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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Company comments on the Evaluation Consultation Document (ECD)**

3. **Consultee and commentator comments on the Evaluation Consultation Document (ECD) from:**
   a. Muscular Dystrophy UK and Action Duchenne

4. **Comments on the Evaluation Consultation Document (ECD) from experts:**
   a. Katherine Wedell – patient expert, nominated by Action Duchenne
   b. Mark Silverman – patient expert, nominated by Action Duchenne

5. **Evidence Review Group critique of the company's response to the Evaluation Consultation Document (ECD)**

6. **Evidence Review Group updated cost-effectiveness results post-first committee meeting**

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 Technology Evaluation

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

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
PTC therapeutics	***General comment / cover letter*** Dear Committee Members, PTC Therapeutics welcomes the opportunity to comment on this Evaluation Consultation Document (ECD) and kindly ask the Committee to reconsider the recommendation published in the ECD. PTC Therapeutics would like to outline the full extent of the unmet need. Nonsense-mutation Duchenne muscular dystrophy (nmDMD) is a rare, inherited, degenerative disease characterised by a progressive loss of muscle function beginning in early childhood, resulting in declining ambulatory ability, pulmonary function, cardiac function, and upper body function.[1] This progressive muscle wasting eventually results in early mortality, typically before the age of 30.[1] Both patients and their caregivers therefore suffer from a severely reduced quality of life (QoL), as daily activities become impossible for patients to perform independently, especially after patients lose their ability to walk and become wheelchair-bound typically at the age of 12-13 years.[2,3] In England, it is estimated that [redacted] nmDMD patients are currently receiving ataluren as part of a Managed Access Agreement (MAA) (number of patients in the MAA, as of December 2021). Other than ataluren, no treatments are currently recommended in the UK specifically for the treatment of DMD including nmDMD. Hence, there is a high unmet need for the introduction of a treatment such as ataluren to improve the QoL of patients with nmDMD. Ataluren has been shown to meet this unmet need by delaying disease progression and hence, prolonging time spent in less severe health states. Ataluren has demonstrated a statistically significant delay in loss of ambulation (LoA) of 5.4 years in patients treated in the Real-World STRIDE registry, compared to matched-control patients receiving best supportive care (BSC) in the CINRG DNHS registry.[4] Pulmonary disease milestones were also delayed in the STRIDE registry in ataluren-treated patients. Similarly, patients	Thank you for your comments. The committee acknowledged the severity of the condition and the limited treatment options available (see FED section 3.1 and 3.2). The committee acknowledged that ataluren provided benefits over standard care (see FED section 3.5). Please refer to responses to further points raised elsewhere in this document.

	treated with ataluren in three phase IIb/III clinical trials showed a statistically significant decrease in change in decline in 6MWD from baseline compared to placebo-treated control patients. In Study 020, in the pre-specified subgroup of patients with baseline 6MWD ≥300m to <400m, the change in decline in 6MWD was 42.9m in favour of the ataluren-treated arm compared to the placebo-treated arm at 48 weeks (p=0.007).[5] Similarly in Study 007, the change in decline in 6MWD was 68.2m in favour of the ataluren-treated arm compared to the placebo-treated arm at 48 weeks (p=0.0053), in the subgroup of patients with a baseline 6MWD <350m.[6] In Study 041, the change in decline in 6MWD decreased by 14.4m in favour of the ataluren-treated arm compared to the placebo-treated arm at 72 weeks (p=0.0248) in the ITT population.[7] NSAA linear scores also showed improvements in ambulatory ability in the ataluren-treated groups compared to control groups of 4.5 (p=0.030) in the pre-specified subgroup of patients with baseline 6MWD ≥300m to <400m in Study 020[5] and 2.3 (p=0.0246) in Study 041 ITT population[7]. Thus, there is strong evidence demonstrating ataluren would address the unmet need for a treatment in patients with nmDMD. As part of this response, PTC Therapeutics have addressed the concerns raised by the Committee and External Assessment Group (EAG) in the ECD, specifically: • The use of independent survival modelling has been justified as appropriate based on analysis of the diagnostic plots for each time-to-event outcome using guidance issued in NICE DSU 14, as well as through analysis of goodness-of-fit and clinical expert validation. To further justify this method of survival modelling, flexible analysis of time-to-event outcomes has been performed. This resulted in a better fit to the observed Kaplan Meier (KM) data and a reduction to the ICER however, the company preferred to consider the conservative approach of using independent survival modelling in the base case due to the implausibility of the survival curves for the flexible survival analysis. • The early treatment benefit assumption of two years delay in time to LoA and three years delay in time to pFVC<50% and pFVC<30% has been justified using additional efficacy data from patients aged 2-5 from Study 030, and clinical expert validation. • The company acknowledges that there are limitations with both the positive utility approach for modelling caregiver QoL used in its original base case and the caregiver disutility approach used in the EAG's base case. As such, the company has accepted NICE's proposed approach of excluding caregiver QoL from the economic model and to instead consider the impact of this qualitatively. • The company has presented discontinuation data from the STRIDE registry including the reason for treatment discontinuation and demonstrating that applying both a constant	

	discontinuation rate and stopping rule assumption is appropriate. Additionally, the company has updated its base case to use an adjusted discontinuation rate, removing those who discontinued due to LoA from the recently published 2021 data-cut of the STRIDE registry. • A later stopping rule at pFVC<30% has been included in the company's updated base case to reflect clinical expert opinion and that of NHS England, which is aligned with NICE's preferred base case. • The company's updated base case analysis shows that ataluren treatment results in a gain of more than 10 undiscounted quality-adjusted life years (QALYs), therefore the company has demonstrated that ataluren qualifies for a QALY weighting. Taking into account the suggestions and recommendations from the Committee and the EAG, PTC Therapeutics have provided a revised company base case. Changes include using an updated stopping rule at pFVC<30%, using different survival distributions for each time-to-event outcome, excluding caregiver QoL from the cost-effectiveness analysis, and a revision in the Patient Access Scheme (PAS) discount from [redacted]% to [redacted]%, resulting in changes in the price of ataluren from £[redacted], to £[redacted] per 125 mg sachet, £[redacted] to £[redacted] per 250 mg sachet, and £[redacted] to £[redacted] per 1000 mg sachet. Applying the above changes in the economic model results in a revised base case incremental cost-effectiveness ratio (ICER) of £[redacted]. A detailed summary of the key uncertainties raised by the Committee and how each of these have been addressed can be found in Sections 2 – 10. All new evidence has been provided at the end of this document.	
PTC therapeutics	***Independent survival modelling is appropriate.*** In Section 3.7 of the ECD, it was noted that: *"The committee considered that the company's original base case model choices, as used in the EAG's base case analysis, were the most appropriate to use for decision making. However, it noted that the results were uncertain because of the poor fit of the models to the data."* The company reiterates that the standard parametric models fitted to the STRIDE and CINRG time-to-event data in the updated company base case are the most appropriate modelling approaches for the following reasons: **1. Diagnostic plots of standard parametric models:**	Thank you for your comments. The committee concluded that the survival modelling used in the company's updated base case was the most appropriate for decision-making. However, the committee were also aware of the uncertainties associated with the survival modelling (see FED section 3.7).

In NICE DSU 14, it is recommended that flexible survival analyses should be considered when log-cumulative hazard plots do not show approximate straight lines (see **Error! Reference source not found.**). Other than in the initial period when very few events took place (which was accounted for by the re-base analysis), the log-cumulative hazard plots for time to LoA, pFVC<50%, and pFVC<30% did not show non-straight lines. Therefore, it was considered appropriate to use standard parametric models instead of flexible analyses, in accordance with the NICE DSU 14 selection algorithm.[8]

Additionally, the company tested the plausibility of using proportional hazards. The log-cumulative hazard plots, Schoenfeld residual plots and quantile-quantile plots were evaluated for time to LoA, pFVC<50%, and pFVC<30% (presented in **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.**, respectively). For each outcome, the log-cumulative hazard plot lines for the CINRG and STRIDE datasets did not remain parallel for the majority of the time period, and plot lines crossed multiple times throughout the time horizon. This suggests that independent survival modelling is the most appropriate approach, in accordance with NICE DSU 14.[8] For each outcome, the Schoenfeld residual plots show a linear curve with a zero slope and a p-value greater than 0.05, supporting the proportional hazards assumption. However, proportional hazards assume a treatment effect that is maintained throughout the treatment duration, and although the assumption appears plausible for some endpoints, it is uncertain whether the treatment effect will be maintained at future timepoints. Therefore, independent survival modelling was considered to be the most appropriate modelling approach.

Furthermore, the fit of the standard parametric models to the observed time-to-event data has already been improved by performing re-based analyses, in which the survival models were applied to the observed Kaplan-Meier (KM) curves only from 5 years and 3.5 years for the BSC and ataluren cohorts, respectively. This approach was used as very few events were observed during the initial period of each registry due to the young age and hence, low rate of disease progression in patients during this period. Therefore, the re-based analysis allowed extrapolations to be made only from the period in which events occurred. However, this re-based analysis has little effect on the company base case ICER. Using non-rebased survival curves results in a change in the ICER of only +£[redacted], to £[redacted].

2. Goodness-of-fit of standard parametric models to KM data:

The log-logistic survival curves to model time to LoA and time to pFVC<50%, and log-normal curves to model time to pFVC<30% in both the ataluren and BSC cohorts have the best goodness of fit. The goodness

	of fit was determined by considering the lowest AIC and BIC, as well as visual inspection of the survival function. The log-logistic and log-normal curves showed the best fit to the observed KM data from the STRIDE and CINRG registries for time to LoA and pFVC<50%, and time to pFVC<30%, respectively, when the rebased analyses at 5 years and 3.5 years for the STRIDE and CINRG datasets, respectively (as described above) were performed. **3. Clinical expert validation of standard parametric curves:** The plausibility of each of the standard parametric survival curves (log-logistic, log-normal, exponential, Weibull, Gompertz and generalised gamma) for time to LoA, pFVC<50%, and pFVC<30% has been validated by two independent UK clinical experts. Clinical expert input indicated the Weibull survival curve distribution is most appropriate in all outcomes, as this is most representative of the disease progression course in clinical practice. Hence, in the company's previous base case, the Weibull curve was selected to model each time-to-event outcome. However, to align with the preferred assumption of NICE and the EAG, the company has chosen to revise their base case for each outcome to the survival curve distributions with the best fit. These are log-logistic for time to LoA and time to pFVC<50%, and log-normal for time to pFVC<30%. A scenario analysis has been included using the Weibull distribution to model each outcome, which increases the ICER slightly to £[redacted], in **Error! Reference source not found.**.	
PTC therapeutics	***Cost-effectiveness analysis results were relatively insensitive to the modelling approach and parametric model selection.*** In Section 3.7 of the ECD, it was noted that: *"[The EAG] noted that the models selected did not appear to provide a good fit to the data for several of the modelled health states. The EAG also noted that the company had not considered more flexible models, which may have provided a better fit to the data."* To investigate further the effect of alternative survival modelling, a flexible modelling analysis was performed. Under this approach, flexible spline models were fitted to the observed KM data from the STRIDE and CINRG registries (2021 data-cut) for the following time-to-event outcomes: • Age at LoA	Thank you for your comments. The committee welcomed the additional analysis provided by the company. The committee concluded that the survival modelling used in the company's updated base case was the most appropriate for decision-making. However, the committee were also aware of the uncertainties

	• Age at pFVC<50% • Age at pFVC<30% This approach was taken to address concerns by the EAG/Committee that the standard parametric survival modelling in the cost-effectiveness model do not show a good fit to the observed data. Spline models are a more flexible class of survival model than standard parametric models, as they allow the survival curve to differ between time intervals, which is determined by the number of knots specified. These models therefore have the flexibility to reflect changes in hazard functions over time. The following three 1-, 2- and 3-knot spline models were considered for each time-to-event outcome, providing extensions to the previously assessed standard parametric models: • The proportional hazards spline model; an extension to the parametric survival model based on the Weibull distribution. • The proportional odds spline model; an extension to the parametric survival model based on the log-logistic distribution. • The normal spline model; an extension to the parametric survival model based on the log-normal distribution. Survival plots for time to LoA, pFVC<50%, and pFVC<30% with each of the above flexible spline models fitted are presented in **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.**, respectively. In line with NICE DSU 14, model selection was based on assessment of goodness-of-fit by considering AIC/BIC (lowest AIC/BIC indicates best fit), through visual inspection, and assessment of the clinical plausibility of the hazard function. Goodness of fit statistics for each model are presented in **Error! Reference source not found.**. For each outcome, the 1-knot flexible spline model showed best fit and was therefore selected for the analysis. The following flexible spline models showed the best fit to the observed KM data and were therefore selected for the flexible analysis: • Time to LoA (ataluren): proportional hazards spline model (1-knot) • Time to LoA (BSC): proportional odds spline model (1-knot) • Time to pFVC<50% (ataluren): proportional normal spline model (1-knot) • Time to pFVC<50% (BSC): proportional odds spline model (1-knot)	associated with the survival modelling (see FED section 3.7).

	• Time to pFVC<30% (BSC): proportional hazards spline model (1-knot). For each time-to-event outcome, the above flexible curves of best fit were compared against the respective standard parametric models of best fit (log-logistic for time to LoA and time to pFVC<50%, and log-normal for pFVC<30%). To assess whether the flexible analyses improved the fit of the extrapolations to the observed KM data, the goodness-of-fit statistics of the best-fitting flexible models were compared against those of the independent models of best fit. Goodness-of-fit statistics are presented for each outcome for the best-fitting standard parametric and flexible spline curves in **Error! Reference source not found.**. Comparisons between the observed KM data and the best-fitting flexible and best-fitting standard parametric models are presented in **Error! Reference source not found.** to **Error! Reference source not found.**. As shown by the goodness-of-fit statistics and comparison of modelled median survival against median survival from the observed KM data (as shown in **Error! Reference source not found.**), the flexible analysis improved goodness-of-fit of the modelled survival curves compared to the standard parametric curves. However, the survival plots for the flexible analyses reveal that a limitation of this approach is that the time to LoA extrapolated curve intersects with the time to pFVC<50% extrapolated curve, resulting in a proportion of patients reaching the night-time ventilation milestone (approximated by reaching the pFVC<50% milestone) before losing ambulation in the model. Survival modelling for each outcome using the flexible analysis approach is presented in **Error! Reference source not found.** and **Error! Reference source not found.** for the ataluren and BSC cohorts, respectively. The effect of using the flexible survival modelling approach on the cost-effectiveness of ataluren is presented in **Error! Reference source not found.**. Using flexible survival modelling instead of independent survival modelling decreases the company base case ICER by £[redacted] to £[redacted]. Despite the fact that including flexible survival analysis improved the fit of the survival curves to the observed KM data and decreased the company base case ICER, the company prefers to remain conservative by using independent survival curves for all time-to-event outcomes, as applied in the NICE base case due to the limitations identified in the flexible analysis.	
PTC therapeutics	***Although only a small number of patients under the age of five have received ataluren, it is plausible to assume early treatment will lead to additional benefits.*** In Section 3.8 of the ECD, it was noted that:	Thank you for your comment. The committee considered the additional information on age of

	"The EAG noted that very few people had received ataluren in STRIDE before the age of 5 and that there was no other direct evidence to show that starting treatment early provided additional benefit. The committee was aware that the company's economic model assumed everyone would have treatment with ataluren at 2 years of age. They considered that this was inconsistent with published evidence and clinical expert opinion that most diagnoses of DMD in England are at around 4 years, and that there is currently no national screening programme for DMD." It should be noted that the Medicines and Healthcare products Regulatory Agency (MHRA) license for ataluren was only extended to the 2-4 year age group in 2018 after the initiation of the STRIDE registry, hence the proportion of patients in this age group in the registry is lower than what would be expected in clinical practice. This also means that the 20 patients in the STRIDE registry who did initiate treatment in the 2-4 year age range have not yet been followed-up for a sufficient duration to make any conclusions about delays in time to LoA, as this typically occurs in patients receiving BSC at around the age of 12 to 13 years.[2,3] Due to this limitation of the available data, the use of clinical expert validated assumptions regarding an early treatment benefit in the model was deemed necessary. Since 2020, [redacted] patients in England have been diagnosed with nmDMD and subsequently treated with ataluren.[9] Of these patients, [redacted] were aged 2-4 years, and [redacted] were two years old at diagnosis. These data show that it is plausible to assume that patients would initiate ataluren treatment before the age of five years in clinical practice. Treatment initiation at two years of age is also the most clinically relevant scenario to model, as this aligns with both the conditional marketing authorisation for ataluren, and the preference of the independent clinicians consulted by the company, who expressed a desire to treat patients as early as possible to maximise the benefit they receive from treatment. Additionally, between 2021 and 2022, there was a [redacted]% increase in the number of children diagnosed with nmDMD below the age of five years, suggesting diagnosis in younger patients is improving. This will allow patients to initiate treatment at an earlier age. Initiating treatment at two years of age in the model is the most conservative approach to modelling the cost-effectiveness of ataluren, as this assumes all patients are on treatment (and therefore accumulating treatment costs) for the longest possible duration within the license. A scenario analysis has been performed assessing the cost-effectiveness in a cohort of patients starting treatment at four years old, with the early treatment benefit removed. This results in an increase of £[redacted] to the ICER from the company's updated base case to £[redacted].	diagnosis. It concluded that it was not appropriate to assume that all children would be treated at 2 years of age. Therefore, the assumed additional benefits were not appropriate (see FED section 3.8).

The company acknowledges that there is uncertainty regarding the magnitude of the early treatment benefit included in the economic model. However, the company reiterates the point that this assumption and the early treatment delay values applied to each outcome were validated by an international Delphi panel of nine clinical experts.[10] Additionally, the company presents further evidence supporting the assumption of an early treatment benefit with earlier initiation of ataluren treatment at an age of two years old.

To evaluate the safety and pharmacokinetics of ataluren in patients aged 2-5 years, a phase II, open-label study (Study 030[11]) was carried out in 14 males aged 2-5 years with a mean age of 3.4 years, weighing ≥12 kg and with a confirmed genotypic diagnosis of nmDMD. As a secondary endpoint, the study measured changes from baseline to week 52 in timed function tests (TFTs), the North Star Ambulatory Assessment (NSAA) 16-part scale, and the 3-part and 8-part NSAA scale, adapted for children <5 years of age.[11] The TFT and NSAA results of Study 030 are presented in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. The study results show that over 28 and 52 weeks of ataluren treatment, patients aged 2-5 years exhibited an improvement in ambulatory ability as demonstrated by decreased time to run/walk 10 metres, decreased time to climb and descend four stairs, time to stand from supine, and increased NSAA scores from baseline. This demonstrates the clinical efficacy of ataluren in patients aged 2-5 years.

in addition, the assumption of an early treatment benefit was supported by both an external clinical expert consulted by the company and the clinical expert present at the ataluren NICE committee meeting. The expert at the committee noted that although she did not have specific data to support the benefit of early treatment, there is a biological rationale behind the assumption, as starting treatment at an earlier age has a protective effect against muscle deterioration, which results in muscle function being preserved for longer during the pubescent stage of childhood. This means that patients are more likely to avoid conditions that develop alongside muscle weakness, for example scoliosis, later in life. By avoiding comorbidities such as scoliosis, the QoL of patients is preserved for a longer duration. The clinical expert also mentioned that it makes sense from a biological perspective to diagnose patients at an earlier age to allow earlier initiation of ataluren treatment, as this would improve their prognosis during later life. Indeed, in recent decades, the medical management of DMD has shifted to more anticipatory diagnostic and therapeutic strategies, to achieve prevention, early identification, and treatment of disease complications.

Furthermore, early genetic testing also allows newborn siblings of patients with an nmDMD diagnosis to be tested and diagnosed, meaning more patients are able to start treatment earlier, assuming that patients are

	eligible for genetic testing procedures that identify the nonsense mutation that causes nmDMD. In a DMD care considerations article published by Birnkrant *et al.* in 2018 it is stated that "*contemporary care has been shaped by the availability of more sensitive diagnostic techniques and the earlier use of therapeutic interventions, which have the potential to improve patients' duration and quality of life*".[12] Birnkrant *et al.* also stated that the use of standardised testing in children with DMD is increasing, and that there "*renewed interest in newborn screening has been building as a result of support among stakeholders and because emerging DMD therapies might prove to be most effective if they are initiated before symptom onset*"[13] supporting the assumption that early diagnosis and hence early treatment initiation is beneficial for patients with DMD in later life, as this rationale is likely to apply to nmDMD. The results from Study 030 demonstrating improved ambulatory ability in patients aged 2-5 years following 28 and 52 weeks of ataluren treatment and the biological rationale behind the early treatment benefit validated by an independent clinical expert suggests that treating patients at 2-5 years of age would have a protective effect against muscle loss and improve patient QoL in more advanced stages of the disease. Thus, the company believes there is strong support for the assumption of an early treatment benefit and has included a two year delay in time to LoA and three year delay in time to pFVC<50% and time to pFVC<30% in its updated base case. To address the Committee's concerns that the early treatment benefit in the model overestimates the actual benefit observed in patients treated with ataluren, the company has also included a scenario analysis in which the assumed early treatment benefit is halved. This results in an ICER of £[redacted], an increase of £[redacted] compared to the company base case.	
PTC therapeutics	***Treatment-dependant utilities are plausible and appropriate for both ambulatory and non-ambulatory disease states due to quality of life improvements observed in ataluren patients that cannot be effectively modelled based on the defined health states in the economic model.*** In section 3.9 of the ECD, it was noted that: *"The committee considered that the company had not provided robust evidence to support the use of treatment-dependent utility values in the ambulatory health state. The committee concluded that treatment-dependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory health states."* The company reiterates that the treatment-dependent utilities are sourced from the Landfeldt *et al.* 2020	Thank you for your comments. The committee considered that the company's treatment-dependent utility values were not appropriate for the ambulatory health state. The committee considered that the company's model structure may not have captured changes in

	Delphi panel,[14] and supported by another independent Delphi panel,[10] as well as an independent UK clinical expert. Both Delphi panels found that clinicians consider there to be differences in cognition, emotion, pain, ambulation and dexterity of patients receiving ataluren and BSC, in both the ambulatory and non-ambulatory health states. Consensus estimates for the mobility, upper limb function (i.e., dexterity), emotion and pain and discomfort domains for ambulatory patients are presented in **Error! Reference source not found.** and **Error! Reference source not found.** (Landfeldt *et al.* 2020[14] and Landfeldt *et al.* 2022[10], respectively). As shown, the clinical experts considered patients treated with ataluren to have different levels of function compared to those receiving BSC. Additionally, treatment-dependent utilities are supported by clinical evidence of improvements in functional ability in patients receiving ataluren compared with BSC within the ambulatory health state. Specifically, lower and upper extremity function among ambulatory patients receiving ataluren and BSC were recorded in Study 041[7] using two extensively validated and frequently employed clinical measures: • The North Star Ambulatory Assessment (NSAA); and • The Performance of the Upper Limb Module (PUL), in a subgroup of patients with a 6-minute walk distance (6MWD) between 300m and 400m. All patients were ambulatory in the trial and only a small number lost ambulation during the trial in each arm. Outcomes from these instruments are presented in **Error! Reference source not found.** and **Error! Reference source not found.**. The data shows a reduced loss (i.e., improvement) in functional ability across [redacted] of the NSAA measured at week 72 in patients receiving ataluren vs. BSC. Additionally, the data shows a relative change of [redacted] in upper limb function among ambulatory patients treated with ataluren vs. BSC from baseline to week 72 (mean change from baseline in total upper limb score: [redacted][ataluren] vs. [redacted] [BSC], [redacted]). These improvements in lower and upper extremity function, as captured in the two Delphi panels,[10,14] results in higher QoL of patients treated with ataluren vs. BSC also within ambulatory disease stages. This is further supported by several studies exploring the association between distal and proximal muscle weakness and QoL domains in DMD, for example Williams *et al*.[15] Additionally, clinical and patient experts were supportive of the company's base case assumption to apply treatment-dependant utilities in all health states, concluding in their response to the technical engagement *"That they [clinical and patient experts] believed it was appropriate to use treatment-dependent utilities*	quality of life across the ambulatory health state and that a model with additional ambulatory health states would have allowed a better estimation of quality of life (see FED section 3.10)

because of the benefits of treatment with ataluren".

Outcomes from the EQ-5D visual analogue scale (VAS) recorded in Study 041 are presented in **Error! Reference source not found.**. Patients with DMD treated with ataluren reported a mean increase in subjective QoL from baseline to month 1 of follow-up of +1.2 scores. In contrast, patients receiving BSC reported a change of +0.1 scores. These data indicate that ataluren has an impact on patient QoL within a very short duration of time after treatment initiation and provide further support for the use of treatment-dependent utilities in ambulatory patients.

Furthermore, evidence from Study 046 includes data on the expression of full-length dystrophin, measured in [redacted] DMD patients before and after ataluren treatment. Dystrophin measurements were recorded at baseline, prior to ataluren treatment, and compared to measurements at week 40 of ataluren treatment. The results show a [redacted] increase in mean dystrophin ([redacted]). As the absence of functional dystrophin protein leads to long-term irreparable damage in muscles of DMD patients with limited potential to regain function, increased dystrophin has the potential to improve, or preserve, muscle function in ataluren-treated patients (as shown in Study 041).[16] Study 046 also reported improved muscle function in ataluren-treated patients measured using the timed function test associated with key functions of daily life, as well as decreases in serum creatine kinase levels, which suggests potential preservation of muscle tissue.

In section 3.9 of the ECD, it was noted that:

"The EAG noted that the company applied treatment-dependent utilities from the beginning of the model time horizon and applied them throughout the model, even when treatment with ataluren had been stopped."

As ataluren delays LoA, the company expects those patients that receive ataluren to have improved physical and mental development during their early and adolescent years (as captured in the Delphi panels). There are common secondary conditions to DMD which contribute to patient QoL, for example scoliosis, which has been linked to reduced QoL and life expectancy, primarily because of detrimental effects on respiratory function.[17]

Published literature indicates that prolonged ambulation reduces scoliosis risk in DMD patients, and that progression occurs most rapidly during the adolescent years.[18] A published study has shown that older age at LoA relates to older age of scoliosis onset ($p<0.0001$) and age at LoA is inversely related to scoliosis

	severity at 17 years ($p<0.005$).[19] This evidence suggests it is plausible that by delaying LoA in patients receiving ataluren, development of scoliosis can be prevented until post-puberty, resulting in prolonged improvements in patient QoL when compared to BSC. The hypothesis that ataluren is likely to reduce the risk of scoliosis was supported by an external UK clinical expert, and both the clinical expert and EAG expert at the committee meeting, where it was noted as follows: *"One EAG expert said that ataluren may improve quality of life in non-ambulant health states because of a reduced risk of scoliosis."* *"The clinical expert at the committee meeting said that ataluren could reduce the risk of developing scoliosis and delay respiratory symptoms in non-ambulatory health states because it would allow muscle strength to be preserved for longer during puberty."* The potential benefits associated with ataluren treatment, such as reduced risk of scoliosis, improved cardiac function, and delayed loss of upper limb function have not been included in the model, as data to inform the post-LoA states based on these factors was not available from the clinical trials at the time of initial submission. In addition, maintaining ambulation longer may improve patient quality of life in later stages of the disease. According to an external clinical expert, factors such as mental health and quality of life can be improved when ambulation loss is delayed until after adolescence due to cognitive maturation, and by delaying progression post-puberty, long-term benefits such as bone health may also be affected as an active lifestyle plays a crucial role in bone health overall. For reasons outlined above, the company considers treatment-dependent utilities to be plausible and appropriate for both ambulatory and non-ambulatory disease states. Furthermore, the treatment benefit is anticipated to translate to a lasting effect for all patients, even after discontinuation of treatment.	
PTC therapeutics	***It is important to incorporate the impact of ataluren on caregiver QoL; however, the company accepts this to be considered in a qualitative way instead of within the model estimation of the ICER.*** In section 3.10 of the ECD, it was noted that:	Thank you for your comments. The committee took into account caregiver quality of life in depth in its decision-

	"It [the committee] therefore concluded that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way." To align with NICE and expert opinion, the company accepts the Committee's preferred assumption by removing caregiver utilities in the revised base case. However, the company continues to note the importance of incorporating the impact on caregivers in decision making. There is a significant, progressively increasing caregiver burden for the vast majority of a DMD patient's lifetime. DMD patients have significant challenges in performing day-to-day activities, particularly in later stages of the disease when the disease has progressed and patients are non-ambulatory, requiring ventilation support and full dependency on support from multiple caregivers.[20,15] Furthermore, the detrimental impact on parents or guardian caregivers is expected to continue even after a patient dies, as despite the daily burden being relieved, these caregivers are likely to experience a bereavement-related disutility.[21] A Delphi panel of nine neuromuscular specialists, adult and paediatric neurologists, and paediatricians from five European countries agreed that both ambulatory and non-ambulatory patients will often have two informal caregivers involved in their day-to-day care and support.[10] The impact of ataluren treatment on changes in caregiver QoL, including reduced anxiety, stress, and a positive impact on productivity, are demonstrated in the results of a qualitative study on the impact of caring for DMD patients,[15] as follows: *"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."* *"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."* Further, caregivers have stated that there is a tangible benefit from delaying disease progressing as it allows	making. This was informed by the information provided by clinical and patient experts, as well as the company (see FED section 3.11).

	time to prepare themselves for the next stage. Additionally, caregivers find that there is greater anxiety surrounding steroid use due to reduced bone density reducing bone strength – caregivers may find they prefer to stop their patient walking to mitigate risk of broken bones. For the reasons outlined above, the company continues to emphasise the appropriateness of incorporating caregiver QoL in the assessment of ataluren from a qualitative perspective. Furthermore, based on the difference in QoL likely to be observed in patients that receive ataluren, the company believes it is also plausible to assume that caregiver QoL is likely to be higher in each health state for those treated with ataluren compared to those that receive BSC.	
PTC therapeutics	***The company has agreed to revise the stopping rule to the Committee's preferred assumption at pFVC<30%, so that patient time on ataluren treatment and the potential benefits received are maximised.*** In section 3.12 of the ECD, it was noted that: *"The clinical expert said that clinicians would want to continue using ataluren after their patients lost the ability to walk because of the benefits in upper limb and respiratory function…For the purposes of cost-effectiveness modelling, the committee preferred to use the time when predicted FVC reached less than 30%. But it acknowledged that this may not align with how treatment is stopped in clinical practice."* To align with NICE and expert opinion, the company chooses to accept the Committee's preferred stopping rule assumption, using the stopping rule at pFVC<30% in the revised base case, as presented in **Error! Reference source not found.**. The ICER increases when this stopping rule assumption of pFVC<30% is used, however the company believes this is necessary to align with NHS England's, the clinicians' and the company's aspirations for patients continuing to receive and benefit from ataluren treatment for as long as possible. Supportive to this, within the ACM an NHSE representative noted that any stopping rule must be guided by clinicians and based on the treatments specific benefit, response, and/or safety profile. **Error! Reference source not found.** also presents the results for a scenario analysis when the stopping rule is pFVC<50%.	
PTC therapeutics	***The treatment discontinuation rate does not lead to double counting of events with the company's proposed stopping rule. The company accept comments from the Committee and have revised the discontinuation rate to align with expert opinion.*** In section 3.11 of the ECD, it was noted that:	Thank you for your comment. The committee concluded that the company's updated treatment discontinuation

	"The EAG said the observed treatment discontinuation rate may have double counted the events that would be captured in the company's proposed stopping rule." The proposed stopping rule implemented in the economic model allows patients to continue treatment until they require full-time ventilation support, estimated by pFVC<30%. Within the STRIDE cohort, only [redacted] of [redacted] non-ambulatory patients reached the pFVC<50% endpoint and only one non-ambulatory patient reached the pFVC<30% endpoint. Therefore, most patients remained on treatment beyond LoA but very few remained on treatment beyond achieving pFVC<30%, as they had not yet reached this endpoint or a later endpoint. As the discontinuation rates used in the previous and current base cases do not include any patients stopping treatment once they have reached either pFVC<50% or pFVC<30%, the application of both the treatment discontinuation rate and the proposed stopping rule in either case does not represent double counting. In section 3.11 of the ECD, it was noted that: *"The EAG provided an analysis that reduced the discontinuation rate by 50% to explore the impact of this on cost effectiveness… The committee concluded that the company's estimated discontinuation rate likely overestimated treatment discontinuation and therefore underestimated ataluren treatment costs. The committee preferred the EAG's scenario analysis, which reduced the discontinuation rate for decision making. But it noted that this reduction was arbitrary and added to the uncertainty."* To address the concerns from the Committee regarding a potential over-estimation of the discontinuation rate, the company have used an adjusted discontinuation rate in the revised base case. Analysis from the STRIDE 2021 data-cut has been used to inform this revised discontinuation rate. Using data from the STRIDE registry overcomes the uncertainty in the EAG suggestion of using an arbitrary 50% reduction to the previous base case discontinuation rate. Within the STRIDE registry, as of January 2021, [redacted] patients were followed for a median follow-up of [redacted] days. As shown in **Error! Reference source not found.**, [redacted] patients within the cohort discontinued treatment with [redacted] being due to LoA and the remaining [redacted] due to other factors. This calculates as a treatment discontinuation rate of [redacted], which overall is a [redacted] reduction on the previous base case discontinuation rate ([redacted] in the revised base case vs. [redacted] in the previous base case), and in-line with the discontinuation rate of [redacted] used in the EAG's scenario analysis.	rate was appropriate for decision-making (see FED section 3.12).

PTC therapeutics	***A QALY weighting should be applied in the base case.*** In section 3.13, it was noted that: *"The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs."* The revised base case assumptions result in an estimated number of additional undiscounted QALYs gained of [redacted] ([redacted] for ataluren, [redacted] for BSC). The estimated number of undiscounted QALYs gained is greater than 10, therefore the company suggests that ataluren meets the criteria for applying a QALY weighting. Therefore, a QALY weighting of [redacted] has been applied in the revised base case.	Thank you for your comment. The committee's preferred assumptions (listed in FED section 3.14) resulted in an analysis which did not meet the criteria for QALY weighing (see FED section 3.15).
PTC therapeutics	***Revised base case*** The company have carefully considered the perceived uncertainties raised by the Committee in the ECD. With this in mind, the company have revised the base case to capture the Committee's preferences with respect to the following assumptions, that should be considered for decision making: • Stopping rule is extended from pFVC<50% to pFVC<30%. • Survival curve distributions are changed from Weibull to the Committee's preferred distributions (log-logistic for LoA and pFVC<50%, log-normal for pFVC<30%). • No caregiver utilities are considered. • Treatment discontinuation rate is reduced from [redacted] to [redacted]. • The PAS discount is increased from [redacted] to [redacted] of the ataluren list price. As outlined in this document, the company have addressed the remaining areas of uncertainty raised by the Committee, including the following: • Treatment-dependent utilities are appropriate in all health states. • Independent survival modelling is appropriate. • Early treatment benefits are plausible. • Treatment discontinuation rate. With the revised assumptions above incorporated into the economic model, the revised company base case results in an ICER of [redacted] (presented in Table 1 below).	Thank you for your comment. The committee's preferred assumptions resulted in an ICER estimate of under £100,000 per QALY gained (see FED section 3.14).
Muscular	We are concerned that the conclusions of the ECD do not reflect the impact of living with Duchenne	Thank you for your

Dystrophy UK and Action Duchenne	muscular dystrophy or the benefits that patients and caregivers experience from receiving ataluren. Throughout the appraisal process we have liaised closely with families in receipt of ataluren and have built our responses based on the input we have received from them. For this response we once again reached out to families through a survey and through a virtual community briefing session held on 5 October 2022. The survey received 17 responses, 100% of which were from parents of a child with Duchenne muscular dystrophy. One family were not in receipt of ataluren. 18% of responses related to a child aged 2-4; 12% related to a child aged 5-9; 35% related to a child aged 10-14; 24% related to a child aged 15-19; 12% related to a child aged over 19. Of the families in receipt of ataluren, 23% had begun receiving it at age 2; 15% had begun receiving it at age 5; 8% had begun receiving it at age 6; 15% had begun receiving it at age 7; 8% had begun receiving it at age 8; 8% had begun receiving it at age 9; 8% had begun receiving it at age 10; 15% had begun receiving it at age 11. In terms of duration on the treatment, 8% had been receiving ataluren for <1 year; 8% had been receiving ataluren for 2 years; 8% had been receiving ataluren for 3 years; 8% had been receiving ataluren for 4 years; 8% had been receiving ataluren for 5 years; 46% had been receiving ataluren for 6 years; 15% had been receiving ataluren for 9 years.	comments. The committee considered the nature of the condition and the impact on caregivers and families (see FED section 3.2). The committee also took into account testimonies from patient experts and considered in depth the impact of caregiver quality of life in its decision-making (see FED sections 3.10, 3.11, 3.13 and 3.16).
Muscular Dystrophy UK and Action Duchenne	We welcome the recognition in the ECD of both the clinical effectiveness of ataluren and that the treatment is likely to slow the progression of Duchenne muscular dystrophy. We also welcome the recognition that ataluren has a positive impact on the lives of people receiving it and on caregivers and that the ECD recommends that anyone currently receiving ataluren should continue to do so after the Managed Access Agreement ends in January 2023	Thank you for your comment. No response needed.
Muscular Dystrophy UK and Action Duchenne	We are, however, very concerned by the fact that the ECD does not recommend that ataluren should be made available for people diagnosed after January 2023. This is the only treatment available to people with Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene, and the decision is counter to the evidence we have presented throughout the appraisal process on the impact of the lived experience of Duchenne muscular dystrophy; or of the positive impact of the treatment that is experienced by both patients and caregivers.	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were

		below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Muscular Dystrophy UK and Action Duchenne	We are highly concerned by the suggestion in the ECD that an ambulant patient receiving ataluren is not experiencing any additional quality of life differences from the treatment when compared to an ambulant patient with Duchenne muscular dystrophy not in receipt of the treatment. Our technical engagement response presented clear evidence from the community on this point, and we explored this once again in the community survey used to help shape this response; 75% of responses to this most recent survey related to a child who is still ambulant. 93% of respondents to this part of the survey either disagreed strongly or disagreed with the ECD conclusion that there was unlikely to be 'significant quality of life differences' between an ambulant person with Duchenne muscular dystrophy who is receiving ataluren; and an ambulant person with Duchenne muscular dystrophy who is not receiving ataluren. 100% of survey respondents on this issue stated that ataluren had meant their child required less supervision or support when walking; enabled their child to have more stamina when walking; enabled their child to have more stamina to complete everyday tasks e.g. dressing; and stated that improvements to their child's mobility as a result of taking ataluren had benefitted them psychologically. 88% of survey respondents on this issue said that ataluren had enabled their child to walk with greater stability; 88% said it had reduced the risk of falls and associated fractures when walking; 75% of survey respondents on this issue said that ataluren had enabled their child to walk at greater pace and/or keep up with their peers; and 63% also said that ataluren made their child more confident about the future. 63% felt that ataluren had improved their child's mobility and/or quality of life in other ways, including allowing participation in sporting activities and improving behaviour. *"Translarna has immensely improved our child's health and quality of life. Other Duchenne children, whom we know of the same age, are completely wheelchair-bound; often bed-bound and have undergone several major surgeries, including tendon cutting and spinal fusion; our boy has not had any surgical interventions, and he is nineteen, still walking quite well and able to enjoy social activities, like disability cricket and swimming, attending shows and concerts, travelling abroad for holidays, etc".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years.	Thank you for your comment. The committee considered that the company had not provided robust evidence to support its use of treatment-dependent utility values in the ambulatory health state. However, it agreed that people treated with ataluren may experience health-related quality of life benefits in the ambulatory health state that were not captured fully in the company's model (due to it having only 1 ambulatory health state). But the size of any such health utility gains would likely be substantially lower than that estimated by the company's modelling. The committee also agreed that treatment-dependent utilities were plausible in the non-ambulatory health

	"The view expressed by the NICE committee is illogical and too simplistic. Walking is a daily struggle for children with Duchenne, physically and emotionally. If they are receiving the drug, the walking experience is transformed. There are clearly walking-related quality of life improvements for those who are receiving the drug and are still ambulant". Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"Definitely an improved quality of life. [Child's name – still ambulant] knows he is receiving the medication available for his condition, rather than feeling he is not receiving the treatment he needs, which is a psychological benefit. His ability to keep up with his peers and feel 'normal' also has a positive impact on his wellbeing".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Translarna has given my child much more independence. We saw no benefit from physio and no changes in his physical development until he started taking Translarna. He is now able to walk much faster for longer, climb the stairs, get in and out of bed and get up from the floor without support. I am confident in the next few months he will be able to run; most children with Duchenne will never be able to run".* Parent of child aged 2-4, in receipt of ataluren for 4 months.	states, because of a reduced risk of scoliosis. (see FED section 3.10).
Muscular Dystrophy UK and Action Duchenne	We are concerned that the way in which caregiver quality of life has been treated in the ECD drastically underplays the essential benefit that ataluren brings to caregivers. We have presented clear and compelling testimony from caregivers about the crucial positive impact that ataluren has on their quality of life throughout the appraisal process (including but not limited to their mental health, their ability to continue with work and the delaying of adaptation costs) and we explored this once again in the community survey used to help shape this response. The impact we set out cannot be captured quantitatively; and it is imperative that this does not mean it is overlooked. While we recognise the challenges of quantitatively assessing this, it is not clear how the qualitative approach that has been taken on this issue has been meaningfully incorporated into the conclusions of the ECD. Some of the benefits to caregiver quality of life that were shared with us by the community, such as hope and reduction in anxiety, are of huge significance on an individual level but are simply too complex to measure or quantify in the evaluation process as it is currently structured. Respondents to our survey raised concerns that failure to suitably measure caregiver quality of life undermines the overall evaluation process and risks discriminating against patients. They also emphasised	Thank you for your comments. The committee took into account caregiver quality of life in depth in its decision-making. This was informed by the information provided by clinical and patient experts, as well as the company (see FED section 3.11).

	the need to give full weight to the experience of caregivers themselves. 93% of survey respondents were either 'very concerned' or 'concerned' by the approach taken in the ECD, with the remaining 7% saying they 'didn't know'. Survey respondents were asked, in light of the challenges faced in assessing this in a quantitative way, how they thought quality of life impacts for caregivers could be measured. *"If caregiver quality of life improvements cannot be measured, resulting in it not being factored into cost-effectiveness calculations, this undermines the overall evaluation process for Translarna. The benefits for caregivers for the drug are significant given the severity of the condition, the burden on those providing daily care and the absence of any other treatments for Duchenne - it is a relentless, degenerative and life-limiting condition. A suitable way of measuring the benefits for caregivers needs to be used for the evaluation of Translarna; otherwise the process risks discriminating against patients by not properly measuring cost-effectiveness".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"I think it should be based alone on what the care giver says; if they say it has positively impacted their life and they have given a reason that should be enough!".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. Respondent also reiterated some of the essential benefits that ataluren has brought to them as caregivers. *"As Translarna has given our child a degree of very good health, he is able to attend college three days a week and to go out one afternoon a week without us. As the main caregiver, this means that I have some respite during this time to meet a friend for lunch, go swimming/for walks, or just to rest and relax. This enables me to continue with my caring role without intervention in our household, giving us more privacy as a family. It also helps me psychologically, as it gives me time to be 'me' for a while".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. Several respondents shared a range of caregiver quality of life impacts that simply may not be measurable. *"I believe that I have less physical health problems than would be expected of a person of my age (I am 65) and less psychological issues, because our boy is keeping so well, due to Translarna, as it takes a tremendous amount of pressure off of me. He has had no hospitalisations or medical emergencies, and that also places less demands on me".*	

	Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"Translarna gives us hope. I believe without this drug my son would not be doing as well as he is now. There are less falls, he is able to walk without it I don't think he would be as strong. It makes us feel more positive to us it feels like a little miracle drug".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. *"My son has benefited considerably from receiving Translarna. The benefits are not just related to ambulation but also to upper body strength and respiratory strength. This has reduced the extent of hospital admissions, enabled us to maintain a quality of life for ourselves and allowed us to continue working as parents - paying taxes and supporting the economy in the same way as parents who do not have the same carer responsibilities".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"Our experience is that we can live as `normally' as possible - we are happier in the knowledge that [child's name] is getting the most up to date medication for his condition - it is an enormous weight off our minds. We can continue caring for [child's name] feeling he has what he needs, which enables us all to continue with family life and be as close to a 'normal' family as we can".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Since my child has been on Translarna I have so much more hope for the future. I don't have to worry about my child being scared of peers knocking him over".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"I am confident that Translarna has greatly helped my son. This in turn helps with my anxiety about my son's disability… Your child's quality of life impacts a parent carer's quality of life".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"The least parents and children with Duchenne deserve is hope and Translarna has given us that hope. I would not have coped with my child's diagnosis if I hadn't been told about Translarna on the day of his diagnosis. Not providing this medication when it has been proven to help is cruel".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"Having a child that is non ambulant is so much harder physically and mentally on caregivers and other family members".*	

	Parent of child aged 10-14, in receipt of ataluren for 6 years.	
Muscular Dystrophy UK and Action Duchenne	We are concerned that although ataluren is available for children under 5 years of age, the ECD concludes that the assumed benefits for 2-4 year olds should not be included in its analysis. 100% of survey respondents either disagreed or strongly disagreed with this position, which seems to run counter to the recognition in the ECD itself that "Dystrophin production is usually affected from birth and symptoms of DMD often appear by age 3 years". 18% of respondents were parents of a child currently aged 2-4 and 23% of respondents were parents of children who had begun receiving ataluren before the age of 4. *"Our boy was diagnosed at the age of two and some are diagnosed during pregnancy now. Our boy was delayed in all his milestones: turning over, sitting up, crawling and walking. He was far below the normal achievement range for his age and I wish Translarna had been available to help him then".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"I think it is relevant to include ALL children on Translarna. My son was diagnosed at 11 months old so we was able to start Translarna at 2. Our experience on Translarna is so amazing and so beneficial to be included as it was such a positive experience".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. *"If children are typically diagnosed with Duchenne at age 4 (or sometimes younger), it is wrong to exclude all age years between 2 and 4 when assessing the benefits of Translarna. Excluding the benefit for 4-year-olds, the average age of diagnosis, risks supressing the overall cost-effectiveness calculation for Translarna".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"We feel that it's due to how early [child's name] started Translarna that he remains so well now - if it should be diagnosed earlier than age 4 then the benefits for children aged 2-4 ought to be included as a benefit in the analysis".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"A lot of work is being done to ensure that Duchenne is part of newborn screening by the World Duchenne Organisation and other organisations; my son was diagnosed at 3 and I know plenty of other families where children were diagnosed under 2 years of age. I feel it imperative to look at the average age of diagnosis - much like an increase in life expectancy I believe we see a decrease in the age of diagnosis".*	Thank you for your comment. The committee considered the additional information on age of diagnosis. It concluded that it was not appropriate to assume that all children would be treated at 2 years of age. Therefore, the assumed additional benefits were not appropriate (see FED section 3.8).

	Parent of child aged 10-14, not in receipt of ataluren. *"Most parents will recognise Duchenne very early on. I recognised my child was behind in his physical development from 9 months of age. We received a diagnosis at 2 years of age. There is absolutely no reason why a 4 year old would not be diagnosed yet!".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"This doesn't take account of children diagnosed at early age, due to mother being a carrier or family history. This is unfair".* Parent of child aged 10-14, in receipt of ataluren for 6 years.	
Muscular Dystrophy UK and Action Duchenne	We are concerned that there could be some wider cost benefits of ataluren that have not been taken into account when assessing it's cost effectiveness. Several survey respondents and one participant in a community briefing session held by MDUK and Action Duchenne on 5 October 2022 spoke of needing far fewer medical interventions linked to their Duchenne muscular dystrophy than peers not receiving ataluren. *"I strongly disagree with the assertion that Translarna isn't cost-effective, as the cost of surgeries and hospitalisations/additional care and support services, etc. that are necessary in the deterioration suffered by boys with Duchenne muscular dystrophy is extremely high also, and the cost to quality of life for both sufferers and carers just cannot be measured in monetary terms, although the ability to continue to provide long-term care at home by family members does save the government a massive amount of money".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"I believe that I have less physical health problems than would be expected of a person of my age (I am 65) and less psychological issues, because our boy is keeping so well, due to Translarna, as it takes a tremendous amount of pressure off of me. He has had no hospitalisations or medical emergencies, and that also places less demands on me".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"Duchenne muscular dystrophy comes with a significant burden on the family, NHS network in terms of cost and time. My son does not take Translarna as unfortunately his mutation cannot be treated with Translarna. I would urge that if this is a cost issue then NICE / NHS England works with PTC to lower the price where it is believed would be cost effective".* Parent of child aged 10-14, not in receipt of ataluren.	

Muscular Dystrophy UK and Action Duchenne	We welcome the ECD's recognition of ataluren as an innovative treatment and are therefore concerned that despite its recognition that it is both clinically effective and that it is likely to slow the progression of Duchenne muscular dystrophy, as well its recognition of the positive impact on the lives of people receiving it and on caregivers, the ECD does not recommend it for patients diagnosed after January 2023. The rare disease community is reliant on the development of innovative treatments, which are highly likely to be relatively expensive, and we are concerned that innovation will be stifled and access to future treatments across a wide range of rare diseases will be made less likely if treatments such as ataluren are not made available.	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Muscular Dystrophy UK and Action Duchenne	We are concerned that the ECD's recommendation that ataluren should not be made available to newly diagnosed patients after January 2023 despite its recognition that it is both clinically effective and that is likely to slow the progression of Duchenne muscular dystrophy, as well its recognition of the positive impact on the lives of people receiving it and on caregivers, could be discriminatory on the grounds of age and disability; both protected characteristics under the Equality Act 2010.	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Muscular Dystrophy UK and Action Duchenne	We recognise the difficult role of the Committee and NICE more broadly in decisions about access to treatments. In representing the community, it is important that we highlight the frustration felt by many that an effective treatment will not be made available based on cost effectiveness. *"Money should not be an issue in relation to children's lives. Especially when the drug is proven to*	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the

	work!". Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Please don't let this come down to cost. You can't put a price on a child's life".* Parent of child aged 10-14, in receipt of ataluren for 6 years. We urge NICE to work with PTC to find a solution that ensures that ataluren can be made available to patients diagnosed after January 2023 and for all parties to show flexibility to enable this. We reiterate the point made in our Technical Engagement response that 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[1]". We feel that this is a positive pragmatic approach and one that would be applicable in this instance.	committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Action Duchenne	The committee concluded that treatmentdependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory health states. In my opinion as a parent, this conclusion does not adequately reflect the evidence from patients' experience including that of my family. • Stamina – the evidence from the 6mwd may not have adequately captured the capacity of patients on ataluren to keep going for longer than those on best supportive care. Compared to his walking before he started taking ataluren, once on ataluren our son had more stamina, i.e. he was able to keep going for a longer time when walking. That meant he was able to do things that are very significant, for example keep going with his peers in the playground, or climb a hill and gaze out at the view. • Energy - not only could he keep going for longer, but he also had more energy than he had had before for additional activities over the week, such as swimming and an after-school club. Before he took ataluren, he would be too tired for these additional activities, thus limiting his social contact, fitness, and self-development.	Thank you for your comment. The committee considered that the company had not provided robust evidence to support its use of treatment-dependent utility values in the ambulatory health state. However, it agreed that people treated with ataluren may experience health-related quality of life benefits in the ambulatory health state

	• Psycho-social benefits - extra years of ambulation lead to knock-on psycho-social benefits additional to those related simply to ambulation. Thanks to ataluren, my son is able to look back on years of meaningful daily experiences of inclusion, for example going to the playground after school with the other children and going round to friends' houses. He can draw on years of being out in the natural world, with all of its well-known psychological benefits. Just yesterday we were recalling a walk in the hills when we went wild swimming by a waterfall. Extra years of ambulation made possible that psychological foundation of inclusion and being out in the natural world and as a result have had a lasting impact on his self-esteem and wellbeing • If you're still walking into your teenage years, you're able to accrue significant social benefits at this crucial formative time in life. As a teenager, if you can sit on the sofa with someone, and hang out at friends' houses, you are at a significant psycho-social advantage in comparison with someone who uses a powered wheelchair full time. Friendships, relationships, and a positive self-image are crucial aspects of teenage development. Friends don't invite you round to their houses if they know you can't get in, and without such social opportunities, those friendships and potential relationships, and the foundational emotional wellbeing that they provide, are in danger of falling away. • Cost benefit of fitness for longer – if people living with DMD are walking, they are fitter and have the health benefits of that fitness. If walking continues for more years, that is likely to lead to fewer physical complications over years, requiring less medical intervention and fewer hospital admissions, and therefore resulting in a cost benefit to the health service for longer.	that were not captured fully in the company's model (due to it having only 1 ambulatory health state). But the size of any such health utility gains would likely be substantially lower than that estimated by the company's modelling. The committee also agreed that treatment-dependent utilities were plausible in the non-ambulatory health states, because of a reduced risk of scoliosis. (see FED section 3.10).
Action Duchenne	The committee concluded that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way. I am concerned that this decision should give appropriate weighting to the qualitative evidence of the impact of ataluren on caregivers. • Even apparently marginal benefits in mobility over longer timescales than would otherwise be the case make a significant difference to the quality of life of caregivers. Transfers using a hoist take much longer than if a person can weight-bear briefly or transfer using a sliding board. If you're supporting transfers from bed to chair, or chair to shower chair, six times a day, and each of those transfers take two minutes instead of fifteen minutes, that is 12 minutes spent on supporting transfers rather than an hour and a half. If a person can shift their weight to take off or put on clothes while sitting on a shower chair, you can also cut out two additional transfers, from wheelchair to bed/changing table and then to shower chair. That's another chunk of time you're not spending on care work twice a day. • If a person can also feed themselves and has the upper body strength to get themselves a snack,	Thank you for your comments. The committee took into account caregiver quality of life in depth in its decision-making. This was informed by the information provided by clinical and patient experts, as well as the company (see FED section 3.11).

	that's another roughly three and a half hours a day saved on care support. • If a person stays in a stable health state for longer, that reduces significantly the impact of all the admin and training involved in caregiving. Getting your head around each stage of a progressive condition is a lot of work. • If those benefits continue for additional years, you're talking about a different kind of life that families are living over years – one that is not dominated by care work. This has very significant impacts. • Caregivers are able to go out to work. Caregivers can be financially independent. They can have a life beyond care work, with all the mental health benefits that brings. • Family relationships aren't skewed by care needs. Relentless need and relentless care duties can lead to mental health crises, to abuse, and to family breakdown. • If a person does not have the upper body strength to feed themselves, that means that either you can't have a family meal with everyone eating together, or you have a carer coming in to help the person eat. Both of those can tear the fabric of family life.	
Action Duchenne	In my experience, the evidence of the impact of ataluren beyond direct health benefits needs to include significant cost savings in social care, dependence on state benefits, and the wider economy. • When our son was able to transfer using a sliding board, rather than a hoist, he was awarded **5 hours per week** funded care support from the local authority through direct payments. Now that he needs hoisted transfers, he has been awarded **52.5 hours per week** funded care support from the local authority – ten times more care support. Currently our son aged 18 can feed himself, does not need peg feeding, does not need additional ventilation, and is able to shift position in bed during the night and meet his own toileting needs overnight. If he did need this additional support, he would need **24/7 care support – 168 hours per week.** • Reducing the burden of care on caregivers significantly reduces the stress on families. Stress has cost implications for families and the wider economy, in terms of mental health and work days lost • The difference between care work taking minutes versus hours, plus the time saved on planning and admin when a patient's condition is stable for longer, is the difference between parents being able to work or not work.	Thank you for your comment. Impact on caregiver quality of life was discussed in depth in the committee's decision-making. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).

Action Duchenne	I welcome NICE's recognition that ataluren is effective. The interpretation of the evidence needs to take into account that uncertainty of evidence is in the nature of investigating treatments for rare conditions including DMD where sample sizes are small. Our son was on Study 020; his walk speed stabilised for a year and then declined at a slower rate than before the study (he was on the active drug during the study). Given that ataluren is an orphan drug for a devastating condition in a situation where statistically significant evidence is challenging to identify: in this situation the uncertainty of evidence needs to be weighted in relation to the very significant need of patients and the recognition that the drug is effective.	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Action Duchenne	I am concerned that the provisional recommendation should give appropriate weighting to the fact that the drug is innovative, reflecting the following points: • The community of people living with rare diseases with no currently known effective treatment relies on innovative medicine. Innovative medicine is always going to be more expensive than other medicines. Not funding innovative medicine disproportionately affects families like ours living with a rare condition. • Funding innovative medicine supports investment, research, and development into innovative medicine and so benefits the economy more widely.	Thank you for your comment. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Action Duchenne	The committee's acknowledgement around the efficacy of Ataluren is welcomed but I cannot support the conclusion of the committee in paragraph 3.9 that 'treatment-dependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory'. This represents an over-simplistic and binary understanding of the reality of the ambulatory health state in Duchenne. For patients living with Duchenne (LWD), and their carers, the *quality* of ambulation is critical and the benefits of	Thank you for your comment. The committee considered that the company had not provided robust evidence to support

	Ataluren, in improving the ambulatory experience, must be compared to the experience for those LWD who are not receiving the drug during the ambulatory health state. It is unreasonable and irrational to disregard the benefits of *improved* ambulation when attributing utility values to the ambulatory health state in Duchenne; from our own personal experience and others whose children have received the drug, Ataluren has demonstrated benefits in relation to the actual quality of ambulation including: - Stamina: the quality of ambulation cannot be measured through a test which only captures distance walked over 6 minutes. The greater stamina which Ataluren has provided for those LWD means that that more experiences can be enjoyed, compared to those who may still be in the ambulatory health state but who are not receiving the drug. This is a direct consequence of receiving the drug. We know from our own experience that our son played more football outside – with family and friends - when he was receiving the drug than when (we subsequently discovered) he had been previously receiving the placebo. This was at an age when those LWD, whilst still potentially ambulatory, would be seeing their overall mobility rapidly *declining*, including their ability to participate in ambulatory-based sport. The increased stamina levels when taking Ataluren in the ambulatory health state form a key part of the improved ambulatory experience compared to those who are not receipt of the drug. - Stability when walking: Our son's ability to walk with greater stability and balance, following commencement of treatment with Ataluren, meant that he was less prone to falls with the associated risk of fractures, given the reduced bone density caused by long-term steroid use. This is one of the greatest fear of parents/carers and their children because fractures in Duchenne can accelerate or directly lead to the end of ambulation; fractures require hospital interventions and also present other risks including, for example, fat embolism syndrome. We were hugely grateful and relieved that our son did not experience limb fractures. There are children LWD whose walking is so unsteady and have such a risk of falls and fractures, that they have expressed some relief when they are no longer ambulatory and can rely on a wheelchair. The quality of the ambulatory experience for those LWD as they get older, when it is continuously linked to a greater likelihood of fractures, differs from those receiving Ataluren and who have greater stability and balance when walking. - Keeping up with peers: Children LWD typically walk much more slowly than those who do not have Duchenne. The physiological effects of Duchenne mean that as they get older, typically from age 7, children LWD literally lag behind their friends and peers at school. This in itself makes the walking experience frustrating and demoralising as able-bodied children become physically stronger and quicker. Ataluren has meant children like my son have been able to keep up with their peers for longer when walking and playing (in the playground and	its use of treatment-dependent utility values in the ambulatory health state. However, it agreed that people treated with ataluren may experience health-related quality of life benefits in the ambulatory health state that were not captured fully in the company's model (due to it having only 1 ambulatory health state). But the size of any such health utility gains would likely be substantially lower than that estimated by the company's modelling. The committee also agreed that treatment-dependent utilities were plausible in the non-ambulatory health states, because of a reduced risk of scoliosis. (see FED section 3.10).

	participating in sports and physical education) compared to those LWD who are not receiving the drug but are still in the ambulatory health state. Outdoor play and socialising, particularly in between lessons at school, is not a sedentary activity and as children LWD get older, the ability to keep up with friends so that these experiences can be shared is significant. It is simplistic and counter-intuitive to discount treatment-dependent utility values for children LWD who are still walking and are in receipt of the drug. - More independent walking: Greater stability and balance when walking also reduces the need to hold onto a rail or hold onto someone's hand when walking. Our son did not need to hold an adult's hand in school when walking which itself had psychological benefits, given the desire to 'fit in' at mainstream school. It meant his teaching assistant did not need to be 'velcroed' to him wherever he went but could walk nearby, giving him more dignity and a greater feeling of independence. This would not have been the case if he was not receiving Ataluren. - Pyschological benefits: The psycho-social benefits associated additional years of *improved* ambulation compared to those not in receipt of Ataluren, show that it not just the impact on walking during the ambulatory health state which need to be factored into utility values. Our son's mental health and emotional well-being was enhanced through taking Ataluren and being able to participate in the same activities and experiences as his peers with minimal need for adjustments or concessions – inside and outside of school. This included youth clubs, cub scouts and after-school arrangements at friends' house; some of these activities were on the upper floor of buildings with no lift but for many years he was able to access these facilities. The impact of Ataluren on our son's ambulation has meant he could experience a more inclusive childhood and adolescence – well into his teenage years - with direct, positive consequences for his emotional well-being. - Other health benefits: Children LWD who are in receipt of Ataluren during the ambulatory health state will be more mobile for more of the day and over a longer period of time. Children and teenagers LWD who struggle to walk, but are still classified as ambulatory, will invariably be less active impacting on their overall fitness, weight (exacerbated by steroids) and general physical and mental health. This reduces and/or delays the considerable financial costs associated with hospital admissions, medical equipment and other interventions which are typically required as children LWD enter their teens.	
Action Duchenne	I do not support the conclusion of the committee in paragraph 3.10 'that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way.'	Thank you for your comments. The committee took into account caregiver quality of life in

	The benefits for caregivers from Ataluren have previously been highlighted in the submissions from patients, patient organisations and clinical experts. These are significant given the absence of any other approved treatments for those LWD but although the substantial impact on caregivers is acknowledged by the committee in paragraph 3.2, it is concerning that the committee has simply recommended that caregiver QALYs should be calculated qualitatively. The committee has highlighted certain issues with the calculation of caregiver QALYs whilst also highlighting that the ECD refers to 'apparent difficulties between differences between the outcomes of the EAG approach and the testimonies of the patient experts in relation to QALY loss for caregivers'. However, caregiver benefits are quite capable of being measured and a range of lived scenarios allow for this to be done, as highlighted in the submission made by myself and others caring for those LWD. Whereas there are measurable quantitative caregiver benefits, there is no clarity about how any 'qualitative way', as described in the ECD, has been or could be included in the recommendations of the committee. For example, my son is nearly 18 and has only recently started to require more regular use of a hoist for transfers, particularly in relation to personal care. Whereas previously, a transfer to or from the toilet or showerchair would only take 2-3 minutes self-transferring or using a commode seat, the safe and comfortable fitting of a sling, use of a hoist and tracking system and other assistance, typically takes around 15 minutes each time, 5-6 times daily. This can take up to an hour and half every day simply to carry out the transfers for personal care. In prolonging ambulation and maintaining upper body strength, the use of Ataluren has delayed by several years the need for this additional 7-10 hours per week of personal care support. Our son still has the upper body strength to feed himself or drink including, for example, going to the fridge, taking out and opening a can of soft drink and pouring the contents into a cup. He does not require ventilation, turning at night or many of the other interventions which would essentially require 24 hour care. Delaying the progression of Duchenne has measurable benefits – in terms of time, financial and health (physical and psychological) costs for caregivers. Clearly these benefits – or health splill overs – do need to be reflected in economic valuations and the issue has been addressed in recently published reviews on the subject , including in relation to NICE's own 'reference case' which states that such assessments should include direct health effects for carers. A suitable way of measuring caregiver QALYs needs to be agreed for Ataluren so that these benefits can be appropriately included in actual calculations of cost-effectiveness. This needs to cover both health and non-health benefits given the medical, social and financial costs savings associated with delays to the	depth in its decision-making. This was informed by the information provided by clinical and patient experts, as well as the company (see FED section 3.11).

	progression of Duchenne.	
Action Duchenne	I do not support the conclusion of the committee in paragraph 3.8 that 'it would not include the additional assumed treatment benefits related to early treatment of ataluren in its preferred analysis.' There is currently limited data in the under 5 age group because the label change, allowing for use of Ataluren in this age group was only agreed in 2018 and more recently in other territories. The typical age at which a DMD diagnosis is made in England is stated by the committee as being 4 years. Even on the basis of an average age of a diagnosis of 4 years, there will be more children – over time – receiving the drug *before* the age of 5. My own son was diagnosed at 2.5 years in 2008 and there are now families in England whose children have started receiving the drug by the age of 3; the committee itself noted in paragraph 3.1 that 'DMD symptoms often appear by age 3. It is not accurate or reasonable, particularly in a life-limiting condition where the age-span of those receiving the drug is already limited, to disregard the assumed treatment benefits for all under 5s.	Thank you for your comment. The committee considered the additional information on age of diagnosis. It concluded that it was not appropriate to assume that all children would be treated at 2 years of age. Therefore, the assumed additional benefits were not appropriate (see FED section 3.8).
Action Duchenne	An important aspect of Duchenne which appears to have been overlooked in the ECD are the cognitive and behavioural symptoms associated with the condition and in particular, the higher prevalence of Autism and ADHD amongst those LWD. The EAG touched on the higher rates of autism and obsessive-compulsive disorder for those LWD but the impact of the relentless progression of Duchenne, unchecked without access to Ataluren, is compounded by a diagnosis of Autism and other cognitive impairments. My own son who was diagnosed as having ASD when he was 12, although in many cases an ASM diagnosis for those LWD is made earlier. The anxiety and distress of LWD is often manifested and amplified through debilitating and time-consuming rituals and patterns of behaviour; for example, repetitive handwashing (which occurred well before Covid-hygiene requirements) has not just been time-consuming for my son but also for my wife and I who are sometimes asked to wash our hands repeatedly. Similarly, at times of heightened anxiety, we can be asked an identical question seeking reassurance about a particular point 10-20 times consecutively. We have no doubt that had our son not been receiving Ataluren and the progression of Duchenne accelerated more rapidly, the cognitive and behavioural challenges of LWD would have been even more profound due to his neurodivergence.	Thank you for your comments. The committee considered the nature of the condition and the impact on caregivers and families (see FED section 3.2). The committee also took into account testimonies from patient experts and considered in depth the impact of caregiver quality of life in its decision-making (see FED sections 3.10, 3.11, 3.13 and 3.16). Following an updated

		commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).
Action Duchenne	The conclusion of the committee that Ataluren is innovative is welcomed, together with its recognition of its efficacy and positive impact beyond direct health benefits. As the first drug to be made available in England to address the underlying cause of Duchenne, it is critical that the cost benefits are fairly and accurately assessed in a very small population whose only other option is best supportive care. Innovative treatments for those living with a very rare condition will invariably be more expensive; families affected by the devastating diagnosis of Duchenne must never be penalised due to their small overall number and an initial inability to agree with the company on an appropriate way of measuring its cost effectiveness. Duchenne predominantly affects particularly young people who, with a severe disability, face a shortened lifespan. The draft recommendation set out in the ECD risks adversely impacting on a group, protected by the Equalities Act, for whom there are presently no treatments to address the underlying cause of their condition.	Thank you for your comments. Following an updated commercial arrangement agreed after the second meeting, the committee concluded that the cost-effectiveness estimates for ataluren were below the range that NICE usually considers acceptable for highly specialised technologies (see FED section 3.15).

Comments received from commentators

Commentator	Comment	Response
	None received.	

Comments received from members of the public

Role*	Comment	Response
	None received.	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

NICE National Institute for Health and Care Excellence

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

Consultation on the evaluation consultation document – deadline for comments 5pm on 21 October 2022. Please submit via NICE Docs.

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.	**N/A**
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	***General comment / cover letter*** Dear Committee Members, PTC Therapeutics welcomes the opportunity to comment on this Evaluation Consultation Document (ECD) and kindly ask the Committee to reconsider the recommendation published in the ECD. PTC Therapeutics would like to outline the full extent of the unmet need. Nonsense-mutation Duchenne muscular dystrophy (nmDMD) is a rare, inherited, degenerative disease characterised by a progressive loss of muscle function beginning in early childhood, resulting in declining ambulatory ability, pulmonary function, cardiac function, and upper body function.[1] This progressive muscle wasting eventually results in early mortality, typically before the age of 30.[1] Both patients and their caregivers therefore suffer from a severely reduced quality of life (QoL), as daily activities become impossible for patients to perform independently, especially after patients lose their ability to walk and become wheelchair-bound typically at the age of 12-13 years.[2,3] In England, it is estimated that [redacted] nmDMD patients are currently receiving ataluren as part of a Managed Access Agreement (MAA) (number of patients in the MAA, as of December 2021). Other than ataluren, no treatments are currently recommended in the UK specifically for the treatment of DMD including nmDMD. Hence, there is a high unmet need for the introduction of a treatment such as ataluren to improve the QoL of patients with nmDMD. Ataluren has been shown to meet this unmet need by delaying disease progression and hence, prolonging time spent in less severe health states. Ataluren has demonstrated a

	statistically significant delay in loss of ambulation (LoA) of 5.4 years in patients treated in the Real-World STRIDE registry, compared to matched-control patients receiving best supportive care (BSC) in the CINRG DNHS registry.[4] Pulmonary disease milestones were also delayed in the STRIDE registry in ataluren-treated patients. Similarly, patients treated with ataluren in three phase IIb/III clinical trials showed a statistically significant decrease in change in decline in 6MWD from baseline compared to placebo-treated control patients. In Study 020, in the pre-specified subgroup of patients with baseline 6MWD ≥300m to <400m, the change in decline in 6MWD was 42.9m in favour of the ataluren-treated arm compared to the placebo-treated arm at 48 weeks (p=0.007).[5] Similarly in Study 007, the change in decline in 6MWD was 68.2m in favour of the ataluren-treated arm compared to the placebo-treated arm at 48 weeks (p=0.0053), in the subgroup of patients with a baseline 6MWD <350m.[6] In Study 041, the change in decline in 6MWD decreased by 14.4m in favour of the ataluren-treated arm compared to the placebo-treated arm at 72 weeks (p=0.0248) in the ITT population.[7] NSAA linear scores also showed improvements in ambulatory ability in the ataluren-treated groups compared to control groups of 4.5 (p=0.030) in the pre-specified subgroup of patients with baseline 6MWD ≥300m to <400m in Study 020[5] and 2.3 (p=0.0246) in Study 041 ITT population[7]. Thus, there is strong evidence demonstrating ataluren would address the unmet need for a treatment in patients with nmDMD. As part of this response, PTC Therapeutics have addressed the concerns raised by the Committee and External Assessment Group (EAG) in the ECD, specifically: • The use of independent survival modelling has been justified as appropriate based on analysis of the diagnostic plots for each time-to-event outcome using guidance issued in NICE DSU 14, as well as through analysis of goodness-of-fit and clinical expert validation. To further justify this method of survival modelling, flexible analysis of time-to-event outcomes has been performed. This resulted in a better fit to the observed Kaplan Meier (KM) data and a reduction to the ICER however, the company preferred to consider the conservative approach of using independent survival modelling in the base case due to the implausibility of the survival curves for the flexible survival analysis. • The early treatment benefit assumption of two years delay in time to LoA and three years delay in time to pFVC<50% and pFVC<30% has been justified using additional efficacy data from patients aged 2-5 from Study 030, and clinical expert validation. • The company acknowledges that there are limitations with both the positive utility approach for modelling caregiver QoL used in its original base case and the caregiver disutility approach used in the EAG's base case. As such, the company has accepted NICE's proposed approach of excluding caregiver QoL from the economic model and to instead consider the impact of this qualitatively. • The company has presented discontinuation data from the STRIDE registry including the reason for treatment discontinuation and demonstrating that applying both a constant discontinuation rate and stopping rule assumption is appropriate. Additionally, the company has updated its base case to use an adjusted

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	discontinuation rate, removing those who discontinued due to LoA from the recently published 2021 data-cut of the STRIDE registry. • A later stopping rule at pFVC<30% has been included in the company's updated base case to reflect clinical expert opinion and that of NHS England, which is aligned with NICE's preferred base case. • The company's updated base case analysis shows that ataluren treatment results in a gain of more than 10 undiscounted quality-adjusted life years (QALYs), therefore the company has demonstrated that ataluren qualifies for a QALY weighting. Taking into account the suggestions and recommendations from the Committee and the EAG, PTC Therapeutics have provided a revised company base case. Changes include using an updated stopping rule at pFVC<30%, using different survival distributions for each time-to-event outcome, excluding caregiver QoL from the cost-effectiveness analysis, and a revision in the Patient Access Scheme (PAS) discount from [redacted]% to [redacted]%, resulting in changes in the price of ataluren from £[redacted], to £[redacted] per 125 mg sachet, £[redacted] to £[redacted] per 250 mg sachet, and £[redacted] to £[redacted] per 1000 mg sachet. Applying the above changes in the economic model results in a revised base case incremental cost-effectiveness ratio (ICER) of £[redacted]. A detailed summary of the key uncertainties raised by the Committee and how each of these have been addressed can be found in Sections 2 – 10. All new evidence has been provided at the end of this document.
2	***Independent survival modelling is appropriate.*** In Section 3.7 of the ECD, it was noted that: *"The committee considered that the company's original base case model choices, as used in the EAG's base case analysis, were the most appropriate to use for decision making. However, it noted that the results were uncertain because of the poor fit of the models to the data."* The company reiterates that the standard parametric models fitted to the STRIDE and CINRG time-to-event data in the updated company base case are the most appropriate modelling approaches for the following reasons: **1. Diagnostic plots of standard parametric models:** In NICE DSU 14, it is recommended that flexible survival analyses should be considered when log-cumulative hazard plots do not show approximate straight lines (see Figure 1). Other than in the initial period when very few events took place (which was accounted for by the re-base analysis), the log-cumulative hazard plots for time to LoA, pFVC<50%, and pFVC<30% did not show non-straight lines. Therefore, it was considered appropriate to use standard parametric models instead of flexible analyses, in accordance with the NICE DSU 14 selection algorithm.[8]

	Additionally, the company tested the plausibility of using proportional hazards. The log-cumulative hazard plots, Schoenfeld residual plots and quantile-quantile plots were evaluated for time to LoA, pFVC<50%, and pFVC<30% (presented in Figure 2, Figure 3, and Figure 4, respectively). For each outcome, the log-cumulative hazard plot lines for the CINRG and STRIDE datasets did not remain parallel for the majority of the time period, and plot lines crossed multiple times throughout the time horizon. This suggests that independent survival modelling is the most appropriate approach, in accordance with NICE DSU 14.[8] For each outcome, the Schoenfeld residual plots show a linear curve with a zero slope and a p-value greater than 0.05, supporting the proportional hazards assumption. However, proportional hazards assume a treatment effect that is maintained throughout the treatment duration, and although the assumption appears plausible for some endpoints, it is uncertain whether the treatment effect will be maintained at future timepoints. Therefore, independent survival modelling was considered to be the most appropriate modelling approach. Furthermore, the fit of the standard parametric models to the observed time-to-event data has already been improved by performing re-based analyses, in which the survival models were applied to the observed Kaplan-Meier (KM) curves only from 5 years and 3.5 years for the BSC and ataluren cohorts, respectively. This approach was used as very few events were observed during the initial period of each registry due to the young age and hence, low rate of disease progression in patients during this period. Therefore, the re-based analysis allowed extrapolations to be made only from the period in which events occurred. However, this re-based analysis has little effect on the company base case ICER. Using non-rebased survival curves results in a change in the ICER of only +£[redacted], to £[redacted]. **2. Goodness-of-fit of standard parametric models to KM data:** The log-logistic survival curves to model time to LoA and time to pFVC<50%, and log-normal curves to model time to pFVC<30% in both the ataluren and BSC cohorts have the best goodness of fit. The goodness of fit was determined by considering the lowest AIC and BIC, as well as visual inspection of the survival function. The log-logistic and log-normal curves showed the best fit to the observed KM data from the STRIDE and CINRG registries for time to LoA and pFVC<50%, and time to pFVC<30%, respectively, when the rebased analyses at 5 years and 3.5 years for the STRIDE and CINRG datasets, respectively (as described above) were performed. **3. Clinical expert validation of standard parametric curves:** The plausibility of each of the standard parametric survival curves (log-logistic, log-normal, exponential, Weibull, Gompertz and generalised gamma) for time to LoA, pFVC<50%, and pFVC<30% has been validated by two independent UK clinical experts. Clinical expert input indicated the Weibull survival curve distribution is most appropriate in all outcomes, as this is most representative of the disease progression course in clinical practice. Hence, in the company's previous base case, the Weibull curve was selected to model each time-to-event outcome. However, to align with the preferred assumption of NICE and the EAG, the company has chosen to revise their base case for each outcome to the survival curve distributions with the best fit. These are log-logistic for time to LoA and time to pFVC<50%, and log-normal

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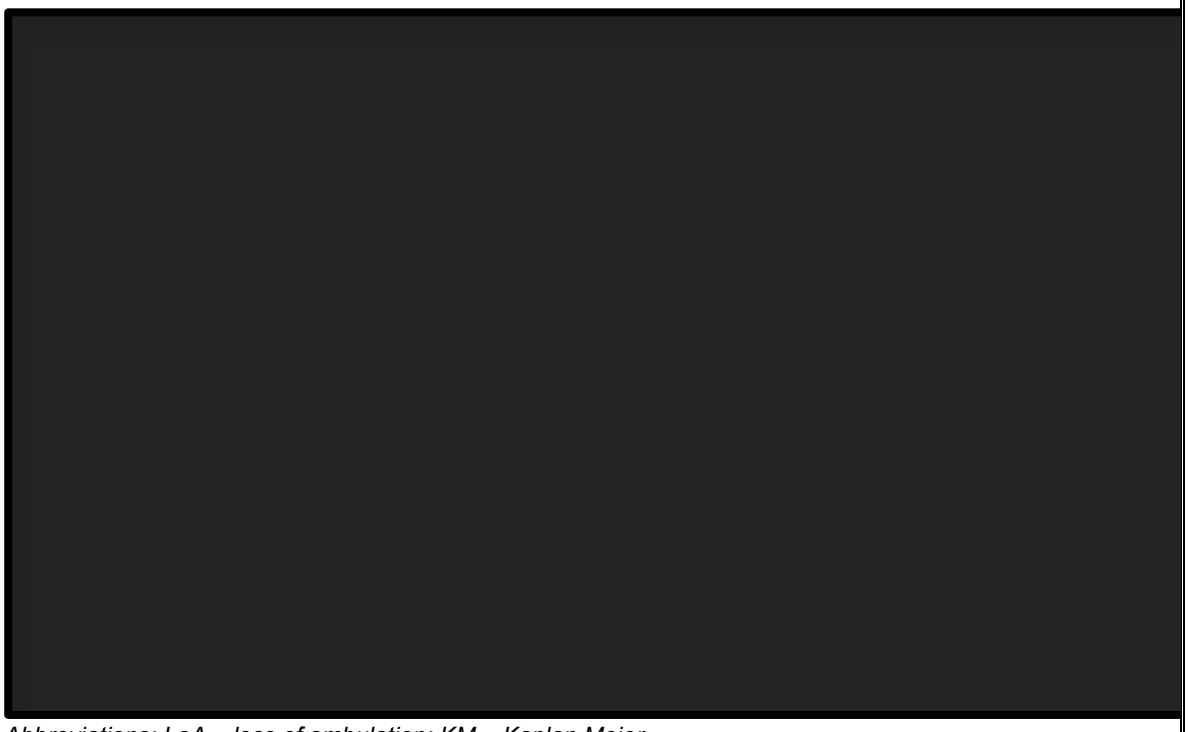
	for time to pFVC<30%. A scenario analysis has been included using the Weibull distribution to model each outcome, which increases the ICER slightly to £[redacted], in *Table **2***.
3	***Cost-effectiveness analysis results were relatively insensitive to the modelling approach and parametric model selection.*** In Section 3.7 of the ECD, it was noted that: *"[The EAG] noted that the models selected did not appear to provide a good fit to the data for several of the modelled health states. The EAG also noted that the company had not considered more flexible models, which may have provided a better fit to the data."* To investigate further the effect of alternative survival modelling, a flexible modelling analysis was performed. Under this approach, flexible spline models were fitted to the observed KM data from the STRIDE and CINRG registries (2021 data-cut) for the following time-to-event outcomes: • Age at LoA • Age at pFVC<50% • Age at pFVC<30% This approach was taken to address concerns by the EAG/Committee that the standard parametric survival modelling in the cost-effectiveness model do not show a good fit to the observed data. Spline models are a more flexible class of survival model than standard parametric models, as they allow the survival curve to differ between time intervals, which is determined by the number of knots specified. These models therefore have the flexibility to reflect changes in hazard functions over time. The following three 1-, 2- and 3-knot spline models were considered for each time-to-event outcome, providing extensions to the previously assessed standard parametric models: • The proportional hazards spline model; an extension to the parametric survival model based on the Weibull distribution. • The proportional odds spline model; an extension to the parametric survival model based on the log-logistic distribution. • The normal spline model; an extension to the parametric survival model based on the log-normal distribution. Survival plots for time to LoA, pFVC<50%, and pFVC<30% with each of the above flexible spline models fitted are presented in Figure 5, **Figure 6**, and Figure 7, respectively. In line with NICE DSU 14, model selection was based on assessment of goodness-of-fit by considering AIC/BIC (lowest AIC/BIC indicates best fit), through visual inspection, and assessment of the clinical plausibility of the hazard function. Goodness of fit statistics for each model are presented in Table 4. For each outcome, the 1-knot flexible spline model showed best fit and was therefore selected for the analysis. The following flexible spline models showed the best fit to the observed KM data and were therefore selected for the flexible analysis:

- Time to LoA (ataluren): proportional hazards spline model (1-knot)
- Time to LoA (BSC): proportional odds spline model (1-knot)
- Time to pFVC<50% (ataluren): proportional normal spline model (1-knot)
- Time to pFVC<50% (BSC): proportional odds spline model (1-knot)
- Time to pFVC<30% (BSC): proportional hazards spline model (1-knot).

For each time-to-event outcome, the above flexible curves of best fit were compared against the respective standard parametric models of best fit (log-logistic for time to LoA and time to pFVC<50%, and log-normal for pFVC<30%). To assess whether the flexible analyses improved the fit of the extrapolations to the observed KM data, the goodness-of-fit statistics of the best-fitting flexible models were compared against those of the independent models of best fit. Goodness-of-fit statistics are presented for each outcome for the best-fitting standard parametric and flexible spline curves in Table 5. Comparisons between the observed KM data and the best-fitting flexible and best-fitting standard parametric models are presented in

Figure 8: Comparison of best fitting standard parametric model (log-logistic) and flexible (hazard spline) model against observed KM data - Time to LoA (BSC+Ataluren)



Abbreviations: LoA – loss of ambulation; KM – Kaplan Meier

Figure *9* to Figure 12.

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	As shown by the goodness-of-fit statistics and comparison of modelled median survival against median survival from the observed KM data (as shown in Table 5), the flexible analysis improved goodness-of-fit of the modelled survival curves compared to the standard parametric curves. However, the survival plots for the flexible analyses reveal that a limitation of this approach is that the time to LoA extrapolated curve intersects with the time to pFVC<50% extrapolated curve, resulting in a proportion of patients reaching the night-time ventilation milestone (approximated by reaching the pFVC<50% milestone) before losing ambulation in the model. Survival modelling for each outcome using the flexible analysis approach is presented in Figure 13 and Figure 14 for the ataluren and BSC cohorts, respectively. The effect of using the flexible survival modelling approach on the cost-effectiveness of ataluren is presented in Table 6. Using flexible survival modelling instead of independent survival modelling decreases the company base case ICER by £[redacted] to £[redacted]. Despite the fact that including flexible survival analysis improved the fit of the survival curves to the observed KM data and decreased the company base case ICER, the company prefers to remain conservative by using independent survival curves for all time-to-event outcomes, as applied in the NICE base case due to the limitations identified in the flexible analysis.
4	***Although only a small number of patients under the age of five have received ataluren, it is plausible to assume early treatment will lead to additional benefits.*** In Section 3.8 of the ECD, it was noted that: *"The EAG noted that very few people had received ataluren in STRIDE before the age of 5 and that there was no other direct evidence to show that starting treatment early provided additional benefit. The committee was aware that the company's economic model assumed everyone would have treatment with ataluren at 2 years of age. They considered that this was inconsistent with published evidence and clinical expert opinion that most diagnoses of DMD in England are at around 4 years, and that there is currently no national screening programme for DMD."* It should be noted that the Medicines and Healthcare products Regulatory Agency (MHRA) license for ataluren was only extended to the 2-4 year age group in 2018 after the initiation of the STRIDE registry, hence the proportion of patients in this age group in the registry is lower than what would be expected in clinical practice. This also means that the 20 patients in the STRIDE registry who did initiate treatment in the 2-4 year age range have not yet been followed-up for a sufficient duration to make any conclusions about delays in time to LoA, as this typically occurs in patients receiving BSC at around the age of 12 to 13 years.[2,3] Due to this limitation of the available data, the use of clinical expert validated assumptions regarding an early treatment benefit in the model was deemed necessary. Since 2020, [redacted] patients in England have been diagnosed with nmDMD and subsequently treated with ataluren.[9] Of these patients, [redacted] were aged 2-4 years, and [redacted] were two years old at diagnosis. These data show that it is plausible to assume that patients would initiate ataluren treatment before the age of five years in clinical practice. Treatment initiation at two years of age is also the most clinically relevant scenario to model, as this aligns with both the conditional marketing authorisation for ataluren, and the preference of the independent clinicians consulted by the company, who expressed a desire to treat

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	patients as early as possible to maximise the benefit they receive from treatment. Additionally, between 2021 and 2022, there was a [redacted]% increase in the number of children diagnosed with nmDMD below the age of five years, suggesting diagnosis in younger patients is improving. This will allow patients to initiate treatment at an earlier age. Initiating treatment at two years of age in the model is the most conservative approach to modelling the cost-effectiveness of ataluren, as this assumes all patients are on treatment (and therefore accumulating treatment costs) for the longest possible duration within the license. A scenario analysis has been performed assessing the cost-effectiveness in a cohort of patients starting treatment at four years old, with the early treatment benefit removed. This results in an increase of £[redacted] to the ICER from the company's updated base case to £[redacted]. The company acknowledges that there is uncertainty regarding the magnitude of the early treatment benefit included in the economic model. However, the company reiterates the point that this assumption and the early treatment delay values applied to each outcome were validated by an international Delphi panel of nine clinical experts.[10] Additionally, the company presents further evidence supporting the assumption of an early treatment benefit with earlier initiation of ataluren treatment at an age of two years old. To evaluate the safety and pharmacokinetics of ataluren in patients aged 2-5 years, a phase II, open-label study (Study 030[11]) was carried out in 14 males aged 2-5 years with a mean age of 3.4 years, weighing ≥12 kg and with a confirmed genotypic diagnosis of nmDMD. As a secondary endpoint, the study measured changes from baseline to week 52 in timed function tests (TFTs), the North Star Ambulatory Assessment (NSAA) 16-part scale, and the 3-part and 8-part NSAA scale, adapted for children <5 years of age.[11] The TFT and NSAA results of Study 030 are presented in Table 7 and Table 8, respectively. The study results show that over 28 and 52 weeks of ataluren treatment, patients aged 2-5 years exhibited an improvement in ambulatory ability as demonstrated by decreased time to run/walk 10 metres, decreased time to climb and descend four stairs, time to stand from supine, and increased NSAA scores from baseline. This demonstrates the clinical efficacy of ataluren in patients aged 2-5 years. in addition, the assumption of an early treatment benefit was supported by both an external clinical expert consulted by the company and the clinical expert present at the ataluren NICE committee meeting. The expert at the committee noted that although she did not have specific data to support the benefit of early treatment, there is a biological rationale behind the assumption, as starting treatment at an earlier age has a protective effect against muscle deterioration, which results in muscle function being preserved for longer during the pubescent stage of childhood. This means that patients are more likely to avoid conditions that develop alongside muscle weakness, for example scoliosis, later in life. By avoiding comorbidities such as scoliosis, the QoL of patients is preserved for a longer duration. The clinical expert also mentioned that it makes sense from a biological perspective to diagnose patients at an earlier age to allow earlier initiation of ataluren treatment, as this would improve their prognosis during later life. Indeed, in recent decades, the medical management of DMD has shifted to more anticipatory diagnostic and therapeutic strategies, to achieve prevention, early identification, and treatment of disease complications.

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	Furthermore, early genetic testing also allows newborn siblings of patients with an nmDMD diagnosis to be tested and diagnosed, meaning more patients are able to start treatment earlier, assuming that patients are eligible for genetic testing procedures that identify the nonsense mutation that causes nmDMD. In a DMD care considerations article published by Birnkrant *et al.* in 2018 it is stated that "*contemporary care has been shaped by the availability of more sensitive diagnostic techniques and the earlier use of therapeutic interventions, which have the potential to improve patients' duration and quality of life*".[12] Birnkrant *et al.* also stated that the use of standardised testing in children with DMD is increasing, and that there "*renewed interest in newborn screening has been building as a result of support among stakeholders and because emerging DMD therapies might prove to be most effective if they are initiated before symptom onset*"[13] supporting the assumption that early diagnosis and hence early treatment initiation is beneficial for patients with DMD in later life, as this rationale is likely to apply to nmDMD. The results from Study 030 demonstrating improved ambulatory ability in patients aged 2-5 years following 28 and 52 weeks of ataluren treatment and the biological rationale behind the early treatment benefit validated by an independent clinical expert suggests that treating patients at 2-5 years of age would have a protective effect against muscle loss and improve patient QoL in more advanced stages of the disease. Thus, the company believes there is strong support for the assumption of an early treatment benefit and has included a two year delay in time to LoA and three year delay in time to pFVC<50% and time to pFVC<30% in its updated base case. To address the Committee's concerns that the early treatment benefit in the model overestimates the actual benefit observed in patients treated with ataluren, the company has also included a scenario analysis in which the assumed early treatment benefit is halved. This results in an ICER of £[redacted], an increase of £[redacted] compared to the company base case.
5	***Treatment-dependant utilities are plausible and appropriate for both ambulatory and non-ambulatory disease states due to quality of life improvements observed in ataluren patients that cannot be effectively modelled based on the defined health states in the economic model.*** In section 3.9 of the ECD, it was noted that: *"The committee considered that the company had not provided robust evidence to support the use of treatment-dependent utility values in the ambulatory health state. The committee concluded that treatment-dependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory health states."* The company reiterates that the treatment-dependent utilities are sourced from the Landfeldt *et al.* 2020 Delphi panel,[14] and supported by another independent Delphi panel,[10] as well as an independent UK clinical expert. Both Delphi panels found that clinicians consider there to be differences in cognition, emotion, pain, ambulation and dexterity of patients receiving ataluren and BSC, in both the ambulatory and non-ambulatory health states. Consensus estimates for the mobility, upper limb function (i.e., dexterity), emotion and pain and discomfort domains for ambulatory patients are presented in Table 9 and Table 10 (Landfeldt *et al.* 2020[14] and Landfeldt *et al.* 2022[10], respectively). As shown, the clinical experts considered patients treated with ataluren to have different levels of function compared to those receiving BSC.

Additionally, treatment-dependent utilities are supported by clinical evidence of improvements in functional ability in patients receiving ataluren compared with BSC within the ambulatory health state. Specifically, lower and upper extremity function among ambulatory patients receiving ataluren and BSC were recorded in Study 041[7] using two extensively validated and frequently employed clinical measures:

- The North Star Ambulatory Assessment (NSAA); and
- The Performance of the Upper Limb Module (PUL), in a subgroup of patients with a 6-minute walk distance (6MWD) between 300m and 400m. All patients were ambulatory in the trial and only a small number lost ambulation during the trial in each arm.

Outcomes from these instruments are presented in Table 11 and Table 12. The data shows a reduced loss (i.e., improvement) in functional ability across [redacted] of the NSAA measured at week 72 in patients receiving ataluren vs. BSC. Additionally, the data shows a relative change of [redacted] in upper limb function among ambulatory patients treated with ataluren vs. BSC from baseline to week 72 (mean change from baseline in total upper limb score: [redacted][ataluren] vs. [redacted] [BSC], [redacted]).

These improvements in lower and upper extremity function, as captured in the two Delphi panels,[10,14] results in higher QoL of patients treated with ataluren vs. BSC also within ambulatory disease stages. This is further supported by several studies exploring the association between distal and proximal muscle weakness and QoL domains in DMD, for example Williams *et al*.[15]

Additionally, clinical and patient experts were supportive of the company's base case assumption to apply treatment-dependant utilities in all health states, concluding in their response to the technical engagement *"That they [clinical and patient experts] believed it was appropriate to use treatment-dependent utilities because of the benefits of treatment with ataluren".*

Outcomes from the EQ-5D visual analogue scale (VAS) recorded in Study 041 are presented in Table 13. Patients with DMD treated with ataluren reported a mean increase in subjective QoL from baseline to month 1 of follow-up of +1.2 scores. In contrast, patients receiving BSC reported a change of +0.1 scores. These data indicate that ataluren has an impact on patient QoL within a very short duration of time after treatment initiation and provide further support for the use of treatment-dependent utilities in ambulatory patients.

Furthermore, evidence from Study 046 includes data on the expression of full-length dystrophin, measured in [redacted] DMD patients before and after ataluren treatment. Dystrophin measurements were recorded at baseline, prior to ataluren treatment, and compared to measurements at week 40 of ataluren treatment. The results show a [redacted] increase in mean dystrophin ([redacted]). As the absence of functional dystrophin protein leads to long-term irreparable damage in muscles of DMD patients with limited potential to regain function, increased dystrophin has the potential to improve, or preserve, muscle function in ataluren-treated patients (as shown in Study 041).[16] Study 046 also reported improved muscle function in ataluren-treated patients measured using the timed function test

	associated with key functions of daily life, as well as decreases in serum creatine kinase levels, which suggests potential preservation of muscle tissue. In section 3.9 of the ECD, it was noted that: *"The EAG noted that the company applied treatment-dependent utilities from the beginning of the model time horizon and applied them throughout the model, even when treatment with ataluren had been stopped."* As ataluren delays LoA, the company expects those patients that receive ataluren to have improved physical and mental development during their early and adolescent years (as captured in the Delphi panels). There are common secondary conditions to DMD which contribute to patient QoL, for example scoliosis, which has been linked to reduced QoL and life expectancy, primarily because of detrimental effects on respiratory function.[17] Published literature indicates that prolonged ambulation reduces scoliosis risk in DMD patients, and that progression occurs most rapidly during the adolescent years.[18] A published study has shown that older age at LoA relates to older age of scoliosis onset ($p<0.0001$) and age at LoA is inversely related to scoliosis severity at 17 years ($p<0.005$).[19] This evidence suggests it is plausible that by delaying LoA in patients receiving ataluren, development of scoliosis can be prevented until post-puberty, resulting in prolonged improvements in patient QoL when compared to BSC. The hypothesis that ataluren is likely to reduce the risk of scoliosis was supported by an external UK clinical expert, and both the clinical expert and EAG expert at the committee meeting, where it was noted as follows: *"One EAG expert said that ataluren may improve quality of life in non-ambulant health states because of a reduced risk of scoliosis."* *"The clinical expert at the committee meeting said that ataluren could reduce the risk of developing scoliosis and delay respiratory symptoms in non-ambulatory health states because it would allow muscle strength to be preserved for longer during puberty."* The potential benefits associated with ataluren treatment, such as reduced risk of scoliosis, improved cardiac function, and delayed loss of upper limb function have not been included in the model, as data to inform the post-LoA states based on these factors was not available from the clinical trials at the time of initial submission. In addition, maintaining ambulation longer may improve patient quality of life in later stages of the disease. According to an external clinical expert, factors such as mental health and quality of life can be improved when ambulation loss is delayed until after adolescence due to cognitive maturation, and by delaying progression post-puberty, long-term benefits such as bone health may also be affected as an active lifestyle plays a crucial role in bone health overall. For reasons outlined above, the company considers treatment-dependent utilities to be plausible and appropriate for both ambulatory and non-ambulatory disease states. Furthermore, the treatment benefit is anticipated to translate to a lasting effect for all patients, even after discontinuation of treatment.

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6	***It is important to incorporate the impact of ataluren on caregiver QoL; however, the company accepts this to be considered in a qualitative way instead of within the model estimation of the ICER.*** In section 3.10 of the ECD, it was noted that: *"It [the committee] therefore concluded that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way."* To align with NICE and expert opinion, the company accepts the Committee's preferred assumption by removing caregiver utilities in the revised base case. However, the company continues to note the importance of incorporating the impact on caregivers in decision making. There is a significant, progressively increasing caregiver burden for the vast majority of a DMD patient's lifetime. DMD patients have significant challenges in performing day-to-day activities, particularly in later stages of the disease when the disease has progressed and patients are non-ambulatory, requiring ventilation support and full dependency on support from multiple caregivers.[20,15] Furthermore, the detrimental impact on parents or guardian caregivers is expected to continue even after a patient dies, as despite the daily burden being relieved, these caregivers are likely to experience a bereavement-related disutility.[21] A Delphi panel of nine neuromuscular specialists, adult and paediatric neurologists, and paediatricians from five European countries agreed that both ambulatory and non-ambulatory patients will often have two informal caregivers involved in their day-to-day care and support.[10] The impact of ataluren treatment on changes in caregiver QoL, including reduced anxiety, stress, and a positive impact on productivity, are demonstrated in the results of a qualitative study on the impact of caring for DMD patients,[15] as follows: *"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."* *"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."* Further, caregivers have stated that there is a tangible benefit from delaying disease progressing as it allows time to prepare themselves for the next stage. Additionally, caregivers find that there is greater anxiety surrounding steroid use due to reduced bone density reducing bone strength – caregivers may find they prefer to stop their patient walking to mitigate risk of broken bones.

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	For the reasons outlined above, the company continues to emphasise the appropriateness of incorporating caregiver QoL in the assessment of ataluren from a qualitative perspective. Furthermore, based on the difference in QoL likely to be observed in patients that receive ataluren, the company believes it is also plausible to assume that caregiver QoL is likely to be higher in each health state for those treated with ataluren compared to those that receive BSC.
7	***The company has agreed to revise the stopping rule to the Committee's preferred assumption at pFVC<30%, so that patient time on ataluren treatment and the potential benefits received are maximised.*** In section 3.12 of the ECD, it was noted that: *"The clinical expert said that clinicians would want to continue using ataluren after their patients lost the ability to walk because of the benefits in upper limb and respiratory function…For the purposes of cost-effectiveness modelling, the committee preferred to use the time when predicted FVC reached less than 30%. But it acknowledged that this may not align with how treatment is stopped in clinical practice."* To align with NICE and expert opinion, the company chooses to accept the Committee's preferred stopping rule assumption, using the stopping rule at pFVC<30% in the revised base case, as presented in Table 1. The ICER increases when this stopping rule assumption of pFVC<30% is used, however the company believes this is necessary to align with NHS England's, the clinicians' and the company's aspirations for patients continuing to receive and benefit from ataluren treatment for as long as possible. Supportive to this, within the ACM an NHSE representative noted that any stopping rule must be guided by clinicians and based on the treatments specific benefit, response, and/or safety profile. *Table **2*** also presents the results for a scenario analysis when the stopping rule is pFVC<50%.
8	***The treatment discontinuation rate does not lead to double counting of events with the company's proposed stopping rule. The company accept comments from the Committee and have revised the discontinuation rate to align with expert opinion.*** In section 3.11 of the ECD, it was noted that: *"The EAG said the observed treatment discontinuation rate may have double counted the events that would be captured in the company's proposed stopping rule."* The proposed stopping rule implemented in the economic model allows patients to continue treatment until they require full-time ventilation support, estimated by pFVC<30%. Within the STRIDE cohort, only [redacted] of [redacted] non-ambulatory patients reached the pFVC<50% endpoint and only one non-ambulatory patient reached the pFVC<30% endpoint. Therefore, most patients remained on treatment beyond LoA but very few remained on treatment beyond achieving pFVC<30%, as they had not yet reached this endpoint or a later endpoint. As the discontinuation rates used in the previous and current base cases do not include any patients stopping treatment once they have reached either pFVC<50%

	or pFVC<30%, the application of both the treatment discontinuation rate and the proposed stopping rule in either case does not represent double counting. In section 3.11 of the ECD, it was noted that: *"The EAG provided an analysis that reduced the discontinuation rate by 50% to explore the impact of this on cost effectiveness… The committee concluded that the company's estimated discontinuation rate likely overestimated treatment discontinuation and therefore underestimated ataluren treatment costs. The committee preferred the EAG's scenario analysis, which reduced the discontinuation rate for decision making. But it noted that this reduction was arbitrary and added to the uncertainty."* To address the concerns from the Committee regarding a potential over-estimation of the discontinuation rate, the company have used an adjusted discontinuation rate in the revised base case. Analysis from the STRIDE 2021 data-cut has been used to inform this revised discontinuation rate. Using data from the STRIDE registry overcomes the uncertainty in the EAG suggestion of using an arbitrary 50% reduction to the previous base case discontinuation rate. Within the STRIDE registry, as of January 2021, [redacted] patients were followed for a median follow-up of [redacted] days. As shown in Table 14, [redacted] patients within the cohort discontinued treatment with [redacted] being due to LoA and the remaining [redacted] due to other factors. This calculates as a treatment discontinuation rate of [redacted], which overall is a [redacted] reduction on the previous base case discontinuation rate ([redacted] in the revised base case vs. [redacted] in the previous base case), and in-line with the discontinuation rate of [redacted] used in the EAG's scenario analysis.
9	***A QALY weighting should be applied in the base case.*** In section 3.13, it was noted that: *"The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs."* The revised base case assumptions result in an estimated number of additional undiscounted QALYs gained of [redacted] ([redacted] for ataluren, [redacted] for BSC). The estimated number of undiscounted QALYs gained is greater than 10, therefore the company suggests that ataluren meets the criteria for applying a QALY weighting. Therefore, a QALY weighting of [redacted] has been applied in the revised base case.
10	***Revised base case*** The company have carefully considered the perceived uncertainties raised by the Committee in the ECD. With this in mind, the company have revised the base case to capture the Committee's preferences with respect to the following assumptions, that should be considered for decision making: • Stopping rule is extended from pFVC<50% to pFVC<30%. • Survival curve distributions are changed from Weibull to the Committee's preferred distributions (log-logistic for LoA and pFVC<50%, log-normal for pFVC<30%). • No caregiver utilities are considered. • Treatment discontinuation rate is reduced from [redacted] to [redacted].

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	• The PAS discount is increased from [redacted] to [redacted] of the ataluren list price. As outlined in this document, the company have addressed the remaining areas of uncertainty raised by the Committee, including the following: • Treatment-dependent utilities are appropriate in all health states. • Independent survival modelling is appropriate. • Early treatment benefits are plausible. • Treatment discontinuation rate. With the revised assumptions above incorporated into the economic model, the revised company base case results in an ICER of [redacted] (presented in Table 1 below).

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Revised base case results

Table 1: Revised base case results *(Stopping rule at pFVC<30%, log-logistic for LoA and pFVC<50%, log-normal for pFVC<30% [survival curve distributions], treatment discontinuation at [redacted], no caregiver utilities considered, [redacted] PAS discount)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – Patient access scheme; QALYs – quality-adjusted life years.

Table 2: Scenario analysis *Table to show ICERs for scenarios, with assumptions varied from the revised base case (see Table 1)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Stopping rule at pFVC <50%							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull survival curve distributions for all health states							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flexible survival analysis							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early treatment benefit reduced by half (LoA: 1 year, pFVC <50% and <30%: 1.5 years)							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIDE 2020 discontinuation rate							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – incremental cost effectiveness ratio; LYG – life years gained; LoA – loss of ambulation; pFVC – predicted forced vital capacity; QALYs – quality-adjusted life years

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Table 3: Previous base case results *(Stopping rule at pFVC<50%, Weibull for all health states [survival curve distributions], treatment discontinuation at [redacted], caregiver utilities considered [absolute approach], [redacted] PAS discount)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – Patient access scheme; QALYs – quality-adjusted life years

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

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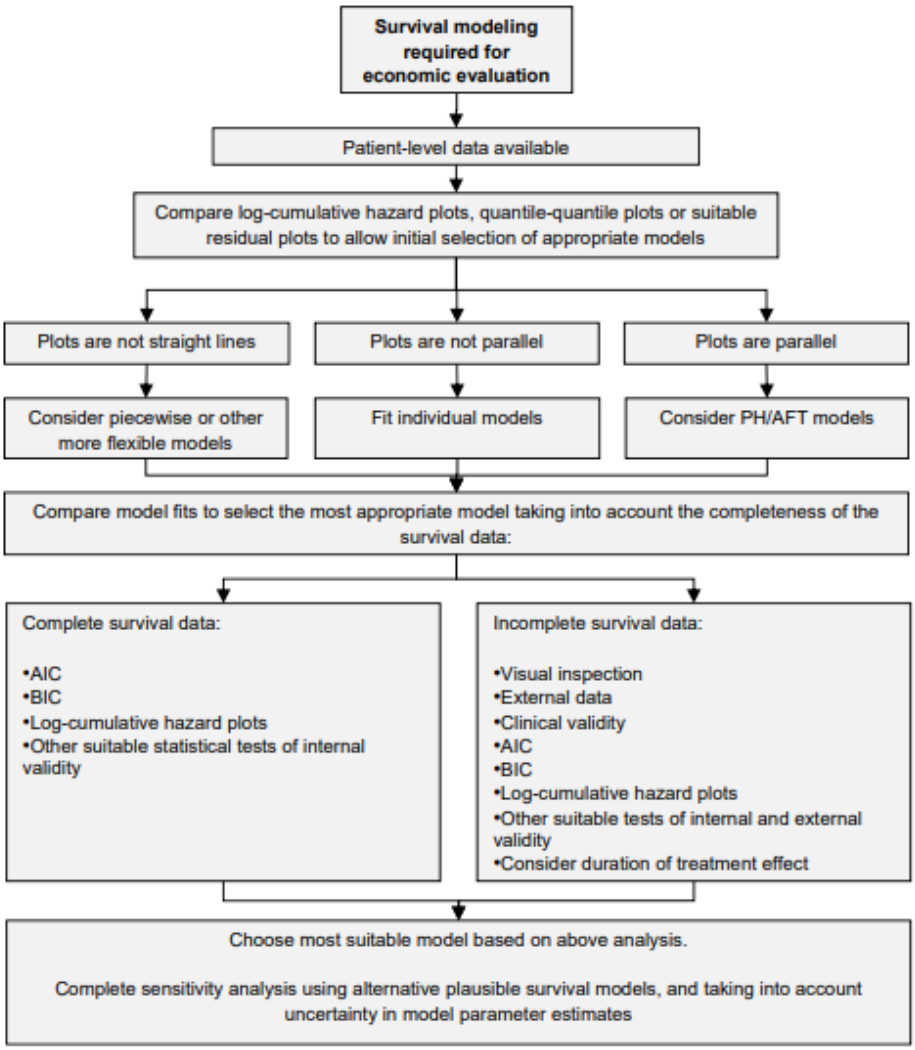
New Evidence

Figure 1: NICE DSU 14 survival model selection process algorithm[8]



Abbreviations: AFT – accelerated failure time; AIC – Akaike information criterion; BIC – Bayesian information criterion; PH – proportional hazards

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Figure 2: Survival analysis diagnostic plots (time to LoA)

Abbreviations: 025, ataluren treatment arm from STRIDE registry; CNG, control arm; LoA – loss of ambulation

Figure 3: Survival analysis diagnostic plots (time to pFVC<50%)

Abbreviations: 025, ataluren treatment arm from STRIDE registry; CNG, control arm; FVC – forced vital capacity

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

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Figure 4: Survival analysis diagnostic plots (time to pFVC<30%)

Abbreviations: 025, ataluren treatment arm from STRIDE registry; CNG, control arm; FVC – forced vital capacity

Figure 5: Survival plots for fitted 1-knot spline models (time to LoA)

Abbreviations: 025, ataluren treatment arm from STRIDE registry; AALOA – age at loss of ambulation; CNG, control arm ; LoA – loss of ambulation

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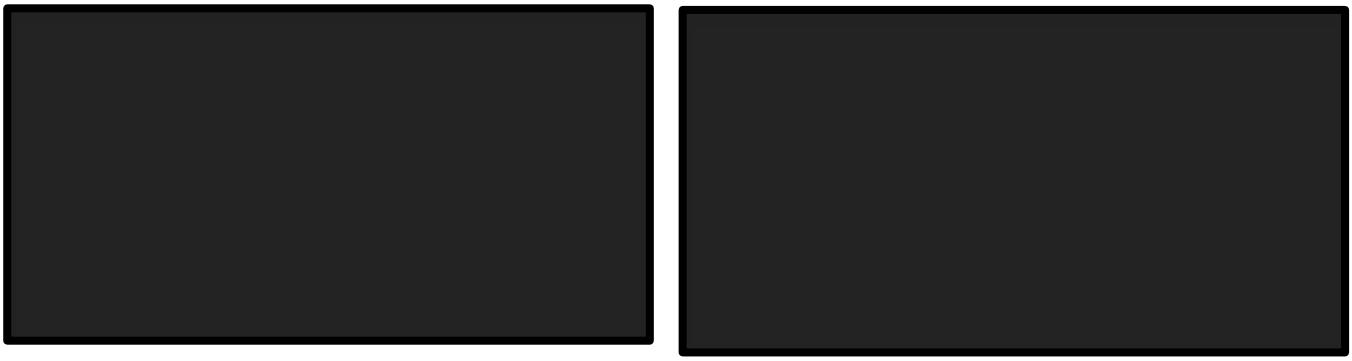
Figure 6: Survival plots for fitted 1-knot spline models (time to pFVC<50%)

Abbreviations: 025, ataluren treatment arm from STRIDE registry; AAPFV50 – age at predicted forced vital capacity <50%; CNG, control arm

Figure 7: Survival plots for fitted 1-knot spline models (time to pFVC<30%)



Abbreviations: 025, ataluren treatment arm from STRIDE registry; AAPFV30 – age at predicted forced vital capacity <30%; CNG, control arm

Table 4: Goodness-of-fit statistics for flexible spline models

Outcome	Model*	025 – AIC	025 – BIC	CNG – AIC	CNG – BIC	AIC	BIC
Time to LoA	Spline hazard K = 1						
	Spline odds K = 1						
	Spline normal K = 1						
	Spline hazard K = 2						
	Spline odds K = 2						
	Spline normal K = 2						
	Spline hazard K = 3						
	Spline odds K = 3						
	Spline normal K = 3						
Time to pFVC<50%	Spline hazard K = 1			-	-	-	-
	Spline odds K = 1						
	Spline normal K = 1						
	Spline hazard K = 2	-	-	-	-	-	-
	Spline odds K = 2						
	Spline normal K = 2						

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Outcome	Model*	025 – AIC	025 – BIC	CNG – AIC	CNG – BIC	AIC	BIC
	Spline hazard K = 3	-	-	-	-	-	-
	Spline odds K = 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline normal K = 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to pFVC<30%**	Spline hazard K = 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline odds K = 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline normal K = 1	-	-	[redacted]	[redacted]	-	-
	Spline hazard K = 2	-	-	-	-	-	-
	Spline odds K = 2	-	-	-	-	-	-
	Spline normal K = 2	-	-	-	-	-	-
	Spline hazard K = 3	-	-	-	-	-	-
	Spline odds K = 3	-	-	-	-	-	-
	Spline normal K = 3	-	-	-	-	-	-

Notes: *Colour coding: best statistically fitting model; within 2; within 5. **Only spline models with one internal knot can be fit to time to pFVC<30% data due to the low number of events.
Key: 025, ataluren treatment arm from STRIDE registry; CNG, control arm; AIC, Akaike information criterion; BIC, Bayesian information criterion; LoA, loss of ambulation; pFVC, predicted forced vital capacity

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Table 5: Comparison of goodness-of-fit between best fitting spline and independent survival models

Outcome	KM median survival (years)	Survival analysis	Modelled median survival (years)	AIC	BIC
Time to LoA (ataluren+BSC)	[redacted]	Log-logistic (standard parametric)	[redacted]	[redacted]	[redacted]
		Proportional hazards spline	[redacted]	[redacted]	[redacted]
Time to LoA (BSC)	[redacted]	Log-logistic (standard parametric)	[redacted]	[redacted]	[redacted]
		Proportional odds spline	[redacted]	[redacted]	[redacted]
Time to pFVC<50% (ataluren+BSC)	[redacted]	Log-logistic (standard parametric)	[redacted]	[redacted]	[redacted]
		Proportional normal spline	[redacted]	[redacted]	[redacted]
Time to pFVC<50% (BSC)	[redacted]	Log-logistic (standard parametric)	[redacted]	[redacted]	[redacted]
		Proportional odds spline	[redacted]	[redacted]	[redacted]
Time to pFVC<30% (BSC)	[redacted]	Log-normal (standard parametric)	[redacted]	[redacted]	[redacted]
		Proportional hazards spline	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; BSC – best supportive care; LoA – loss of ambulation; pFVC – predicted forced vital capacity

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Figure 8: Comparison of best fitting standard parametric model (log-logistic) and flexible (hazard spline) model against observed KM data - Time to LoA (BSC+Ataluren)

Abbreviations: LoA – loss of ambulation; KM – Kaplan Meier

Figure 9: Comparison of best fitting standard parametric model (log-logistic) and flexible (odds spline) model against observed KM data - Time to LoA (BSC)

Abbreviations: LoA – loss of ambulation; KM – Kaplan Meier

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Figure 10: Comparison of best fitting standard parametric model (log-logistic) and flexible (normal spline) model against observed KM data - Time to pFVC<50% (Ataluren + BSC)

Abbreviations: KM – Kaplan Meier; pFVC – predicted forced vital capacity

Figure 11: Comparison of best fitting standard parametric model (log-logistic) and flexible (odds spline) model against observed KM data - Time to pFVC<50% (BSC)

Abbreviations: KM – Kaplan Meier; pFVC – predicted forced vital capacity

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Figure 12: Comparison of best fitting standard parametric model (log-normal) and flexible (normal spline) model against observed KM data - Time to pFVC<30% (BSC)

Abbreviations: KM – Kaplan Meier; pFVC – predicted forced vital capacity

Figure 13: Survival modelling using flexible analyses of best fit in the ataluren+BSC-treated population

Abbreviations: BSC – best supportive care; LoA – loss of ambulation

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Figure 14: Survival modelling using flexible analyses of best fit in the BSC-treated population

Abbreviations: BSC – best supportive care; LoA – loss of ambulation

Table 6: Incremental cost-effectiveness ratio of ataluren vs. BSC using independent or flexible survival models

Survival modelling approach	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£)
Independent analysis	BSC							
	Ataluren + BSC							
Flexible analysis	BSC							
	Ataluren + BSC							

Abbreviations: BSC – best supportive care; ICER – incremental cost effectiveness ratio; LYG – life years gained; QALY – quality adjusted life year

Table 7: Summary of change in TFTs from baseline to week 28 and 52 in Study 030[11]

	TFTs			
	Baseline (N=14)	**Week 28[a,b] (N=13)**	**Week 52 (N=14)**	**Change from baseline to Week 52 (N=14)**
Time to run/walk 10 metres, s (SD)	6.6 ( )	5.9 ( )	6.2 ( )	-0.4 ( )
Time to climb 4 stairs, s (SD)	7.1 ( )[c]	5.3 ( )	4.5 ( )	-2.6 ( )
Time to descend 4 stairs, s (SD)	7.5 ( )[c]	6.5 ( )[d]	5.3 ( )[d]	-2.2 ( )[d]

Time to Stand from a Supine Position, s (SD)	7.1 ([redacted])	4.3 ([redacted])	4.1 ([redacted])	-3.0 ([redacted])

Abbreviations: TFT – timed function test; SD – standard deviation
[a] Baseline TFT measure for week 28 time point 7.1; [b] After the original analysis TFT results were re-examined with data from one subject removed as a result of data being of questionable reliability due to poor listening; [c] N=13; [d] N=12

Table 8: Summary of change in NSAA scores from baseline to week 28 and 52 in Study 030[11]

NSAA[a]	
NSAA 16-item total Score	
Baseline, mean (SD). N=14	16.2 ([redacted])
Week 28, mean (SD), N=13	19.8 ([redacted])
Increase from Baseline to Week 28, mean	3.8
Week 52, mean (SD), N=13	21.5 ([redacted])
Increase from Baseline to Week 52[b], mean	5.5
NSAA 8-item Score[c]	
Baseline, mean (SD). N=14	10.5 ([redacted])
Week 28, mean (SD), N=13	12.1 ([redacted])
Increase from Baseline to Week 28, mean (SD)	1.5 ([redacted])
Week 52, mean (SD), N=14	12.8 ([redacted])
Increase from Baseline to Week 52, mean (SD)	2.3 ([redacted])
NSAA 3-item Score[d]	
Baseline, mean (SD). N=14	5.4([redacted])
Week 28, mean (SD), N=13	5.8 ([redacted])
Increase from Baseline to Week 28, mean (SD)	0.5 ([redacted])
Week 52, mean (SD), N=14	5.6 ([redacted])
Increase from Baseline to Week 52, mean (SD)	0.3 ([redacted])

Abbreviations: NSAA – North Star ambulatory assessment; SD – standard deviation
[a] After the original analysis TFT results were re-examined with data from one subject removed as a result of data being of questionable reliability due to poor listening; [b] Baseline value of 16.0 was used for change in NSAA Week 52 calculation. [c]3-item NSAA function scale = the ability to stand, walk 10 metres, and go from sitting in a chair to standing; [d]8-item NSAA function scale = stand, walk 10 metres, go from sitting in a chair to standing, climb a step (with the right and left foot), get to a sitting position, jump, and run

Table 9: Delphi panel results from 6 experts relating to patients in an ambulatory state[22]

	Ataluren	**BSC**
How the patient has been feeling		
Happy and interested in life.	[redacted]	[redacted]
Somewhat happy.	[redacted]	[redacted]
Somewhat unhappy.	[redacted]	[redacted]
The pain and discomfort the patient has experienced		
Free of pain and discomfort.	[redacted]	[redacted]
Mild to moderate pain or discomfort that prevented no activities.	[redacted]	[redacted]
Ability of the patient to walk		
Able to walk around the neighbourhood without difficulty, and without walking equipment.	[redacted]	[redacted]
Able to walk around the neighbourhood with difficulty;	[redacted]	[redacted]

	Ataluren	BSC
but did not require walking equipment or the help of another person.		
Ability of the patient to use their hands and fingers		
Full use of two hands and ten fingers	[redacted]	[redacted]
Limitations in the use of hands or fingers; but did not require special tools or the help of another person.	[redacted]	[redacted]

Abbreviations: BSC – best supportive care

Table 10: Delphi panel results from 9 experts relating to patients in an ambulatory state[23]

	Ataluren	BSC
How the patient has been feeling		
Happy and interested in life.	[redacted]	[redacted]
Somewhat happy.	[redacted]	[redacted]
The pain and discomfort the patient has experienced		
Free of pain and discomfort.	[redacted]	[redacted]
Mild to moderate pain or discomfort that prevented no activities.	[redacted]	[redacted]
Ability of the patient to walk		
Able to walk around the neighbourhood without difficulty, and without walking equipment.	[redacted]	[redacted]
Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.	[redacted]	[redacted]
Able to walk around the neighbourhood with walking equipment, but without the help of another person.	[redacted]	[redacted]
Ability of the patient to use their hands and fingers		
Full use of two hands and ten fingers	[redacted]	[redacted]
Limitations in the use of hands or fingers; but did not require special tools or the help of another person.	[redacted]	[redacted]

Abbreviations: BSC – best supportive care

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Table 11: Function loss of NSAA items in DMD patients at Week 72, receiving ataluren or BSC treatment in Study 041[7]

	Ataluren (N, %)	BSC (N, %)	Relative risk reduction
Stand	[redacted]	[redacted]	0.36
Walk (10 metres)	[redacted]	[redacted]	0.36
Stand up from chair	[redacted]	[redacted]	0.01
Stand on one leg - right	[redacted]	[redacted]	0.05
Stand on one leg – right	[redacted]	[redacted]	0.08
Climb box step – right	[redacted]	[redacted]	0.44
Descend box step – right	[redacted]	[redacted]	0.18
Climb box step – left	[redacted]	[redacted]	0.40
Descend box step – left	[redacted]	[redacted]	0.09
Lifts head	[redacted]	[redacted]	0.35
Gets to sitting	[redacted]	[redacted]	0.43
Rise from floor	[redacted]	[redacted]	0.10
Stand on heels	[redacted]	[redacted]	0.09
Jump	[redacted]	[redacted]	0.08
Hop right	[redacted]	[redacted]	0.18
Hop left	[redacted]	[redacted]	0.17
Run (10 metres)	[redacted]	[redacted]	0.22

Abbreviations: DMD – Duchenne Muscular Dystrophy; N – number of patients; NSAA – North Star Ambulatory Assessment

Table 12: Change in PUL score from baseline to Week 72 in DMD patients with baseline 6MWD ≥ 300 metres and < 400 metres, receiving ataluren or BSC treatment in Study 041[24]

	Ataluren (mean)	BSC (mean)	Treatment difference Ataluren vs BSC (mean)	Relative change Ataluren vs BSC (%)
High level: shoulder	-0.47	-0.92	0.45	48.98%
Mid-level: elbow	-0.20	-0.66	0.46	69.58%
Distal: wrist and hand	0.02	-0.03	0.05	173.67%
Total	-0.64	-1.65	1.00	61.01%

Abbreviations: 6MWD – 6-minute walk distance; BSC – Best supportive care; DMD – Duchenne Muscular Dystrophy; PUL – Performance of Upper Limb Module

Table 13: EQ-5D VAS scores in DMD patients at Baseline and Month 1, in Study 041

	Ataluren (n=183) (mean, sd)	**BSC (n=176)** (mean, sd)
n'	[redacted]	[redacted]
Baseline	[redacted]	[redacted]

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Month 1	[redacted]	[redacted]
Change from Baseline to Month 1	[redacted]	[redacted]

Overall health status was evaluated using the visual analogue scale rated from 0 (worst) to 100 (best).
n' = number of subjects with a result at baseline and the specified visit.
Abbreviations: BSC – best supportive care; DMD – Duchenne Muscular Dystrophy; N – number of patients

Table 14: Cause of study and treatment discontinuation in the STRIDE registry as of January 2021

Disposition	**All (N=269) n (%)**
Stop ataluren or changed dose:	[redacted]
Adverse events	[redacted]
Family/participant request	[redacted]
Non-response	[redacted]
Physician decision	[redacted]
Loss of ambulation	[redacted]
Other	[redacted]

Abbreviations: N – number of patients

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Muscular Dystrophy UK and Action Duchenne** This response has also been endorsed by Patient Experts Katherine Wedell and Mark Silverman and is based on engagement with families living with Duchenne muscular dystrophy with experience of ataluren (see comment 1 for survey information).
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that the conclusions of the ECD do not reflect the impact of living with Duchenne muscular dystrophy or the benefits that patients and caregivers experience from receiving ataluren. Throughout the appraisal process we have liaised closely with families in receipt of ataluren and have built our responses based on the input we have received from them. For this response we once again reached out to families through a survey and through a virtual community briefing session held on 5 October 2022. The survey received 17 responses, 100% of which were from parents of a child with Duchenne muscular dystrophy. One family were not in receipt of ataluren. 18% of responses related to a child aged 2-4; 12% related to a child aged 5-9; 35% related to a child aged 10-14; 24% related to a child aged 15-19; 12% related to a child aged over 19. Of the families in receipt of ataluren, 23% had begun receiving it at age 2; 15% had begun receiving it at age 5; 8% had begun receiving it at age 6; 15% had begun receiving it at age 7; 8% had begun receiving it at age 8; 8% had begun receiving it at age 9; 8% had begun receiving it at age 10; 15% had begun receiving it at age 11. In terms of duration on the treatment, 8% had been receiving ataluren for <1 year; 8% had been receiving ataluren for 2 years; 8% had been receiving ataluren for 3 years; 8% had been receiving ataluren for 4 years; 8% had been receiving ataluren for 5 years; 46% had been receiving ataluren for 6 years; 15% had been receiving ataluren for 9 years.
2	We welcome the recognition in the ECD of both the clinical effectiveness of ataluren and that the treatment is likely to slow the progression of Duchenne muscular dystrophy. We also welcome the recognition that ataluren has a positive impact on the lives of people receiving it and on caregivers and that the ECD recommends that anyone currently receiving ataluren should continue to do so after the Managed Access Agreement ends in January 2023
3	We are, however, very concerned by the fact that the ECD does not recommend that ataluren should be made available for people diagnosed after January 2023. This is the only treatment available to people with Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene, and the decision is counter to the evidence we have presented throughout the appraisal process on the impact of the lived experience of Duchenne muscular dystrophy; or of the positive impact of the treatment that is experienced by both patients and caregivers.
4	We are highly concerned by the suggestion in the ECD that an ambulant patient receiving ataluren is not experiencing any additional quality of life differences from the treatment when compared to an ambulant patient with Duchenne muscular dystrophy not in receipt of the treatment. Our technical engagement response presented clear evidence from the community on this point, and we explored this once again in the community survey used to help shape this response; 75% of responses to this most recent survey related to a child

	who is still ambulant. 93% of respondents to this part of the survey either disagreed strongly or disagreed with the ECD conclusion that there was unlikely to be 'significant quality of life differences' between an ambulant person with Duchenne muscular dystrophy who is receiving ataluren; and an ambulant person with Duchenne muscular dystrophy who is not receiving ataluren. 100% of survey respondents on this issue stated that ataluren had meant their child required less supervision or support when walking; enabled their child to have more stamina when walking; enabled their child to have more stamina to complete everyday tasks e.g. dressing; and stated that improvements to their child's mobility as a result of taking ataluren had benefitted them psychologically. 88% of survey respondents on this issue said that ataluren had enabled their child to walk with greater stability; 88% said it had reduced the risk of falls and associated fractures when walking; 75% of survey respondents on this issue said that ataluren had enabled their child to walk at greater pace and/or keep up with their peers; and 63% also said that ataluren made their child more confident about the future. 63% felt that ataluren had improved their child's mobility and/or quality of life in other ways, including allowing participation in sporting activities and improving behaviour. *"Translarna has immensely improved our child's health and quality of life. Other Duchenne children, whom we know of the same age, are completely wheelchair-bound; often bed-bound and have undergone several major surgeries, including tendon cutting and spinal fusion; our boy has not had any surgical interventions, and he is nineteen, still walking quite well and able to enjoy social activities, like disability cricket and swimming, attending shows and concerts, travelling abroad for holidays, etc".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"The view expressed by the NICE committee is illogical and too simplistic. Walking is a daily struggle for children with Duchenne, physically and emotionally. If they are receiving the drug, the walking experience is transformed. There are clearly walking-related quality of life improvements for those who are receiving the drug and are still ambulant".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"Definitely an improved quality of life. [Child's name – still ambulant] knows he is receiving the medication available for his condition, rather than feeling he is not receiving the treatment he needs, which is a psychological benefit. His ability to keep up with his peers and feel 'normal' also has a positive impact on his wellbeing"*. Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Translarna has given my child much more independence. We saw no benefit from physio and no changes in his physical development until he started taking Translarna. He is now able to walk much faster for longer, climb the stairs, get in and out of bed and get up from the floor without support. I am confident in the next few months he will be able to run; most children with Duchenne will never be able to run".* Parent of child aged 2-4, in receipt of ataluren for 4 months.
5	We are concerned that the way in which caregiver quality of life has been treated in the ECD drastically underplays the essential benefit that ataluren brings to caregivers. We have presented clear and compelling testimony from caregivers about the crucial positive impact that ataluren has on their quality of life throughout the appraisal process (including but not

	limited to their mental health, their ability to continue with work and the delaying of adaptation costs) and we explored this once again in the community survey used to help shape this response. The impact we set out cannot be captured quantitatively; and it is imperative that this does not mean it is overlooked. While we recognise the challenges of quantitatively assessing this, it is not clear how the qualitative approach that has been taken on this issue has been meaningfully incorporated into the conclusions of the ECD. Some of the benefits to caregiver quality of life that were shared with us by the community, such as hope and reduction in anxiety, are of huge significance on an individual level but are simply too complex to measure or quantify in the evaluation process as it is currently structured. Respondents to our survey raised concerns that failure to suitably measure caregiver quality of life undermines the overall evaluation process and risks discriminating against patients. They also emphasised the need to give full weight to the experience of caregivers themselves. 93% of survey respondents were either 'very concerned' or 'concerned' by the approach taken in the ECD, with the remaining 7% saying they 'didn't know'. Survey respondents were asked, in light of the challenges faced in assessing this in a quantitative way, how they thought quality of life impacts for caregivers could be measured. *"If caregiver quality of life improvements cannot be measured, resulting in it not being factored into cost-effectiveness calculations, this undermines the overall evaluation process for Translarna. The benefits for caregivers for the drug are significant given the severity of the condition, the burden on those providing daily care and the absence of any other treatments for Duchenne - it is a relentless, degenerative and life-limiting condition. A suitable way of measuring the benefits for caregivers needs to be used for the evaluation of Translarna; otherwise the process risks discriminating against patients by not properly measuring cost-effectiveness".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"I think it should be based alone on what the care giver says; if they say it has positively impacted their life and they have given a reason that should be enough!".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. Respondent also reiterated some of the essential benefits that ataluren has brought to them as caregivers. *"As Translarna has given our child a degree of very good health, he is able to attend college three days a week and to go out one afternoon a week without us. As the main caregiver, this means that I have some respite during this time to meet a friend for lunch, go swimming/for walks, or just to rest and relax. This enables me to continue with my caring role without intervention in our household, giving us more privacy as a family. It also helps me psychologically, as it gives me time to be 'me' for a while".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. Several respondents shared a range of caregiver quality of life impacts that simply may not be measurable. *"I believe that I have less physical health problems than would be expected of a person of*

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

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	my age (I am 65) and less psychological issues, because our boy is keeping so well, due to Translarna, as it takes a tremendous amount of pressure off of me. He has had no hospitalisations or medical emergencies, and that also places less demands on me". Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"Translarna gives us hope. I believe without this drug my son would not be doing as well as he is now. There are less falls, he is able to walk without it I don't think he would be as strong. It makes us feel more positive to us it feels like a little miracle drug".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. *"My son has benefited considerably from receiving Translarna. The benefits are not just related to ambulation but also to upper body strength and respiratory strength. This has reduced the extent of hospital admissions, enabled us to maintain a quality of life for ourselves and allowed us to continue working as parents - paying taxes and supporting the economy in the same way as parents who do not have the same carer responsibilities".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"Our experience is that we can live as `normally' as possible - we are happier in the knowledge that [child's name] is getting the most up to date medication for his condition - it is an enormous weight off our minds. We can continue caring for [child's name] feeling he has what he needs, which enables us all to continue with family life and be as close to a 'normal' family as we can".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Since my child has been on Translarna I have so much more hope for the future. I don't have to worry about my child being scared of peers knocking him over".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"I am confident that Translarna has greatly helped my son. This in turn helps with my anxiety about my son's disability… Your child's quality of life impacts a parent carer's quality of life".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"The least parents and children with Duchenne deserve is hope and Translarna has given us that hope. I would not have coped with my child's diagnosis if I hadn't been told about Translarna on the day of his diagnosis. Not providing this medication when it has been proven to help is cruel".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"Having a child that is non ambulant is so much harder physically and mentally on caregivers and other family members".* Parent of child aged 10-14, in receipt of ataluren for 6 years.
6	We are concerned that although ataluren is available for children under 5 years of age, the ECD concludes that the assumed benefits for 2-4 year olds should not be included in its analysis. 100% of survey respondents either disagreed or strongly disagreed with this position, which seems to run counter to the recognition in the ECD itself that "Dystrophin production is usually affected from birth and symptoms of DMD often appear by age 3 years". 18% of respondents were parents of a child currently aged 2-4 and 23% of respondents were parents of children who had begun receiving ataluren before the age of 4.

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	"Our boy was diagnosed at the age of two and some are diagnosed during pregnancy now. Our boy was delayed in all his milestones: turning over, sitting up, crawling and walking. He was far below the normal achievement range for his age and I wish Translarna had been available to help him then". Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"I think it is relevant to include ALL children on Translarna. My son was diagnosed at 11 months old so we was able to start Translarna at 2. Our experience on Translarna is so amazing and so beneficial to be included as it was such a positive experience".* Parent of child aged 2-4, in receipt of ataluren for nearly 3 years. *"If children are typically diagnosed with Duchenne at age 4 (or sometimes younger), it is wrong to exclude all age years between 2 and 4 when assessing the benefits of Translarna. Excluding the benefit for 4-year-olds, the average age of diagnosis, risks supressing the overall cost-effectiveness calculation for Translarna".* Parent of child aged 15-19, in receipt of ataluren for over 6 years. *"We feel that it's due to how early [child's name] started Translarna that he remains so well now - if it should be diagnosed earlier than age 4 then the benefits for children aged 2-4 ought to be included as a benefit in the analysis".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"A lot of work is being done to ensure that Duchenne is part of newborn screening by the World Duchenne Organisation and other organisations; my son was diagnosed at 3 and I know plenty of other families where children were diagnosed under 2 years of age. I feel it imperative to look at the average age of diagnosis - much like an increase in life expectancy I believe we see a decrease in the age of diagnosis".* Parent of child aged 10-14, not in receipt of ataluren. *"Most parents will recognise Duchenne very early on. I recognised my child was behind in his physical development from 9 months of age. We received a diagnosis at 2 years of age. There is absolutely no reason why a 4 year old would not be diagnosed yet!".* Parent of child aged 2-4, in receipt of ataluren for 4 months. *"This doesn't take account of children diagnosed at early age, due to mother being a carrier or family history. This is unfair".* Parent of child aged 10-14, in receipt of ataluren for 6 years.
7	We are concerned that there could be some wider cost benefits of ataluren that have not been taken into account when assessing it's cost effectiveness. Several survey respondents and one participant in a community briefing session held by MDUK and Action Duchenne on 5 October 2022 spoke of needing far fewer medical interventions linked to their Duchenne muscular dystrophy than peers not receiving ataluren. *"I strongly disagree with the assertion that Translarna isn't cost-effective, as the cost of surgeries and hospitalisations/additional care and support services, etc. that are necessary in the deterioration suffered by boys with Duchenne muscular dystrophy is extremely high also, and the cost to quality of life for both sufferers and carers just cannot be measured in monetary terms, although the ability to continue to provide long-term care at home by family*

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	members does save the government a massive amount of money". Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"I believe that I have less physical health problems than would be expected of a person of my age (I am 65) and less psychological issues, because our boy is keeping so well, due to Translarna, as it takes a tremendous amount of pressure off of me. He has had no hospitalisations or medical emergencies, and that also places less demands on me".* Parent of child aged 15-19, in receipt of ataluren for 6-9 years. *"Duchenne muscular dystrophy comes with a significant burden on the family, NHS network in terms of cost and time. My son does not take Translarna as unfortunately his mutation cannot be treated with Translarna. I would urge that if this is a cost issue then NICE / NHS England works with PTC to lower the price where it is believed would be cost effective".* Parent of child aged 10-14, not in receipt of ataluren.
8	We welcome the ECD's recognition of ataluren as an innovative treatment and are therefore concerned that despite its recognition that it is both clinically effective and that it is likely to slow the progression of Duchenne muscular dystrophy, as well its recognition of the positive impact on the lives of people receiving it and on caregivers, the ECD does not recommend it for patients diagnosed after January 2023. The rare disease community is reliant on the development of innovative treatments, which are highly likely to be relatively expensive, and we are concerned that innovation will be stifled and access to future treatments across a wide range of rare diseases will be made less likely if treatments such as ataluren are not made available.
9	We are concerned that the ECD's recommendation that ataluren should not be made available to newly diagnosed patients after January 2023 despite its recognition that it is both clinically effective and that is likely to slow the progression of Duchenne muscular dystrophy, as well its recognition of the positive impact on the lives of people receiving it and on caregivers, could be discriminatory on the grounds of age and disability; both protected characteristics under the Equality Act 2010.
10	We recognise the difficult role of the Committee and NICE more broadly in decisions about access to treatments. In representing the community, it is important that we highlight the frustration felt by many that an effective treatment will not be made available based on cost effectiveness. *"Money should not be an issue in relation to children's lives. Especially when the drug is proven to work!".* Parent of child aged 10-14, in receipt of ataluren for 6 years. *"Please don't let this come down to cost. You can't put a price on a child's life".* Parent of child aged 10-14, in receipt of ataluren for 6 years. We urge NICE to work with PTC to find a solution that ensures that ataluren can be made available to patients diagnosed after January 2023 and for all parties to show flexibility to enable this. We reiterate the point made in our Technical Engagement response that 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

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	committee accepted the uncertainties[1]". We feel that this is a positive pragmatic approach and one that would be applicable in this instance.

Insert extra rows as needed

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[1] https://www.nice.org.uk/guidance/gid-ta10876/documents/final-appraisal-determination-document

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Action Duchenne
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Katherine Wedell

Comment number	Comments

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Example 1	We are concerned that this recommendation may imply that ……..
1	The committee concluded that treatmentdependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory health states. In my opinion as a parent, this conclusion does not adequately reflect the evidence from patients' experience including that of my family. • Stamina – the evidence from the 6mwd may not have adequately captured the capacity of patients on ataluren to keep going for longer than those on best supportive care. Compared to his walking before he started taking ataluren, once on ataluren our son had more stamina, i.e. he was able to keep going for a longer time when walking. That meant he was able to do things that are very significant, for example keep going with his peers in the playground, or climb a hill and gaze out at the view. • Energy - not only could he keep going for longer, but he also had more energy than he had had before for additional activities over the week, such as swimming and an after-school club. Before he took ataluren, he would be too tired for these additional activities, thus limiting his social contact, fitness, and self-development. • Psycho-social benefits - extra years of ambulation lead to knock-on psycho-social benefits additional to those related simply to ambulation. Thanks to ataluren, my son is able to look back on years of meaningful daily experiences of inclusion, for example going to the playground after school with the other children and going round to friends' houses. He can draw on years of being out in the natural world, with all of its well-known psychological benefits. Just yesterday we were recalling a walk in the hills when we went wild swimming by a waterfall. Extra years of ambulation made possible that psychological foundation of inclusion and being out in the natural world and as a result have had a lasting impact on his self-esteem and wellbeing • If you're still walking into your teenage years, you're able to accrue significant social benefits at this crucial formative time in life. As a teenager, if you can sit on the sofa with someone, and hang out at friends' houses, you are at a significant psycho-social advantage in comparison with someone who uses a powered wheelchair full time. Friendships, relationships, and a positive self-image are crucial aspects of teenage development. Friends don't invite you round to their houses if they know you can't get in, and without such social opportunities, those friendships and potential relationships, and the foundational emotional wellbeing that they provide, are in danger of falling away. • Cost benefit of fitness for longer – if people living with DMD are walking, they are fitter and have the health benefits of that fitness. If walking continues for more years, that is likely to lead to fewer physical complications over years, requiring less medical intervention and fewer hospital admissions, and therefore resulting in a cost benefit to the health service for longer.
2	The committee concluded that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way.

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	I am concerned that this decision should give appropriate weighting to the qualitative evidence of the impact of ataluren on caregivers. • Even apparently marginal benefits in mobility over longer timescales than would otherwise be the case make a significant difference to the quality of life of caregivers. Transfers using a hoist take much longer than if a person can weight-bear briefly or transfer using a sliding board. If you're supporting transfers from bed to chair, or chair to shower chair, six times a day, and each of those transfers take two minutes instead of fifteen minutes, that is 12 minutes spent on supporting transfers rather than an hour and a half. If a person can shift their weight to take off or put on clothes while sitting on a shower chair, you can also cut out two additional transfers, from wheelchair to bed/changing table and then to shower chair. That's another chunk of time you're not spending on care work twice a day. • If a person can also feed themselves and has the upper body strength to get themselves a snack, that's another roughly three and a half hours a day saved on care support. • If a person stays in a stable health state for longer, that reduces significantly the impact of all the admin and training involved in caregiving. Getting your head around each stage of a progressive condition is a lot of work. • If those benefits continue for additional years, you're talking about a different kind of life that families are living over years – one that is not dominated by care work. This has very significant impacts. • Caregivers are able to go out to work. Caregivers can be financially independent. They can have a life beyond care work, with all the mental health benefits that brings. • Family relationships aren't skewed by care needs. Relentless need and relentless care duties can lead to mental health crises, to abuse, and to family breakdown. • If a person does not have the upper body strength to feed themselves, that means that either you can't have a family meal with everyone eating together, or you have a carer coming in to help the person eat. Both of those can tear the fabric of family life.
3	In my experience, the evidence of the impact of ataluren beyond direct health benefits needs to include significant cost savings in social care, dependence on state benefits, and the wider economy. • When our son was able to transfer using a sliding board, rather than a hoist, he was awarded **5 hours per week** funded care support from the local authority through direct payments. Now that he needs hoisted transfers, he has been awarded **52.5 hours per week** funded care support from the local authority – ten times more care support. Currently our son aged 18 can feed himself, does not need peg feeding, does not need additional ventilation, and is able to shift position in bed during the night and meet his own toileting needs overnight. If he did need this additional support, he would need **24/7 care support – 168 hours per week.** • Reducing the burden of care on caregivers significantly reduces the stress on families. Stress has cost implications for families and the wider economy, in terms of mental health and work days lost • The difference between care work taking minutes versus hours, plus the time saved on planning and admin when a patient's condition is stable for longer, is the difference between parents being able to work or not work.
4	I welcome NICE's recognition that ataluren is effective. The interpretation of the evidence needs to take into account that uncertainty of evidence is in the nature of investigating treatments for rare

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	conditions including DMD where sample sizes are small. Our son was on Study 020; his walk speed stabilised for a year and then declined at a slower rate than before the study (he was on the active drug during the study). Given that ataluren is an orphan drug for a devastating condition in a situation where statistically significant evidence is challenging to identify: in this situation the uncertainty of evidence needs to be weighted in relation to the very significant need of patients and the recognition that the drug is effective.
5	I am concerned that the provisional recommendation should give appropriate weighting to the fact that the drug is innovative, reflecting the following points: • The community of people living with rare diseases with no currently known effective treatment relies on innovative medicine. Innovative medicine is always going to be more expensive than other medicines. Not funding innovative medicine disproportionately affects families like ours living with a rare condition. • Funding innovative medicine supports investment, research, and development into innovative medicine and so benefits the economy more widely.
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Action Duchenne
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Mark Silverman

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

Consultation on the evaluation consultation document – deadline for comments 5pm on 21 October 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The committee's acknowledgement around the efficacy of Ataluren is welcomed but I cannot support the conclusion of the committee in paragraph 3.9 that 'treatment-dependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory'. This represents an over-simplistic and binary understanding of the reality of the ambulatory health state in Duchenne. For patients living with Duchenne (LWD), and their carers, the *quality* of ambulation is critical and the benefits of Ataluren, in improving the ambulatory experience, must be compared to the experience for those LWD who are not receiving the drug during the ambulatory health state. It is unreasonable and irrational to disregard the benefits of *improved* ambulation when attributing utility values to the ambulatory health state in Duchenne; from our own personal experience and others whose children have received the drug, Ataluren has demonstrated benefits in relation to the actual quality of ambulation including: - Stamina: the quality of ambulation cannot be measured through a test which only captures distance walked over 6 minutes. The greater stamina which Ataluren has provided for those LWD means that that more experiences can be enjoyed, compared to those who may still be in the ambulatory health state but who are not receiving the drug. This is a direct consequence of receiving the drug. We know from our own experience that our son played more football outside – with family and friends - when he was receiving the drug than when (we subsequently discovered) he had been previously receiving the placebo. This was at an age when those LWD, whilst still potentially ambulatory, would be seeing their overall mobility rapidly *declining*, including their ability to participate in ambulatory-based sport. The increased stamina levels when taking Ataluren in the ambulatory health state form a key part of the improved ambulatory experience compared to those who are not receipt of the drug. - Stability when walking: Our son's ability to walk with greater stability and balance, following commencement of treatment with Ataluren, meant that he was less prone to falls with the associated risk of fractures, given the reduced bone density caused by long-term steroid use. This is one of the greatest fear of parents/carers and their children because fractures in Duchenne can accelerate or directly lead to the end of ambulation; fractures require hospital interventions and also present other risks including, for example, fat embolism syndrome. We were hugely grateful and relieved that our son did not experience limb fractures. There are children LWD whose walking is so unsteady and have such a risk of falls and fractures, that they have expressed some relief when they are no longer ambulatory and can rely on a wheelchair. The quality of the ambulatory experience for those LWD as they get older, when it is continuously linked to a greater likelihood of fractures, differs from those receiving Ataluren and who have greater stability and balance when walking.

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	- Keeping up with peers: Children LWD typically walk much more slowly than those who do not have Duchenne. The physiological effects of Duchenne mean that as they get older, typically from age 7, children LWD literally lag behind their friends and peers at school. This in itself makes the walking experience frustrating and demoralising as able-bodied children become physically stronger and quicker. Ataluren has meant children like my son have been able to keep up with their peers for longer when walking and playing (in the playground and participating in sports and physical education) compared to those LWD who are not receiving the drug but are still in the ambulatory health state. Outdoor play and socialising, particularly in between lessons at school, is not a sedentary activity and as children LWD get older, the ability to keep up with friends so that these experiences can be shared is significant. It is simplistic and counter-intuitive to discount treatment-dependent utility values for children LWD who are still walking and are in receipt of the drug. - More independent walking: Greater stability and balance when walking also reduces the need to hold onto a rail or hold onto someone's hand when walking. Our son did not need to hold an adult's hand in school when walking which itself had psychological benefits, given the desire to 'fit in' at mainstream school. It meant his teaching assistant did not need to be 'velcroed' to him wherever he went but could walk nearby, giving him more dignity and a greater feeling of independence. This would not have been the case if he was not receiving Ataluren. - Pyschological benefits: The psycho-social benefits associated additional years of *improved* ambulation compared to those not in receipt of Ataluren, show that it not just the impact on walking during the ambulatory health state which need to be factored into utility values. Our son's mental health and emotional well-being was enhanced through taking Ataluren and being able to participate in the same activities and experiences as his peers with minimal need for adjustments or concessions – inside and outside of school. This included youth clubs, cub scouts and after-school arrangements at friends' house; some of these activities were on the upper floor of buildings with no lift but for many years he was able to access these facilities. The impact of Ataluren on our son's ambulation has meant he could experience a more inclusive childhood and adolescence – well into his teenage years - with direct, positive consequences for his emotional well-being. - Other health benefits: Children LWD who are in receipt of Ataluren during the ambulatory health state will be more mobile for more of the day and over a longer period of time. Children and teenagers LWD who struggle to walk, but are still classified as ambulatory, will invariably be less active impacting on their overall fitness, weight (exacerbated by steroids) and general physical and mental health. This reduces and/or delays the considerable financial costs associated with hospital admissions, medical equipment and other interventions which are typically required as children LWD enter their teens.
2	I do not support the conclusion of the committee in paragraph 3.10 'that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way.'

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	The benefits for caregivers from Ataluren have previously been highlighted in the submissions from patients, patient organisations and clinical experts. These are significant given the absence of any other approved treatments for those LWD but although the substantial impact on caregivers is acknowledged by the committee in paragraph 3.2, it is concerning that the committee has simply recommended that caregiver QALYs should be calculated qualitatively. The committee has highlighted certain issues with the calculation of caregiver QALYs whilst also highlighting that the ECD refers to 'apparent difficulties between differences between the outcomes of the EAG approach and the testimonies of the patient experts in relation to QALY loss for caregivers'. However, caregiver benefits are quite capable of being measured and a range of lived scenarios allow for this to be done, as highlighted in the submission made by myself and others caring for those LWD. Whereas there are measurable quantitative caregiver benefits, there is no clarity about how any 'qualitative way', as described in the ECD, has been or could be included in the recommendations of the committee. For example, my son is nearly 18 and has only recently started to require more regular use of a hoist for transfers, particularly in relation to personal care. Whereas previously, a transfer to or from the toilet or showerchair would only take 2-3 minutes self-transferring or using a commode seat, the safe and comfortable fitting of a sling, use of a hoist and tracking system and other assistance, typically takes around 15 minutes each time, 5-6 times daily. This can take up to an hour and half every day simply to carry out the transfers for personal care. In prolonging ambulation and maintaining upper body strength, the use of Ataluren has delayed by several years the need for this additional 7-10 hours per week of personal care support. Our son still has the upper body strength to feed himself or drink including, for example, going to the fridge, taking out and opening a can of soft drink and pouring the contents into a cup. He does not require ventilation, turning at night or many of the other interventions which would essentially require 24 hour care. Delaying the progression of Duchenne has measurable benefits – in terms of time, financial and health (physical and psychological) costs for caregivers. Clearly these benefits – or health splillovers – do need to be reflected in economic valuations and the issue has been addressed in recently published reviews on the subject[1], including in relation to NICE's own 'reference case' which states that such assessments should include direct health effects for carers.[2] A suitable way of measuring caregiver QALYs needs to be agreed for Ataluren so that these benefits can be appropriately included in actual calculations of cost-effectiveness. This needs to cover both health and non-health benefits given the medical, social and financial costs savings associated with delays to the progression of Duchenne.

[1] Systematic Review of Cost-Utility Analyses That Have Included Carer and Family Member Health-Related Quality of Life, A. Scope, A. Bhadhuri and B. Pennington (2022)
[2] Inclusion of Carer Health-Related Quality of Life in National Institute for Health and Care Excellence Appraisals, B. Pennington (2022)

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3	I do not support the conclusion of the committee in paragraph 3.8 that 'it would not include the additional assumed treatment benefits related to early treatment of ataluren in its preferred analysis.' There is currently limited data in the under 5 age group because the label change, allowing for use of Ataluren in this age group was only agreed in 2018 and more recently in other territories. The typical age at which a DMD diagnosis is made in England is stated by the committee as being 4 years. Even on the basis of an average age of a diagnosis of 4 years, there will be more children – over time – receiving the drug *before* the age of 5. My own son was diagnosed at 2.5 years in 2008 and there are now families in England whose children have started receiving the drug by the age of 3; the committee itself noted in paragraph 3.1 that 'DMD symptoms often appear by age 3. It is not accurate or reasonable, particularly in a life-limiting condition where the age-span of those receiving the drug is already limited, to disregard the assumed treatment benefits for all under 5s.
4	An important aspect of Duchenne which appears to have been overlooked in the ECD are the cognitive and behavioural symptoms associated with the condition and in particular, the higher prevalence of Autism and ADHD amongst those LWD. The EAG touched on the higher rates of autism and obsessive-compulsive disorder for those LWD but the impact of the relentless progression of Duchenne, unchecked without access to Ataluren, is compounded by a diagnosis of Autism and other cognitive impairments. My own son who was diagnosed as having ASD when he was 12, although in many cases an ASM diagnosis for those LWD is made earlier. The anxiety and distress of LWD is often manifested and amplified through debilitating and time-consuming rituals and patterns of behaviour; for example, repetitive handwashing (which occurred well before Covid-hygiene requirements) has not just been time-consuming for my son but also for my wife and I who are sometimes asked to wash our hands repeatedly. Similarly, at times of heightened anxiety, we can be asked an identical question seeking reassurance about a particular point 10-20 times consecutively. We have no doubt that had our son not been receiving Ataluren and the progression of Duchenne accelerated more rapidly, the cognitive and behavioural challenges of LWD would have been even more profound due to his neurodivergence.
5	The conclusion of the committee that Ataluren is innovative is welcomed, together with its recognition of its efficacy and positive impact beyond direct health benefits. As the first drug to be made available in England to address the underlying cause of Duchenne, it is critical that the cost benefits are fairly and accurately assessed in a very small population whose only other option is best supportive care. Innovative treatments for those living with a very rare condition will invariably be more expensive; families affected by the devastating diagnosis of Duchenne must never be penalised due to their small overall number and an initial inability to agree with the company on an appropriate way of measuring its cost effectiveness.

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	Duchenne predominantly affects particularly young people who, with a severe disability, face a shortened lifespan. The draft recommendation set out in the ECD risks adversely impacting on a group, protected by the Equalities Act, for whom there are presently no treatments to address the underlying cause of their condition. .

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

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Addendum: EAG critique of the company's response to the NICE Evaluation Consultation Document

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	31st October 2022

Introduction

In September 2022, the National Institute for Health and Care Excellence (NICE) issued a negative Evaluation Consutation Document (ECD) for ataluren for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (nmDMD) in people aged 2 years and over who can walk.[1] The ECD states that the cost-effectiveness estimates for ataluren are uncertain because of how treatment benefits were estimated in the company's model and due to the limitations of the clinical effectiveness data, and that the costs of ataluren are uncertain. The ECD also states that based on its preferred assumptions, the cost-effectiveness estimates for ataluren are substantially above the range that NICE considers acceptable for highly specialised technologies.[1]

In October 2022, the company submitted a response to the NICE ECD.[2] The company's response includes a written document and a revised base case model which includes some of the Appraisal Committee's preferred assumptions. The company's response document provides additional discussion around seven key factors which impact on the incremental cost-effectiveness ratio (ICER) for ataluren: (i) survival modelling; (ii) early treatment benefit assumptions; (iii) treatment-dependent utility values; (iv) caregiver quality-adjusted life years (QALYs); (v) the stopping rule; (vi) the ataluren discontinuation rate and (vii) the decision modifier. Additional scenario analyses are presented around several of these issues. The company has also increased the Patient Access Scheme (PAS) discount for ataluren to [redacted].

The Appraisal Committee's preferred scenario and the key features of the company's revised base case model are summarised in Table 1. The results of the company's revised base case analysis and additional scenario analyses are summarised in Table 2. The company's revised deterministic base case ICER is [redacted] per QALY gained (decision modifier = [redacted]). The probabilistic ICER is similar at [redacted].

Table 1: Summary of Appraisal Committee's preferred scenario and company's revised model

Aspect of model	Committee's preferred scenario	Company's revised post-ECD model
Survival models	Original base case models: • Age at loss of ambulation - log-logistic • Age at FVC<50% - log-logistic • Age at FVC<30% - log-normal	Distributions applied in company's original base case. Scenario analyses conducted for alternative parametric survival models.
Early treatment benefits	Excluded	Included in base case. Scenario analyses presented in which early treatment benefits are halved or removed.
Patient utility values	Treatment-dependent utility values in non-ambulatory states only.	Treatment-dependent utility values in all states.
Caregiver QALYs	Excluded - to be considered qualitatively.	Caregiver health state utility values excluded. Bereavement-related QALY losses included.
Stopping rule	FVC<30%	FVC<30%
Treatment discontinuation rate	EAG's scenario analysis (STRIDE[3] probability halved [value = [redacted]])	Re-analysis of STRIDE data excluding discontinuations due to loss of ambulation [probability = [redacted]]

ECD - Evaluation Consultation Document; FVC - forced vital capacity; QALY - quality-adjusted life year; EAG - External Assessment Group; STRIDE - Strategic Targeting of Registries and International Database of Excellence

Table 2: Results of company's revised base case and scenario analyses presented in ECD response (excludes QALY weighting)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's revised base case model following ECD (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base case model following ECD (probabilistic)†								
Ataluren+BSC	[redacted]	NR	NR	[redacted]	[redacted]	-	-	
BSC	[redacted]	NR	NR	[redacted]	[redacted]	-	-	
Incremental	[redacted]	NR	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]
SA1: Weibull survival distributions for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA2: 1-knot restricted cubic spline model for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA3: Early treatment benefit removed, ataluren start age = 4 years								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA4: Early treatment benefit reduced by half ([redacted])								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA5: STRIDE discontinuation rate = [redacted]								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA6: Stopping rule at pFVC <50%								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SA7: Company's previous base case at technical engagement (including previous PAS)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SA - scenario analysis; DM - decision modifier; LoA - loss of ambulation; pFVC - predicted forced vital capacity; STRIDE - Strategic Targeting of Registries and International Database of Excellence; NR - not reported
† QALYs accrued by patients and carers are not recorded separately in the company's PSA sub-routine

This addendum provides a critique of the company's ECD response[2] and the company's revised base case model (Section 2) and presents additional exploratory analyses undertaken by the External Assessment Group (EAG) (Section 3). Unless otherwise stated, all ICERs presented in this addendum include the updated PAS for ataluren and exclude QALY weighting associated with the decision modifier. Cost-effectiveness results including QALY weighting are presented in Appendix 1.

2. EAG summary and critique of key points raised in company's ECD response

(i) Survival modelling

Section 3.7 of the NICE ECD[1] states: *"The committee considered that the company's original base case model choices, as used in the EAG's base case analysis, were the most appropriate to use for decision making. However, it noted that the results were uncertain because of the poor fit of the models to the data."*

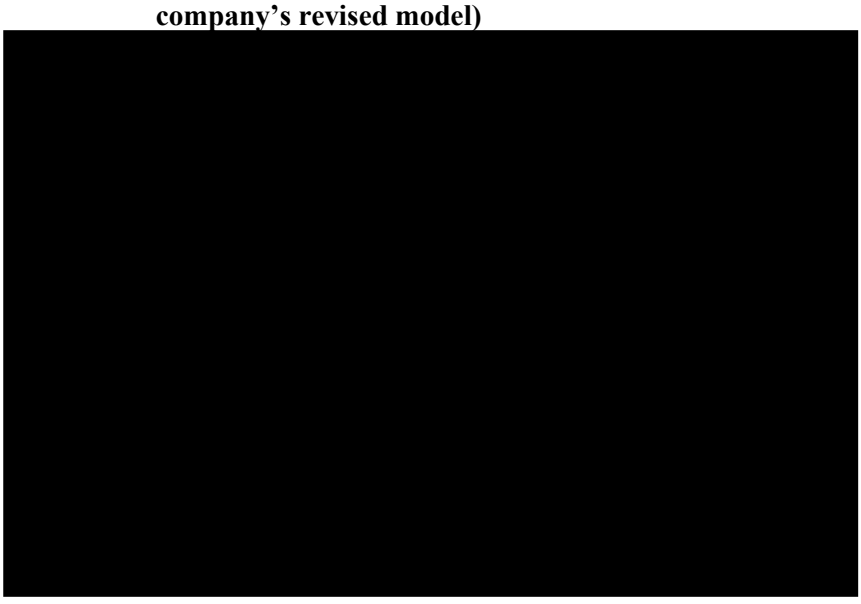
The company's updated base case analysis uses independent log-logistic distributions fitted to time-to-event data on age at loss of ambulation and age at forced vital capacity (FVC)<50% from the Strategic Targeting of Registries and International Database of Excellence (STRIDE) and propensity score-matched Cooperative International Neuromuscular Research Group (CINRG) datasets.[3, 4] Age at FVC<30% is modelled using a log-normal distribution fitted to data from CINRG. This is the same as the company's original base case analysis.[5] The EAG report[6] highlighted concerns that the company had only considered a limited range of parametric survival models and that the models selected for use in the company's base case analysis did not provide a good representation of the observed data, particularly with respect to age at loss of ambulation in STRIDE and time to FVC<50% in STRIDE and CINRG (see EAG report, Section 5.3.5, critical appraisal point [4]). In addition, the EAG's clinical advisors commented that the mean delays in reaching DMD milestones predicted by the company's economic model, which are a function of the selected parametric survival distributions and early/relative treatment benefit assumptions, appear to be optimistic.

The company's ECD response[2] argues that the approach taken in the company's original base case analysis is appropriate. The company's response makes the following points:

- The company argues that the log-cumulative hazard plots for age at loss of ambulation, age at FVC<50% and age at FVC<30% (company's ECD response, Figures 2-4) *"did not show non-straight lines"*; hence, it was appropriate to consider standard parametric models rather than flexible models, based on guidance from NICE Technical Support Document (TSD) Number 14.[7]
- The log-cumulative hazard plots for the ataluren and best supportive care (BSC) groups are not parallel at all time points; hence, it is more appropriate to use independent models rather than jointly-fitted models which assume a constant hazard ratio (HR) or acceleration factor (AF).[7]
- The use of a "re-based" analysis, whereby no events are assumed to occur in the ataluren and BSC groups until after 5 and 3.5 years, respectively, has a very limited impact on the ICER for ataluren versus BSC.
- The log-logistic and log-normal distributions used in the company's original base case analysis are the best-fitting models (amongst the standard parametric models considered in the company's original submission[5]).

- Input from two independent UK clinical experts was used to determine the plausibility of the model predictions beyond the observed period of the data. The experts indicated that the Weibull distribution was the most appropriate function to use for all three endpoints (time to loss of ambulation, FVC<50% and FVC<30%). Weibull distributions were used to model all three endpoints in the company's revised base case at the technical engagement stage of the appraisal.[8] However, the company's revised base case model following the ECD reverts back to the log-logistic and log-normal distributions used in the company's original model, with Weibull distributions considered in additional scenario analyses (see Table 2, company's revised base case, ICER = [redacted] per QALY gained; Scenario SA1 using Weibull distributions, ICER = [redacted] per QALY gained).
- In response to the Appraisal Committee's concerns regarding poor model fit described in the ECD,[1] the company subsequently explored the use of restricted cubic spline (RCS) models using 1, 2 or 3 knots, with models fitted to the log cumulative hazard, log cumulative odds, or the inverse normal survival distributions. The company's ECD response includes a scenario analysis using 1-knot RCS models for each endpoint. The company's ECD response notes that the use of RCS models improved model fit and reduced the ICER for ataluren from [redacted] to [redacted] per QALY gained (see Table 2, Scenario SA2). However, the company's response highlights problems regarding the plausibility of the extrapolation using the RCS models, whereby the modelled survival function for age at loss of ambulation crosses the survival function for age at FVC<50% at around age 23 years (see Figure 1, orange and blue lines), which is logically inconsistent. For this reason, RCS models are not included in the company's revised base case analysis.

Figure 1: Company's model trace using 1-knot RCS models (generated by the EAG using the company's revised model)



RCS - restricted cubic spline; BSC - best supportive care; FVC - forced vital capacity

The EAG notes the following points regarding the company's original and updated survival analysis:

- The company's original survival models did not provide a good representation of the available time-to-event data for some of the modelled endpoints. Plots of the empirical and modelled hazards provided in the company's clarification response[9] also suggested that none of the standard parametric models reflected the shape of the underlying hazard for age at loss of ambulation in STRIDE or for time to FVC<50% in STRIDE and CINRG.[3, 4] The EAG considers it questionable as to whether the log-cumulative hazard plots and/or quantile-quantile plots for age at loss of ambulation and age at FVC<50% suggest straight lines. Therefore, the EAG considers it reasonable to explore the use of more flexible parametric models which might better represent the underlying hazard of reaching each DMD milestone.
- The company's ECD response[2] indicates that clinical experts stated that the Weibull model was the most appropriate distribution for all endpoints. It is unclear when this clinical input was obtained or what was asked of the clinical experts as no details were provided in the company's TE response[8] or ECD response.[2] Without additional information, the EAG is unable to comment further.
- The EAG appreciates that the company has undertaken additional survival analysis to attempt to resolve the issues raised in the EAG report[6] and the NICE ECD.[1] The EAG agrees with the company that the selected RCS models are problematic in this case due to the survival models for age at loss of ambulation and age at FVC<50% crossing.
- Whilst the company has fitted a range of RCS models wth 1, 2 or 3 knots, the executable model only includes functionality to select the 1-knot RCS models. Given the company's concerns regarding the plausibility of the model predictions for the 1-knot models, it would have been useful to explore whether the same problem of crossing curves also applies to the 2- and 3-knot RCS models. The presence and extent of this problem is likely to be dependent on where the knots are placed for each model.
- Given the problems regarding the plausibility of the extrapolations from the RCS models highlighted by the company, the EAG believes that the most reasonable course of action may be to instead rely on the standard parametric survival models which were used in the company's original base case model. However, this means that the EAG's original concerns regarding poor model fit and potential overestimation of overall modelled delays in reaching DMD milestones in the company's original base case analysis still apply to the revised base case analysis.

(ii) Early treatment benefits

Section 3.9 of the NICE ECD[1] states *"The committee therefore concluded that it would not include the additional assumed treatment benefits related to early treatment of ataluren in its preferred analysis."*

The company's revised base case analysis retains the company's original assumptions regarding early/relative treatment benefits, whereby the modelled survival distributions are shifted 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 (note – the shift in FEV<30% includes a [redacted]-year gain in relative effect versus BSC and a [redacted]-year gain associated with early treatment with ataluren).

The company's ECD response[2] highlights the following points in support of the assumptions of early treatment benefits and the age of ataluren initiation in the company's economic model:

- The license for ataluren was extended to the 2-4 year age group in 2018.[10] As such, the mean age of patients in STRIDE[3] is older than would be expected in current clinical practice, and the duration of follow-up in STRIDE for the [redacted] patients who initiated ataluren at age 2-4 years is insufficient to draw conclusions regarding delays in time to loss of ambulation associated with early treatment initiation.
- The company states that [redacted] patients in England have been diagnosed with nmDMD since 2020 and that of these, [redacted] patients were aged 2-4 years and [redacted] patients were aged 2 years at diagnosis. The company argues that these data show that it is plausible to assume that patients would initiate ataluren before the age of 5 years in clinical practice.
- Between 2021 and 2022, there was an increase of [redacted] in the number of children diagnosed with nmDMD below the age of 5 years, which suggests that diagnosis in younger patients is improving.
- The company argues that initiating treatment with ataluren at age 2 years is the most clinically relevant scenario to reflect in the economic model. The company's ECD response states that this is a conservative approach and presents the results of a scenario analysis in which early treatment benefits were removed and the model start age was set equal to 4 years (see Table 2, Scenario SA3). This analysis increased the company's revised base case ICER from [redacted] to [redacted] per QALY gained.
- The company reiterates that the estimates of early treatment benefits used in the model were obtained from an international Delphi panel comprised of 9 clinical experts.[11]
- The company's response highlights that in Study 030,[12] over 28 and 52 weeks of treatment with ataluren, patients aged 2-5 years showed improvements in ambulatory ability as demonstrated by decreased time to run/walk 10 metres, decreased time to climb and descend four stairs, time to stand from supine, and increased North Star Ambulatory Assessment (NSAA) scores from baseline. These data have been presented previously (see EAG report,[6] Figures 3 and 4).
- The company's ECD response presents an additional scenario analysis in which the assumed early treatment benefits are halved (see Table 2, Scenario SA4). This analysis increased the base case ICER from [redacted] to [redacted] per QALY gained.

The EAG notes the following points regarding the assumed benefits of early treatment with ataluren:

- The company's revised model is not in line with the Appraisal Committee's preferred assumptions, although the company has presented additional scenario analyses in which the assumed early treatment benefits are reduced or removed (see Table 2, Scenarios S3 and S4).
- The EAG's clinical advisors agreed that it is plausible that earlier treatment would lead to additional benefits compared with later treatment.[6]
- The EAG agrees with the company that owing to the older age of patients at initiation of ataluren in STRIDE[3] (mean age in the evaluable population = [redacted] years), any additional benefits associated with earlier treatment will not be reflected in the 2021 data-cut.
- The company's ECD response[2] indicates that the proportion of patients who are diagnosed at an earlier age is increasing over time, which the company uses to justify the assumption of a model start age of 2 years. The ECD[1] refers to published evidence and expert clinical opinion that most diagnoses of DMD in England are at around 4 years of age. It is not fully clear what might be achievable in terms of reducing the age of diagnosis of nmDMD in practice and how earlier treatment might delay patients reaching disease milestones. As such, the EAG is uncertain regarding to the most appropriate treatment start age to apply in the economic model, but notes that applying outcomes data from STRIDE without additional assumptions may underestimate the clinical benefit of ataluren.
- The company's ECD response describes the use of an earlier initiation age as being conservative because it accumulates treatment costs for the longest possible duration. However, earlier initiation also results in additional modelled benefits. Increasing the model start age has the potential to increase the ICER for ataluren more than the inclusion of early treatment benefit assumptions (see Figure 2).

Figure 2: Impact of age and early treatment benefit assumptions on the ICER for ataluren versus BSC (generated by the EAG using the company's revised model)

ICER - incremental cost-effectiveness ratio; BSC - best supportive care

(iii) Treatment-dependent utility values

Section 3.9 of the NICE ECD[1] states *"The committee considered that the company had not provided robust evidence to support the use of treatment-dependent utility values in the ambulatory health state. The committee concluded that treatment-dependent utility values were not appropriate for the ambulatory health state but were plausible in the non-ambulatory health states."*

The company's revised base case model retains the company's original assumptions of treatment-dependent utility values in all health states. The company's ECD response[2] presents the following arguments in support of the assumption of treatment-dependent utility values:

- The treatment-dependent utility values used in the model were taken from a published Delphi study reported by Landfeldt *et al.*[13] and are supported by a second Delphi study[11] and additional UK expert opinion. The company's ECD response states that clinicians consider that ataluren provides benefits over BSC in terms of cognition, emotion, pain, ambulation and dexterity in both the ambulatory and non-ambulatory health states.
- Additional data on the NSAA and the Performance of the Upper Limb Module (PUL) from Study 041[14] suggest a reduced loss in functional ability across [redacted] of the NSAA measured at week 72 and a relative gain of [redacted] in upper limb function for ambulatory patients receiving ataluren over BSC. The company's response argues that this *"results in higher QoL of patients treated with ataluren vs. BSC also within ambulatory disease stages."*
- Additional Euroqol 5-Dimensions Visual Analogue Scale (EQ-5D VAS) data from Study 041[14] indicate a mean increase from baseline to month 1 of [redacted] points for ataluren and [redacted] points for placebo (difference in mean change from baseline = [redacted] points). The company's ECD response states that *"These data indicate that ataluren has an impact on patient QoL within a very short duration of time after treatment initiation"*
- At the technical engagement stage of the appraisal, submissions from clinical and patient experts were supportive of the assumption of treatment-dependent utility values.
- Additional data from Study 046 show an increase in mean dystrophin levels from baseline to week 40 of [redacted] in patients treated with ataluren. Additional data on timed function tests (TFTs), outcomes related to functions of daily life, and decreases in serum creatine kinase levels suggest potential preservation of muscle tissue.
- The company's response also puts forward additional arguments supporting the assumption of treatment-dependent utility values in the non-ambulant health states. The ECD suggests that the Appraisal Committee has already accepted this assumption; for brevity, the company's discussion around this issue is not presented here.

The EAG notes the following points:

- The company's revised model is not in line with the Appraisal Committee's preferred scenario.
- The inclusion of treatment-dependent utility values in the ambulatory health state remains a key model driver.
- The company's original and revised models apply utility values of 0.93 for ambulant patients receiving ataluren and 0.61 for ambulant patients receiving BSC (utility gain for ambulant patients receiving ataluren = 0.32).[13] These estimates were obtained from a Delphi panel involving six neuromuscular experts in Sweden who assessed health status for ambulant and non-ambulant nmDMD patients using the Health Utilities Index Mark 3 (HUI-3). For the assessment of the ambulant health state, panelists were instructed to assess health status assuming a mean patient age of 13 years, with a 6-minute walk test (6MWT) distance of 410 metres for those treated with ataluren and 316 metres for those treated with BSC, based on observed and extrapolated efficacy data.[15] These utility values are applied in the economic model in all cycles in which the patient remains ambulatory, regardless of their actual level of functioning and endurance, as the model structure only contains a single ambulatory health state.
- The published Delphi studies discussed in the company's ECD response[11, 13] both support the assumption of treatment-dependent utility values. However, the EAG's clinical advisors were uncertain about whether it would be reasonable to apply treatment-dependent utility values, particularly with respect to impacts on physical functioning, for patients who are still ambulant (see EAG report,[6] Section 5.3.5, critical appraisal point [6a]). In addition, one of the UK clinical experts consulted by the company suggested that there would be [redacted]
- The EQ-5D VAS data from Study 041[14] might support an assumption of treatment-dependent utility values; however, the time period for assessment is short (one month), the between-group difference in change from baseline is small and the instrument used is not preference-based.
- The additional data from Study 046 might also support an assumption of treatment-dependent utility values; however, this evidence is limited to TFTs and serum tests which are not preference-based measures of HRQoL.
- Whilst the company has presented further evidence to support the hypothesis that HRQoL will be improved for ambulatory patients receiving ataluren compared with those receiving BSC alone, there is no empirical evidence of a gain in HRQoL measured in ambulatory nmDMD patients using a preference-based method. Given this absence of this evidence, the EAG is unsure whether the utility values applied in the company's model are reasonable. The EAG has undertaken additional exploratory analyses around this assumption (see Section 3). A judgement by the Appraisal Committee is required regarding whether the additional evidence presented in the company's ECD response is sufficient to warrant the inclusion of treatment-dependent utility values for ambulatory patients.

(iv) Caregiver HRQoL

Section 3.10 of the NICE ECD[1] states that the Appraisal Committee *"concluded that it would exclude estimated caregiver QALYs from its preferred analysis and instead would consider the impact on caregivers in its decision making in a qualitative way."*

In line with the Appraisal Committee's preferred scenario,[1] the company has removed caregiver utility values associated with the patient health states from the economic model. The company's ECD response[2] highlights that there is a significant, progressively increasing caregiver burden for the vast majority of a DMD patient's lifetime. The company emphasises the need to incorporate these factors into the assessment of ataluren from a qualitative perspective.

The EAG notes that bereavement-related QALY losses associated with the patient's death, which are also assumed to apply to caregivers,[9] are still included in the company's revised model. The inclusion of this aspect of the model results in a small incremental QALY gain for ataluren versus BSC. The impact of removing this aspect of the model is explored in the additional analyses undertaken by the EAG (see Section 3).

(v) Ataluren stopping rule

Section 3.12 of the NICE ECD[1] states *"…for the purposes of cost-effectiveness modelling, the committee preferred to use the time when predicted FVC reached less than 30%. But it acknowledged that this may not align with how treatment is stopped in clinical practice."*

The company's original base case model assumed that all patients who are still on treatment when they reach FVC<50% discontinue at this point. In line with the Appraisal Committee's preferred scenario,[1] the company's model has been amended to apply a stopping rule at FVC<30%. The company's ECD response includes a scenario analysis assuming the original proposed stopping rule of FVC<50% (see Table 2, Scenario SA6). This earlier stopping rule reduces the company's revised base case ICER from [redacted] to [redacted] per QALY gained.

The EAG notes that owing to the use of a partitioned survival model approach, extending the stopping rule to later milestones increases costs but does not impact on QALYs. Offering ataluren beyond FVC<50% may lead to additional health gains which are not captured in the model, although the magnitude of these benefits are uncertain.

(vi) Ataluren discontinuation rate

Section 3.11 of the NICE ECD[1] states *"The committee concluded that the company's estimated discontinuation rate likely overestimated treatment discontinuation and therefore underestimated*

ataluren treatment costs. The committee preferred the EAG's scenario analysis, which reduced the discontinuation rate for decision making. But it noted that this reduction was arbitrary and added to the uncertainty."

The company's revised base case model includes an amended estimate of the ataluren discontinuation rate in STRIDE[3] (January 2021 data-cut). The company's original estimate of [redacted] per 3-months was based on [redacted] out of [redacted] patients discontinuing ataluren over a median follow-up duration of [redacted] days, assuming a constant underlying rate. [redacted] of these [redacted] patients discontinued due to loss of ambulation. The company has removed these [redacted] patients from the analysis which results in an updated estimate of the discontinuation rate of [redacted]. This discontinuation rate is markedly lower than the company's original estimate, which increases total costs for the ataluren group.

The EAG believes that the updated estimate of [redacted] is more appropriate than the company's original estimate.

(vii) Decision modifier

The company's ECD response[1] highlights that the revised base case model suggests that ataluren will generate an additional [redacted] QALYs and therefore a QALY weighting of [redacted] has been applied in the base case analysis. The results of the company's revised base case and scenario analyses including QALY weighting are reported in Appendix 1.

3. Additional analyses undertaken by the EAG

This section presents the results of additional exploratory analyses (EAs) undertaken by the EAG. Seven additional analyses were undertaken to explore the areas of uncertainty discussed in Section 2:

- *EA1:* This scenario reflects the Appraisal Committee's preferred assumptions stated in the ECD. This analysis is the same as the company's revised base case analysis, but also includes treatment-independent utility values for the ambulant state (utility value = 0.62), removes the early treatment benefit assumptions and removes the bereavement-related QALY losses.
- *EA2:* EA1 + treatment-dependent utility values applied in the ambulatory state.
- *EA3:* EA1 + treatment-dependent utility gain halved in ambulatory state (utility value = 0.77).
- *EA4:* EA1 + model start age = 4 years
- *EA5:* EA1 + bereavement-related QALY losses included
- *EA6:* EA1 + Weibull models used for all time-to-event endpoints.
- *EA7:* EA1 + FVC<50% stopping rule.

The results of the EAG's additional analyses are presented in Table 3. The Appraisal Committee's preferred scenario leads to a deterministic ICER for ataluren versus BSC of [redacted] per QALY gained; the probabilistic ICER is lower at [redacted] per QALY gained. These ICERs are considerably higher

than the company's revised base case ICER of [redacted] per QALY gained. The key driver of the higher ICERs relates to the assumption of treatment-dependent utility values in the ambulatory health state of the model. Most of the other EAG scenarios have a smaller impact on the ICER. The use of a stopping rule at earlier DMD milestones has the potential to improve the ICER, although as noted above, this only impacts only on costs within the model. The decision modifier is estimated to be [redacted] across all of the EAG's additional analyses.

Table 3: Results of additional exploratory analyses undertaken by the EAG

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's revised 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]	[redacted]
EA1: Appraisal Committee's preferred assumptions (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1: Appraisal Committee's preferred assumptions (probabilistic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2: Appraisal Committee's preferred scenario + treatment-dependent utility values								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA3: Appraisal Committee's preferred scenario + treatment-dependent utility gain in ambulatory state halved								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA4: Appraisal Committee's preferred scenario + start age = 4 years								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA5: Appraisal Committee's preferred scenario + bereavement QALY loss included								

Ataluren+BSC						-	-	
BSC						-	-	
Incremental								
EA6: Appraisal Committee's preferred scenario + Weibull models								
Ataluren+BSC						-	-	
BSC						-	-	
Incremental								
EA7: Appraisal Committee's preferred scenario + FVC<50% stopping rule								
Ataluren+BSC						-	-	
BSC						-	-	
Incremental								

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; BSC - best supportive care; EA - exploratory analysis; QALY - quality-adjusted life year; FVC - forced vital capacity

4. References

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Appendix 1: Company's revised base case and scenario analyses including QALY weighting

Table 4 presents the results of the company's revised base case and scenario analyses including QALY weighting. The results of the EAG's additional analyses are not presented here as the decision modifier is estimated to be [redacted] across all analyses.

Table 4: Results of company's revised base case and scenario analyses presented in ECD response (includes QALY weighting)

Scenario	Decision modifier*	Weighted ICER†
Company's revised base case model following ECD (deterministic)	[redacted]	[redacted]
Company's revised base case model following ECD (probabilistic)	[redacted]	[redacted]
SA1: Weibull survival distributions for all time-to-event endpoints	[redacted]	[redacted]
SA2: 1-knot restricted cubic spline model for all time-to-event endpoints	[redacted]	[redacted]
SA3: Early treatment benefit removed, ataluren start age = 4 years	[redacted]	[redacted]
SA4: Early treatment benefit reduced by half ([redacted])	[redacted]	[redacted]
SA5: STRIDE discontinuation rate = [redacted]	[redacted]	[redacted]
SA6: Stopping rule at pFVC <50%	[redacted]	[redacted]
SA7: Company's previous base case at technical engagement (including previous PAS)	[redacted]	[redacted]

ICER - incremental cost-effectiveness ratio; SA - scenario analysis; ECD - Evaluation Consultation Document; LoA - loss of ambulation; pFVC - predicted forced vital capacity; STRIDE - Strategic Targeting of Registries and International Database of Excellence; PAS - Patient Access Scheme
** Decision modifiers are rounded down to 1 decimal place*
† Includes patient QALYs and bereavement-related QALY losses

Updated company and EAG results using 5-year STRIDE cut-point plus updated proposed commerical arrangement of [redacted]

12th December 2022

Table 1: Results of company's revised base case and scenario analyses presented in ECD response (excludes QALY weighting)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's revised base case model following ECD (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base case model following ECD (probabilistic)†								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA1: Weibull survival distributions for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA2: 1-knot restricted cubic spline model for all time-to-event endpoints								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA3: Early treatment benefit removed, ataluren start age = 4 years								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA4: Early treatment benefit reduced by half ([redacted])								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA5: STRIDE discontinuation rate = [redacted]								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA6: Stopping rule at pFVC <50%								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA7: Company's previous base case at technical engagement (including previous PAS)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SA - scenario analysis; DM - decision modifier; LoA - loss of ambulation; pFVC - predicted forced vital capacity; STRIDE - Strategic Targeting of Registries and International Database of Excellence; NR - not reported

† QALYs accrued by patients and carers are not recorded separately in the company's PSA sub-routine

Table 2: Results of additional exploratory analyses undertaken by the EAG

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs - total	Costs	ICER (patients)	ICER (patients + carers)	DM
Company's revised 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]	[redacted]
EA1: Appraisal Committee's preferred assumptions (deterministic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA1: Appraisal Committee's preferred assumptions (probabilistic)								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA2: Appraisal Committee's preferred scenario + treatment-dependent utility values								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA3: Appraisal Committee's preferred scenario + treatment-dependent utility gain in ambulatory state halved								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA4: Appraisal Committee's preferred scenario + start age = 4 years								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA5: Appraisal Committee's preferred scenario + bereavement QALY loss included								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA6: Appraisal Committee's preferred scenario + Weibull models								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EA7: Appraisal Committee's preferred scenario + FVC<50% stopping rule								
Ataluren+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Incremental	[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; BSC - best supportive care; EA - exploratory analysis; QALY - quality-adjusted life year; FVC - forced vital capacity

Table 3: Results of company's revised base case and scenario analyses presented in ECD response (includes QALY weighting)

Scenario	Decision modifier*	Weighted ICER†
Company's revised base case model following ECD (deterministic)	[redacted]	[redacted]
Company's revised base case model following ECD (probabilistic)	[redacted]	[redacted]
SA1: Weibull survival distributions for all time-to-event endpoints	[redacted]	[redacted]
SA2: 1-knot restricted cubic spline model for all time-to-event endpoints	[redacted]	[redacted]
SA3: Early treatment benefit removed, ataluren start age = 4 years	[redacted]	[redacted]
SA4: Early treatment benefit reduced by half ([redacted])	[redacted]	[redacted]
SA5: STRIDE discontinuation rate = [redacted]	[redacted]	[redacted]
SA6: Stopping rule at pFVC <50%	[redacted]	[redacted]
SA7: Company's previous base case at technical engagement (including previous PAS)	[redacted]	[redacted]

ICER - incremental cost-effectiveness ratio; SA - scenario analysis; ECD - Evaluation Consultation Document; LoA - loss of ambulation; pFVC - predicted forced vital capacity; STRIDE - Strategic Targeting of Registries and International Database of Excellence; PAS - Patient Access Scheme

** Decision modifiers are rounded down to 1 decimal place*

† Includes patient QALYs and bereavement-related QALY losses

Figure 1: Impact of age and early treatment benefit assumptions on the ICER for ataluren versus BSC (generated by the EAG using the company's revised model)

Additional Figure: ICERs according to ataluren ambulatory utility value and FVC stopping rule