henricson EK, Duong T, Hoffman EP*, et al.* Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology* 2015;85:1048-55.

49. Finkel RS, Flanigan KM, Wong B, Bönnemann C, Sampson J, Sweeney HL*, et al.* Phase 2a study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. *PLoS One* 2013;8:e81302.
50. Campbell C, Barohn RJ, Bertini E, Chabrol B, Comi GP, Darras BT*, et al.* Meta-analyses of ataluren randomized controlled trials in nonsense mutation Duchenne muscular dystrophy. *Journal of Comparative Effectiveness Research* 2020;9:973-84.
51. Centre for Reviews and Dissemination (CRD). Systematic review: CRD's guidance for undertaking reviews in health care. CRD, University of York; 2009.
52. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.* Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane; 2022.
53. National Institute for Health and Care Excellence (NICE). Contract variation agreement no. 1 to Managed Access Agreement for ataluren (TranslarnaTM) for treating nonsense mutation Duchenne muscular dystrophy.; 2021. https://www.nice.org.uk/guidance/hst3/resources/contract-variation-agreement-no-1-to-managed-access-agreement-pdf-9202767661 (Accessed 9 May 2021).
54. European Medicines Agency. Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006. 2019. https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-p46-0025-epar-assessment-report_en.pdf (Accessed 04 May 2022).
55. European Medicines Agency. CHMP extension of indication variation assessment report. Procedure No. EMEA/H/C/002720/II/0037. 2018. https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-ii-0037-epar-assessment-report-variation_en.pdf (Accessed 04 May 2022).
56. European Medicines Agency. Assessment report - Translarna. Procedure no. EMEA/H/C/002720/II/0049. 2019. https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-ii-0049-epar-assessment-report-variation_en.pdf (Accessed 04 May 2022).
57. European Medicines Agency. Assessment report - Translarna. Procedure no. EMEA/H/C/002720/II/0047. 2019. https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-ii-0047-epar-assessment-report-variation_en.pdf (Accessed 09 May 2022).
58. Clinicaltrials.gov. NCT02369731. Registry of Translarna (ataluren) in nonsense mutation Duchenne muscular dystrophy (nmDMD). https://clinicaltrials.gov/ct2/show/NCT02369731 (Accessed 04 May 2022).
59. National Institute for Health and Care Excellence (NICE). Addendum to Managed Access Agreement Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD) in patients aged between 2 years and 5 years. 2019. https://www.nice.org.uk/guidance/hst3/resources/addendum-to-managed-access-agreement-pdf-6779076589 (Accessed 09 May 2022).
60. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399-424.
61. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci* 2010;25:1-21.
62. Ciafaloni E, Kumar A, Liu K, Pandya S, Westfield C, Fox DJ*, et al.* Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker muscular dystrophy: Data from the MD STARnet. *Journal of Pediatric Rehabilitation Medicine* 2016;9:5-11.
63. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F*, et al.* Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet* 2018;391:451-61.
64. Zhang Z, Kim HJ, Lonjon G, Zhu Y, written on behalf of AMEB-DCTCG. Balance diagnostics after propensity score matching. *Ann Transl Med* 2019;7:16.

65. PTC Therapeutics Inc. Clinical Study Report. PTC124-GD-025o-DMD. Long-term observational study of Translarna safety and effectiveness in usual care. Interim clinical study report. PTC Therapeutics: Guildford, UK; 2019.
66. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Statistics in Medicine* 2008;27:2037-49.
67. Austin PC, Fine JP. Propensity-score matching with competing risks in survival analysis. *Statistics in Medicine* 2019;38:751-77.
68. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Statistics in Medicine* 2014;33:1057-69.
69. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis* 2017;15:199-236.
70. Austin PC, Schuster T. The performance of different propensity score methods for estimating absolute effects of treatments on survival outcomes: A simulation study. *Statistical Methods in Medical Research* 2016;25:2214-37.
71. Gayat E, Resche-Rigon M, Mary JY, Porcher R., et al. Propensity score applied to survival data analysis through proportional hazards models: a Monte Carlo study. *Pharmaceutical Statistics* 2012;11:222-9.
72. Schiava M, Amos R, VanRuiten H, McDermott MP, Martens WB, Gregory S*, et al.* Clinical and genetic characteristics in young, glucocorticoid-naive boys with Duchenne muscular dystrophy. *Neurology* 2021;98:390-401.
73. European Medicines Agency. Translarna - EPAR. Procedural steps taken and scientific information after the authorisation. 2021. https://www.ema.europa.eu/en/documents/procedural-steps-after/translarna-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf (Accessed 08 May 2022).
74. Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V*, et al.* The burden of Duchenne muscular dystrophy: an international, cross-sectional study. *Neurology* 2014;83:529-36.
75. Humbertclaude V, Hamroun D, Bezzou K, Bérard C, Boespflug-Tanguy O, Bommelaer C*, et al.* Motor and respiratory heterogeneity in Duchenne patients: implication for clinical trials. *European Journal of Paediatric Neurology* 2012;16:129-60.
76. Duchenne UK. About Project HERCULES (https://hercules.duchenneuk.org/about-project-hercules/); 2022.
77. Office for National Statistics. National life tables: England 2018-2020. London, UK; 2021.
78. Ara R, Brazier JE. Populating an economic model with health state utility values: Moving toward better practice. *Value in Health* 2010;13:509-18.
79. National Institute for Health and Care Excellence. HST7: Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. Committee papers; 2018.
80. Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. *British Medical Journal* 2014;9.
81. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th edn. New York: Oxford University Press; 2015.
82. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C*, et al.* Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value in Health* 2004;6:9-17.
83. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. NICE: London, UK; 2022.

84. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. NICE Decision Support Unit, Sheffield, UK; 2013.
85. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders* 2002;12:926-9.
86. Crossnohere NL, Fischer R, Lloyd A, Prosser LA, Bridges JFP. Assessing the appropriateness of the EQ-5D for Duchenne muscular dystrophy: A patient-centered study. *Medical Decision Making* 2021;41:209-21.
87. National Institute for Health and Care Excellence. NICE TA755: Risdiplam for treating spinal muscular atrophy. NICE: London, UK; 2021.
88. Hernández Alava M., Pudney S., Wailoo A. Estimating EQ-5D by age and sex for the UK. NICE Decision Support Unit, Sheffield; 2022.
89. Royal College of Paediatrics and Child Health. Growth charts. Available from: https://www.rcpch.ac.uk/resources/growth-charts. RCPCH: London; 2022.
90. Rodger S, Woods KL, Bladen CL, Stringer A, Vry J, Gramsch K*, et al.* Adult care for Duchenne muscular dystrophy in the UK. *Journal of Neurology* 2015;262:629-41.
91. Landfeldt E, Edström J, Buccella F, Kirschner J, Lochmüller H. Duchenne muscular dystrophy and caregiver burden: a systematic review. *Developmental Medicine & Child Neurology* 2018;60:987-96.

8. APPENDICES

Appendix 1: Instructions for implementing the EAG's exploratory analyses using the company's original submitted model

This appendix explains how to implement each of the ERG's exploratory analyses. All analyses should be undertaken using the version of the model which has been modified by the EAG.

EA1: Correction of errors

The following corrections have been made to the original version of the submitted model.

In worksheet "Ataluren plus BSC":

- The formulae in cells AQ12, AS12, AU12, AW12 and AY12 have been amended to refer to the first row of the half-cycle adjusted LYG contributions for each cycle (row 11, not 12). The formulae have been filled down.
- The formulae in the cells in row 12 of columns CG:CP have been amended to refer to the first row of the half-cycle adjusted model trace (columns AF:AK). The formulae have been filled down.
- The formulae in cells DI12 and DJ12 have been amended to refer to cells AB11 and AC11, respectively. Fill the formulae down.

In the worksheet "BSC":

- The formulae in cells AI12, AK12, AM12, AO12 and AQ12 have been amended to refer to the first row of the half-cycle adjusted LYG contributions for each cycle (row 11, not 12). The formulae have been filled down.
- The formulae in the cells in row 12 of columns BY:CH have been amended to refer to the first row of the half-cycle adjusted model trace (columns AF:AK). The formulae have been filled down.

EA2: Use of caregiver disutilities

Additional functionality has been added to the model. Go to worksheet "EAG_analysis." Amend the values in cells AG4 and AG6 to 1.

EA3: Inclusion of age-adjusted utilities

Additional functionality has been added to the model. Go to worksheet "EAG_analysis." Amend the value in cell AG5 to 1.

EA4: Use of age-specific weight data from RCPCH

Go to worksheet "Settings." Use the drop-down menu in cell D9 to select the "RCPCH" option.

ASA1a: Use of treatment-independent patient utility values in ambulatory state

Go to worksheet "Utilities", cell E9. Amend formula to read "=late_BSC_utility"

ASA1b: Assume BSC patient utility values after ataluren discontinuation

Additional functionality has been added to the model. Go to worksheet "EAG_analysis." Amend the value in cell AG7 to 1.

ASA1c: Use of treatment-independent utility values

Go to worksheet "Utilities". Apply the following utility values:

- Cells E9 and F9 – 0.49
- Cells E10 and F10 – 0.31
- Cells E11:F12 - 0.26

ASA2a: Early treatment benefits halved

Go to worksheet "Settings". In cells D35, D48 and D60, apply values of [redacted], respectively.

ASA2b: Early treatment benefits removed

Go to worksheet "Settings". In cells D35, D48 and D60, apply values of 0.

ASA3a: Survival gain assumed to be equal to gain in delay in loss of ambulation

Go to worksheet "Settings". In cell D60, apply a value of [redacted].

ASA3b: Survival gain removed

Go to worksheet "Settings". In cells D58 and D60, apply a value of 0.

ASA4: Use of Weibull model for all time-to-event endpoints

Go to worksheet "Settings". For drop-down menus in cells D32, D33, D45, D46 and D56, select "Weibull".

ASA5: Discontinuation rate reduced by 50%

Go to worksheet "Model Parameters". Amend the formula in cell F12 to "=CHOOSE(model_mode,G12,J12)/2"

ASA6a: Discontinuation at 6 months after loss of ambulation

Go to worksheet "Settings". Go to the drop-down menu in cell D77 and select "6 months post LoA"

ASA6b: Discontinuation at FVC<30%

Go to worksheet "Settings". Go to the drop-down menu in cell D77 and select "At FVC<1 litre"

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology evaluation process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology evaluations).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 8 June 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Table summarising Issue 1: The bullet point discussing “No evidence of OS benefit” repeats the expression “are available” twice. This is a typographical error.	Remove one set of “**are available**” from the sentence such that the sentence starts “No data are available to demonstrate…”	Corrects typographical error.	The EAG agrees. The text has been amended

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Table summarising Issue 3: There is a statement which writes “Clinical experts were not asked to provide estimates of expected survival or judgements about the plausibility of the final modelled functions”. This is not true as stated in the company response to the clarification questions Appendix 1.	The sentence would be more accurate if it was re-worded to say: “A clinical expert was asked to provide judgements about the clinical plausibility of the final modelled functions, however as they were a paediatrician, they felt they were not in a position to pass judgement on patient progression beyond 18 years of age.”	This is a more accurate summary of the input from a clinical expert approached by the company.	The EAG agrees. The text has been amended to read: [redacted] *The CS and the company’s clarification response do not provide any further detail on how clinical input was used to inform model selection.”*

			The text on page 128 has also been amended to include this additional text.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	
Page 20, Table summarising Issue 7: There is a statement which writes "The company's economic model adopts a partitioned survival approach whereby treatment discontinuation is structurally unrelated to clinical outcomes". This statement is true when considering the impact of "per cycle natural discontinuation", however it is not true when the impact of the stopping rule is considered. This is because the health states are based on clinical outcomes and then treatment stopping is informed when patients reach a specific health state.	The accuracy of the statement could be improved if it was reworded to say: "The Company's economic model adopts a partitioned survival approach whereby background treatment discontinuation is structurally unrelated to clinical outcomes."	This is a more accurate description of the model functionality.	The EAG agrees that this text could have been slightly clearer. The issue is not only about background discontinuation – it is that clinical outcomes are not dependent on whether the patient is still receiving treatment. For this reason, we have applied a different amendment to that suggested by the company. The text has been amended to read: *"The company's economic model adopts a partitioned survival approach whereby clinical outcomes are not structurally dependent on whether the patient is still receiving treatment."*

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Table summarising Issue 7:	Replace the sentence to write "A different model structure would be	Corrects typographical error.	The EAG agrees. This typographical error has been fixed.

The word “to” is missing from the sentence “A different model structure would be required estimate the impact of treatment discontinuation on outcomes associated with subsequent disease milestones.”	required **to** estimate the impact of treatment discontinuation on outcomes associated with subsequent disease milestones.”		

Issue 4

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 21, Table summarising Issue 8: There is a statement that writes “All of the company’s deterministic and probabilistic sensitivity analyses apply QALY weighting based on the number of additional undiscounted QALYs gained in the base case analysis.” It is the company’s understanding that this statement is not true. The functionality in the model is set up such that the QALY weighting varies based on the number of undiscounted incremental QALYs that are generated for each scenario.	The company proposes that the bullet point containing this statement is removed, or is corrected to say: “All of the Company’s deterministic and probabilistic sensitivity analyses apply QALY weighting based on the number of undiscounted QALYs gained for that scenario”.	This is a more accurate description of the model functionality.	The EAG agrees. We had misunderstood the wording in the CS. The text has been removed throughout the report as it is no longer a valid criticism.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25, Final paragraph: The specific sub-group of nonsense mutation DMD patients is not specified within the following sentence. "The CS cites a UK qualitative study in which interviews were conducted with the parents of 10 individuals with DMD aged 4 to 19 years."	Rewrite the sentence as follows: "The CS cites a UK qualitative study in which interviews were conducted with the parents of 10 individuals with **nm**DMD aged 4 to 19 years."	Includes relevant specific information regarding the patient sub-group.	The EAG has amended the text in line with the company's suggestion.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, Second paragraph: The baseline age inclusion criteria for studies 007 and 020 are stated incorrectly as "5 to 20 and 7 to 16".	Update the text to state: "The pivotal RCTs of ataluren, Study 007 and Study 020, which formed the basis of the original European Medicines Agency (EMA) conditional marketing authorisation issued in 2014, were undertaken in patients who were aged 5 years or greater and between 7 to 14 years, respectively".	Corrects typographical error.	The EAG has amended the text in line with the company's suggestion.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42, third paragraph: The p-value associated with the difference between the 6MWD distance for ataluren and placebo patients is presented incorrectly as "(p=0.561)"	Update the text to write "(**p=0.056**)". Please refer to: Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 2014 Oct;50(4):477–87.	Corrected typographical error.	The EAG agrees. This typographical error has been fixed.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 77, Table 18 Heading: The heading of this table describes it as "reproduced from CS, Table C-25". This refers to the incorrect table from the CS. The data in the table is from Table C-35 of the CS.	The heading of Table 18 should be re-worded as "Baseline characteristics after matching, MAA and control cohort (reproduced from CS, Table **C-35**)"	This refers to the correct table from the CS.	The EAG agrees. This typographical error has been fixed.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102, Table 26: Data in this table has been transcribed to the incorrect columns.	An amended version of Table 26 is presented below: **Distribution** / **BSC group (CINRG)** / **Ataluren group (STRIDE)** **AIC** / **BIC** / **AIC** / **BIC** Exponential [redacted] Weibull [redacted]	This amendment accurately represents the AIC and BIC values for each group as presented in CS Appendix 6 Tables 41 and 42.	The EAG agrees. This was a transposition error. The table has been amended as suggested by the company.

	Gompertz	[redacted]	[redacted]	We have also amended the text in critical appraisal point 4(c) regarding similar fitting models.
	Log-normal			
	Log-logistic (base case)			
	Generalised gamma			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 104, Table 27: Data in this table has been transcribed to the incorrect columns.	An amended version of Table 27 is presented below: **Distribution** / **BSC group (CINRG)** / **Ataluren group (STRIDE)** **AIC** / **BIC** / **AIC** / **BIC** Exponential Weibull Gompertz Log-normal Log-logistic (base case) Generalised gamma [redacted]	This amendment accurately represents the AIC and BIC values for each group as presented in CS Appendix 6 Tables 43 and 44.	The EAG agrees. This was a transposition error. The table has been amended as suggested by the company. We have also amended the text in critical appraisal point 4(c) regarding similar fitting models. Note - the values for the log-logistic and log-normal distributions in the suggested table have been pasted in the wrong rows. The values used in the EAG report have been taken from the CS appendices.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 112, Table 34: The final column on the right-hand side is titled “Delay attributable to early treatment benefit assumptions”. Technically this is not what the bottom two rows represent. For the bottom two rows, FVC <30% and Death, the number presented represents an overall delay in reaching these health states for ataluren patients compared to BSC based on two simultaneous contributing factors. These are the assumed treatment benefit due to active ataluren treatment of approximately 4 years, and due to early treatment contributing approximately 3 years. Also, the company are unsure of the exact method used to calculate the mean age of reaching each disease milestone and therefore are unable to confirm if the numbers presented are correct.	The delay assumed because of active treatment with ataluren should be presented in the column one to the left, titled “Delay attributable to STRIDE/ CINRG ITC”, and then only the delay experienced due to the early treatment assumed benefit should be included in the final column. Alternatively. the title of the final column should be updated to include mention of both contributing assumptions.	This is a more accurate description of the model functionality.	The EAG agrees. We have amended the final column heading to read: *“Delay attributable to assumptions about early and/or relative treatment benefit”* The table footnotes have been amended to improve clarity. There was a minor error in the model calculations. This has been rectified and the figures have been updated. Note that the quantity estimated is the mean time to reach each endpoint (from model entry), not mean patient age. Because all milestones are sequential, the mean time to each milestone can be calculated as the sum of the AUC for cumulative states from the half-cycle corrected model trace.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 117 Table 37, Element of HTA – "Measuring and valuing health effects" The EAG comments state that the patient utility values were sourced from "Landfeldt et al. (2017)" whereas they were actually sourced from "Landfeldt et al. (2020)" Also, the specific Landfeldt publication used to inform the caregiver utilities is not stated.	Correct "Health state utility values for patients were taken from Landfeldt et al. (2017)[33]" To: "Health state utility values for patients were taken from Landfeldt et al. **(2020)**[33]" And correct "Health state utility values for caregivers are based on values reported by Landfeldt et al.,[31]" To: "Health state utility values for caregivers are based on values reported by Landfeldt et al. **(2017)**,[31]"	Corrects typographical error and improves clarity.	The EAG agrees. These typographical errors have been fixed.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 117, Table 37, Element of HTA – "Equity considerations" This issues links to **Error! Reference source not found.** where the text states "All sensitivity analysis results presented in the CS[1] include the decision modifier estimated from the base case analysis."	Remove this sentence or correct it to state: "All sensitivity analysis results presented in the CS[1] Automatically update the decision modifier depending on the number of undiscounted incremental QALYs gained in each scenario"	A more accurate description of the model functionality.	As described in our response to Issue 4, we had misunderstood the wording in the CS. The text has been removed throughout the report as it is no longer a valid criticism.

As written within the description of **Error! Reference source not found.**, it is the company's opinion this is not true.			

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 120, middle paragraph: The following sentence is arguably ambitious: "[redacted]" The ambiguity could result in the reader interpreting the statement that both experts did not believe that the HRQoL would differ between treatment groups, rather than that the experts had differing opinions.	The company suggest re-phrasing the statement to say: "[redacted]"	Improves clarity of the statement and reduces the chance of misinterpretation.	The EAG agrees. The text has been amended in line with the company's suggestion.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 122: point (d) *Additional assumptions regarding early treatment with ataluren:* The comments from the clinical experts cited by the EAG are discussing opinions not specifically related to the early treatment delay, but rather the assumption that observed delays in reaching earlier disease milestones translate to delays in reaching later disease milestones. It is worth noting that these are two distinct assumptions operating in parallel.	The company suggest either removing the AIC marked information within this bullet point, or to introduce another bullet point (e) which discusses the modelling assumption applied to later disease milestones, such as "FVC <50%" and "Death", based on the assumption that an observed delay in reaching earlier disease milestones will likely translate into a delay in reaching later disease milestones.	Helps to clearly distinguish between two distinct modelling assumptions.	The EAG agrees that the clinician's statement is not specifically related to early treatment. However, it is still relevant as the company's model predictions of delays in ataluren-treated patients reaching FVC<30% and death are reliant both on assumptions about relative benefit and early benefit. We have not removed the text or added a new subheading. Instead, we have amended the title of the subheading to "*Additional assumptions regarding the benefits of early treatment with ataluren".* For clarity, we have also amended the text in the paragraph to read: [redacted]

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 124 subheading "*(c) Statistical and visual goodness-of-fit, (i)*"	Correct "The log-normal model has the lowest AIC and BIC for both	Corrects typographical error.	The EAG agrees. This typographical error has been fixed.

The text implies the “Log-normal” model was selected as the base case survival models for age at loss of ambulation. This was in fact the “Log-logistic” model	groups; the company selected this model for inclusion in the base case analysis.” To: “The **log-logistic** model has the lowest AIC and BIC for both groups; the company selected this model for inclusion in the base case analysis.”		

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135, first bullet point: The text states “No information is provided regarding the number of events or the number of patients at risk over time” The company argues that the nature of a Kaplan Meier graph displays the number of events and the number of censored patients even if this is not explicitly stated numerically. The graph does explicitly present the number of patients at risk at various time points above the x-axis.	Remove this sentence or correct to state: “The number of events or number of patients throughout the follow up period are not explicitly stated”	Improves the accuracy of the statement.	The EAG agrees that the number of patients at risk is provided in the plot. However, it remains unclear whether it is reasonable to apply a constant discontinuation over time. We would suggest that this could be informed by examining the empirical hazard plot, fitting parametric survival models to the data and seeking clinical input to support/refute the assumption. As such, the text has been amended to read: *“No information is provided regarding the empirical hazard over time and parametric survival models have not been fitted to the data.”*

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135, subheading "(8) Weak characterisation of uncertainty", first bullet point. This issue links to **Error! Reference source not found.** and **Error! Reference source not found.**. The text states "all of the sensitivity and scenario analyses presented in the CS1 include the decision modifier, based on the estimated number of incremental undiscounted QALYs gained in the base case analysis". As mentioned within **Error! Reference source not found.** and **Error! Reference source not found.**, It is the company's position that this is untrue.	Remove this bullet point or correct to state: "all of the sensitivity and scenario analyses presented in the CS1 include the decision modifier, based on the estimated number of incremental undiscounted QALYs gained in each explored scenario"	Provides a more accurate description of the model functionality.	The EAG agrees. The text has been removed. In addition, there were two other instances in which this was mentioned which have been removed for accuracy (pages 111 and 118).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642] External Assessment Group report **Pages 15, 32, 59, 122** **STRIDE Evaluable population number marked as AIC**	The number of patients in the evaluable population from the STRIDE registry were not marked as AIC in the CS.	269	All marking has been updated in line with the company's request.
Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642] External Assessment Group report **Page 60** **STRIDE Effectiveness population number marked as AIC**	The number of patients in the effectiveness population from the STRIDE registry were not marked as AIC in the CS.	241	

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642] External Assessment Group report **Pages 59** **STRIDE As-treated population number marked as AIC**	The number of patients in the as-treated population from the STRIDE registry were not marked as AIC in the CS.	286	

Note: The post-FAC version of the EAG report also includes the correction of a small number of additional typographical errors.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this evaluation.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology evaluation (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **15 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Table 1: About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	PTC Therapeutics
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population (ERG report sections 4.3 and 5.3.5)	Yes	**The clinical efficacy of ataluren is further supported by results from Study 041** To reduce the uncertainty regarding the relative effectiveness of ataluren and BSC compared to BSC alone, the company has included the recently presented top-line results from Study 041, a randomised, double-blind, placebo-controlled, clinical trial comparing ataluren treatment against placebo over a 72-week period. These results further add to the clinical efficacy and safety-profile of ataluren. In the ITT population of Study 041, ataluren treated patients showed a statistically significant reduced decline from baseline in 6MWD compared to placebo treated patients (-53.0m vs -67.4m; difference=14.4m; p=0.0248) and a reduced rate of change (-0.74m/week vs -0.94m/week; difference=0.20m/week; p=0.0248). Additionally, ataluren treated patients demonstrated a statistically significant difference in NSAA scores versus placebo treated patients (total score -3.7 vs -4.5; difference = 0.9; p=0.0235 and linear score -9.6 vs -11.9; difference = 2.3; p=0.0246). Ataluren treated patients also demonstrated statistically significant reductions in 10m walk times (3.04s vs 3.82s; difference = -0.78s; p=0.0422) and stair ascend times (4.98s vs 6.04s; difference = -1.06s; p=0.0293) versus placebo.

		Ataluren has demonstrated consistent treatment effect across multiple clinical endpoints in previous trials. Analysis from the pooled Studies 007, 020 and 041 dataset also showed a statistically significant difference in ambulatory function between the ataluren-treated and placebo-treated groups. The reduction in 6MWD was smaller in ataluren treated patients by 19.3m versus placebo (-28.1 vs. -47.4) (p=0.0002), NSAA total and linear scores also favoured ataluren treated patients by 1.01 (p=0.002) and 2.28 (p=0.005). The 10m walk time was reduced by 1.30s (p=0.0001), stair ascend was reduced by 1.43s (p=0.0004) and stair descend time was reduced by 1.51s (p=0.0004) in ataluren treated patients compared to placebo treated patients. **Assumptions regarding the clinical efficacy of ataluren are supported by clinical expert opinion and findings from both Study 041 and the STRIDE/CINRG analysis** The company's submission presented an early benefit for patients starting treatment at two years old instead of five years old. Although a relatively small proportion of patients in the STRIDE registry received treatment below the age of five years (7.4%), it is expected that early treatment will result in a two-year delay in loss of ambulation (LoA), and a three-year delay in night-time and full-time ventilation support, based on the results of a global Delphi panel of nine clinical experts, with experience of using ataluren to treat DMD patients. The company acknowledges that there is uncertainty regarding the magnitude of delay in treatment effect but notes that this is a limitation of generating real-world evidence in a rare disease, particularly in such a young patient population that would need to be observed over their lifetime. Given the natural history of DMD, it could take approximately 20+ years to reach LoA or pulmonary endpoints when treatment is started at two years of age. The company strongly believes there is an early benefit in treating patients with ataluren at two years of age. However, to account for the uncertainty regarding the magnitude of delay in treatment effect, we have conducted a scenario analysis of the cost-effectiveness model in which the early treatment benefit assumption has been removed from the non-ambulatory health state transitions only (maintaining

		the delay in loss of ambulation), to provide a very conservative estimation of treatment benefit. As the table of incremental cost-effectiveness ratios (ICER) at the end of this response shows, this results in a relatively small increase in the ICER, suggesting that delays in non-ambulatory milestones because of treating earlier are not a key model driver. The company also highlights that a delay in disease progression, such as that demonstrated in Study 041, is plausible given the nature of DMD and the mechanism of action of ataluren. DMD is a progressive degenerative disease in which muscle function declines monotonically over a patient's life due to the insufficient production of dystrophin. Ataluren restores dystrophin production and therefore would be expected to have a protective effect against muscular degeneration and slow the decline in muscle function. It is therefore plausible that delays in subsequent disease milestones are associated with ataluren treatment. This is supported by the results of Study 041 presented above, in which ataluren treated patients showed significant improvement in several ambulatory parameters compared to placebo treated patients within the ITT population. The STRIDE/CINRG comparison (data-cut from 31st January 2021) did demonstrate evidence of significant delays in the LoA and decline in pulmonary function. STRIDE patients demonstrated significant delays in ambulatory function decline compared to those in the propensity score matched CINRG DNHS population. Ataluren treatment was associated with a delay in LoA of 5.4 years (17.9 years of age vs 12.5 years of age) and reduced the risk of LoA by 63% compared to BSC alone ($p<0.0001$, HR 0.374). The median age at pFVC<60% was 17.6 years in the STRIDE registry versus 15.8 years in the propensity score matched CINRG DNHS population ($p=0.0051$, HR 0.544). The STRIDE/CINRG comparison controlled for known confounding factors through propensity score matching, such as age at first symptom, age at steroid initiation and duration of steroid use. The endpoints

		measured in the STRIDE/CINRG comparison are likely to be more representative of the disease and clinical practice. In the STRIDE registry, no patients receiving ataluren had died as of the 31st January 2021 data-cut. In contrast 45 deaths occurred in the CINRG DNHS (although it has not been reported how many of these occurred within the propensity score matched cohort). This suggests that a delay in mortality is observed in ataluren-treated patients. However, the mortality data is immature and so the impact of ataluren on delaying death is uncertain. Thus, the economic analysis modelled a delay in mortality for ataluren, as this endpoint is linked to decline in respiratory endpoints. A recent systematic literature review in DMD patients found that mortality increases with age and disease progression, with rates of up to 16% reported in those up to the age of 20 years, and among those surviving to adulthood, mortality was up to 60% by the age of 30.[1] **The data from the Managed Access Agreement (MAA)/NorthStar Registry comparison would not be appropriate to use in the cost-effectiveness model** The company also notes that while results from the MAA support the clinical efficacy of ataluren, the nature of these data makes them inappropriate for use in the cost-effectiveness model. This is primarily due to the limitations associated with the NorthStar Ambulatory Assessment (NSAA) method used in the MAA data collection. In young patients, NSAA typically improves in patients until the age of seven years and is therefore not appropriate for assessing delays in declining ambulatory function in this age group. The matching of MAA patients to control subjects from the NorthStar registry was not able to include age at first symptom, as this variable was not recorded. In addition, it should also be noted that the MAA was designed only to show a difference in trajectory of NSAA decline between the ataluren and control group and not to collect data to inform a health economic model. LoA was regarded as a more appropriate ambulatory endpoint to include in the model and to capture the efficacy of ataluren, as it is a clearly defined and measurable milestone

		in clinical practice. Therefore, the company preferred to use the STRIDE/CINRG comparison as a more comprehensive assessment (and larger patient dataset) of the clinical efficacy of ataluren. The company notes that because the majority of patients from the MAA were also included in the STRIDE registry, data from these patients does inform the cost-effectiveness model.
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs (ERG report section 5.3.5)	Yes	In the company submission, caregiver QALYs were estimated using an absolute caregiver utility approach, in which QALYs are accrued for each caregiver during a patient's life. While most HST assessments have used a disutility approach to estimate caregiver QALYs, it was not adopted in the company submission because it results in a counterintuitive situation wherein improved patient survival decreases the cost-effectiveness of ataluren. More specifically, ataluren-treated patients spend longer in severe health states and accrue additional caregiver disutility, whereas BSC-treated patients die earlier, and their caregivers therefore return to the general population utility sooner and therefore accrue fewer negative QALYs. The company acknowledges that there are also limitations with the approach taken to implement positive caregiver utilities in the model. The QALY gains in ataluren-treated patients may be exaggerated because positive utilities stop accruing when patients die, and an additional bereavement disutility is applied. Despite the limitations of this method, the company believes it is a more plausible implementation than the caregiver disutility approach suggested by the EAG as it implies that it would be more cost-effective not to seek to prolong the lives of patients with DMD. Indeed, removing the survival gain modelled for ataluren compared with BSC decreases the EAG's ICER to £[redacted], implying that prolonging survival is not cost-effective. The company also notes that the EAG's proposed approach applies age adjustments to caregiver disutilities. As a result of the way this has been implemented in the model (a positive age-adjusted caregiver utility weight applied to a disutility value), the caregiver disutility and therefore quality of life, improves over time and is likely to be underestimated, especially as patients progress to more severe health states.

		To resolve these issues, the company has explored several approaches to estimating caregiver QALYs to address this point: • Implementing positive caregiver utilities beyond patient death and a bereavement disutility that is applied to the caregiver upon the patient's death. This approach ensures that the effect of DMD on a caregiver's lifetime is accurately captured. However, the model is highly sensitive to the caregiver utilities, and modelling caregiver QALYs beyond patient death cannot be complete as the model only considers the lifetime of the cohort of patients. • Adapting the caregiver disutility approach proposed by the EAG, by applying a cap in the ataluren group to prevent the caregiver disutility in the ataluren arm from exceeding that in the BSC arm. This approach prevents a situation arising where it is no longer beneficial to prolong survival in DMD patients and was explored in TA755, as the Committee preferred that the inclusion of carer disutility did not result in fewer accumulated QALYs.[2] The impact of this cap is presented in the table of ICERs at the end of this response, and shows that it is reduced to £[redacted] (including the other relevant changes proposed in the company base case – use of Weibull parametric curves). • Removing caregiver QALYs completely presents an alternative to implementing a caregiver disutility approach that makes patient death preferable to extension of life however, this ignores the significant impact of the disease on caregiver quality of life. • Finally, the company investigated using the original approach of using positive caregiver utilities but only applying these **until patients reach the age of joint median survival for the two treatment arms in the model (ataluren plus BSC vs. BSC)**, rather than assuming that QALYs accrue until patient death (as per the original approach). This approach avoids the overestimation of caregiver utilities when QALYs are accrued beyond patient

		death, whilst also avoiding the counterintuitive result that is associated with the EAG's disutility approach. The company presents a revised base case using the median survival approach applied to absolute caregiver QALYs, as it is preferable to the disutility approach and it's limitations, and to neglecting the impact on caregiver quality of life altogether. At the original [redacted]% PAS discount, this results in an ICER of £[redacted], including the changes proposed by the EAG (modelling ataluren acquisition costs based on patient weight and age-adjusted utilities). In recognition of the uncertainty that remains in the economic modelling, the company have increased the PAS discount to [redacted]%, which further reduces the ICER to £[redacted] meeting the cost-effectiveness threshold for HST appraisals with the decision-modifier applied.
Issue 3: Limitations surrounding the company's survival modelling (ERG report section 5.3.5)	Yes	Regarding the parametric survival functions used to model health state transitions, independent curves were fitted to the patient-level data as the most parsimonious choice, as this does not rely on the proportional hazards assumption. Proportional hazards assume a treatment effect that is maintained throughout time and, although the assumption appeared reasonable for some endpoints (see Appendix), it was decided to select independent models as it is uncertain if this would be maintained at future timepoints. The EAG suggests that consideration should have been given to a broader range of models, including flexible parametric survival distributions. However, because the economic model is relatively insensitive to the survival function used, the company has not undertaken such analyses at this time. The EAG's preferred distribution of the Weibull curve is adopted in the company's revised base case. The company acknowledges that there is uncertainty regarding the cut-points used in the parametric survival modelling of each group. Therefore as a scenario analysis, the company has included analyses using a 3.5 cut-point for both BSC and ataluren. Using a cut-point of 3.5 for both BSC and ataluren has a minimal impact on the

		model results, with the ICER being either £[redacted] or £[redacted], without and with the QALY modifier respectively.
Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values (ERG report section 5.3.5)	No	The company maintains that treatment-dependent utilities are applied appropriately in the company's model. The assumption of improved health-related quality of life (HRQoL) in ataluren-treated patients compared to BSC-treated patients in all health states is strongly supported by clinical experts from two Delphi panels (described in the company's submission) and one independent UK clinical expert who we sought feedback from during the technical engagement phase. They mentioned that in addition to reaching key disease milestones, the HRQoL of patients is also influenced by additional disease symptoms such as pain, fatigue, problems with self-care, cognitive function, emotional stress, sadness and sleep, which cannot be fully captured within the economic model. Therefore, patients of the same age and in the same health state will experience a different burden of disease. The company believes that the assumption of treatment-dependent patient utility values is plausible in the context of ataluren's effect on delaying disease progression from ambulatory to non-ambulatory states compared to BSC and the limited data defining utility within the ambulatory state. It was agreed within the Delphi panel and with a UK clinical expert that there is likely to be progression through different ambulatory functionalities, and therefore there is likely to be variation in HRQoL values within each state. For example, an ambulatory patient who can largely ambulate unassisted is likely to have significantly greater HRQoL than an ambulatory patient who is only capable of short periods of ambulation, despite technically being in the same health state as each other. Furthermore, the former patient is more likely to be able to fully participate in activities common in early adolescence, which is important for the development of self-esteem, social relationships and self-identity. As ataluren delays progression to the non-ambulatory health state, the clinical experts noted that it is plausible that progression *within* health states is also delayed

		and therefore it is likely that ataluren-treated patients have improved HRQoL compared to BSC-treated patients across all health states. This improvement in HRQoL in ataluren-treated patients is also supported by statements from patient organisations. As reported by Muscular Dystrophy UK and Action Duchenne in the Patient organisation submission (Section 3) regarding a patient and caregiver experience survey, *"88% of respondents stated that being on Translarna [ataluren] had improved the individuals' overall quality of life. These patients were able to participate more in activities, found attending school much easier and were able to follow the workload (due to improvements in fatigue). Several respondents also noted the improvement in their child's behaviour as Translarna would lessen the number of emotional outbursts."* One respondent to the survey commented that *"He has more energy he's literally never tired. He can play for longer periods with his friends and join in without any problems. He has less falls, can walk long distances without getting tired. He can do lots of fun things that he enjoys doing which greatly improve the quality of his life."* Another respondent reported that: *"My son's behaviour improved almost immediately after taking Translarna and this made a fantastic difference to the whole family in terms of what we were able to do. He is not able to tolerate a full steroid dose but with Translarna there was an increase in ability as much as when he started taking steroids."* Additionally, 72% of respondents in the survey reported that ataluren treatment had a positive impact on their mental health, as it had given them "*hope for the future*" and allowed them to participate in everyday activities. One respondent reported that ataluren treatment had "*a huge positive impact; being able to be mobile, to do more every day activities have given him so much happiness and enjoyment of life, and also hope for the future has increased with taking Translarna*".

		The evidence provided from both clinicians and the patient and caregiver survey supports the use of treatment dependent utilities across all health states, as patients gain additional benefits from treatment as well as improved ambulatory function.
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age (ERG report section 5.3.5)	No	The company acknowledges that the modelling of ataluren acquisition costs based on the mean patient weight in the STRIDE registry introduces uncertainty into the model, as the use of a constant weight disregards potential differences in weight by age between each treatment group, and the overestimation of patient weights in younger patients may bias the results due to the discount rate multiplier. The company therefore proposes to instead use the results of the scenario analysis using RCPH patient weights to reflect the changes in weight distribution by age group and adjust this by [redacted]% based on the average weight reduction in DMD patients from the STRIDE registry compared to the general population. This is a more plausible scenario to consider as it assumes that patients gain weight as they age, but with a reduction applied to factor in the weight loss DMD patients experience as a result of the disease.
Issue 6: Uncertainty surrounding the discontinuation rate in patients with FVC>50% (ERG report section 5.3.5)	No	The company acknowledges that there is some uncertainty over the discontinuation rate of ataluren used in the model and the potential that it contains patients who are already included in the stopping rule. The discontinuation rate was sourced from the STRIDE registry which is the most appropriate source of evidence to use as it contains patients who received ataluren in a real-world clinical setting. The rate of discontinuation in the STRIDE registry has also been validated by an independent UK clinical expert as an appropriate estimate of discontinuation in clinical practice. As of January 2021, [redacted] out of 269 patients discontinued ataluren or changed dose in the STRIDE registry. Patients were treated for a median of [redacted] days ([redacted] years, range: [redacted] to [redacted] days). Reasons for discontinuation were: physician decision, n=[redacted]; loss of ambulation, n=[redacted]; family/participant request, n=[redacted]; AEs, n=[redacted]; non-response, n=[redacted], and other, n=[redacted]. The Kaplan-Meier plot of treatment duration in the STRIDE registry is presented below in Figure 1. As shown in the graph,

		discontinuations occurred consistently suggesting that the assumption of a constant discontinuation rate is appropriate. The company base case uses a discontinuation rate of [redacted]% per 3-month cycle, based on the STRIDE discontinuation rate of [redacted] patients who discontinued ataluren out of [redacted] over a period of [redacted] years. **Figure 1: Kaplan-Meier graph for time on ataluren in STRIDE** 
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule (ERG report section 5.3.5)	No	The company acknowledges that no stopping rule was implemented consistently, at least for all patients, in the STRIDE registry. This creates an issue of proposing any particular rule as this will be fraught with uncertainty. However, independent UK clinical experts have highlighted that applying stopping rules based on pFVC is a challenge, due to the difficulties in obtaining accurate height measurements for patients. A preferred option might be to focus on ventilation status and stopping treatment once patients require night-time or full-time ventilation. Given this uncertainty and the impact it has on cost-effectiveness, the company is open to considering different stopping rules. The current approach of using a

		stopping rule when pFVC<50% (i.e., patients are non-ambulatory and on night-time ventilation) is consistent with clinical opinion and practice, whereas an earlier stopping rule may reduce ataluren costs, thereby improving cost-effectiveness, but is less consistent with the clinical data. As such, the company presents revised estimates of cost-effectiveness based on both approaches.
Issue 8: Weak characterisation of uncertainty (ERG report section 5.3.5)	Yes	The company acknowledges that there are several parameters in the model for which uncertainty has not been extensively characterised. The company has therefore considered additional scenarios in the updated model, which can be found below. To improve the accuracy of the model's characterisation of uncertainty, standard errors have also been added to the model for patient and caregiver utility values, health state costs and patient weights where they are available in the referenced literature. Additionally, the company acknowledges that the shifted gamma distributions assigned to patient and caregiver utility values permit samples outside the range of the HUI3 and EQ-5D. To resolve this, the company has changed these parameters to use beta distributions in its updated base case. This limits variation to within the bounds of the HUI and EQ-5D instruments. The results of the probabilistic and one-way sensitivity analyses are presented at the end of this response (Figure 2 - Figure 7).

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

There are no additional issues from the EAG report that have not been discussed above.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 3: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	Impact on the company's base-case incremental cost-effectiveness ratio (ICER) (with decision modifier applied)
Company ICERs				
Initial company base case (at time of the NICE submission) at [redacted]% PAS discount	Incremental QALYs: [redacted]	Incremental costs: £ [redacted]	Company base-case ICER: £[redacted]	Company base-case ICER (with decision modifier applied): £[redacted]
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age	STRIDE patient weight	RCPCH weight for patients	£[redacted]	£[redacted]
EAG amendment to company base case	Patient and caregiver utilities not adjusted for age	Patient and caregiver utilities adjusted for age	£[redacted]	£[redacted]

Issue 3: Limitations surrounding the company's survival modelling	Log-logistic distribution applied to ambulatory health state transitions and non-ambulatory pFVC<50% health state transitions, lognormal distribution applied to pFVC<30% health state transitions.	Weibull distribution applied to all health state transitions (absolute caregiver utility approach)	£[redacted]	£[redacted]
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Absolute caregiver utilities only accrue until patient death	Positive caregiver utility approach applied until patients reach the age of joint median survival for the two treatment arms in the model (ataluren plus BSC vs. BSC)	£[redacted]	£[redacted]
Revised company base case following technical engagement (absolute caregiver utility approach and above changes) at [redacted]% PAS discount	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	Company revised base-case ICER: £[redacted]	Company revised base-case ICER (with decision modifier applied): £[redacted]
Revised company base case following technical	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	Company revised base-case ICER:	Company revised base-case ICER (with decision modifier applied):

engagement (absolute caregiver utility approach and above changes) at [redacted]% PAS discount			£[redacted]	£[redacted]
EAG ICERs				
EAG preferred base case (caregiver disutility approach)	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	EAG base-case ICER: £[redacted]	EAG base-case ICER (with decision modifier applied): £[redacted]
EAG preferred base case with Weibull parametric curves and cap applied to caregiver disutility approach	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	EAG base-case ICER: £[redacted]	EAG base-case ICER (with decision modifier applied): £[redacted]
EAG model – assuming no survival benefit	Incremental QALYs: [redacted]	Incremental costs: £[redacted]	EAG revised base-case ICER: £[redacted]	EAG revised base-case ICER (with decision modifier applied): £[redacted]

Table 4: Scenario analyses around revised company base case

Key issue(s) in the ERG report that the change relates to	Company's base case:	Change(s) made in scenario	Impact on the company's incremental cost-effectiveness ratio (ICER)	Impact on the company's incremental cost-effectiveness ratio (ICER) (with decision modifier applied)
Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population	Assumed 3-year delay to pFVC<50% and pFVC<30% health state transitions with early treatment	Early treatment benefit assumption removed for non-ambulatory health state transitions	£[redacted]	£[redacted]
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Absolute caregiver utilities only accrue until patient death	Absolute caregiver utilities accrue beyond patient death	£[redacted]	£[redacted]
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Caregiver mortality not applied as caregivers are only modelled until patient death	Caregiver background mortality applied after patient death	£[redacted]	£[redacted]
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Absolute caregiver utilities only accrue until patient death and caregiver mortality not applied as caregivers are only modelled until patient death	Absolute caregiver utilities accrue beyond patient death and caregiver background mortality applied after patient death	£[redacted]	£[redacted]

Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Absolute caregiver utilities applied	Caregiver utilities excluded	£[redacted]	£[redacted]
Issue 3: Limitations surrounding the company's survival modelling	Original data-cut points of 3.5 and 5 years for ataluren and BSC respectively.	3.5 analysis (applied to revised company base case)	£[redacted]	£[redacted]
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule	Stopping rule at pFVC<50%	Stopping rule at pFVC<30%	£[redacted]	£[redacted]
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule	Stopping rule at pFVC<50%	Stopping rule at 6 months post-LoA	£[redacted]	£[redacted]
PSA of revised company base case following technical engagement (absolute caregiver utility approach)	Incremental QALYs: [redacted] (modifier OFF) [redacted] (modifier ON)	Incremental costs: £[redacted] (modifier OFF) £[redacted] (modifier ON)	Company revised base-case ICER: £[redacted]	Company revised base-case ICER (with decision modifier applied): £[redacted]

References

1. Szabo SM, Salhany RM, Deighton A, *et al.* The clinical course of Duchenne muscular dystrophy in the corticosteroid treatment era: a systematic literature review. *Orphanet Journal of Rare Diseases* 2021. 16: 237.
2. National Institute for Health and Care Excellence. TA755: Risdiplam for treating spinal muscular atrophy - final appraisal document. 2021. at <https://www.nice.org.uk/guidance/ta755/documents/final-appraisal-determination-document-6>

Appendix

Figure 2: Incremental costs versus incremental QALYs (QALY modifier off)

Figure 3: Incremental costs versus incremental QALYs (QALY modifier on)

Figure 4: Cost-effectiveness acceptability curve (QALY modifier off)

Figure 5: Cost-effectiveness acceptability curve (QALY modifier on)

Figure 6: OWSA tornado diagram (QALY modifier off)

Figure 7: OWSA tornado diagram (QALY modifier on)

Issue 3: Limitations surrounding the company's survival modelling (ERG report section 5.3.5); proportional hazards testing

Proportion of patients with pFVC>30%	
Log-cumulative hazard plot	Schoenfeld residuals plot
[redacted]	[redacted]

Proportion of patients with pFVC>50%	
Log-cumulative hazard plot	Schoenfeld residuals plot
	

Proportion of patients without loss of ambulation	
Log-cumulative hazard plot	Schoenfeld residuals plot
	

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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

Thank you for agreeing to comment on the evidence review group (ERG) report for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology evaluation (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

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

Deadline for comments by **5pm** on **15 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Anne-Marie Childs
2. Name of organisation	Leeds teaching Hospitals
3. Job title or position	Consultant Paedaitric neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene? ☐ A specialist in the clinical evidence base for Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other : I have not seen the document submitted on behalf of the Northstar network of clinicians
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of treatment with Ataluren is to slow down the rate of progression in muscle weakness that occurs in DMD associated with NS mutation seen with best supportive care There is no evidence that boys with NS mutations have a different disease trajectory than those with other mutations resulting in a truncated protein. Therefore the expected disease trajectory with BSC, including the use of long term steroids, is that boys will lose ambulation between 12-14 yrs on average and that this will be followed by progressive weakness in trunk and upper limb muscles and finally weakness of the respiratory muscles. Slowing down the rate of progression in NS mediated DMD will delay the loss of ambulation, and allow affected individuals to preserve their independence for longer. This means that young people are more able to participate in activities at school, are growing and going through puberty in an upright position which is better for long term spinal posture and respiratory function and are able to maintain their confidence and social engagement. Preserving trunk and upper limb mobility, supports independent transfers from chair to bed and vice versa and to toilets and shower chairs. This preserves independence and self care, with individuals retaining the ability to feed independently for longer, to manage their own toileting with simple adaptations rather than with 1-2 carers and to record their written work , engage in other fine motor tasks more effectively on their own Studies have shown that the deterioration in respiratory muscle in DMD mirrors the weakness in other skeletal muscles and occurs later in the disease course.

	Slowing down the rate of progressive weakness will delay the onset of respiratory muscle weakness and reduce the requirement for additional ventilatory support and hospital admission with recurrent infection in adolescents and older children meaning that they have achieved full lung growth and are more mature when they face these complications
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Delaying loss of ambulation by more than 1-2 years is a significant benefit for the reasons stated above. The Stride study has confirmed that Ataluren delays loss of ambulation by 5 yrs. This means that boys overall function will be preserved through a critical time of physical and emotional development Delaying loss of upper limb function and the development of scoliosis means that young men are more functional at the time of entering high school. Lack of respiratory symptoms and preserved muscle strength and ability to maintain sitting posture and head control mean that teenagers will enjoy better general health at key points ie GCSE and A levels and are more likely to fulfil their potential. This in turn should give better opportunities for employment and tertiary education. In addition young men with better muscle function can engage in relevant social activities without fatigue and without needing high levels of supervision and adaptation. This is critical to emotional health and overall well being.
10. In your view, is there an unmet need for patients and healthcare professionals in Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene?	In my personal experience boys treated with Ataluren have followed a better disease trajectory with slower progression, maintaining their functional motor skills for longer. This has also been evident in the Stride dataset
11. How is Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are	There is no 'curative' treatment for DMD, but all boys with DMD should be managed within specialist NM centres offering BSC in line with current standards of care recommendations. These international guidelines are currently being reviewed and updated in the UK as part of the DMDCareUK project which was started in response to variations in resource allocation and access to specific elements of care in different parts of the country. It is likely that the evidenced based recommendations provided by the project will form the basis for care

there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	going forward and hopefully help address gaps in provision of care. At present it is recommended that all boys are started and maintained on glucocorticoid treatment and this is the case for those with NS mediated DMD Currently ambulant boys with NS mutations over tha ge of 2 yrs are able to access treatment with Ataluren via the NHSE managed access agreement. Treatment cannot be continued once the boys/young men have lost independent standing and so non ambulant boys with DMD are precluded from treatment even if there is evidence of sustained upper limb function
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	I would envisage being able to continue treating young men with NS DMD who have been shown to benefit from Ataluren once they have lost their independent standing for the reasons stated above and the potential benefits in terms of upper limb and respiratory function I think Ataluren should continue to be prescribed through specialist NM centres who have the expertise to manage all elements of the condition. This means that if treatment is continued following loss of ambulation the adult NM centres will need to develop their experience in using the drug and monitoring for benefits and risks of treatment The adult Northstar network is not as comprehensive as the paediatric network and typically does not have access to the same multidisciplinary resources as children's services. This is a wider issue/concern as it effects all those with DMD now living in adulthood and not just those with NS DMD.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes - I have outlined the benefits above on the basis of the data from post trial patients and the Stride database.

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	If we preserve muscle strength and delay the onset of respiratory muscle weakness this is likely to improve life expectancy Young men with DMD are living longer as a result of improvements in supportive care. Steroid use has delayed rate of progression in DMD and the onset of respiratory failure further increasing the life expectancy as evidenced in surivial studies over the last 5 decades. Other medication that further delays the rate of decline is likely to translate into improved life expectancy, although the effect of Ataluren on cardiac muscle and the dilated cardiomyopathy seen in DMD is not yet clear. Cardiac involvement in DMD does not typically mirror skeletal muscle weakness. Although the incidence increases with age, there are some younger patients with significant cardiac disease and this is why the mean age of death in DMD has remained lower than the mean rate of survival. This may still be the case for Ataluren
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are likely to be some boys who respond less well to Ataluren than others, but the factors predicting response to treatment are not clear. This will need to be monitored and it will be important to ensure that the benefits of treatment outweigh any side effects for an individual patient
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The drug is given orally 3 times a day. The dosing is complex and the drug comes in a sachet that needs to be mixed with a liquid or semi solid. Complying with a 3 x daily dose regime for medication that needs preparation may be daunting for some patients and monitoring compliance will be really important. All those with NS DMD should be seen in their NM centres at 6monthly intervals according to Standards of care and so monitoring of Ataluren should be feasible in this context. However not all units have the resources to meet this standard of care. Monitoring specific blood tests including lipids is also advised and is not

	currently part of routine testing
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	At present we are following the terms of the MAA in the UK Given that the treated patients are still expected to decline, albeit more slowly than untreated patients, it will be difficult to set specific functional test to confirm benefit However if there is a sense that AEs/difficulty taking the medication outweigh the expected benefits, then it would be appropriate to stop treatment Similarly if there is poor compliance I do think we need to reconsider the possibility of continuing treatment in those who have clearly benefited when ambulant for reasons stated above.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	See above re likely better attainment and improved emotional/psychological well being if we can retain postural control, good upper limb function and delay respiratory failure This could have benefits for individual QofL and that of the patients carers if independence an ability to participate and engage in activities is preserved for longer QofL tools used in standards assessments do not reflect the true picture in DMD. Project Hercules has produced new PROMs that may be more relevant for assessing benefits in DMD
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Ataluren is a step change in the management of NS related DMD, but this is a small part of the affected population, the majority of whom have a different genetic mechanism underlying their DMD. The data from Stride and the LTE shows significant difference in the treated NS

• Does the use of the technology address any particular unmet need of the patient population?	patients in comparison to others with DMD As there are no other options for genetic modification in this cohort at present then yes Ataluren is addresses an unmet need in this population
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most individuals tolerate the drug well, but there are some patients who have developed problems during treatment, although it is not clear whether these changes in lipid, thyroid parameters are disease related, steroid related or a direct consequence of Ataluren use As mentioned before , it does require preparation and planning to take the drug 3 times a day
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Our knowledge of the natural history in DMD is evolving as evidenced by the recent publication from the Northstar group in Dev Med Child Neurology 2022, 64;979-989. The original clinical trials had not targeted boys at the time when we would expect a significant difference in disease trajectory between the treated and control group. Greater clarity about the functional abilities of boys with DMD has refined the criteria for subsequent clinical trials in DMD. Boys are now selected if there are in the 'late ambulatory' disease phase as this is time when difference can be seen within the time frame of most RCTs. The phase 3 study used predetermined subgroup analysis to identify the differences between control and treated groups. The Stride dataset has also used case matched controls The MAA Northstar matching has not shown significant change but the numbers are smaller and the Covid pandemic meant that many boys with DMD were not able to undergo their routine functional assessments in face to face clinic, or to access their usual therapy regimes.

	The MAA matching was done prior to the most recent evaluation (ref above) that has identified 4 disease trajectories each of which has a different rate of decline and can make control groups varyingly representative of the actual disease process
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I have reference the Stride dataset, MAA and longer term extension studies. I am not aware of any other datasets other than the clinical trials and personal observations from expert clinicians There has been a publication using Delphi panel model to assess the validity of the disease model to capture the effects of Ataluren (https://doi.org/10.1080/13696998.2022.2085444) of which I am a co-author
22. How do data on real-world experience compare with the trial data?	Real world experience mirrors what has been shown in the Stride dataset. This is consistent with patient feedback on a personal level, as part of this technology appraisal and within the Delphi panel The trial data was impacted by the selection of patients at different stages in the disease course, although the predetermined subgroup analysis attempted to offset this
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other	I think the issue of discriminating against older more severely affected patients needs to be considered The current MAA does not allow continued treatment in non ambulant patients although there is no biological reasons why the upper limb , trunk and respiratory muscles of non ambulant patients would not respond to treatment. These patients were not included in the original study and so it is difficult to provide 'trial' data to support this use Evidence from other disease modifying drug treatments that slow down but do not stop the rate of progression - - steroids, some of the exon skipping drugs is that the benefits on lower limb function as measured by delayed Loss of ambulation are mirrored by delay in the rate of progression in other skeletal muscles.

shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	There are patients who have remained on treatment despite losing ambulation post trial who report sustained benefits I have also had patients who are happy to discontinue treatment at the point of losing mobility It is really important not to deny weaker and older patients with NSDMD the opportunity of preserving their motor function despite the fact they were not included in the original trials Maintaining fine motor skills can be critical in independent operation of controls , computer use, communication all of which have a major impact on overall well being and ability to participate in work and social activites

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the evaluation committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population (ERG report sections 4.3 and 5.3.5)	I am not an expert on disease modelling but I do think the curves looking at relative shift of age at which particular milestones of decline in DMD are reasonable There are significant differences noted in the functional outcomes of those treated in the Stride dataset in comparisons to matched controls, which are reflected in patient experience and those of their treating clinicians In terms of motor function, this is not just about a step wise change in function ie walking to sitting to not sitting independently There are stages in between that have clear impacts on quality of life - walking long distances outside v walking short distances outside to get into the car of from the car to a building without aids, walking effectively inside - at school or home, walking short distances and crossing a room independently v not being able to do this, to being able to stand to PU - each of these stages has

Clinical expert statement

	functional benefits and staying in these states for longer is associated with more independence, improved participation and in turn better over all well-being There are similar stages to being a 'sitter' - from one who can independently transfer, feed themselves, reach for objects at suitable heights through to a 'sitter' one who cannot sit unsupported without full head control and cannot operate standard controls. Clearly preserving someone in the state of being an independent sitter has significant benefits of quality life of both the individuals and carers. The respiratory data is difficult in both the MAA and Stride as the patients have not all reached the age at which respiratory decline is seen and many patients can not be included in analysis I have highlighted some of the challenges with the Northstar dataset above and the potential bias that can result from using a a relatively small dataset for the control group Similarly I have commented above on the issue regarding survival and the fact that in my view the extrapolation of improved OS is reasonable on the basis of the natural history and survival studies The issue regarding younger children is also challenging as in the short term - again on basis of Northstar publications we recognise that all children - irrespective of their subsequent disease course will achieve higher scores on the NSAA as they mature and make overall developmental progress. This makes it difficult to show a benefit in the younger patients if they have not reached an age where we start to see decline in NSAA - typically after 7 years. The numbers are small. However, if, as has been shown, Ataluren does have an effect at modifying the disease process and slowing down the rate of decline in muscle powere, it would not make biological sense to delay treatment to a point where there has been further muscle fibrosis and necrosis as the greatest benefits are likely to be seen in the 'strongest/best preserved muscles where restoring the dystrophin protein can have an effect on the muscle function.

	Regarding optimistic milestone prediction, I think it is likely that some boys will demonstrate better response than others, but the predictions come from the results of LTE and Stride which have followed boys /young men for the longest periods on steroids. These have been validated by the Delphi process among a number of clinical experts treating both children and adults with NS DMD
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs (ERG report section 5.3.5)	This is always challenging and I don't feel I can comment on the detail of the economic model It is reasonable to assume that carer needs increase as the muscle weakness progresses and the individuals independence declines.
Issue 3: Limitations surrounding the company's survival modelling (ERG report section 5.3.5)	I am not sure what clinical feedback I can give other than what I have stated above regarding the impact on OS of delaying muscle weakness and how this mirrors a delay in loss of ambulation I am happy to respond to specific questions from the panel
Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values (ERG report section 5.3.5)	I have set out why I believe there are differences in health utilities for patients in both ambulatory and non ambulatory. These differences reflect how their overall muscle strength and function impacts on their functioning and quality of life - I have given examples above Thus a stronger ambulant or indeed non ambulant patient with DMD has a higher utility score than a weaker ambulant or non ambulant patient. It is therefore reasonable to assume a patient whose muscle function is declining more slowly will remain more functional than someone who is still in the same health state but considerable weaker and more dependent on aids/adaptations and carers to compete the same functional tasks.

	I have explained in the previous section why maintaining postural control (delaying onset of scoliosis) and respiratory function has a positive impact on well being
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age (ERG report section 5.3.5)	Again, I am not an expert of modelling but the pattern of weight gain in patients with DMD is somewhat different to the unaffected population At presentation boys with reduced muscle bulk may be lighter than expected for height. With restricted mobility and steroid use, the majority of boys will gain weight above expected rate whilst experiencing restriction in their height such that their BMI increases. Boys with DMD on steroids have delayed puberty and restricted height which results in high BMI but not necessarily body weight at the expected level for age As the disease progresses and eating becomes more challenging , older boys /young men can lose weight dramatically
Issue 6: Uncertainty surrounding the discontinuation rate in patients with FVC>50% (ERG report section 5.3.5)	From a clinical perspective, I think that using a stopping rule that is dependent on a measurement such as FVC% which can be challenging to capture in certain patients and is dependent on accurate height estimate which is particular difficult in non ambulant patients, it would be better to use a clinical end point FVC< 50% is felt to be the point at which patients may require overnight ventilatory support so it would be more practical to use initiation of routine non invasive ventilation at night for more than 21 days (to allow short term use in the face of infection/post operatively) as a stopping criteria In my experience given the fact that this is a 3 x a day medication that has to be mixed or dissolved in a palatable solution, patients do not want to continue treatment if they don't feel it is beneficial so they will be some discontinuation outside the stopping rule above.

	I think there may be challenges in compliance with some of the younger patients and this must be considered as a reason for stopping if the treating clinician is not confident that the medicine is being taken as advised.
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule (ERG report section 5.3.5)	I have addressed the issue of treating non ambulant patients already and the fact that this is potentially denying a cohort of patients effective care
Issue 8: Weak characterisation of uncertainty (ERG report section 5.3.5)	This is outside my area of expertise
Are there any important issues that have been missed in ERG report?	Not to my knowledge, other than the clarifications and issues I have raised already

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert technical engagement response form

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

Thank you for providing us with a patient expert statement or on behalf of your nominating organisation a patient organisation submission.

We are now asking for your input to the technical engagement stage of the evaluation. The evidence review group (ERG) report and stakeholder responses are used by the evaluation committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

In part 1 we are asking you to provide answers to questions that are specific to the evaluation that were not included in your patient expert statement.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Deadline for comments by **5pm** on **15 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 1. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report (section 1.1), the patient organisation responses will also be considered by the committee.

Table 1 Issues arising from ERG report

Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population (ERG report sections 4.3 and 5.3.5)	
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	Here is a summary, followed by more detailed information about each stage. My son [redacted] is 18 and has been taking Ataluren since January 2014, when he had just turned 10. I can't comment on the stage of needing assistance with ventilation, or assistance with eating, as [redacted] does not need assistance with ventilation or with eating.

How is caregiver quality of life affected by the condition at different disease stages?
 	
we consider patient perspectives may particularly help to address this issue
(ERG report section 5.3.5)
	Summary:
	• Caregiver burden increases significantly at
	  ○ Loss of ambulation
	  ○ Needing to transfer using a hoist and sling rather than a sliding board
	  ○ Loss of upper body/limb strength
	• The increase of the care burden is mainly due to
	  ○ Ensuring things are within reach ongoingly throughout the day
	  ○ The frequency, duration, and complexity of transfers
	  ○ Providing personal care support
	  ○ The level of detailed advanced planning needed
	• Social isolation significantly increases
	  ○ At loss of ambulation
	  ○ At needing to transfer using a hoist and sling
	• Stress and anxiety/depression is caused by, and increases due to
	  ○ Watching your child's condition deteriorate
	  ○ The learning curve needed to master the management of DMD at each new stage of the condition
	  ○ The increased care burden at each new stage
	
	Caregiver quality of life at different disease stages:
	
	Factors affecting caregiver quality of life at different disease stages are listed below. First, however, I would say that two factors affect caregiver quality of life throughout every disease stage:
	• Overriding anxiety to slow down the rate of progression of DMD – because it increases life expectancy and enables your child to do more for longer; and also because if you can slow things down, if there is even some stability, it gives you time to manage the condition more successfully at each stage and prepare for upcoming changes in the condition.

	• Concern to maximise your child's quality of life and for them to be able to live life to the full, socially, creatively, and in terms of independent living and employment. The greater mobility you have, the easier this is – even if you use a wheelchair, if you can transfer independently and have upper limb mobility it makes a huge difference **Diagnosis / Early ambulation** • devastation at our son [redacted]'s diagnosis (he was 4 years old); profound grief, depression, and anxiety in the years following diagnosis. • a steep learning curve at that time as we researched the condition, its prognosis and possible treatments; navigated the 19 or so specialists involved in our son's care; researched/negotiated to find a wheelchair accessible school with an inclusive ethos; applied for a Statement of Special Educational Need; applied for Disability Living Allowance; learned how to do the daily physiotherapy, and occupational therapy exercises; and researched possible clinical trials and their inclusion criteria. • A steep learning curve to understand [redacted]'s complex learning and behaviour profile and how to meet his learning needs. DMD affects [redacted] cognitively as well as physically and he transferred aged 8 from mainstream to special education. • Physical care work involved daily physiotherapy stretches but otherwise was not significantly different from having an able-bodied child, as [redacted] was independently able to for example get in and out of the bath, get in and out of bed, get things that he needed, pick things up off the floor, and meet his personal care needs including going to the toilet and dressing/undressing. • Social isolation was not an issue as [redacted] could access friends' houses and have sleepovers. While he was slower physically than his peers it didn't make a significant difference socially.

	As his parents, we were able to leave [redacted] with friends and grandparents and so have breaks and time for our own relationship. • I had to cut my work hours to cope with the emotional impact of DMD (on myself and to support our family to cope), manage the number and frequency of appointments, and address the steep learning curve of understanding how to manage DMD and support [redacted]'s learning and behaviour needs. • I am a teacher and write educational materials freelance. It has been difficult to hold on to my work and any sense of career progression in the face of [redacted]'s care and educational needs. This difficulty increased at [redacted]'s loss of ambulation and increased again with him needing a hoist to transfer. • Stuart, [redacted]'s dad, continued and still continues to work full time. He is a university academic. He has not been able to have the career progression that he would otherwise have had, due to the impact of care work at home and the psychological demands of coping with [redacted]'s DMD. **Late ambulation** • Stressful and ongoing concern for [redacted] to walk for as long as possible, because we knew that delaying loss of ambulation would increase his life expectancy • This stress included a hugely difficult decision about increasing the dose of steroids to support [redacted]'s ambulation. We were between a rock and a hard place because of worry about the side effects of an increased steroid dose. • The stress also included great anxiety that [redacted] would continue to walk long enough to be included in a clinical trial for a potential treatment.

	• Physical care work involved daily physiotherapy stretches but otherwise was not significantly different from or more time-consuming than having an able-bodied child as [redacted] was still independently able to for example get in and out of the bath, get in and out of bed, get things that he needed, pick things up off the floor (with long-handled tweezers), and meet his personal care needs – including going to the toilet and dressing/undressing. • [redacted] had mobility equipment at this time to support him: a powered wheelchair for longer distances, an electric adjustable bed to support him to sit up in bed, a bath chair so he didn't have to sit down and stand up in the bath, a supportive frame for the toilet and urine bottles so he didn't always have to walk to the toilet. This equipment was provided by the local authority and enabled [redacted] to meet his needs independently and not have continuous care support from carers. • We had to adapt our house, as it became difficult and potentially dangerous for [redacted] to use the stairs (though he could still walk around the house on the level and manage a step or two), and additionally we were anticipating his future full-time wheelchair use. Adaptations included a level access entrance and a downstairs bedroom and bathroom. The local authority provided a £30k grant but the adaptations cost more than that – we met the additional cost ourselves. • [redacted] could independently walk around the house, sit on the sofa, and sit at the table. Being able to use ordinary domestic furniture/space along with other members of the family makes you feel included – a big positive psychological impact. • Social isolation was not a significant issue for us as parents or for [redacted], as [redacted] could still visit friends and extended family. Sleepovers were possible where friends/relatives had downstairs facilities, hired equipment such as a toilet frame, and had a clear understanding of [redacted]'s physical limitations. Therefore, arranging an overnight break for us as parents involved increased planning but was possible with friends/family. Also, as parents we could

	leave [redacted] with a sitter and go out for the evening, so we could still relatively easily have breaks and time for our own relationship. • We made sure we got out and did the things that [redacted] could still do reasonably easily – e.g playing on the beach, swimming in the sea, going on holiday by train and plane, climbing hills, visiting castles, climbing an observatory to look at the stars. [redacted] took a Dreamflight trip to Disneyland in Florida. We felt that such experiences would build his resilience for later in life, giving him self-esteem, zest for life, and feeling like he had not missed out when these things were possible. • I was able to work 17 hours per week and manage care work at this stage. **Early non-ambulation** • Grief and trauma at [redacted]'s loss of ambulation, particularly because it was preventable and earlier than it would otherwise have been. He was able to walk and got up to use the urine bottle. His carer hadn't put the bottle within reach, and because of his cognitive impairment [redacted] forgot that his shorts were round his ankles, and he tripped up. It was just before his 14th birthday. He had osteoporosis due to steroid use and sustained a spinal compression fracture**.** Standing up was painful after this and he never recovered his walking. • It was a quite steep learning curve at this stage, to understand how to support [redacted] to transfer and how not to risk physical damage by trying to lift [redacted] • Very significant anxiety, depression, and anger as we began to experience the lack of wheelchair accessibility in the world around us – eg [redacted] is no longer being able to visit friends in their houses unless the house was wheelchair accessible. • Care work was more demanding in terms of time and planning. Transfers are a big factor. [redacted] used a slide-board to transfer, e.g. from bed to wheelchair or shower chair, or from shower chair into the bath chair. Every transfer needed to be supported by a carer, to place

	and support the slide-board and gently support [redacted] to shuffle across the board. Over the day there are numerous transfers: getting out of bed, going to the toilet, getting into the wheelchair, transferring out and back again to have a break from the wheelchair, then transfers to get ready for bed – out of the wheelchair, into the shower chair, then into bed. Additionally, swimming several times a week is crucial for exercise and physiotherapy; this involves transfers from wheelchair to poolside chair, poolside chair to changing table, then back into the wheelchair. • With good upper body strength, [redacted] continued to be able to do his usual activities independently, even though he was in a wheelchair. These activities included cooking, drawing and painting, playing the keyboard, picking up the phone to answer it, getting things from that he needs from shelves, and lifting books to read them • Good upper body strength meant that, apart from transfers, independent self-care was fairly straightforward - [redacted] could shuffle forward in the wheelchair to use a bottle to urinate during the day and use a bottle to urinate overnight. He had strength to wash himself, clean his teeth, and dress/undress himself. • We had to get the kitchen adapted to enable [redacted] to access the kitchen independently in a wheelchair, e.g. fit his legs under the hob, or drive alongside the oven. These adaptations cost £9k and were funded mainly by the local authority. • Psycho-social care work significantly increased at this stage, as the side effects of steroids became more problematic for [redacted]. These included delayed puberty, managing hunger / potential weight gain, and increased behavioural challenges when combined with the teenage years. I would say that half of managing DMD is just managing the side effects of steroids. Weight management is particularly psychologically challenging for a non-ambulant teen, especially given that chocolate / burgers / chips are everywhere. • Social isolation became much more of an issue for [redacted] and for us as parent carers. Once [redacted] lost ambulation, he could not spend the night anywhere without a carer to support the

	transfers. It was not appropriate or safe to ask family and friends to undertake this care work – it needed to be a trained person such as ourselves as parent carers or a trained professional carer. This means that as parents we are quite isolated, unable to go out unless we have professional carers to take over the care work. • The time and mental/emotional challenge of care work increased after [redacted] lost ambulation. We got a carer for 10 hours a week and with that support I was able to work 15 hours a week. **Later non-ambulation ([redacted] is now 18)** • Hoisted transfers - [redacted] now needs to be hoisted to transfer. This is not because his condition has significantly deteriorated; it is because [redacted]'s physiotherapist is pro-active in taking measures to prevent scoliosis, by ensuring that all the teenagers she sees with DMD are fitted with moulded wheelchair seats. These seats are designed to supporting a healthy posture and spine by fitting very snugly. With his moulded wheelchair seat, [redacted] can't transfer by sliding sideways because the moulded seat has high immovable sides. • Increased time on care work: when a person needs to be hoisted rather than use a sliding board transfers take much longer. Transfers can take 15 minutes with a hoist instead of 2 minutes with a sliding board. • [redacted] has less independence with personal care. Because of the moulded seat, [redacted] can't shuffle forward in his chair to urinate. He uses a sheath catheter with a leg bag and needs a carer to empty the leg bag whenever he urinates. • There is a learning curve involved in learning to use a sling and hoist to do a transfer, and to fit and manage the sheath catheter system. We and everyone who works with [redacted] needs to be trained to use this equipment. • [redacted] has now been allocated 52.5 hours per week care support and he has a team of five carers covering 48 of those hours. I manage [redacted]'s care team and that takes time and

	mental energy – recruiting, sorting hours, pay, holidays, and other admin, liaising with the payroll company, and making sure carers have the right training and support. When [redacted] was more mobile and had just one or two carers this took much less time and effort. • Due to the problems in social care provision we can't find enough carers to fill the slots we need, so Stuart ([redacted]'s Dad) and I fill in the gaps. We are also the backstop any time one of [redacted]'s carers is absent. It's relentless and exhausting. • We are vulnerable to physical impacts, for example I have had three hernia operations and Stuart has back problems. • Care work impacts on our relationship with [redacted]. We have to work hard to have a healthy relationship as parents with our teenage / young adult son. It is challenging to support [redacted]'s increasing independence as an adult while also being in a caring role in relation to him. • The extra time needed for care work means that as partners, [redacted]'s dad and I have less time with each other. • The need for increased care support means that we have much less time as a family. Either we do the care work ourselves, or we have carers coming to the house. [redacted] has some wonderful carers who he and we love; however, the situation is that they are at work in our home, our domestic space, and managing that situation can be challenging. • Increased social isolation: once a person can't transfer using a slide board, the access difficulties which already exist increase further and social isolation increases as a result. For example, [redacted] can't use local swimming pools which have a poolside hoist, but no hoist to transfer from a wheelchair to the poolside hoist chair. If travelling by car, [redacted] has to use our adapted wheelchair accessible vehicle; he can't just slide onto a seat into a regular car and get a lift somewhere with a friend.

	• Travel becomes much more difficult. Everything has to be planned in detail in advance, with very significant anxiety if plans fail. If we hire equipment eg profiling bed and hoist, is it going to turn up? Will someone be there with a ramp so [redacted] can get off the train? Will his wheelchair get damaged in the hold of the plane? That anxiety is a deterrent to heading out, so [redacted]'s world gets smaller. • Going on holiday, either as a family or [redacted] accessing eg a summer school with his peers, is a major challenge and expense – we have to ensure that the accommodation is wheelchair accessible, pay for an extra room for a PA, pay for hiring an adjustable bed, a mattress, a hoist, and a shower chair, and either have enough direct payment hours from the local authority to pay for PA time, or pay for it ourselves. • Physiotherapy is more demanding and costly for non-ambulant people who need a hoist to transfer and who are at a later stage of DMD, for example travelling a distance to use a pool with a changing room hoist, travelling to access a hydrotherapy pool (at £50 a time). • Being less mobile means that [redacted] is much more vulnerable and dependent. It's harder to access study and employment opportunities. For example, [redacted] wanted to go to a residential college that offered his choice of course, but is unable to because the college can't accommodate a student who needs hoisted transfers. Much of my time is taken up as his advocate, supporting him to access study, work experience, and social opportunities. We haven't embarked yet on the questions of employment or independent living. • It is frustrating for [redacted] and for us to live with this level of vulnerability and dependence and it takes a toll on mental health. • The pressure of care work, managing a care team, and advocacy means that the hours I can work have reduced to approximately ten per week.

Issue 3: Limitations surrounding the company's survival modelling (ERG report section 5.3.5)	
Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values How appropriate is it to assume different quality of life estimates between the treatment and comparator group for the same disease stage? (i.e higher quality of life for the treatment group in the same disease stage) **we consider patient perspectives may particularly help to address this issue** (ERG report section 5.3.5)	It is appropriate to assume different quality of life estimates between the treatment and comparator group for the same disease stage, for the following reasons: • The stages of the condition are happening later and more slowly • More years of relative mobility give children living with DMD early and ongoing experience of being able to do physical activities such as playing on playground equipment, riding a bike or trike, and walking. Those physical experiences develop neural pathways, thereby supporting physical and neural development; they help to develop self-esteem and a can-do attitude; and give children the experience of social inclusion. • More years of ambulation correlate with a longer life expectancy for people living with DMD • More years of relative mobility in turn provide a foundation for greater emotional resilience for patients when dealing with the later stages of the condition. This is partly due to the developmental and psychological foundation they provide and also because a person can look back on years that were not 'eaten' by DMD. • It makes a huge difference emotionally and psychologically to know that you are on a treatment that is slowing the condition – you've feel you've got some power to fight the condition • Because the decline is slower, you are looking forward to a longer life expectancy. And this includes being able to dream, plan, and achieve your goals. • If each stage of the condition is longer, this enables both patients and carers to manage the condition better. With a progressive condition it's always a moving target: physio, moving and handling, equipment and adaptations, nutrition, bone health, endocrine issues, occupational therapy, respiratory support, cardiology – the management of all the aspects of

	this complex condition change as the condition progresses. If each stage lasts longer, and the progression is slower, there is more time to master what you need to know at any given stage. You know what you are doing and can manage it better. You also have time to learn about and prepare yourself for the next stage. • There is longer time to get the equipment you will need. With the current challenges in social care, getting the right equipment can take a long time – we have been told it will take a year to get approval and funding from the local authority to install a level access shower in our new house. • Having longer to prepare for and master the management of each stage means in my case that I am less anxious. It's hard to underestimate both the mental effort needed to learn the optimal management of DMD at each stage and also the emotional strain of anticipating the progress of the condition. This effort and strain, as well as the sheer time needed for care work, impact on carer's mental health and their capacity for paid work over and above being a carer. • Parents and adult patients are employers of Personal Assistants (PAs) and in the position of training PAs. Each progression in the condition requires PAs to be trained in the optimal management of that stage of progression. The training is ongoing work for parents and adults living with DMD, work which takes planning and time. Slower progression means that PAs can get on with the job and parents/patients have more time to get on with their lives before addressing the demands of the next stage.
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age	

(ERG report section 5.3.5)	
Issue 6: Uncertainty surrounding the discontinuation rate in patients with FVC>50% (ERG report section 5.3.5)	
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule (ERG report section 5.3.5)	The treatment should be continued for as long as it benefits the recipient.
Issue 8: Weak characterisation of uncertainty (ERG report section 5.3.5)	
Are there any important issues that have been missed in the ERG report?	

Part 2: Topic specific questions

What do patients or carers think about the current treatment stopping rules in the managed access agreement?

Patient expert technical engagement response

I think that the current treatment stopping rules are inappropriate. If Ataluren slows disease progression in ambulant patients there is no reason why it should not slow disease progression in non-ambulant patients. Because [redacted] took part in a clinical trial for Ataluren, he is still on Ataluren even though he has lost ambulation. He is 18, doesn't need additional ventilation, and has relatively strong upper limb function. In particular, the fact that he doesn't need support with eating and drinking vastly increases his independence and reduces the burden of care work. In my opinion it is likely that Ataluren has made this possible.

In the context of there being no other treatment available which targets the underlying cause of nmDMD, and no reason to suppose that Ataluren is not effective in non-ambulant patients, I think it is unethical to stop treatment when a patient loses ambulation.

What do patients or carers think about the removal of the following wording from section 4.1 of the Summary of Product Characteristics (SmPC) for ataluren: "Efficacy has not been demonstrated in non-ambulatory patients"

I can only speak from our personal experience. [redacted] has lost ambulation. He is 18 and a half and does not need ventilation or support with eating. He is able to lift a cup to his mouth, demonstrating functional upper limb strength. He has been taking Ataluren since he just turned 10.

What do patients or carers feel are the benefits and disadvantages of the potential continuation of treatment in people who have lost the ability to walk?

Benefits:

- Ataluren continuing to slow disease progression in non-ambulant patients (as outlined in the answer to the previous question)

- The psychological advantage for patients and their families of patients of continuing to take a treatment that is slowing disease progression. The significance of this can't be overstated. It reduces anxiety, empowers people, and gives hope for a longer, more fulfilled life.
- The creation of a broader evidence base, over time, for the impact of the treatment on non-ambulant patients with nmDMD

Disadvantages:
No disadvantages.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert technical engagement response form

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

Thank you for providing us with a patient expert statement or on behalf of your nominating organisation a patient organisation submission.

We are now asking for your input to the technical engagement stage of the evaluation. The evidence review group (ERG) report and stakeholder responses are used by the evaluation committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

In part 1 we are asking you to provide answers to questions that are specific to the evaluation that were not included in your patient expert statement.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Deadline for comments by **5pm** on **15 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 1. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report (section 1.1), the patient organisation responses will also be considered by the committee.

Table 1 Issues arising from ERG report

Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population (ERG report sections 4.3 and 5.3.5)	No detailed response but support the response to this issue provided by MDUK.
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs	For parents/carers, Ataluren has delayed the progression of the condition and the associated milestones which Duchenne families have to face. This has provided us – on a practical level –with more time to prepare adaptations and acquire the necessary equipment. There is no doubt that caregiver quality of life is impacted as the condition progresses. The number of medical

How is caregiver quality of life affected by the condition at different disease stages? **we consider patient perspectives may particularly help to address this issue** (ERG report section 5.3.5)	interventions and amount of support and caregiver time was relatively modest for much of [redacted]' time at primary school but since then, it has steadily increased to the extent that it is now demanding for us across a range of areas. However, caregiver responsibilities were relatively manageable throughout most of secondary school with many of the greatest challenges being presented by the Covid pandemic. The impact on [redacted]' and our own routine can be summarised as follows: (i) early ambulatory (age 2-8); [redacted]: - other than needing help to climb or be carried up the stairs, no other assistance to get around the then two-storey house - occasional falls when walking - able to participate in nursery and primary school with limited support, in terms of teaching assistants being 'attached' to him - able to do a full day and a full week at school arriving at 8.40am with his peers each morning - attends an after-school childminder all the way through primary school - no obvious psychological impact on [redacted] despite the severity of the diagnosis - despite being subsequently diagnosed (aged 12) as being autistic – Duchenne frequently affecting cognitive function - very few traits were apparent as anxiety levels remained low - able to form and maintain friendships without thinking about his condition - limited number of medical appointments - minimal medication or other medical interventions

		Parents
	-	immense shock, disbelief and sadness followed by anticipatory grief in the months after [redacted]' diagnosis
	-	several months where each day was a struggle and there appeared to be no light at the end of tunnel, despite all of the 'promising' research being undertaken
	-	large amounts of time and meetings spent putting some early arrangements in place including the various bureaucratic process associated with applying for support at school, disability living allowance and – given the need to plan well in advance – housing requirements
	-	decide to relocate to a bungalow at a young age; a stressful process which ultimately required leafleting all suitable looking bungalows in the area to see if they wanted to sell their home; fortunately, this approach eventually worked. Actual further adaptations to the bungalow were not required until 8 years after we moved in, assisted by the delayed progression of Duchenne which we consider is down to taking Ataluren
	-	despite the above, I was able to progress with my career and take on additional responsibilities in the workplace, as a chartered Town Planning, including taking over the overall management of the planning department where I worked. My wife was also able to continue to work part-time in a local college, maintaining her work pattern.
	(ii)	mid-ambulatory; (9-13)
		[redacted]:
	-	largely able to 'keep up' with his peers, both physically and socially, in many areas, but as other friends gain independence from their families – starting to meet up without adults – [redacted] requires greater supervision
	-	more time spent doing physio and attending medical appointments but no complaints
	-	able to move around the house independently and get in and out of bed himself

	- some increased anxiety, linked to growing awareness of his condition, manifesting itself in some repetitive phrases and outbursts when particularly anxious; referred for and received a diagnosis of autism aged 12 - able to remain in a mainstream school with the right support - declines to use a wheelchair or mobility scooter at school but gradually becomes accepting of using a Wombat R82 chair, in some lessons, to aid his posture **Parents** - gradual increase in medical appointments requiring more time off work but manageable - very limited support from wider family network requested or offered; although not needed regularly, the amount of time my wife and I get to spend together is impacted due to lack of people available to care in the evenings or at weekends - the main other family carer – my mother – who used to help once a week collecting and caring after school passed away in 2018, meaning we have had no regular family support since then - adaptations now required to the home to create an en-suite wetroom, ramps etc The wetroom was relatively straightforward but the stress of nearly three years of unresolved snagging issues with the Council was a strain - as [redacted] starts secondary school able to find a much closer childminder which initially provides some after-care support for [redacted] - still able to progress our respective careers but have started to rely on a local charity to provide some limited respite as it has become apparent that we need to be giving ourselves a break (iii) Late ambulatory (14-16)

	- able to walk between lessons at school etc, still declining to use a wheelchair or mobility scooter - Covid lockdowns start when [redacted] is 15; a year of shielding and not being at school significantly reduced [redacted]' motivation or need to walk but still able to maintain ambulation - initially unable to cope with remote online teaching which affects his ability to complete coursework for GCSEs - further lockdowns and increases in Covid cases make return to school very protracted - increased anxiety linked to shielding and no apparent end in sight for those who are clinically extremely vulnerable; his autism makes coping with this and the progression of his condition very difficult - prescribed anti-depressants when 16½ which coupled with regular counselling (provided through a charity) has helped - [redacted] applies for and receives a place in the autism special resource provision at his school for the sixth form - by the time [redacted] starts returning to school more regularly in the sixth form, he has lost much of the confidence to walk and starts to rely more on his manual chair **Parents** - throughout the lockdown/shielding period, the stress on us as [redacted]' sole carers became extremely high - as [redacted] didn't yet have a powerchair, he frequently relied on us to push him round the house in his Wombat R82 - stress caused by [redacted]' medical appointments being cancelled due to Covid and very frustrated and upset that he was no longer able to do weekly swimming, which provided the best exercise for him - after the first year of Covid, we both started seeing counsellors given how the situation, coupled with the progression of [redacted]' condition, was impacting on our mental health

	- the process of getting [redacted] a place in the special resource provision was incredibly stressful due to covid, local authority bureaucracy and a failure of all parties to understand [redacted]' situation properly - increasingly difficult to transfer [redacted] into the car due to his weight and suddenly have to look at wheelchair accessible vehicles after he turns 16½ - start trying to find a carer/PA for [redacted] to give him more independence but process takes over 12 months from first receiving funding from local authority which is immensely frustrating as we need more help and respite - increasing impact on our relationship due to the lack of time together (iv) Early non-ambulatory (late 16/17+) - by the time [redacted] starts attending school more regularly in the first term of sixth form, he is only able to stand and relies on the wheelchair to get around - his mental health has improved by being back in school and finally being around his peers on a fairly regular basis - acknowledges to us that he finds it physically tiring being in school – a combination of the progression of his condition and the fact that he is not used to being in school - A PA starts supporting [redacted] for 6 hours a week. Although it is only two afternoons a week, [redacted] has really started enjoying the greater independence and is now able to go out independently, for example to a local café - Generally [redacted] is positive and upbeat although he can get frustrated about the fact that he can do less than he used to

	Parents - increasing amount of time taken to help [redacted] get ready in the morning, due to greater range of tasks with which he needs assistance (e.g. getting dressed, toileting, transfers) - financial burden of buying more specialist equipment, including a profiling bed which costs over £10k, meaning we rely on family financial support to pay for this - further increase in medical appointments, resulting in more time off my work, necessitating further discussions with my own employer who don't have a carer's policy - I am not able to comply with my employer's new post-Covid hybrid working policy which requires me in the office three days per week; I can now only commit to two days per due to carer responsibilities and have also now had to turn down promotion opportunities Despite the progression of the condition and the impact that it has had on us as parents, partners and carers, [redacted] is still fiercely independent wherever possible. He typically sorts out brushing his own teeth in the morning or will give himself his own medication – a large number of tablets, including medication to manage the multiple side-effects of steroids. The fact that he is able to carry out some of these tasks, in terms of his own dignity, makes us as parents feel positive and that he is doing everything he possibly can independently. However, as [redacted] as get older and more of the straightforward care tasks require assistance throughout the day, we find ourselves more physically and emotionally worn down. We are also 15 years older than when he was first diagnosed. The slower progression of the condition has enabled my wife and I to hold down jobs and maintain a modest social life, despite the fact that our careers and lives are centred on and shaped by [redacted]' needs. That is becoming more difficult now but we have been in employment (except for 12 months maternity leave) since [redacted] was born, which has (a) assisted those organisations for whom we

	work (I have been a manager/team leader for the past twenty years) (b) enabled us to pay back into the system i.e. taxes (c) maintained our own self-esteem and self-worth and (d) provided us with a valuable 'diversion' given the seriousness of [redacted]' diagnosis.
Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values How appropriate is it to assume different quality of life estimates between the treatment and comparator group for the same disease stage? (i.e higher quality of life for the treatment group in the same disease stage) **we consider patient perspectives may particularly help to address this issue** (ERG report section 5.3.5)	Slowing the progression of the condition through a treatment which has demonstrated its efficacy in trials and real-world data means it is entirely appropriate to use different quality of life estimates. When [redacted] was first diagnosed, we expected – based on the prevailing information and advice at the time – that he would cease walking by age 11 or 12 and would rapidly lose upper body function by his late teens. This prognosis remains the case for a large proportion of young people living with Duchenne and despite many receiving steroids over many years. Delaying each milestone in the progression of the condition has multiple, tangible physical, practical and psychological benefits for the patient and carer. For example, we only had to buy a wheelchair accessible vehicle when [redacted] was nearly 17 as it was becoming difficult for him to walk to and climb into the car. It has also meant that [redacted] has been able to enjoy our back garden for longer; I only removed the goal nets last summer because after many years, they were falling apart. [redacted] still enjoys playing cricket in the garden, hitting sixes, despite the loss of ambulation. Slowing the progression of the condition enables life events to be enjoyed more fully. [redacted] was able to participate in a wide range of sports with able-bodied peers well into his teens, including football, cricket, snooker, swimming and table tennis. He was able to participate fully in his own Bar Mitzvah celebrations when he was 13 including dancing on his feet at his own Bar Mitzvah party with

	his family and friends and standing to deliver a speech in front of 150 guests. This level of participation reduced the extent to which [redacted] has experienced the social isolation, increased anxiety and psychological difficulties which so many other teenagers living with Duchenne experience. For [redacted] this only became problematic during and largely because of the Covid pandemic, when he was forced to shield at home, his OCD escalated and he was not able to attend school for a year or mix with his peers. It was only during Covid that [redacted]' mental health was affected to the extent that he had to start taking anti-depressants. Since returning to school, he has largely reverted to his usual upbeat self and can be heard singing to himself in the bathroom most mornings. He knows that in receiving Ataluren, he is taking medication which has helped to maintain quality of life, sometimes comparing himself to how others living with Duchenne – who aren't receiving the drug – are progressing.
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age (ERG report section 5.3.5)	Not in a position to respond to this issue.
Issue 6:	Not in a position to respond to this issue.

Uncertainty surrounding the discontinuation rate in patients with FVC>50% (ERG report section 5.3.5)	
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule (ERG report section 5.3.5)	No detailed response but support the response to this issue provided by MDUK.
Issue 8: Weak characterisation of uncertainty (ERG report section 5.3.5)	No detailed response but support the response to this issue provided by MDUK.
Are there any important issues that have been missed in the ERG report?	The ERG report appears to not reflect or have given consideration to the significant side effects associated with current BSC, namely the very substantial side-effects of steroid treatment. Steroids were never trialled in Duchenne but the side effects (see below) are considerable and frequently observed regardless of whether Deflazacort or Prednisoline is taken. This should be compared with Ataluren which has a very good safety profile.

Part 2: Topic specific questions

What do patients or carers think about the current treatment stopping rules in the managed access agreement?

Patient expert technical engagement response

The current discontinuation rules reflects the emphasis in earlier clinical trials on the 6 minute walk test and the fact that there was insufficient data on efficacy in non-ambulant patients at the time. However, the discontinuation rules do not reflect the critically important role Ataluren has in slowing the progression of the condition, regardless of whether the patient is still walking. This is not just borne out in the real-world data which has since been published and which, for example, demonstrated slower pulmonary function decline. It is also reflected in the real-world observations of families like my own, who have noticed the retention of functional upper body strength, fewer respiratory infections despite a loss of ambulation and the ability to carry out physical tasks which would not otherwise be possible simply through the use of steroids. For examples, my son still takes great pride in those aspects of personal care he is able to carry out himself such as applying toothbrush to his electric brush, cleaning his teeth and wiping his mouth or taking cotton buds from the bathroom shelf, cleaning his ears and throwing the buds into the bin.

It would be counter-intuitive and unethical to continue to remove access to a drug which targets the underlying cause of a muscle wasting condition, simply because one set of muscles are no longer able to bear the weight of a patient and support ambulation. There are millions of non-ambulant adults and children who enjoy a very good quality of life and given the progression of Duchenne, it is vital that this is retained for as long as possible where a drug exists.

The current discontinuation rules will not be appropriate moving forward. Unless the drug can no longer by physically administered, it should be available where there is benefit to the recipient and it may simply not be appropriate to have a discontinuation rule post-MAA. There is no reason why an intervention to slow the progression of muscle wasting throughout the body – which includes respiratory muscles – should not continue to be made available.

What do patients or carers think about the removal of the following wording from section 4.1 of the Summary of Product Characteristics (SmPC) for ataluren: “Efficacy has not been demonstrated in non-ambulatory patients”

The removal of this wording is strongly welcomed and in doing so, reflects the importance of access to Ataluren for patients who become non-ambulatory. Access to a drug which targets the underlying cause of a muscle wasting condition should not be dependent on which muscles have declined first. However, Ataluren should be made available to patients who are non-ambulant already, rather than only in instances where they have lost ambulation since commencement of treatment.

What do patients or carers feel are the benefits and disadvantages of the potential continuation of treatment in people who have lost the ability to walk?

When children are diagnosed with Duchenne – and it is typically when they are very young and may have only just *started* walking – the focus of parents/carers is typically on two outcomes from that initial diagnosis: the loss of ambulation and the severely reduced life expectancy. Anticipatory grief and continuous visualisation of the decline of one’s child follows. The use of a wheelchair is a recurring theme in those first few years post-diagnosis but in time, both parents and the child living with Duchenne become somewhat adjusted to a future loss of ambulation. Ambulation is no longer the way in which one’s own child and their future is defined.

[redacted] is now in a powerchair (he can stand with support from others) but only became a full-time wheelchair user just before his 17th birthday, a stage we feel was accelerated due to the Covid pandemic and the lack of motivation or need to keep up with his peers, when shielding at home for an entire year. . However, being in a powerchair has not changed [redacted] fundamentally and has given him additional independence. We are immensely grateful that he enjoyed 4-5 years of ambulation than we originally thought would be the case. He does occasionally express frustration that he can no longer walk but this has not stopped [redacted] maintaining a good quality of life. He is still able to do many regular activities such as writing out a birthday card for his grandparents, rapidly assembling complex lego sets and hitting a cricket ball in the garden. He can also walk independently in a swimming or hydrotherapy pool now that he is able to get back into the water following Covid restrictions. Ensuring that Ataluren remains available to those who are non-ambulant means extending how long this significant sub-group can maintain their quality of life and are not discriminated against, simply because they are no longer walking.

Conversely, there are no disadvantages to continuing treatment in the non-ambulant population. The drug has been demonstrated to be safe and simple to administer; being in a wheelchair does not prevent [redacted] from being able to receive the drug. By way of comparison, the disadvantages to continuing steroid treatment – despite being widely prescribed – are numerous and over time, capable of outweighing the advantages. [redacted] has cataracts, compression fractures, reduced bone density and cushingoid features. He has experienced no side-effects to taking Ataluren.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this evaluation.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology evaluation (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **15 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Muscular Dystrophy UK **Please note that this response has been shared with and endorsed by the other Patient Experts ahead of being submitted.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population (ERG report sections 4.3 and 5.3.5)	Yes	The ERG report concludes that the three studies cited in the company's submission do all demonstrate effectiveness. As a patient group, we feel that we play an important role at this stage in the appraisal process in showing what the effectiveness of a treatment means in practical terms to the people in receipt of it. Academic discussion about 'relative effectiveness' is far removed from the experience of families receiving ataluren who have experienced the effectiveness of ataluren versus BSC. The 'real-world' effectiveness of a treatment that delays the progression of Duchenne muscular dystrophy cannot be overstated. It is important to recognise that data points about the distance someone has the ability to walk or an above average age of loss of ambulation can translate to significant treatment effectiveness in terms of someone's ability to live independently. As part of this response we conducted a survey of families with experience of receiving ataluren. 22 people responded to the survey, 18 of whom were parents; one a carer; one a grandparent; one a friend; and one someone receiving the

		treatment themselves. Three responses were linked to a child aged 2-4 years of age; two responses were linked to a child aged 5-9 years of age; eight responses were linked to a child aged 10-14 years of age; five responses were linked to a child aged 15-19 years of age; and four responses were linked to a child aged 19 and over. Names have been redacted from the responses quoted. There was a wide range of time in receipt of ataluren, with many respondents having first accessed the treatment through a clinical trial. Respondents were asked whether the anticipated age of loss of ambulation at diagnosis had been exceeded and 68 per cent of respondents said that this had been the case. *"Definitely. I thought by the age of 10 [child's name] would start to struggle but he is nearly that now and still doing so well. I would hope he will still be walking even a little until he is 15 or older!"* Parent of child aged 5-9, in receipt of ataluren for 3 years. *"[Anticipated loss of ambulation was] 11 or 12, so ambulation was exceeded by at least four years as he continued walking until he was nearly 17."* Parent of child aged 15-19, in receipt of ataluren for 10 years. *"We were told [child was likely to lose ambulation at]12 years of age. Far exceeded. [Child's name] walked independently until October 2018 when he broke his left femur aged 17."* Parent of child aged 19 or over, in receipt of ataluren for 14 years.

		"We were told he could need to use a wheelchair by age 8, and [child's name] is now 12 years old, so that age has been exceeded, and he still seems to be far from needing one right now." Parent of child aged 10-14, in receipt of ataluren for 6 years. *"When first diagnosed we thought he would be ambulant until he was around 10-12yrs, but he was ambulant up until he was 18-19 years of age which we believe translarna has made the difference in a huge way".* Parent of child aged 19 or over, in receipt of ataluren for 13 years. *"My son was selected for the Translarna trial on the basis he would become non ambulant by 8 1/2yrs - 9 years old. My son became non ambulant at 14 1/2years old during shielding. We believe he would have continued to walk for longer had he not needed to shield and could have gone out more."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"We were originally told he would stop walking around the age of 10 years old, he is 14 next month and still ambulant".* Parent of child aged 10-14, in receipt of ataluren for almost 6 years. *"We were told about 8 years old; he is now coming up for 12. He is slowing down now but can still walk for a mile or so."* Grandparent of child aged 10-14, in receipt of ataluren for 6 years. *"We were told he would cease to be ambulant between the ages of 8 and 12, so that age limit has been exceeded by almost seven years, as he will be 19 in September this year, and he is still walking well over short distances."*

		Carer of child aged 15-19, in receipt of ataluren for 5 years. *"10-12 he walking until he was almost 15".* Parent of child aged 15-19, in receipt of ataluren for 9 years. *"Until 9. Still ambulant at 11.5"* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. As stated above, it is important to recognise the real-world impact of the effectiveness of ataluren versus BSC. Respondents were asked to describe what any delay in the loss of ambulation meant for the individual receiving ataluren. *"It has helped him to maintain independence and dignity for longer, as well as giving him longer to adjust as his condition progresses. On a practical level, that has meant - for example - walking between lessons at school and around the house, playing indoor and outdoor sports with his peers and being able to carry out more of the personal care himself, for longer. He is still able to brush his teeth, wash his hands and cut up food for example."* Parent of child aged 15-19, length of time on ataluren not provided. *"EVERYTHING! Losing independence hit [name of child] hard both around the house and outside. His world has recently become much smaller as access to family and friends' houses is much more limited. EVERYTHING now needs planning in advance and in detail."* Parent of child aged 19 or over, in receipt of ataluren for 14 years.

		"Any delay in this condition is a little win, a small victory, taking a little something back. Our hope has always been to keep our son walking for as long as possible, any delay in loss of ambulation we believe, physically has a direct benefit to his posture, circulation, digestion etc. To watch our son be able to play with his friends and brother has always filled us with such joy, for him to be able to walk into his classroom with his friends, play and be like his peers you cannot put into words." Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"Delay in losing the ability to walk has a huge impact. My son has learned to ride a bike, gotten his cycling proficiency, he has learned to surf, he has been able to feel normal as far as that's possible, building friendships and not feeling defined by his condition. People meeting him are not even aware he has Duchenne unless they've been told. I think losing the ability to walk aged 8 would have devastated him and required a huge adjustment, both for him and for our family…"* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Access to everywhere. Allowed my son to attend mainstream school and attain his full potential in terms of qualifications. Social development. Better quality of life. Maintain key family relationships and friendships."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"Ambulation has a massive effect on [child's name] mental health and wellbeing, he has been able to keep active, carry-on fishing, trying new activities. He is still able to walk and independently get in the family car."* Parent of child aged 10-14, in receipt of ataluren for almost 6 years.

		"It means his overall health, including respiration and muscle strength has been, and is still, very good. This has helped him to manage a full week at school and to gain a place on a full-time college course; it has also meant he can maintain social relationships via school and he can still participate in disability sports." Carer of child aged 15-19, in receipt of ataluren for 5 years. *"He is still able to dress and toilet independently. He can continue to play with his younger brother and friends outside…and he can still visit his grandparents' homes that have stairs and no adaptions."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. *"Been able to finish primary school whilst still be ambulant."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Any loss of ambulation would result in consequences for [child's name] independence and mental health."* Parent of child aged 10-14, in receipt of ataluren for 5 years. *"It made him feel like he was like his other peers of his age as he was able to walk along side of them."* Parent of child aged 19 or over, in receipt of ataluren for 13 years. *"He can still climb stairs, albeit slowly, he is still independent and this is important particularly to his brother."* Grandparent of child aged 10-14, in receipt of ataluren for 6 years.

		As well as ambulation, respondents were asked what any delay in loss of upper body strength would mean for their child, and what they thought it has or would help them do or achieve. *"He loves playing with Lego and gaming and can currently do this with ease. These are things he enjoys and so having the strength to do them in turn makes him happy."* Parent of child aged 5-9, in receipt of ataluren for 3 years. *"The ability to carry out personal care and eating for much longer. Our son can apply toothpaste onto the brush to clean his teeth or reach for earbuds on the shelf to clean his ears. Or in the current very hot weather, he can open the freezer door, take out a box of ice lollies, remove one for himself and put the box back. He is also able to enjoy assembling complex Lego builds or take a book off the shelf to read."* Parent of child aged 15-19, in receipt of ataluren for 10 years. *"This is our next big challenge and potentially as great as losing ambulation. Small things to abled bodied people such as washing your own hair, putting your own glasses on or cutting food will become a challenge."* Parent of child aged 19 or over, in receipt of ataluren for 14 years. *"It's also very significant that he's retained upper body strength, and strength in his arms and hands. He enjoys drawing and makes his own beautiful cards for us on birthdays which we treasure. He loves gaming, on a console and on his phone. He hugs us, he picks up and hugs our cat, Ginger. He has been learning to play the saxophone and then the clarinet. He loves animation will be doing a course at Bournemouth University in October to learn how to do it.*

		It's a critical time for him in finding what he wants to do with his life, and he's not limited at the moment by his condition." Parent of child aged 10-14, in receipt of ataluren for 6 years. *"It allows my son to be independent and feed himself and communicate via written form. It allows him to touch his face, play and participate in school. All the things we take for granted."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"Good upper body strength means he can still feed himself, and wash and dress himself at a basic level with a limited amount of help, although help is required with showering. It also helps to keep the heart and lungs healthy, as I believe scoliosis has been prevented by the use of Translarna."* Carer of child aged 15-19, in receipt of ataluren for 5 years. *"They can still dress and toilet themselves. Brush their own teeth and eat independently. This means as he transitions to high school there is less stigma and difference at this very difficult time whilst his peers mature. By delaying these differences, he and his peers will be able to accept these differences more easily."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. Respondents were asked whether they felt there was any difference between what their child and their family could do compared to other Duchenne families they know who don't receive ataluren. 64 per cent said that they felt this to be the case.

		"I feel [child's name] is definitely more able than other boys his age not on Translarna." Parent of child aged 5-9, in receipt of ataluren for 3 years. *"We think that our son's upper body strength, fine motor skills and respiratory strength are markedly greater than many of the non-ambulant children/teens his age. This is reflected in the real word data which has been published comparing Translarna and non-Translarna patients."* Parent of child aged 15-19, length of time on ataluren not provided. *"Yes. I feel that there are lots of things physically that my child can do compared to other children who do not receive Translarna. As a family it is a very positive experience."* Parent of child aged 2-4, in receipt of ataluren for 2.5 years. *"We did notice huge differences for a long period of time. Friends (who we made at Duchenne events) who had Duchenne boys were losing ambulation in their early teens while [child's name] could still walk."* Parent of child aged 19 or over, in receipt of ataluren for 14 years (beginning with a clinical trial). *"For certain. With [child's name], he lives currently unaided and taking ownership of his own independence."* Parent of child aged 10-14, in receipt of ataluren for 5 years. *"Very much so, younger lads are in their chairs at very young age."* Parent of child aged 19 or over, in receipt of ataluren for 13 years.

		"Yes. We have witnessed boys without Translarna deteriorate and die. We have seen many families who don't have Translarna require anti-depressants and require much more mental health support." Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"Yes, most definitely. We are a "normal" family and do not have to take his illness into account all the time."* Grandparent of child aged 10-14, in receipt of ataluren for 6 years. *"Definitely. We have, tragically, seen many cases of boys who have passed away at a much younger age, and also so many who are bed bound/housebound, who require twenty-four-hour care, whose survival depends on oxygen, etc., whereas our family still has a lot of opportunity to live almost 'normal' lives, by going out for meals, concerts, theatre visits and holidays at home/abroad."* Carer of child aged 15-19, in receipt of ataluren for 5 years. *"Yes. Holidays don't require adapted rooms or special travel arrangements. Hire cars are simple. He can visit friends and family without worry about home suitability. He can be left unattended as there's no assistance needed for toileting etc."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. *"A lot of children the same age as [redacted] are already non ambulant with a great loss of upper body function."* Parent of child aged 10-14, in receipt of ataluren for 5 years.

		Looking at the wider benefit of receiving ataluren, respondents were asked whether they felt that being on ataluren has had a role in reducing their and their child's social isolation and benefiting their family's general wellbeing. 77 per cent said that they felt this has been the case. *"[Child's name] is still ambulant and with two younger siblings means we can still get out and about."* Parent of child aged 5-9, in receipt of ataluren for 3 years. *"My son is still ambulant and able to ride a bicycle, swim and last a whole day doing things without getting tired."* Parent of child aged 10-14, in receipt of ataluren for 5 years. *"Being on the drug we felt he didn't feel embarrassed as much as he could walk longer and falling had stopped which he found the most difficult when people watched him fall."* Parent of child aged 19 or over, in receipt of ataluren for 13 years. *"Translarna kept my son ambulant for approximately 4 years beyond the time he was expected to be in a wheelchair. This has benefited our family and my son immensely. It allowed my son to maintain social interactions with friends and family. Now that he is no longer ambulant social isolation is brutal and devastating. It allowed my son to attend mainstream school. It has prevented my son developing scoliosis. His lung function is in the normal range and meant no intervention from the respiratory team. His consultant said my son was first boy to get to 15 years without needing any additional support. He attributes this to Translarna. Heart function is good and again heart consultant*

		has confirmed she would expect more advanced fibrosis at my son's age, but it has not occurred to the extent other boys without Translarna have experienced." Parent of child aged 19 or over, in receipt of ataluren for 13 years. *"Maintaining the function [child's name] has, has helped us carry on with family holidays and enabled him to access friends' houses."* Parent of child aged 10-14, in receipt of ataluren for almost 6 years. *"He has remained on his feet, does not feel different to other children and the family have benefited greatly."* Grandparent of child aged 10-14, in receipt of ataluren for 6 years. *"It has benefited all of us, as he is still ambulant over short distances, which makes it easier to access relatives' houses for visits; he is still keeping very well and is able to participate in disability sports, although he is almost nineteen, and he will be going to college soon, which allows me, as his carer, some daily respite to participate in my social activities. As a family, we can still travel abroad, as he is not on daily oxygen and he can drive his wheelchair/mobility scooter independently, which makes travel much easier for all of us."* Carer of child aged 15-19, in receipt of ataluren for 5 years. *"Obviously, my son being able to do more for longer has helped us be able to do more as a family and spend quality time together."* Parent of child aged 10-14, in receipt of ataluren for 6 years.

		Respondents were also asked, if they had taken part in an ataluren trial and subsequently found out that their child was on a placebo arm, whether they had noticed a difference between their energy and activity levels after they switched to ataluren. Only two respondents said that this applied to them, and both reported a noticeable difference. *"My son seemed to have lots of energy, even after a long day at school he'd still be doing laps of our living room, he continually surprised us how he kept going. His mood and behaviour seemed to improve as well."* Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"Yes he was on a placebo for a year with no difference, but as soon as he started Translarna within 2-3 months there was a huge improvement i.e. falling had eased and he had more energy."* Parent of child aged 19 or over, in receipt of ataluren for 13 years. Whilst we anticipate that the company will go into the detail of this in their submission, we are also aware of new evidence that has been published further demonstrating the effectiveness of ataluren[1]. The data from PTC Therapeutics' Study 041 indicate that children in the placebo arm lost more function than those treated with ataluren. So, whilst participants treated with ataluren demonstrated reduction of functional ability, this was significantly less than the reduction in function in the placebo arm. In addition to the clinical benefit, the drug is tolerated and safe.

[1] https://ir.ptcbio.com/static-files/d4bfdc71-df47-4776-8fac-8fd166761baf

		With regards to concerns raised in the ERG report relating to the strength of the data from the Managed Access Agreement (MAA), as far as we understand, the MAA was an observational study and as such it was not expected that the data collected would be subjected to the kinds of statistical rigour that more traditional clinical trial data undergoes. In relation to the concerns raised in the ERG report regarding NorthStar data collection, it is important to recognise the impact that COVID-19 had on this. MDUK's July 2021 report 'Shining a Light' – the Impact of COVID-19 on Neuromuscular Services'[2] was built on input from 400 people with a neuromuscular condition and 32 neuromuscular clinical teams. The overall findings showed that people living with muscle-wasting conditions struggled to access critical services such as specialist muscle clinical appointments (75%) and specialist neuromuscular physiotherapy (54%) because of the pandemic and shielding. 97 per cent of neuromuscular services had to cancel routine face-to-face neuromuscular clinics. While services pivoted to virtual appointments, in many cases these simply are not suitable for collecting the kind of data collected for the NorthStar database. Finally, although as set-out above there is little uncertainty from families receiving ataluren regarding its effectiveness versus BSC, we note with interest the approach taken by NICE in relation to avalglucosidase alfa for treating Pompe disease. The final appraisal document for that treatment states "Given the high burden of Pompe disease on children and their carers, and the rarity of the condition, the committee accepted the uncertainties[3]". We feel that this is a

[2] https://www.musculardystrophyuk.org/static/s3fs-public/2021-07/POL14%20-%20Impact%20of%20COVID%20report.v4.pdf?VersionId=apq4P8Je32l.hgaQFd0h8HyzX_DMxWw9
[3] https://www.nice.org.uk/guidance/gid-ta10876/documents/final-appraisal-determination-document

		positive pragmatic approach and one that would be applicable in this instance, should the Committee feel there is any uncertainty.
Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs (ERG report section 5.3.5)	Yes	We are not in a position to analyse different QALY models and the benefits of their use. From our perspective as a patient group, it is essential that any debate about the approach that should be taken to demonstrating the impact of ataluren on caregivers does not lose sight of the real-world benefit that caregivers experience from the treatment. It is important to recognise the wide range of formal and informal caregivers who support people living with Duchenne muscular dystrophy, and therefore whose quality of life is impacted by access to a treatment that slows the progression of the condition. 68 per cent of survey respondents referred to caregivers other than parents, the vast majority of whom were other family members, including siblings. Survey respondents were asked what impact has/would any delay in loss of ambulation for their child mean to them as caregivers. 73 per cent said that it had improved their mental wellbeing; 73 per cent said that it had prolonged how long their child is able to undertake tasks or activities independently (i.e. reduced the amount of support they have needed to provide); 55 per cent said that it had provided them with additional time to concentrate on their work/career and/or social life; 41 per cent said that it had delayed the cost of housing adaptations. Respondents also shared that it had allowed other family members to provide respite rather than having to use paid care support and that they had not yet had to provide or acquire extra medical equipment, breathing equipment or “extensive care”. *“I strongly agree with all of the above statements. Delaying the cost of housing adaptations gives you more time to prepare, save and plan your adaptations.*

		I'm not sure I need to explain the importance of your child being able to maintain independence, it goes without saying that maintaining any independence is beyond important. This is also true of how it affects your and your child's well-being. Any decline in your child's condition is heart-breaking for everyone in your life, friends, family your child's friends everyone! Being able to delay any decline, whatever it may be is so so imperative. As a parent and primary caregiver, it is the biggest juggling act you'll ever undertake, balancing DMD, work and social life can at times be overwhelming. Any time you have to yourself is so precious and you have to learn to look after yourself as well." Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"Our house has stairs and our son's room is upstairs, and there's limited options in terms of creating a downstairs bedroom and accessible bathroom, so moving house would most likely be necessary. Our son loves the independence he currently has, and his appearance really matters to him, and he prefers not to be helped wherever possible. He hates people fussing over him. In terms of mental wellbeing it's priceless, as it reassures us as parents that we're doing all we can, and not failing our son. My husband and I can still both work, which matters as it enables us to save more, to afford to take the family away and make memories, to save for the next stage if we have to move in the future. Working also give us a sense of self-worth and personal achievement."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"…adaptions have been delayed; expensive WAV [Wheelchair Accessible Vehicle] is not yet required. Holidays don't require special considerations…"* Parent of child aged 10-14, in receipt of ataluren for 6.5 years.

		"We didn't need to do adaptations for 5 years after we were advised to do so. This allowed us to save and plan exactly what was required first time. No interim or regret spend was needed. Good Mental health is vital. Being able to participate in school and after school activities provides social development, better quality of life for the child and indirect respite for the parents e.g. my son went to scouts and after school clubs. Feeding himself was very important to my son. My husband and I have continued to work full time. We have provided my son's care by ourselves with limited support from family members. This has meant we have not needed paid carers and kept our family safer doing lockdown/ shielding." Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"It makes life easier for the whole family, and especially for the young person themselves, as it helps them to participate socially and reduces the need for extra equipment in the home, as well as allowing family carers to have some respite."* Carer of child aged 15-19, in receipt of ataluren for 5 years. *"We are still on low mobility allowance on DLA and don't require any major adaptions in the home. As mentioned he is independent and able to dress, toilet and eat independently."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. *"I am a full-time worker, I actually thought I would have had to get extra help a lot sooner."* Parent of child aged 15-19, in receipt of ataluren for 9 years.

		"Although we moved to a bungalow when our son was much younger, we didn't need to start carrying out physical adaptations until he was 14. Tracking [hoists] did not need to be installed until he was nearly 17." Parent of child aged 15-19, in receipt of ataluren for 10 years. *"Been able to stay in family home longer."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"In general life can continue as we know. We are in the process of moving to a home more suitable for [child's name] which we may have needed to do much sooner. Independence is so important and being ambulant and having the upper body strength can only help with this."* Parent of child aged 10-14, in receipt of ataluren for 5 years. Survey respondents were also asked what has/would any delay in loss of upper body strength for their child mean to them as caregivers. 73 per cent said that it had improved their mental wellbeing; 73 per cent said that it had prolonged how long their child is able to undertake tasks or activities independently (i.e. reduced the amount of support they have needed to provide); 50 per cent said that it had provided them with additional time to concentrate on their work/career and/or social life; 23 per cent said that it had delayed the cost of housing adaptations. One respondent also shared that it had Reduced extra care needs and led to less difference to his siblings. *"My son's upper body strength is weakening now and the full realisation of the additional care he needs is now evident. It is incredibly time consuming, and I can see how exhausting it is going to be in the future."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years.

		Survey respondents were also asked about the additional level of support needed from caregivers, and therefore the increasing impact on their quality of life, as the condition continues to progress in the person living with Duchenne muscular dystrophy. 73% of respondents cited an increasing impact on caregivers as the condition progressed. *"Several hours more each day. The amount of time it takes to get [up] and get ready in the morning has increased from about 45m/1hr to at least 2hrs. Every time he needs the toilet, can take 15-20 minutes (or longer, if as sometimes occurs, he soils himself), whereas previously he could do this all himself. Even going out to the shops takes longer, due to getting all the equipment ready, loading the car up, going to the toilet again (to reduce the risk/need of going when we are out) etc."* Parent of child aged 15-19, in receipt of ataluren for 10 years. *"When [name of child] was ambulant he would take himself to the toilet during the night and turn himself. Now, if he needs the loo, it takes around 10 minutes. He also needs turning (sometimes several times) during the night. Sleep is much reduced and has massive consequence on quality of life.* Parent of child aged 19 or over, in receipt of ataluren for 14 years. *"Our son requires more and more of our time, it's 24/7… from turning him during the night to getting him dressed/undressed, bathing, washing, teeth brushing, hair doing and transferring."* *Parent of a child aged 5-9, in receipt of ataluren for almost 5 years.*

		"[Child's name] needing help more and more over the time. For example on and off the loo, in and out of chairs / sofa, keeping a close eye when he's walking in case of trip hazards or falls. It's difficult to process what's happening and adjusting to being needed more. But obviously as things change, we learnt to adapt what we need to do with / for him." *Parent of child aged 10-14, in receipt of ataluren for 5 years.* *"I would say since he stopped walking caring has increased 50%"* Parent of child aged 15-19, in receipt of ataluren for 9 years. *"Translarna gave my son 4 extra years of independence. He could go and do anything he wanted. Now he is older and the disease has progressed we now need to dress and wash my son. We have to lift him onto the toilet and into bed. We help him sit up in bed or move position. We have to cut his food and help him position a glass. We have to help him write. If my son needs any equipment or items we need to get them for him."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"Increased anxiety due to decreased mobility at school is meaning later starts, regular phone calls home and spending time catching up on lessons at home has led to more time spent caring including Dad reducing working hours to enable support at home."* Parent of child aged 10-14, in receipt of ataluren for almost 6 years. *"Help with toileting, washing, dressing, chopping up food, transporting wheelchair/scooter; attending hospital appointments; dealing with care managers/school/college (extensive paperwork, etc./help with financial*

		management)/government agencies for benefits/cooking/cleaning/laundry, etc./assisting with and escorting to and from social activities, etc." Carer of child aged 15-19, in receipt of ataluren for 5 years. *"Helping with dressing and fetching things are small but constant reminders. More care in planning trips and visits. Planning future adaptions."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. *"Help with getting dressed, showering. Things that 11 year old should do unsupported."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Getting in and out of bed, in and out of bath, wheelchair, car etc."* Parent of child aged 10-14, in receipt of ataluren for 5 years. One survey respondent commented that without ataluren, they may not have decided to have further children. *"…we may even have decided not to try to have another child, but we have managed to with IVF and genetic diagnosis - and when our son was 8 we had his little brother who is now 4 years old."* Parent of child aged 10-14, in receipt of ataluren for 6 years. An important aspect for caregivers of the slowing of progression of Duchenne muscular dystrophy thanks to ataluren that came through the survey was providing time to delay conversations with their children regarding their long-term prognosis until they were more mature and better equipped to handle these discussions.

		"I believe [child's name] is still ambulant due to Translarna and this has helped postpone inevitable questions re his condition." Parent of child aged 10-14, in receipt of ataluren for 5 years. *"[Child's name] is struggling mentally that he is different to others. With age comes maturity and hopefully a better understanding."* Parent of child aged 5-9, in receipt of ataluren for 3 years.
Issue 3: Limitations surrounding the company's survival modelling (ERG report section 5.3.5)	No	We are not in a position to comment on this issue.
Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values (ERG report section 5.3.5)	Yes	While this is a technical point that we are not in a position to provide in depth analysis of, as a patient group we can provide insight as to the positive impact that knowing your child is on a treatment that is slowing the progression of Duchenne muscular dystrophy can have versus a whose child may be, or appears to be, at the same point in the progression of Duchenne muscular dystrophy and only able to access BSC *"We are lucky to have the possibility / hope that translarna is and will continue to help."* Parent of child aged 10-14, in reciept of ataluren for 5 years. *"I cannot explain how much any delay in loss of function means. It goes beyond words to think you have the means to stop this condition ruining some other precious part of your child's life even if it's only for a time. Having*

		access to a drug such as Translarna is imperative, you would move mountains to "buy" more time. It's hard enough to come to terms with this diagnosis and watch your child slowly lose abilities when they should be getting stronger, it goes against nature and we as a family would fight to access this drug for as long as possible." Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"Knowing that our son is accessing a treatment, when the alternative would have simply to continue with steroids alone, gave us a significant boost."* Parent of child aged 15-19, in receipt of ataluren for 10 years. *"Knowing your child has access to a drug that can help slow the progression of DMD is amazing, each delivery we have we call our little box of miracles. To believe that you're taking a small victory back from this devastating condition brings you all hope."* Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"It has given us confidence to get on with living life as we know our son is getting the right medical care and medication. [Child's name] has been able to live as 'normal' a life as possible and do things we never thought he'd be able to."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"I feel as a family we generally feel better about things due to him being on a treatment that may help with his condition."* Parent of child aged 10-14, in receipt of ataluren for 5 years.

		"Being able to access Translarna is life changing! As unlucky as we are that this condition is in our lives we are determined to make the most of life and give our son the best we possibly can. We do however consider ourselves very lucky that we have this drug and a chance to delay the progression of this disease. It's a massive boost to know that we are able to do something to take back a little victory over this devastating condition. We would fight over and over to keep this drug available to all families whose child is eligible for it. We 100% believe this has helped our son and would urge you to continue its distribution." Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"I feel we are a different family because of Translarna - we have hope that our oldest son may continue to walk for years longer, and be fitter and healthier even if a time comes where he needs to use a wheelchair. We can contribute, by working, taking care of our sons, being a family. I'm not sure we would have had our youngest child if things had been different."* Parent of child aged 10-14, in receipt of ataluren for 6 years. The limitations and side-effects of BSC must also be taken into account e.g. the effect of steroid use.
Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age (ERG report section 5.3.5)	No	We are not in a position to comment on this issue.
Issue 6:	No	We are not in a position to comment on this issue.

Uncertainty surrounding the discontinuation rate in patients with FVC>50% (ERG report section 5.3.5)		
Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule (ERG report section 5.3.5)	Yes	We believe that access to ataluren should continue for as long as there is any benefit to the recipient. Survey recipients were asked whether they thought there should be a point where ataluren is discontinued for patients or whether it should be made available regardless of the progression of the condition. 73 per cent said that it should continue for as long as there is benefit; 18 per cent of respondents did not answer this question; 9 per cent did not feel they knew enough about benefits beyond ambulation to comment. *"If the patient should wish to continue taking Translarna then I think it should be available to them. Upper body strength is important too."* Parent of child aged 5-9, in receipt of ataluren for 3 years. *"No - Translarna has been demonstrated to show efficacy, via real world data, in non-ambulant patients. Its mechanism of action doesn't target one particular muscle and Duchenne affects all muscles. It would be unethical to discontinue Translarna for patients at any stage so long as it is able to be administered to/for them."* Parent of child aged 15-19, in receipt of ataluren for 10 years. *"I think it should be made available regardless as it could still help with upper body strength, lung function and other things too."* Parent of child aged 2-4, in receipt of ataluren for 2.5 years.

		"The loss of arm function potentially could be an even bigger issue than losing ambulation. As mentioned before, may accelerate loss of independence and increase mental health problems." Parent of child aged 19 or over, in receipt of ataluren for 14 years (beginning with a clinical trial). *"No, do not discontinue Translarna!! We 100% believe it should be available regardless of progression. Any production of a functioning protein is beneficial. It seems madness to discontinue it due to loss of ambulation. We are fighting to gain our children time, we fight every day to delay deterioration and the need for more invasive support, any drug which can help this is surely a benefit for our children not to mention our National Health Service, our carers and support network."* Parent of a child aged 5-9, in receipt of ataluren for almost 5 years. *"I think it should be made available regardless of progression because Duchenne is a muscle wasting condition, not a leg muscle wasting condition only affecting only the legs - maintenance of upper body strength is also vital in overall health and well-being."* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Translarna has been shown to have positive impact on lung and heart function and should be continued after ambulating."* Parent of child aged 15-19, in receipt of ataluren for 8.5 years. *"This drug is a life changer and should be made available even after the child stops walking. If it helps other muscles in the body then it should be continued."*

		Grandparent of child aged 10-14, in receipt of ataluren for 6 years. *"I think Translarna should still be made available for the benefit of upper body strength and heart and lung functions."* Carer of child aged 15-19, in receipt of ataluren for 5 years. *"In line with EMA guidance Translarna should continue due to the benefits to upper body strength, the diaphragm, heart, and the brain. Translarna cross the blood brain barrier and can help with behaviour and other difficulties through the lack of dystrophin in the brain."* Parent of child aged 10-14, in receipt of ataluren for 6.5 years. *"Translarna has been proven to help upper body function too so I feel it should be allowed."* Parent of child aged 10-14, in receipt of ataluren for 5 years. *"We believe that although our son is now non-ambulant if we are able to access Translarna for longer this will help him maintain upper body strength, we believe this will help protect his lungs and heart going forward and potentially delay and need for more intrusive support. Any production of a functioning protein is beneficial to all parts of the body; ultimately, we are trying to preserve the heart and lungs, delaying the onset of more serious complications and if Translarna can help that it is so important. Our boys have to endure so much that giving them the ability to be able to do simple things such as feed themselves is beyond important. It's their dignity. Losing the ability to walk is one thing, being able to still use their arms and hands is a massively important part of being able to function independently."* Parent of a child aged 5-9, in receipt of ataluren for almost 5 years.

Issue 8: Weak characterisation of uncertainty (ERG report section 5.3.5)	No	We are not in a position to comment on this issue other than to reiterate the points made above that for families in receipt of ataluren there is no uncertainty as to its effectiveness versus BSC.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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

Addendum: EAG critique of company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	28th July 2022

1. Introduction

This addendum provides a summary and critique of the company's technical engagement (TE) response by the External Assessment Group (EAG). Both the company's TE response and this addendum should be read alongside the company's submission[1] (CS) and the EAG report.[2]

The company's TE response consists of a written response document[3] and a revised version of the company's economic model. The company has increased the Patient Access Scheme (PAS) discount for ataluren to [redacted] (previously [redacted]). The company's TE response includes discussion around all eight key issues raised in the EAG report.[2] A broad overview of the company's TE response is provided in Table 1. The results of additional economic analyses presented in the company's TE response are summarised in Table 2; these results exclude quality-adjusted life year (QALY) weighting based on the decision modifier. A detailed description and critique of the company's responses and new economic analyses is presented in Section 2. Further analyses conducted by the EAG are presented in Section 3.

Table 1: Summary of company's technical engagement response

Key issue	Description of issue	Overview of company's TE response and model amendments
Issue 1	Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population	New results from Study 041[4, 5] are presented. These data are not used in the company's model. The TE response argues that the MAA data should not be used in the model, but that most MAA patients were included in STRIDE.[6]
Issue 2	Inappropriate approach used to estimate incremental caregiver QALYs	The company's TE response[3] provides a description of six alternative approaches for modelling caregiver QALYs applied in the revised model. The company's revised base case analysis estimates absolute caregiver QALYs which are counted only up to the modelled joint median survival time.
Issue 3	Limitations surrounding the company's survival modelling	No new survival analysis has been conducted. The company's revised base case model uses different (Weibull) distributions for all three time-to-event endpoints.
Issue 4	Uncertainty surrounding the appropriateness of treatment-dependent patient utility values	The company's TE response[3] argues that treatment-dependent patient utility values are strongly supported by clinical experts. No new empirical evidence is presented.
Issue 5	Uncertainty surrounding modelled acquisition costs of ataluren by age	The company agrees with the EAG that data from the RCPCH on patient weight by age[7] should be preferred over STRIDE.[6] The company has updated their base case analysis.
Issue 6	Uncertainty surrounding the discontinuation rate in patients with FVC>50%	The company's TE response[3] provides reasons for discontinuation or dose adjustment in STRIDE.[6] No new evidence is presented. The model has not been amended.
Issue 7	Uncertainty surrounding the most appropriate treatment discontinuation rule	The company's TE response[3] includes additional scenario analyses around the discontinuation rule using the revised base case model. No new evidence is presented.
Issue 8	Weak characterisation of uncertainty	The company's PSA has been improved. The company's TE response[3] reports results for a broader range of scenario analyses compared with the CS[1] (see Table 2).

BSC - best supportive care; TE - technical engagement; QALY - quality-adjusted life year; FVC - forced vital capacity; RCPCH - Royal College of Paediatrics and Child Health; MAA - Managed Access Agreement; STRIDE - Strategic Targeting of Registries and International Database of Excellence; PSA - probabilistic sensitivity analysis

Table 2: Results of additional economic analyses presented in the company's TE response, including corrections by the EAG (ICERs exclude QALY weighting using the decision modifier)

Scenario no.	Description of scenario	PAS	ICER	DM	EAG comments
Scenarios presented in Table 3 of the company's TE response[3]					
S1	**Company's original base case**	[redacted]	[redacted]	**2.3**	Company's original base case model,[1] excluding QALY weighting. Excludes correction of errors by the EAG.
S2	RCPCH weight for patients	[redacted]	[redacted]	2.3	Same as S1, but uses patient weight data from RCPCH[7] instead of STRIDE[6] and includes correction of errors by the EAG. Equivalent to the EAG's exploratory analysis EA4 (see EAG report,[2] Table 42).
S3	Patient and caregiver utility values adjusted for age	[redacted]	[redacted]	2.2	Same as S1, plus age-adjusted utility values and EAG's corrections. Equivalent to EAG's EA3.
S4	Weibull distributions applied to all time-to-event endpoints (age at loss of ambulation, FVC<50% and FVC<30%)	[redacted]	[redacted]	2.3	Same as S1, but applies Weibull distributions to all three time-to-event endpoints. Also includes correction of errors by the EAG.
S5	Absolute caregiver utility approach applied until patients reach the age of joint median OS	[redacted]	[redacted]	1.8	Same as S1, but absolute caregiver QALY gains are not counted in either treatment group after patients have reached [redacted] years of age. Also includes correction of errors by the EAG.
S6	Revised company base case with previous PAS	[redacted]	[redacted]	1.7	Same as S1, plus amendments applied in Scenarios S2-S5 above. In addition, utility values used to estimate bereavement-related QALY losses are based on Hernandez Alava *et al.*[8]
S7	**Revised company base case with new PAS (deterministic)**	[redacted]	[redacted]	**1.7**	Same as S6, but includes updated PAS.
S8	**EAG preferred model**	[redacted]	[redacted]	**1.1**	EAG's preferred analysis EA5 using the previous PAS (see EAG report,[2] Table 42). This scenario is the same as the company's revised base case model (S7), except for: (i) the caregiver QALY approach, (ii) the selection of parametric survival models and (iii) the PAS.
S9	EAG preferred model with Weibull models and capped disutility approach	[redacted]	[redacted]	1.1	Same as S8, except that Weibull distributions are applied to all time-to-event endpoints and an assumption that caregiver QALY losses in each cycle in the ataluren group cannot be greater than those in the BSC group.
S10	EAG preferred model with no survival benefit	[redacted]	[redacted]	1.0	Same as S8, except that assumptions regarding early/relative treatment benefits in time to reach FVC<30% for ataluren vs BSC are removed. Equivalent to EAG's ASA3b (see EAG report,[2] Table 43).

Scenario no.	Description of scenario	PAS	ICER	DM	EAG comments
Scenarios presented in Table 4 of the company's TE response[3]					
S11	Early treatment benefit removed	[redacted]	[redacted]	1.3	Same as S7, with early treatment benefit for FVC<50% and FVC<30% removed.
S12	Absolute caregiver utilities, including caregiver utilities accruing beyond patient death	[redacted]	[redacted]	1.2	Same as S7, but excludes median OS cap and includes assumption that bereaved caregivers accrue a utility value which is equivalent to that of caregivers of patients with FVC<30% (the worst alive nmDMD health state).
S13	Absolute caregiver utilities with caregiver background mortality applied after patient death	[redacted]	[redacted]	1.7	Same as S7. Additional assumptions have no effect on model results.
S14	Absolute caregiver utilities capped by median OS, including caregiver utilities accruing beyond patient death, with background mortality to caregivers applied after patient death	[redacted]	[redacted]	1.2	This analysis combines Scenarios S7, S12 and S13. Background mortality is included only for caregivers after the patient has died. Caregiver QALYs are counted only up to the joint modelled median OS time point.
S15	Caregiver QALYs excluded	[redacted]	[redacted]	1.1	Same as S7, but excludes caregiver QALYs attributable to surviving patients. The analysis still includes bereavement-related QALY losses for caregivers elsewhere in the model.
S16	Survival models using 3.5-year cut-point	[redacted]	[redacted]	1.7	Same as S7, but uses alternative parametric survival models for ataluren group with a cut-point of 3.5 years applied to the STRIDE dataset.[6]
S17	Stopping rule at FVC<30%	[redacted]	[redacted]	1.7	Same as S7, but assumes that all patients discontinue ataluren upon reaching FVC<30%. Analysis impacts on costs, but not QALYs.
S18	Stopping rule at FVC<6 months after loss of ambulation	[redacted]	[redacted]	1.7	Same as S7, but assumes that all patients discontinue ataluren 6 months after losing ambulation. Analysis impacts on costs, but not QALYs.
S19	**Revised company base case with updated PAS (probabilistic)**	[redacted]	[redacted]	**1.6**†	Same as S7, results generated using the probabilistic version of the revised model

PAS - Patient Access Scheme; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EAG - External Assessment Group; S - Scenario; QALY - quality-adjusted life year; RCPCH - Royal College of Paediatrics and Child Health; OS - overall survival; FVC - forced vital capacity; nmDMD - nonsense mutation Duchenne muscular dystrophy

** The ICERs for these scenarios in the company's TE response erroneously include an additional amendment whereby EQ-5D-3L estimates reported by Hernandez Alava are used to value bereavement-related QALY losses. The results shown in this table have been corrected by the EAG. The impact of this error is minor.*

† Generated using by the EAG by re-running the company's PSA

2. EAG description and critique of individual issues discussed in the company's TE response

Issue 1: Uncertainty surrounding the relative effectiveness of ataluren versus BSC in the target population

The company's TE response[3] presents top-line results from Study 041,[4, 5] a clinical trial comparing ataluren treatment against placebo over a 72-week period. The EAG has been unable to critique this study in detail as the available data discussed in the company's TE response are limited to an online webcast (21st June 2022), including a brief accompanying slide presentation.[4, 9] A summary of Study 041 and the other pivotal randomised controlled trials (RCTs) of ataluren previously discussed in the EAG report[2] (Study 007[10] and Study 020[11]) is presented in Table 3.

Study 041 was a Phase 3, randomised, double-blind, placebo-controlled study conducted in 359 ambulatory males aged ≥5 years with nonsense mutation Duchenne muscular dystrophy (nmDMD) who were on stable doses of corticosteroids. Participants were recruited at 72 sites across 18 countries (excluding the UK). Patients with a baseline six minute walking distance (6MWD) of ≥150 metres were randomised in a 1:1 ratio to receive ataluren at a total daily dosage of 40mg/kg/day (n=183) or placebo (n=176) for 72 weeks. The EAG assumes that all patients also received BSC. Subsequently, patients were eligible to receive ataluren through an open-label 72-week extension study. Randomisation was stratified by steroid use, baseline 6MWD and supine to stand ≥5 seconds.

The primary outcome was the change in 6MWD from baseline to Week 72. In the intention-to-treat (ITT) population (mean age 8.1 years), ataluren-treated patients showed a statistically significant reduced decline from baseline in 6MWD compared to placebo-treated patients (-53.0m vs. -67.4m, respectively; difference=14.4m; p=0.0248). A more pronounced effect was observed in a subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres, with an observed difference of 24.2 metres in favour of ataluren (-55.8m vs. -80.0m, respectively; p=0.0310). In contrast, no significant difference was observed in a subgroup of patients (the primary analysis population) with a baseline 6MWD of ≥300 metres and ≥5 seconds stand from supine (-81.8m vs. -90.1m, respectively; p=0.3626).

An analysis of secondary endpoints in the ITT population showed statistically significant benefits for ataluren versus placebo for NorthStar Ambulatory Assessment (NSAA) scores (total score: difference = 0.9; p=0.0235 and linear score: difference = 2.3; p=0.0246), 10m walk times (difference = -0.78s; p=0.0422) and stair ascend times (difference = -1.06s; p=0.0293). No statistically significant difference was observed for stair descend times (difference = -0.29s; p=0.5749). In the subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres, ataluren showed significant benefits compared with placebo only in linear NSAA scores (difference = 3.3; p=0.0419), 10m walk times (difference = -1.29s; p=0.0429) and stair ascend times (difference = -2.29s; p=0.0050). In the subgroup of patients with a baseline 6MWD of ≥300 metres and ≥5 seconds stand from supine, a statistically significant difference was only observed in stair ascend times (difference = -1.76s; p=0.0155). Further details of the available results are presented in Table 4 and Table 5.

Table 3: Summary of RCTs of ataluren for nmDMD

Study name	Design	Population	Sample size	Intervention	Comparator	Follow-up period	Primary outcome(s)
Ataluren studies							
Study 041 (unpublished)[4, 5]	• Phase 3, randomised, double-blind, placebo-controlled • 72 sites, 18 countries	• Ambulatory males with nmDMD, • Aged ≥5 years (on corticosteroid treatment)	359	• Ataluren 40mg/kg/day; TID (n=183)	• Placebo; TID (n= 176)	72 weeks	Change in 6MWD from baseline to Week 72
Study 007[10]	• Phase 2b, randomised, double-blind, placebo-controlled • 37 sites, 11 countries, including UK	• Ambulatory males with nmDMD, • Aged ≥5 years (not required to be on corticosteroids at baseline)	174	• Ataluren 40mg/kg/day; TID (n=57) • Ataluren 80mg/kg/day; TID (n=60)	• Placebo, TID (n=57)	48 weeks	Change in 6MWD from baseline to Week 48
Study 020[11]	• Phase 3, randomised, double-blind, placebo-controlled • 54 sites, 18 countries, including UK	• Ambulatory males with nmDMD, • Aged 7 to 16 years (on corticosteroid treatment)	230	• Ataluren 40mg/kg/day; TID (n=115)	• Placebo; TID (n= 115)	48 weeks	Change in 6MWD from baseline to Week 48

6MWD - 6-minute walk distance; nmDMD - nonsense mutation Duchenne muscular dystrophy; TID - three times daily

Table 4: Summary of key results in the ITT population of Study 041

Endpoint	ITT Population		
	Ataluren (n=183)	Placebo (n=176)	Difference
6MWD (metres)			
Change from baseline	-53.0	-67.4	14.4 (*p*=0.0248)
Rate of change (metres/week)	-0.74	-0.94	0.20 (*p*=0.0248)
Loss of ambulation	12 (6.6%)	20 (11.4%)	
NSAA			
Total score	-3.7	-4.5	0.9 (*p*=0.0235)
Linear score	-9.6	-11.9	2.3 (*p*=0.0246)
Timed function tests			
10 metre walk	3.04	3.82	-0.78 (*p*=0.0422)
Stair ascend	4.98	6.04	-1.06 (*p*=0.0293)
Stair descend	4.96	5.25	-0.29 (*p*=0.5749)

6MWD - 6-minute walk distance; ITT, intention-to-treat; NSAA - NorthStar Ambulatory Assessment
Source: PTC Therapeutics Study 041 Top-line results[4]

Table 5: Summary of subgroup results from Study 041

Endpoint	Subgroup					
	6MWD 300m to 400m			6MWD ≥300m and ≥5 seconds supine to stand[a]		
	Ataluren (n=86)	Placebo (n=83)	Difference	Ataluren (n=92)	Placebo (n=93)	Difference
6MWD (metres)						
Change from baseline	-55.8	-80.0	24.2 (*p*=0.0310)	-81.8	-90.1	8.3 (*p*=0.3626)
Rate of change (metres/week)	-0.77	-1.11	0.34 (*p*=0.0310)	-1.14	-1.25	0.11 (*p*=0.3626)
Loss of ambulation	5 (5.7%)	10 (12.0%)	-	5 (5.4%)	9 (9.7%)	-
NSAA						
Total score	-4.4	-5.5	1.1 (*p*=0.0837)	-5.2	-6.1	0.9 (*p*=0.1258)
Linear score	-10.0	-13.3	3.3 (*p*=0.0419)	-11.4	-14.0	2.5 (*p*=0.0656)
Timed function tests						
10 metre walk	2.99	4.28	-1.29 (*p*=0.0429)	3.06	3.79	-0.73 (*p*=0.1877)
Stair ascend	5.26	7.55	-2.29 (*p*=0.0050)	5.19	6.96	-1.76 (*p*=0.0155)
Stair descend	4.62	5.59	-0.97 (*p*=0.2714)	4.58	4.78	-0.19 (*p*=0.7997)

6MWD - 6-minute walk distance; NSAA – NorthStar Ambulatory Assessment
[a] *Primary analysis population*
Source: PTC Therapeutics Study 041 Top-line results[4]

The company's TE response[3] and the top-line slide deck also include a pooled analysis of Studies 007, 020 and 041 (see Table 6), although the EAG is unclear which statistical methods were used to pool the data as no additional information was provided by the company. This analysis showed a statistically significant benefit for ataluren compared to placebo with a mean difference in 6MWD of 19.3 metres

(p=0.0002). A more pronounced effect was observed in the pooled subgroup of patients with a baseline 6MWD of ≥300 metres to <400 metres, with an observed difference of 32.1 metres in favour of ataluren versus placebo (p=0.0005).

Additional analyses of secondary outcomes from the three studies showed statistically significant benefits in favour of ataluren over placebo in NSAA scores (total score: p=0.002; linear score: p=0.005), 10m walk time (p=0.0001), stair ascend (p=0.0004) and stair descend (p=0.0004).

Table 6: Results of pooled analysis of Studies 007, 020 and 041

Endpoint	Overall study population: Studies 007, 020, 041		
	Ataluren (n=354)	Placebo (n=347)	Difference
6MWD (m) (48 weeks)	-28.1	-47.4	19.3 (p=0.0002)
NSAA[a]			
Total score	-	-	1.01 (p=0.002)
Linear score	-	-	2.28 (p=0.005)
Timed function tests			
10m walk	-	-	-1.30 (p=0.0001)
Stair ascend	-	-	-1.43 (p=0.0004)
Stair descend	-	-	-1.51 (p=0.0004)

[a] *Study 020 and study 041 only*
Source: PTC Therapeutics Study 041 Top-line results[4]

In summary, the EAG agrees with the company's view in their TE response[3] that the headline results from Study 041 '*further add to the clinical efficacy and safety-profile of ataluren.*' However, the EAG notes that the evidence from Study 041 has not been used in the company's economic model, nor does it provide any evidence on the efficacy of ataluren beyond the loss of ambulation or in patients aged <5 years old.

Issue 2: Inappropriate approach used to estimate incremental caregiver QALYs

The company's TE response[3] presents the results of scenario analyses using six different approaches for estimating the impact of ataluren versus BSC on QALY impacts for caregivers of patients with nmDMD. Each of these approaches impacts on both the incremental cost-effectiveness ratios (ICERs) for ataluren versus BSC, as well as the decision modifier (DM). Each of these six methods and their underlying assumptions are described and critiqued below.

Approach 1: Absolute caregiver utility approach (used in the company's original base case model, Table 2, Scenario S1)

This approach was used in the company's original base case model.[1] Caregiver QALYs in both groups are calculated by assigning absolute caregiver utility values to patient health states; when patients spend time in the alive health states, their caregivers accrue QALYs. This approach counts caregiver QALYs whilst the nmDMD patient is alive, but stops counting caregiver QALYs when the patient dies. As noted

in the EAG report[2] (Section 5.3.5, critical appraisal point 6c, pages 130 to 132), this approach implicitly makes one of three assumptions: (i) that when the patient dies their caregivers also die; (ii) that when the patient dies their caregivers survive with zero utility, or (iii) that society places value on health gains accrued by caregivers of surviving patients but not on health gains accrued by bereaved caregivers. The EAG does not consider any of these assumptions to be appropriate. As such, the EAG believes that the results of an analysis using this approach are not meaningful.

Approach 2: Absolute caregiver utility approach capped at joint median OS time (used in the company's revised base case model, Table 2, Scenario S5)

This approach is used in the company's revised base case model. Caregiver QALYs in both groups are calculated in the same way as in Approach 1 (described above), except that after some time point, subsequent QALYs accrued by caregivers of surviving patients are not included in the analysis. The time point used in this analysis is the age of joint median overall survival (OS) for the two treatment groups in the model ([redacted] years). The EAG notes that this alternative approach is subject to the same problematic assumption as Approach 1, as QALYs accrued by bereaved caregivers are not counted, as well as an additional arbitrary assumption that QALYs accrued by caregivers of surviving patients should be included up to some time point, but not subsequently. As such, the EAG does not consider the results of the company's revised base case model to be meaningful.

Approach 3: Caregiver disutility approach (used in the EAG's preferred model, Table 2, Scenario S8)

This approach is used in the EAG's preferred model (see EAG report,[2] Table 42, exploratory analysis EA5). The methods used to implement this analysis are described in Section 5.4 of the EAG report (page 136). Under this approach, disutility values for caregivers are assigned to each alive nmDMD patient health state, calculated as the difference between the health state utility values reported by Landfeldt *et al.* (2017)[12] and an estimate of general population utility, based on Euroqol 5-Dimensions 3-Level (EQ-5D-3L) values reported by Hernandez Alava *et al.*[8] In the model, caregiver QALY losses are incurred in each treatment group whilst the patient is still alive; after the patient dies, no further QALY losses are applied. Therefore, this method implicitly assumes that caregiver health-related quality of life (HRQoL) rebounds to the level of the general population after the nmDMD patient dies. This assumption is problematic, but can be avoided through the inclusion of some bereavement-related QALY loss – this factor is already included elsewhere in the company's model, based on the approach used in NICE Highly Specialised Technology (HST) Appraisal Number 7.[13] As noted in the EAG report (Section 5.3.5, critical appraisal point 6c, page 131), with only one exception, all previous HSTs which have included caregiver QALY impacts, including the previous model of ataluren used to inform HST3,[14] have adopted a caregiver disutility approach. This remains the EAG's preferred approach and this is used in the EAG's additional analyses presented in Section 3 of this addendum.

Approach 4: Caregiver disutility approach, with ataluren QALY losses capped by BSC QALY losses (used in the company's TE scenario analysis, Table 2, Scenario S9)

This approach is used in the company's TE Scenario S9 (together with other model amendments). This approach is the same as Approach 3, except that a cap is applied to the caregiver QALY losses in the ataluren group, which ensures that the total caregiver QALY loss in each cycle for caregivers of ataluren-treated patients cannot be greater than the total caregiver QALY loss of caregivers of BSC-treated patients in that same cycle. In each cycle, if the estimated caregiver QALY loss is greater for ataluren than BSC, the caregiver QALY loss in the health state for the BSC group is applied to the equivalent health state for the ataluren group. The estimated caregiver QALY losses in the BSC group remain unaffected by this cap.

The implications of this approach are illustrated in Figure 1. This plot presents the estimated per-cycle caregiver QALY losses for: (i) the BSC group (the solid grey line), (ii) the ataluren group excluding the cap (the solid black line) and (iii) the ataluren group including the cap (the dashed black line). OS for both groups is also shown on the plot to aid interpretation. In the first few model cycles, both treatment groups incur similar caregiver QALY losses because most patients remain alive and ambulant, regardless of which treatment they are receiving. The caregiver QALY losses in both groups initially decrease in these early cycles as a consequence of the inclusion of age-adjustment for caregiver utility values and discounting. After patients reach the age of around [redacted] years, the lines showing caregiver QALY losses for ataluren and BSC separate as the BSC group incurs greater caregiver QALY losses because patients reach more severe DMD milestones at a faster rate than the ataluren group. However, as BSC patients die faster than ataluren patients, the caregiver QALY losses for ataluren exceed those for BSC from the age of [redacted] years. This is when the cap is applied. The difference in caregiver QALYs for ataluren versus BSC up to this time point, denoted Area "A" in Figure 1, is positive (i.e., caregivers of ataluren-treated patients lose fewer QALYs than caregivers of BSC-treated patients). When the cap is excluded from the analysis, the subsequent incremental caregiver QALYs for ataluren versus BSC are shown by Area "B" Figure 1. Over this interval, caregiver QALY losses are greater for ataluren than BSC because although more ataluren patients are in better health states due to delays in reaching more advanced DMD milestones, more BSC patients have died (hence, the model reflects an ongoing caregiver burden associated with extended patient OS). When the cap is excluded, the total incremental caregiver QALYs for ataluren versus BSC (excluding bereavement-related QALY losses which are captured elsewhere in the model) is calculated as the sum of Areas A and B (where A is positive and B is negative). When the cap is included, only Area A is counted and Area B is ignored.

The EAG believes that accepting this approach would require a social value judgement that only positive effects on caregivers should be included in an economic analysis. Such a position would

purposefully exclude the impact of increased OS leading to a continued caregiver burden. The EAG is unsure whether this type of value judgement has been applied in previous HSTs.

Figure 1: Comparison of including or excluding the QALY loss cap (Table 2, Scenario S8 versus Scenario S9)

Note: Area A is estimated to be [redacted] discounted caregiver QALYs and Area B is estimated to be [redacted] discounted caregiver QALYs. The total incremental caregiver QALYs gained for ataluren versus BSC is estimated to be [redacted] QALYs when the cap is excluded (Scenario S8) and [redacted] QALYs when the cap is included (Scenario S9). These total incremental caregiver QALY estimates estimated by the model also include bereavement-related QALY losses which are not represented in the plot.

Approach 5: Absolute caregiver utility approach, including continued caregiver QALY gains after patient death (used in TE scenario analysis, Table 2, Scenario S12)

This approach is used in the company's TE Scenario S12. This approach is the same as the absolute caregiver utility approach used in Approach 1, except that QALYs accrued by caregivers continue to be counted after the patient has died. As such, the caregiver QALYs accrued in the alive health states remain unchanged from Approach 1, but additional QALYs are also included for bereaved caregivers. These additional QALY gains for bereaved caregivers are calculated as the product of: (i) the proportion of nmDMD patients who have died in each cycle; (ii) the number of caregivers per nmDMD patient (n=2) and (iii) the caregiver utility value for the worst patient health state (forced vital capacity [FVC] <30%, utility value = 0.77, taken from Landfeldt *et al.* (2017)[12]). Age-adjustment of caregiver utility values is also included in the calculations. The EAG understands that this approach has been presented as an attempt to avoid the inappropriate assumptions which underpin Approach 1. However, it is unclear why the company has assumed that bereaved caregiver HRQoL would rebound to the level assumed for patients with FVC<30% after the patient has died, as the impact of bereavement is already captured

elsewhere in the model. Including both of these factors therefore appears to be double-counting the impact of bereavement. The EAG notes that when the utility value for bereaved caregivers is set equal to that of the general population (utility = 0.91, from Hernandez Alava *et al.*[8]), this method is conceptually identical to the EAG's preferred caregiver disutility method (Approach 3). Table 7 illustrates this by comparing the results of the EAG's preferred model using disutility values (Table 2, Scenario S8) and the company's absolute caregiver utility approach including continued caregiver QALY gains after patient death (Table 2, Scenario S12) including an alternative assumption whereby bereaved caregivers have a utility value of 0.91 rather than 0.77. As shown in Table 7, the results of the two methods are the same and therefore the EAG considers that this amended absolute caregiver utility approach is appropriate.

Table 7: Comparison of caregiver disutility approach versus approach using absolute caregiver utilities including general population utility for bereaved caregivers (Table 2, Scenarios S8 versus modified Scenario S12, using previous PAS)

EAG-preferred caregiver disutility approach (TE response, Table 2, Scenario S8)							
Option	**LYGs***	**QALYs patients**	**QALYs carers**	**QALYs patients+ carers**	**Costs**	**ICER patient**	**ICER patient + carers**
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute caregiver utility approach including QALY gains for bereaved caregivers (TE response, Table 2, Scenario S12), plus amendment whereby bereaved caregivers have a utility value of 0.91							
Option	**LYGs***	**QALYs patients**	**QALYs carers**	**QALYs patients+ carers**	**Costs**	**ICER patient**	**ICER patient + carers**
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TE - technical engagement; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; S – scenario

Approach 6: Absolute caregiver utility approach capped at joint median OS time, including background mortality for caregivers (used in TE scenario analysis, Table 2, TE Scenario S13)

This approach is used in the company's TE Scenario S13. Caregiver QALYs in both groups are calculated in the same way as in Approach 2, except that background mortality risks are applied to bereaved caregivers, but not caregivers of surviving patients. However, because Approach 2 assumes that bereaved caregivers accrue zero QALYs, applying background mortality to these caregivers has no effect on the model results (ICER = [redacted] per QALY gained). The EAG believes that this approach applies illogical assumptions and should therefore be disregarded.

After submitting their original TE response,[3] the company provided an updated document which included a further analysis which combines Approaches 2, 5 and 6 (Table 2, TE Scenario S14). This

additional analysis: (a) uses absolute caregiver utility values; (b) includes a cap whereby caregiver QALYs are counted only up to the modelled joint median OS time; (c) counts absolute caregiver QALYs for bereaved caregivers (rebounding to the utility value for the FVC<30% health state after the patient dies), and (d) includes background mortality risks for bereaved caregivers. This analysis is subject to the same problems as Approaches 2 and 5, in that it counts caregiver QALYs up to an arbitrary timepoint, but not thereafter, and it likely double counts the impact of bereavement. As background mortality risks in this analysis are only applied to bereaved caregivers, this scenario implies that surviving patients will always have 2 caregivers. This might reflect an underlying assumption that if one caregiver dies, they would be immediately replaced by another caregiver (e.g., a different family member), although this is not discussed in the company's TE response.

EAG's overall conclusions on the company's alternative methods for estimating caregiver QALYs

The EAG's overall view regarding how caregiver QALYs should be estimated remains unchanged. The EAG's preferred analysis uses caregiver disutility values (Approach 3), including the impact of bereavement which is captured elsewhere in the model. This disutility approach is consistent with most previous HSTs, including the earlier NICE appraisal of ataluren in HST3.[14] The absolute caregiver utility approaches used in the company's original and revised base case analyses (Approaches 1 and 2, respectively) do not count QALYs accrued by bereaved caregivers, which the EAG considers to reflect one of several potential unreasonable assumptions. The EAG's analysis in Table 7 illustrates that applying absolute caregiver utility values, including accounting for health gains accrued by bereaved caregivers (Approach 5), is the same as using disutility values (Approach 3), provided that both methods apply consistent assumptions about caregiver HRQoL after the patient has died. Applying a cap on ataluren QALY losses (Approach 4) implies an additional social value judgement – that the positive effects on caregivers should be counted but the negative effects should be ignored; it is unclear whether this position should be considered acceptable. The company's original scenario analysis which includes background mortality risks (Approach 6) is illogical and should be disregarded. The additional scenario analysis using this approach provided in the updated TE response arbitrarily stops counting caregiver QALYs after median OS is reached and likely double counts the impact of bereavement.

Issue 3: Limitations surrounding the company's survival modelling

The company's TE response[3] provides further explanation regarding the company's decision to fit independent parametric survival models to the Strategic Targeting of Registries and International Database of Excellence (STRIDE) and Cooperative International Neuromuscular Research Group (CINRG) Disease Natural History Study (DNHS) datasets[15] and provides plots of log-cumulative hazards and Schoenfeld residuals for each time-to-event endpoint. The company's TE response also notes the EAG's criticism that a broader range of survival distributions, such as restricted cubic spline [RCS] models, should have been assessed. The company's TE response (page 10) states that this further

analysis has not been conducted as the economic model is *"relatively insensitive to the survival function used."* The company's original model used log-logistic models for age at loss of ambulation and age at reaching FVC<50%, and log-normal models for age at reaching FVC<30%. The company's revised base case model (Table 2, Scenario S7) applies Weibull models for all three time-to-event endpoints; the company's TE response states that this was the EAG's preferred distribution. The company's response also presents an additional scenario analysis using a cut-point of 3.5 years in both treatment groups (Table 2, Scenario S16). The results for this scenario analysis are very similar to those generated using for the company's revised base case model (Scenario S7 versus Scenario S16: ICERs = [redacted] versus [redacted] per QALY gained; decision modifier = [redacted] for both scenarios).

The EAG notes the following observations regarding the company's TE response:

- The EAG report[2] (Section 5.3.5, critical appraisal point 4, page 123) noted that the proportional hazards (PH) assumption had not been explored by the company. Despite this, the EAG considered the use of independent survival models to be reasonable.
- The company's model predictions are a function of the parametric survival model predictions as well as additional assumptions regarding early/relative treatment benefits for ataluren. As noted in the EAG report, the models selected by the company do not appear to provide a good representation of the data for age at loss of ambulation from STRIDE, or age at FVC<50% in either the STRIDE or propensity score matched CINRG DNHS datasets.[6, 15] With the exception of age at loss of ambulation in the CINRG DNHS, the selected models for all other endpoints in both treatment groups do not appear to reflect the empirical hazards. The EAG's clinical advisors also had concerns that the model predictions in terms of delays in reaching DMD milestones appeared to be optimistic. As no new analyses have been presented, the concerns discussed in the EAG report remain unchanged.
- The EAG report presented an additional sensitivity analysis using Weibull distributions for all time-to-event endpoints (see EAG report, Table 43, ASA4). However, this was a sensitivity analysis which did not form part of the EAG's preferred model. As such, the EAG is unclear why the company has selected Weibull models for use in their revised base case model.

Issue 4: Uncertainty surrounding the appropriateness of treatment-dependent patient utility values

The company's TE response[3] states that treatment-dependent patient utility values are applied correctly in the company's model. The response also states that the assumption of treatment-dependent utility values is strongly supported by the clinical experts who participated in two Delphi panels (comprised of 6 and [redacted] clinicians) and by one UK clinical expert consulted by the company during the TE stage. The company's response also argues that the modelled health states are too blunt to fully reflect improvements attributable to ataluren relating to functional ability and associated HRQoL impacts on

participation in ambulatory patients. The response also argues that as progression to loss of ambulation is delayed with ataluren, progression within all health states is also likely to be delayed. The company also presents quotes from submissions from patient organisations including Muscular Dystrophy UK and Action Duchenne citing positive patient and caregiver experiences of patients receiving ataluren treatment, including the patient's ability to participate in activities, walking, attending school, increased energy and reduced fatigue, and improved behaviour. The submissions also refer to positive impacts relating to hope.

The EAG notes the following points regarding this issue:

- The EAG does not believe that there is an error in the company's model. This issue relates to the plausibility of assuming treatment-dependent patient utility values.
- The inclusion of treatment-dependent patient utility values is a key model driver. The EAG's exploratory analyses demonstrate that removing this assumption from the ambulatory health state, or from all health states, substantially increases the ICER for ataluren versus BSC.
- As discussed in the EAG report (Section 5.3.5, critical appraisal point 6a), the company has not presented any empirical evidence of HRQoL measured in nmDMD patients to support the assumption of treatment-dependent patient utility values (e.g., a comparison of preference-based HRQoL from an RCT). [redacted] The Delphi panel (Landfeldt *et al.*, 2020[17]) used to inform the company's model assumes treatment-dependent patient utility values in all ambulant and non-ambulant health states, regardless of whether the patient is still receiving ataluren.
- The EAG's clinical advisors commented that it was difficult to comment on the appropriateness of assuming treatment-dependent patient utility values because there is a lack of evidence. The EAG's first clinical advisor commented that ambulant patients receiving ataluren or BSC will have a range of functional abilities and they suggested that it was unlikely that there would be any significant difference in HRQoL between the two groups, even if endurance was slightly increased in those on ataluren. They suggested however that non-ambulant patients who have discontinued ataluren may have comparatively better HRQoL than patients who have never received the drug, as delaying loss of ambulation could reduce the risk of scoliosis. The EAG's second clinical advisor commented that they were not convinced that there would be a marked difference in HRQoL in ambulatory patients receiving ataluren or BSC. They also commented that there is no evidence to support a delay in the effect of ataluren on upper limb involvement.

- The EAG's preferred model[2] retains the company's assumption of treatment-dependent patient utility values in all health states. This may be optimistic given the absence of empirical evidence and the differing views of clinical experts consulted by the EAG and the company.
- The EAG believes that judgements are required by the Appraisal Committee regarding: (i) whether there is sufficient evidence to assume treatment-dependent patient utility values in the model; (ii) whether this assumption should apply to all or some of the model health states, and (iii) whether such benefits should be assumed to persist beyond discontinuation of ataluren.

Issue 5: Uncertainty surrounding modelled acquisition costs of ataluren by age

The company's TE response[3] acknowledges the limitations of using the data from STRIDE[6] to inform estimates of patient weight in the model. This issue is discussed in Section 5.3.5 (critical appraisal point 7a) of the EAG report.[2] The company's revised base case model uses the data on patient weight by age from the Royal College of Paediatrics and Child Health (RCPCH).[7] This is now consistent with the EAG's preferred model (EA5). The EAG believes that this issue can be considered resolved.

Issue 6: Uncertainty surrounding the discontinuation rate in patients with FVC>50%

The company's TE response[3] acknowledges that the discontinuation rate for ataluren used in the model is problematic as it has been estimated from patients in STRIDE[6] who discontinued treatment for any reason, including those which may be already captured by the modelled stopping rule (applied when patients reach FVC<50%). The company's TE response reports data on the number of patients who discontinued ataluren or changed dose at the January 2021 data-cut in STRIDE and presents a Kaplan-Meier plot of time to treatment discontinuation (TTD). These data were previously reported in the company's clarification response (questions A8 and B8) and were reproduced in the EAG report[2] (Section 4.2.4, page 54 and Section 5.3.5, Figure 27). No new analysis has been presented and the company's economic model has not been amended. As such, the EAG remains concerned that the company's model may overestimate the discontinuation rate for ataluren.

Issue 7: Uncertainty surrounding the most appropriate treatment discontinuation rule

The company's TE response[3] acknowledges that STRIDE[6] did not apply a consistent stopping rule to all patients and that any proposed stopping rule will inevitably be subject to uncertainty. The company's TE response also highlights the challenge of implementing a stopping rule based on predicted FVC and suggests that a preferred option might be to focus on ventilation status – with treatment stopping at the point at which patients require night-time or full-time ventilation. The TE response also states that the company is open to exploring alternative stopping rules and notes that their proposed stopping rule at FVC<50%, which is assumed to reflect the time at which patients are non-ambulatory and require night-time ventilation, is consistent with clinical opinion, whereas earlier stopping rules are less consistent with the clinical data but result in lower ICERs for ataluren. The company's TE response includes

economic analyses which explore alternative stopping rules - at FVC<50% (Table 2, Scenarios S1-S16 and S19), FVC<30% (Table 2, Scenario S17) and 6-months after loss of ambulation (Table 2, Scenario S18).

The EAG notes the following issues regarding stopping rules for ataluren:

- The EAG's clinical advisors commented that they would wish to use ataluren beyond the loss of ambulation.
- Data presented in the company's clarification response[16] suggest that up to [redacted] of patients in STRIDE[6] who lost ambulation continued to receive ataluren. However, the extent to which this continued exposure to treatment is consistent with the company's proposed FVC<50% discontinuation rule applied in the model is unclear.
- There are no long-term data which demonstrate the magnitude of clinical benefit on pulmonary endpoints associated with continued ataluren treatment beyond loss of ambulation.
- It is unclear whether the elicited estimates around early treatment benefit for the age at which ataluren-treated patients reach FVC<30% in the model specifically took account of the company's proposed FVC<50% discontinuation rule.
- The company's economic model adopts a partitioned survival approach whereby clinical outcomes are not structurally dependent on whether the patient is still receiving treatment (i.e., the modelled stopping rule applied at earlier DMD milestones cuts costs but does not affect QALYs). The ability of the company's model to explore the costs and clinical consequences of alternative discontinuation rules is therefore limited.

Issue 8: Weak characterisation of uncertainty

The company's TE response[3] acknowledges the limited range of deterministic scenario analyses presented in the CS[1] and the EAG's concerns regarding the weak characterisation of uncertainty for some of the parameters included in the original PSA. The company's response includes a broader range of scenario analyses (see Table 2) and the company's revised model resolves some of the issues in the company's original PSA (using published standard errors for costs and utility parameters and applying beta distributions for utility values). The EAG notes that the ICERs generated using the probabilistic and deterministic versions of the model are similar. However, the probabilistic model produces lower estimates of OS compared with the deterministic model. This discrepancy is caused by the early treatment benefit parameters being rounded down to integer values. This rounding has been removed from the EAG's additional probabilistic analysis presented in Section 3.

3. Additional analyses undertaken by the EAG

This section presents the results of the EAG's exploratory analyses including the updated PAS for ataluren. Table 8 presents the results of the EAG's preferred model. Table 9 presents the results of the EAG's additional sensitivity analyses. The results presented in these tables include the correction of a

minor error in the calculation of the decision modifier for some scenarios; this error was identified after the submission of the EAG report. The probabilistic version of the EAG's preferred model (EA5) suggests that the ICER for ataluren versus BSC is [redacted] per QALY gained (decision modifier = [redacted]). The deterministic version of the EAG's preferred model suggests a slightly higher ICER of [redacted] per QALY gained (decision modifier = [redacted]). These ICERs are substantially higher than the ICERs generated using the company's original and revised deterministic base case models using the new PAS (ICERs = [redacted] and [redacted] per QALY gained, respectively; decision modifiers = [redacted] and [redacted], respectively). The main driver of the differences in the estimated ICERs and decision modifiers across these models relates to the approach used to estimate caregiver QALY impacts. The EAG's additional sensitivity analyses highlight that the ICER is highly sensitive to the assumption of treatment-dependent patient utility values. The decision modifier is estimated to be [redacted] across all additional sensitivity analyses.

Table 8: EAG preferred model results including updated ataluren PAS

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's original base case model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.3**
EA1: Correction of errors								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.3**
EA2: Use of caregiver disutilities								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.1**
EA3: Inclusion of age-adjusted utilities								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.2**
EA4: Use of age-specific weight data from RCPCH								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.3**
EA5: EAG preferred model (deterministic)								

Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.1**
EA5: EAG preferred model (probabilistic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.1**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; BSC - best supportive care; RCPCH - Royal College of Paediatrics and Child Health;
** Undiscounted*

Table 9: EAG additional sensitivity analysis results including updated ataluren PAS

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
EA5: EAG preferred model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.1**
ASA1a: Use of treatment-independent patient utility value in ambulatory state								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA1b: Assume BSC patient utility values after ataluren discontinuation								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA1c: Use of treatment-independent patient utility values								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA2a: Early treatment benefits halved								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA2b: Early treatment benefits removed								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA3a: Survival gain assumed to be equal to delay in loss of ambulation								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA3b: Survival gain removed								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.0**
ASA4: Use of Weibull model for all time-to-event endpoints								

Ataluren+BSC	[redacted]						-	-
BSC	[redacted]						-	-
Incremental	[redacted]						[redacted]	[redacted]	**1.0**
ASA5: Discontinuation rate reduced by 50%								
Ataluren+BSC	[redacted]						-	-
BSC	[redacted]						-	-
Incremental	[redacted]						[redacted]	[redacted]	**1.1**
ASA6a: Discontinuation at 6 months after loss of ambulation								
Ataluren+BSC	[redacted]						-	-
BSC	[redacted]						-	-
Incremental	[redacted]						[redacted]	[redacted]	**1.1**
ASA6b: Discontinuation at FVC<30%								
Ataluren+BSC	[redacted]						-	-
BSC	[redacted]						-	-
Incremental	[redacted]						[redacted]	[redacted]	**1.1**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; ASA – additional sensitivity analysis; BSC - best supportive care; * Undiscounted*

4. References

1. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's submission to NICE. PTC Therapeutics: Guildford; 2022.
2. Tappenden P, Pandor A, Bayley T, Clowes M. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. External Assessment Group Report. University of Sheffield: Sheffield, UK; 2022.
3. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's technical engagement response. PTC Therapeutics: Guildford UK; 2022.
4. PTC Therapeutics. Translarna ™ (ataluren) Study 041 topline results. Available from: https://ir.ptcbio.com/events-presentations. Accessed 25 July 2022; 2022.
5. ClinicalTrials.gov. NCT03179631. Long-term outcomes of ataluren in Duchenne muscular dystrophy. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03179631. Accessed 25 July 2022.; 2022.
6. PTC Therapeutics Inc. Registry of Translarna (ataluren) in nonsense mutation Duchenne muscular dystrophy (nmDMD) (STRIDE); 2022.
7. Royal College of Paediatrics and Child Health. Growth charts. Available from: https://www.rcpch.ac.uk/resources/growth-charts. RCPCH: London; 2022.
8. Hernández Alava M., Pudney S., Wailoo A. Estimating EQ-5D by age and sex for the UK. University of Sheffield: Sheffield, UK; 2022.
9. PTC Therapeutics. PTC Therapeutics to host call to review topline results from Study 041 for Translarna™ (ataluren) in nonsense mutation Duchenne muscular dystrophy. Available from: https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-host-call-review-topline-results-study-041 Accessed 25 July 2022. 2022.

10. Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP*, et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy (Study 007). *Muscle & Nerve* 2014;50:477-87.
11. McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N*, et al.* Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial (Study 020). *Lancet* 2017;390:1489-98.
12. Landfeldt E, Alfredsson L, Straub V, Lochmüller H, Bushby K, Lindgren P. Economic evaluation in Duchenne muscular dystrophy: Model frameworks for cost-effectiveness analysis. *PharmacoEconomics* 2017;35:249-58.
13. National Institute for Health and Care Excellence. HST7: Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. Committee papers; NICE: London, UK; 2018.
14. National Institute for Health and Care Excellence. HST3 - NICE Guidance: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. NICE: London, UK; 2016.
15. The Cooperative International Neuromuscular Research Group (CINRG). CINRG disease natural history dataset. 2022.
16. PTC Therapeutics Inc. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) [ID1642]. Company's response to clarification questions from the EAG. PTC Therapeutics: Guildford; 2022.
17. Landfeldt E, Lindberg C, Sejersen T. Improvements in health status and utility associated with ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy. *Muscle & Nerve* 2020;61:363-8.

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

Appendix 1: Cost-effectiveness results for EAG exploratory analyses using the list price for ataluren

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	18th August 2022

Table 1: EAG preferred model results using ataluren list price (Table 8 in EAG technical engagement response)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's original base case model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£559,636**	**£336,555**	**2.3**
EA1: Correction of errors								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£564,853**	**£341,148**	**2.3**
EA2: Use of caregiver disutilities								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£564,853**	**£580,159**	**1.1**
EA3: Inclusion of age-adjusted utilities								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£567,801**	**£352,113**	**2.2**
EA4: Use of age-specific weight data from RCPCH								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£623,065**	**£376,306**	**2.3**
EA5: EAG preferred model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£626,317**	**£639,644**	**1.1**
EA5: EAG preferred model (probabilistic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£623,002**	**£637,925**	**1.1**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; BSC - best supportive care; RCPCH - Royal College of Paediatrics and Child Health;
** Undiscounted*

Table 2: EAG additional sensitivity analysis results using ataluren list price (Table 9 in EAG technical engagement response)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
EA5: EAG preferred model (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£626,317**	**£639,644**	**1.1**
ASA1a: Use of treatment-independent patient utility value in ambulatory state								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,478,870**	**£1,555,386**	**1.0**
ASA1b: Assume BSC patient utility values after ataluren discontinuation								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£821,786**	**£844,882**	**1.0**
ASA1c: Use of treatment-independent patient utility values								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£3,112,151**	**£3,471,543**	**1.0**
ASA2a: Early treatment benefits halved								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£643,804**	**£658,923**	**1.0**
ASA2b: Early treatment benefits removed								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£661,574**	**£678,870**	**1.0**
ASA3a: Survival gain assumed to be equal to delay in loss of ambulation								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£631,282**	**£640,920**	**1.0**
ASA3b: Survival gain removed								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£678,887**	**£648,411**	**1.0**
ASA4: Use of Weibull model for all time-to-event endpoints								

Ataluren+BSC	[redacted]					-	-	
BSC						-	-	
Incremental						**£588,080**	**£604,428**	**1.0**
ASA5: Discontinuation rate reduced by 50%								
Ataluren+BSC	[redacted]					-	-	
BSC						-	-	
Incremental						**£732,699**	**£748,289**	**1.1**
ASA6a: Discontinuation at 6 months after loss of ambulation								
Ataluren+BSC	[redacted]					-	-	
BSC						-	-	
Incremental						**£548,220**	**£559,885**	**1.1**
ASA6b: Discontinuation at FVC<30%								
Ataluren+BSC	[redacted]					-	-	
BSC						-	-	
Incremental						**£697,608**	**£712,451**	**1.1**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; ASA – additional sensitivity analysis; BSC - best supportive care; * Undiscounted*

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

Appendix 2: Cost-effectiveness results for EAG exploratory analyses including decision modifier weighting

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	18th August 2022

Table 1: Company's base case, EAG preferred model and EAG additional sensitivity analysis results including updated ataluren PAS and ICERs with/without decision modifier weighting

Scenario	Decision modifier	ICER (patients and carers) excluding QALY weighting	ICER (patients and carers) including QALY weighting
Company's base case			
Company's original base case model (deterministic)	2.3	[redacted]	[redacted]
EAG preferred analysis (Table 8 in EAG technical engagement response)			
EA1: Correction of errors	2.3	[redacted]	[redacted]
EA2: Use of caregiver disutilities	1.1	[redacted]	[redacted]
EA3: Inclusion of age-adjusted utilities	2.2	[redacted]	[redacted]
EA4: Use of age-specific weight data from RCPCH	2.3	[redacted]	[redacted]
EA5: EAG preferred model (deterministic)	1.1	[redacted]	[redacted]
EA5: EAG preferred model (probabilistic)	1.1	[redacted]	[redacted]
EAG additional sensitivity analyses (Table 9 in EAG technical engagement response)			
ASA1a: Use of treatment-independent patient utility value in ambulatory state	1.0	[redacted]	[redacted]
ASA1b: Assume BSC patient utility values after ataluren discontinuation	1.0	[redacted]	[redacted]
ASA1c: Use of treatment-independent patient utility values	1.0	[redacted]	[redacted]
ASA2a: Early treatment benefits halved	1.0	[redacted]	[redacted]
ASA2b: Early treatment benefits removed	1.0	[redacted]	[redacted]
ASA3a: Survival gain assumed to be equal to delay in loss of ambulation	1.0	[redacted]	[redacted]
ASA3b: Survival gain removed	1.0	[redacted]	[redacted]
ASA4: Use of Weibull model for all time-to-event endpoints	1.0	[redacted]	[redacted]
ASA5: Discontinuation rate reduced by 50%	1.1	[redacted]	[redacted]
ASA6a: Discontinuation at 6 months after loss of ambulation	1.1	[redacted]	[redacted]
ASA6b: Discontinuation at FVC<30%	1.1	[redacted]	[redacted]

EAG - External Assessment Group; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; EA - exploratory analysis; ASA - additional sensitivity analysis; RCPCH - Royal College of Paediatrics and Child Health; BSC - best supportive care; FVC - forced vital capacity