NICE National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

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

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient access scheme evidence submission template

July 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for highly specialised technologies. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a highly specialised technology evaluation, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical effectiveness and value for money of a technology, in the context of a highly specialised technology evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/hst-interim-evidence-submission-template.doc) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the highly specialised technology evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf). The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technology evaluation, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated.

If you are submitting the patient access scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the highly specialised technology and the disease area to which the patient access scheme applies.

Ataluren (Translarna™) for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation (nmDMD) in the dystrophin gene, in ambulatory patients aged 5 years and older.

3.2 Please outline the rationale for developing the patient access scheme.

This patient access scheme is for provision of Translarna at a discounted price. This scheme is being provided to improve Translarna's value for money with the expectation that it will allow a positive recommendation from NICE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a simple discount (fixed price discount which will not vary with any change to the UK list price).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the whole licensed population: Duchenne muscular dystrophy resulting from a nonsense mutation (nmDMD) in the dystrophin gene, in ambulatory patients aged 5 years and older.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Not applicable – the scheme is not dependent on any criteria. All patients will be eligible to enter the scheme in line with the marketing authorisation for Translarna.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients meeting the licensed indication for Translarna will meet the scheme criteria.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The fixed price discount will be applied from the list price and *applied to all original invoices* for Translarna.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As the scheme is a simple discount there are no administration requirements. NHS organisations will be provided with a notification document regarding the Terms and Conditions at the start of the scheme for reference.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable - The fixed price discount will be applied from the list price and *applied to all original invoices* for Translarna.

3.10 Please provide details of the duration of the scheme.

As this is a simple scheme it would be in place from the date of guidance publication until NICE next reviews the guidance on Translarna and a final decision has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues have been identified.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

NHS organisations will not be required to complete an agreement from prior to participation in the scheme. They will simply be provided with a notification document regarding the Terms and Conditions for reference.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Value for money

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence'. You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable.

4.2 If you are submitting the patient access scheme at the end of the highly specialised technology evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

The economic results presented in this submission are using the model presented to NICE in response to the ECD, which incorporates assumptions requested by NICE and further modifications including the use of additional data from the Phase 3 study (Study 020). This model was submitted to NICE on 6th November 2015.

The base case scenario is that presented in row 2 of Table A2.1 of the ECD response: Linear extrapolation of 6MWD decline from meta-analysis of decline phase population (6MWD 400-300m at baseline).

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

The cost of a 125mg sachet of ataluren has been amended from the list price of £84.40 to the fixed price proposed under the patient access scheme of £[redacted].

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

Not applicable – there are no additional costs envisaged in the implementation and operation of this patient access scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable.

Summary results

Base-case analysis

4.7 Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 1 Base-case value for money results without patient access scheme

	Ataluren	Best supportive care
Intervention cost (£)	8,457,389	0
Other costs (£)	308,555	366,043
Total costs (£)	8,765,944	366,043
Difference in total costs (£)	N/A	8,399,901
LYG	26.520	20.294
LYG difference	N/A	6.226
QALYs	8.512	-3.235
QALY difference	N/A	11.747

LYG: life-year gained; QALY: quality-adjusted life-year

Table 2 Base-case value for money results with patient access scheme

	Ataluren	Best supportive care
Intervention cost (£)	[redacted]	0
Other costs (£)	[redacted]	366,043
Total costs (£)	[redacted]	366,043
Difference in total costs (£)	N/A	[redacted]
LYG	26.520	20.294
LYG difference	N/A	6.226
QALYs	8.512	-3.235
QALY difference	N/A	11.747

LYG: life-year gained; QALY: quality-adjusted life-year

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Incremental results are provided in Tables 1 and 2 above.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation. Consider using tornado diagrams.

Deterministic sensitivity analysis was not presented to NICE in the ECD response.

4.10 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation.

The results for alternative scenarios considered in response to the ECD are detailed in Table 3. The scenarios are as follows:

1. Model with Study 007 data only, incorporating the ERGs preferred scenario and enhancements to further capture the benefit of ataluren
2. Extrapolation of 6MWD decline stratified by patients with >400m, 400-300m and <300m
3. Extrapolation of 6MWD decline stratified by patients with >400m, 400-300m and <300m starting at 450m baseline

[2] For outcome-based schemes, please see section 5.2.9

4. Extrapolation of 6MWD decline stratified by patients with >400m, 400-300m and <300m starting at 500m baseline

5. Extrapolation of 6MWD decline stratified by patients with >400m, 400-300m and <300m starting at 550m baseline

As detailed in Appendix 2 of the ECD response, scenario 1 includes changes 1-10 of Appendix 2 and scenarios 2 to 5 includes changes 1-10 and 11b of Appendix 2.

Table 3 Scenario analysis results

Scenario	Incremental QALYs	Incremental costs without patient access scheme	Incremental costs with patient access scheme
1	8.972	£6,128,102	£[redacted]
2	8.194	£5,532,819	£[redacted]
3	9.666	£6,618,756	£[redacted]
4	13.685	£10,260,303	£[redacted]
5	16.564	£13,176,864	£[redacted]

4.11 If any of the criteria on which the patient access scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme

4.12 For financially based schemes, please present the results of the value for money analyses showing the impact of the patient access scheme on the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

To address the HST Evaluation Committee concerns regarding the average weight of patients likely to be treated with ataluren, the budget impact analysis now utilises a mean patient weight of 27-31kg. This equates to an annual treatment cost of £277,254 without the patient access scheme and [redacted] with the patient access scheme.

In addition, the number of patients known to be diagnosed with nmDMD has increased slightly since the original manufacturer's submission in June 2015. There are currently [redacted] known patients in England, out of a theoretical 68 patients (after accounting for prevalence, incidence and discontinuation due to death / loss of ambulation). This equates to a level of patient identification of [redacted]% in year 1. This is expected to increase up to [redacted]% by year 4.

To address the HST Evaluation Committee concerns regarding the uptake of ataluren in patients with nmDMD, the market uptake is also now assumed to be [redacted]%, such that [redacted] are assumed to be initiated on ataluren.

Assuming a NICE decision will be made in April of 2016, the Year 1 budget impact estimate assumes only [redacted] months of treatment with ataluren. With the patient access scheme, the budget impact in Year 1 is estimated to be approximately [redacted] rising to around [redacted] in Year 5 (Table 4).

Table 4 Budget impact of ataluren in England over 5 years with patient access scheme

	Calendar Year 1	Calendar Year 2	Calendar Year 3	Calendar Year 4	Calendar Year 5
Prevalence	66	[redacted]	[redacted]	[redacted]	[redacted]
Incidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Theoretical available patients based on prevalence and incidence estimates (see manufacturer submission or derivation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Level of patient identification	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Known (diagnosed) patients eligible for ataluren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

The PTC Simple PAS notification to Trusts document has been attached.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.2.8 Please present the value for money results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable.

5.2.9 Please present in separate tables the results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

Not applicable.

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene- ERG critique of cost-effectiveness model submitted 25th January 2016

Produced by ERG: Warwick Evidence

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Contributions of authors: Paul Sutcliffe (Associate Professor) co-ordinated the project. Peter Auguste (Research Fellow in Health Economics) and Joshua Pink (Assistant Professor in Health Economics) conducted, reviewed and evaluated the cost-effectiveness evidence. Jill Colquitt (Senior Researcher) and Emma Loveman (Senior Researcher) co-ordinated and conducted the evaluation of the clinical effectiveness evidence. Karoline Freeman (Research Fellow) conducted the evaluation of the clinical effectiveness. Rachel Court (Information Specialist) conducted the evaluation of the Company searches. Martin Connock (Senior Research Fellow) undertook the survival analyses. Aileen Clarke (Professor of Public Health and Health Services Research) and Andy Clegg (Senior Researcher) contributed in peer review, summaries, conclusions and editing. All authors contributed to the writing of the report.

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Please note that: Sections highlighted in yellow and underlined are [redacted]
Sections highlighted in aqua and underlined are [redacted]

Cost-effectiveness model (25th January 2016)

The Company has submitted an updated cost-effectiveness model, which incorporates the changes made to previous models, whilst also applying a patient access scheme (PAS) at a [redacted] discount rate. The initial cost of 125mg a sachet of ataluren was £84.40, and the discounted cost is [redacted].

Below we present a commentary on the range of scenario analyses whilst applying the new PAS [redacted] discount rate, and discuss the impact these changes have to the results of both modelling approaches (linear extrapolation and stepped-decline).

Changes made by the Company:

1. Updated parametric curves
2. Restriction added to the transition to scoliosis, such that patients do not develop scoliosis after puberty
3. Inclusion of treatment costs for six months post loss of ambulation
4. Increase in the time horizon of the analysis from 40 years to 50 years
5. Discount rates changes from 3.5% to 1.5%, (on the basis of NICE technology appraisal guidance on 'treatments which significantly improve health over a long-period.')
6. Increased disutility due to scoliosis
7. Increased caregiver disutilities- caregiver disutilities were increased from one primary caregiver to the equivalent of three fulltime primary caregivers
8. Non-ambulatory utilities- to account for the possibility that patients may have a higher quality of life post loss of ambulation with ataluren, due to being in a better state at loss of ambulation
9. Inclusion of costs for ventilation assistance
10. The inclusion of the new data from Study 020
11. Stepped-decline of 6MWD
12. Combined changes
13. Different baseline 6MWD (Linear approach)
14. Different baseline 6MWD (Stepped-decline approach)

Company Base-case results with [redacted] PAS discount rate

Table 1: Results based on linear extrapolation

	Best supportive care	**Ataluren**	**Incremental**
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	8.512	11.747

Table 2: Results based on stepped approach

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	4.959	8.194

1. *ERG Updated parametric curves: applying the best-fitting curves*

Table 3: Results based on linear extrapolation

	Best supportive care	Ataluren	Incremental
Costs	£356,734	[redacted]	[redacted]
QALYs	-2.868	8.564	11.432

Table 4: Results based on stepped approach

	Best supportive care	Ataluren	Incremental
Costs	£356,734	[redacted]	[redacted]
QALYs	-2.868	5.194	8.062

2. *Restriction added to the transition to scoliosis, such that patients do not develop scoliosis after puberty*

The inclusion of a PAS discount does not have an impact on the transition to scoliosis, hence the Markov trace plots for the ataluren and the best supportive care arms remain unchanged. The plots below were presented in the ERG's previous critique of additional evidence (Company's Response to the Evaluation Consultation Document) document and our concern about them remains unchanged.

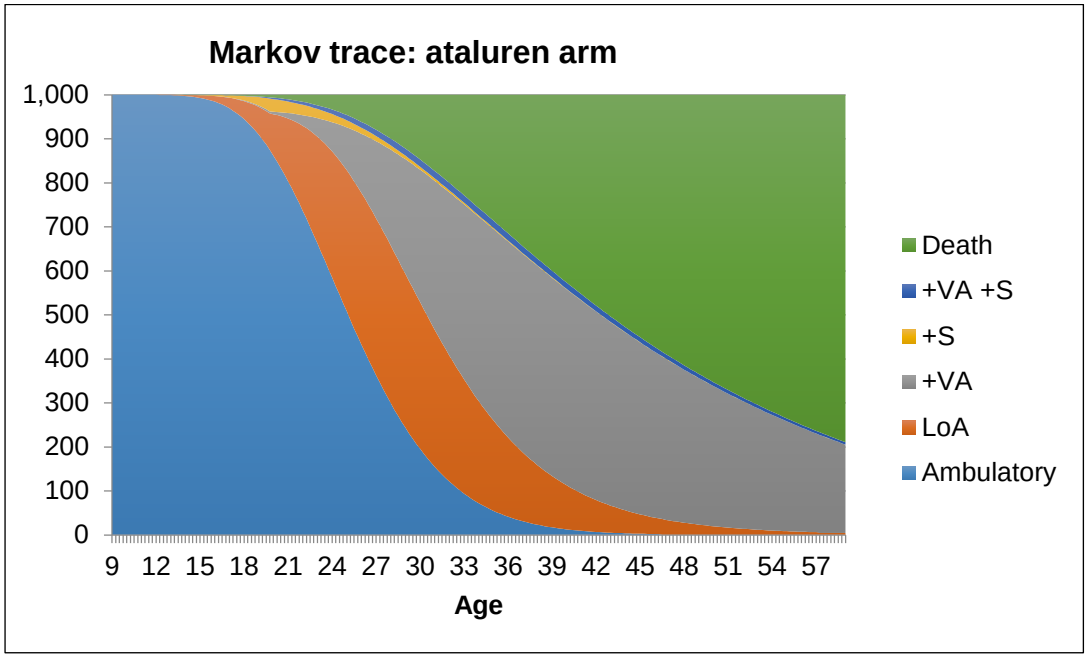

Figure 1: Markov trace plot for the ataluren arm

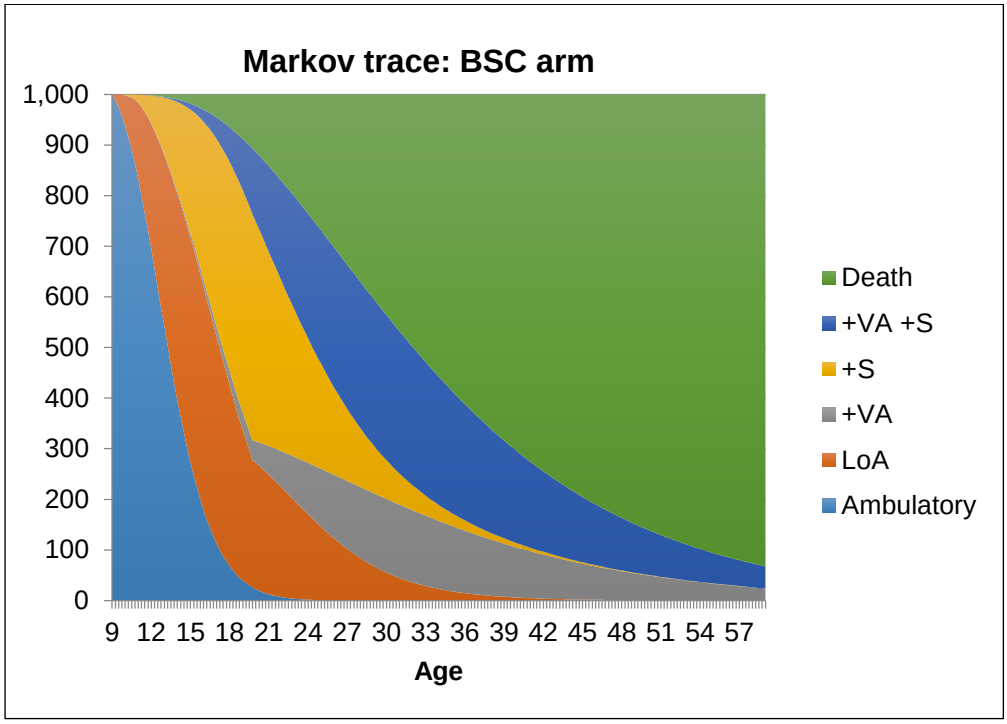

Figure 2: Markov trace plot for the best supportive care arm

3. *Inclusion of treatment costs for six months post loss of ambulation*
4. *Increase in the time horizon of the analysis from 40 years to 50 years*
5. *Discount rates changes from 3.5% to 1.5%, on the basis of NICE technology appraisal on treatments which significantly improve health over a long-period*

The ERG is happy with changes 3 and 4 made to the models. However, should a 3.5% discount rate (see ERG's critique of additional evidence, point 5) be applied to costs and outcomes instead of the 1.5% rate, the following changes to the results would occur:

Table 5: Results based on linear extrapolation

	Best supportive care	**Ataluren**	**Incremental**
Costs	£277,150	[redacted]	[redacted]
QALYs	-1.743	7.590	9.334

Table 6: Results based on stepped approach

	Best supportive care	**Ataluren**	**Incremental**
Costs	£277,150	[redacted]	[redacted]
QALYs	-1.743	4.914	6.657

6. *Increased disutility due to scoliosis*

The current submission uses a disutility of 0.3 instead of 0.1 for people who have scoliosis. Reverting to the original disutility of 0.1 makes the following changes to the results:

Table 7: Results based on linear extrapolation

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.408	8.614	10.021

Table 8: Results based on stepped approach

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.408	5.493	6.901

With the PAS discount of [redacted] the mean cost of treatment for ataluren is [redacted], which equates to an incremental cost of [redacted].

7. *Increased caregiver disabilities- caregiver disabilities were increased from one primary caregiver to the equivalent of three fulltime primary caregivers*

Table 9: Results based on linear extrapolation (equivalent of two caregivers)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.479	9.826	11.305

Table 10: Results based on stepped approach (equivalent of two caregivers)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.479	6.541	8.021

Table 11: Results based on linear extrapolation (equivalent of one caregiver)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	0.277	11.140	10.863

Table 12: Results based on stepped approach (equivalent of one caregiver)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	0.277	8.124	7.847

8. *Non-ambulatory utilities- to account for the possibility that patients may have a higher quality of life post loss of ambulation with ataluren, due to being in a better state at loss of ambulation*

If we use the original utility values which are the same for those in the ataluren group as in the best supportive care group once ambulation is lost, this results in the following changes:

Table 13: Results based on linear extrapolation

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	6.959	10.195

Table 14: Results based on stepped approach

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	3.088	6.323

Applying the Company's PAS discount of [redacted] to the cost of ataluren treatment reduces the mean cost of treatment in the ataluren arm to [redacted], which equates to an incremental cost of [redacted].

9. *Inclusion of costs for ventilation assistance*

The Company has included a cost for ventilation assistance, and we are happy with this change.

10. *The inclusion of the new data from Study 020*

We have conducted a multi-way sensitivity analysis, which is based on the linear extrapolation model, PAS discount of [redacted], and the following changes:

- Using different survival models for the scoliosis and ventilation assistance
- Allowing people to develop scoliosis post puberty
- Applying a 3.5% discount rate for both costs and outcomes
- Using a disutility of 0.1 as opposed to 0.3 for the scoliosis health state
- Reducing the primary caregivers from three to two
- Applying utility values to represent the value placed on occupying a health state as opposed to a utility value based on health state and treatment

Table 15: Results based on linear extrapolation

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	7.212	6.409

The results show that the mean treatment costs for the best supportive care arm and ataluren arm are [redacted] and [redacted], respectively, which equates to a mean incremental cost of [redacted]. Mean QALYs gained in the best supportive care arm and ataluren arm were 0.803 and 7.212, respectively, which equates to a mean incremental gain of 6.409 QALYs over a 50-year time horizon.

11. Stepped-decline of 6MWD

As stated in our previous document (ERG critique of additional evidence) , '*the ERG believes the stepped decline model represents a better approach to long-term extrapolation, as it takes into account what appear to be very different trajectories based on baseline 6MWD. However, there are some specific technical issues with the way the stepped decline model has been implemented, in particular where data from the trials has been replaced by assumed values, and these assumptions have been much more favourable to ataluren than the data from the trial. There are two key issues, to address, which are dealt with sequentially below:*

The >400m subgroup

The pooled data from the studies suggests a [redacted] 48 week decline with placebo for patients in the >400m group at baseline, and an equivalent decline of [redacted] with ataluren. The company has, quite reasonably, suggested these numbers may not be representative of the long-term decline, and hence after two years has replaced this with the average decline from the 300-400m subgroup and the >400m subgroup. However, no such adjustment has been made to the ataluren arm (meaning patients are expected to continue plateauing in this state, but not the placebo state), which means a bias in favour of the ataluren group has been introduced. To show the importance of this effect, the table below shows the values used in the model, and what values would be used if data for the trial were used for he >400m subgroup in the same way as the other subgroups.

Table 16: Post-hoc adjustment to best supportive care (BSC) arm

	Model data		***Trial data***	
	BSC	***Ataluren***	***BSC***	***Ataluren***
Baseline 6MWD	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline first 2 years	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline after 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Annual decline 300-400m baseline	[redacted]	[redacted]	[redacted]	[redacted]
Annual decline <300m baseline	[redacted]	[redacted]	[redacted]	[redacted]
Years to loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]
Difference in loss of ambulation	*7.1*		*2.1*	
Age at loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]

Two alternative approaches, which still account for the expected faster decline over time in the >400m group, but do not introduce such an optimistic assumption for ataluren, would be:

Approach 1: *Making the same adjustment for ataluren as best supportive care (i.e. after two years taking the average of the >400m and 300-400m groups and using that for the >400m group.*

Approach 2: *Taking the [redacted] increase in 48 week decline used for the placebo arm after two years, and applying this same adjustment to the ataluren arm (this assumes the increase in decline rate is related solely to the disease, and is thus treatment independent).'*

Using these two different assumptions in the modelling gives the results below:

Table 17: Post-hoc adjustment to best supportive care (BSC) and ataluren arms

	Approach 1		***Approach 2***	
	BSC	***Ataluren***	***BSC***	***Ataluren***
Baseline 6MWD	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline first 2 years	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline after 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Annual decline 300-400m baseline	[redacted]	[redacted]	[redacted]	[redacted]
Annual decline <300m baseline	[redacted]	[redacted]	[redacted]	[redacted]
Years to loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]
Difference in loss of ambulation	*4.6*		*4.0*	
Age at loss of ambulation	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]*The <300m subgroup*

'The company states that "as the 6MWD is not a sufficiently sensitive tool to measure treatment effect in the <300m group but that the NSAA and TFTs showed ataluren had a treatment effect of approximately [redacted] *on average, a conservative* [redacted] *treatment effect of ataluren on 6MWD decline in the <300m group was applied." Firstly, it is not clear that treatment effects are transferable between different measures, and it is unclear how it can be regarded as conservative to replace trial data with assumptions more favourable to ataluren. Secondly, even if the 6MWD is not sufficiently sensitive for effects measured to be statistically significant, it does not follow that data from the trial for this measure should simply be ignored, particularly when it is the primary outcome used in the model. Making use of actual trial data rather than these post-hoc assumptions makes the following changes to the results above.'*

It should be noted that, since the ERG did not know the exact numbers of patients randomised to each arm across the trials, this analysis involved the simplifying assumption that patient numbers were exactly balanced between the arms of the studies.

12. Combined changes

In its last analysis, the ERG included the impact of these changes, together with the model adjustments from point 11, specifically:

- Adding the above changes – i.e. approaches to 'stepped decline'
- Using different survival models for the scoliosis and ventilation assistance
- Allowing people to develop scoliosis post puberty
- Applying a discount rate of 3.5% for both costs and outcomes
- Using a disutility of 0.1 as opposed to 0.3 for the scoliosis health state
- Reducing the number of equivalent primary caregivers from three to two
- Non-ambulatory utilities set to be the same for both arms of the model

Making these changes to the model produced the following results:

Table 18: Results (Stepped-decline) – Approach 1, trial data for <300m subgroup and other changes

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	3.186	2.383

Table 19: Results (Stepped-decline) – Approach 2, trial data for <300m subgroup and other changes

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	2.831	2.028

These represent substantial QALY reductions compared to the base case results presented by the company in table 2 of this document.

Increasing the baseline 6MWD and how this relates to the population likely to be treated in clinical practice

Increasing the baseline 6MWD may increase the length of time people are on treatment, hence we would expect treatment costs to increase. However, the ERG would like to reiterate that there is simply no data on these higher 6MWD groups. In the Company's trial, ataluren was performing [redacted] than placebo in the >400m group, so the assumption of large treatment benefits for groups with baselines up to 500m or 600m seems questionable. After the first two years, the data on the treatment benefit from ataluren in this higher 6MWD group aren't based on any data, but just an assumption. Therefore, the higher you raise the baseline, the more important the impact of this assumption becomes.

The ERG would like to note that in the updated model, scenario analyses on increasing the 6MWD were not provided by the Company. However, the ERG has undertaken scenario analyses by assuming baseline 6MWD of 500M. Below we present the results for the change in the baseline 6MWD for the linear approach and stepped-decline approach, respectively.

13. Different baseline 6MWD (Linear approach)

Table 20: Results based on linear approach (500M 6MWD)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	11.261	14.496

Increasing the baseline 6MWD to 500M resulted in an incremental cost of approximately [redacted] with correspondingly 14.496 QALYs gained.

Table 21: Results based on linear approach (combined changes and baseline 500M 6MWD)

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	9.181	8.378

Making the combined changes to the model (as in point 10) and increasing the baseline 6MWD to 500M resulted in increased incremental costs and QALYs.

14. Different baseline 6MWD (Stepped-decline)

Table 22: Results based on stepped-decline (baseline 500M 6MWD)

	Best supportive care	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	10.450	13.685

Using the stepped-decline approach and an increase of the baseline 6MWD, the results show an increase in the incremental costs and QALYs compared to the stepped-decline approach in the base-case.

Table 23: Results (Stepped-decline) – Approach 1, trial data for <300m subgroup and other changes

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	5.435	4.632

Using the stepped-decline approach one, combined changes and an increase in the baseline 6MWD, the results show an increase in the incremental costs and QALYs compared to the stepped-decline approach one (Table 18).

Table 24: Results (Stepped-decline) – Approach 2, trial data for <300m subgroup and other changes

	Best supportive care	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	2.779	1.976

Results based on the stepped-decline approach two, combined changes and an increase in the baseline 6MWD, show that there was a decline in the incremental costs and QALYs.

[redacted]

Conclusion

In conclusion, it is relevant to note that first, the model is highly sensitive to a number of assumptions, both in the structure of the model and the parameter values chosen, and that alternative assumptions can result in considerably different estimates on costs and QALYs. Second, there is also quite a high correlation between costs and QALYs, meaning reductions in QALYs (often driven by reductions in time in the ambulatory health state) are accompanied by reductions in costs (the lower treatment costs for a smaller number of people still being on ataluren). Third, applying the PAS discount rate of [redacted] reduces the mean cost of ataluren treatment.

Finally, it should be noted that here the ERG only considered the impact of changes to the model based on the new submission made by the company, and applying a PAS of [redacted] discount for the cost of ataluren. Other comments on the model made in the original ERG report (e.g. the initial cohort used in the model are older than the likely starting age in clinical practice, the model assumes the treatment benefit with ataluren persist beyond the time horizon of the trials), and the ERG critique of additional evidence report remain valid for the new data and model submitted.

Budget impact model

The company has submitted a new budget impact model which is used to estimate the total costs to the NHS over a five-year duration. This model was presented alongside the updated economic model, and the results are presented in terms of the annual absolute costs of using ataluren treatment to the NHS. Table 25 below summarises the information changed in the updated budget impact model compared with information from the original model.

Table 25: Summary of the original and updated information used in the budget impact models

Key model inputs	Original budget impact model	Updated budget impact model
Cost per 125mg sachet	£84.40	£84.40
Patient access scheme discount	-	[redacted]
Cost per 125mg sachet applying patient access scheme discount	-	[redacted]
Daily dose (mg)	1000mg (based on median weight of 24-26kg)	1,125mg (based on median weight 27-31kg)
Annual treatment cost without patient access scheme	£246,448 (based on median weight of 24-26kg)	£277,254
Annual treatment cost with patient access scheme	-	[redacted]
Level of patient identification	[redacted]	[redacted]
Market uptake	[redacted]	[redacted]

The ERG noted that the Company applied a patient access scheme discount rate of [redacted] and derived a cost of [redacted] for a 125mg sachet of ataluren. The Company has updated their budget impact model by increasing the median weight of people they expect to be taking ataluren, from 24-26kg to 27-31kg. Other changes made included an increase in the level of patient identification and an increase in the market uptake of people on ataluren treatment.

In Table 26 below, we present the results of the original, and updated budget impact model based on the changes made to some of the key input parameters. In the updated model, results are presented on the annual budget with/without the patient access scheme.

Table 26: Summary of the original and updated results from the budget impact models

Year	Original budget impact model (£)	Updated budget impact model	
		Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)
Year 1	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]

Results from the original model shows that budget impact for year one is approximately [redacted] million and rises to approximately [redacted] million to year five at an average of [redacted] million per year. The budget required without the patient access scheme is approximately [redacted] million in the first year and rises to approximately [redacted] million in the fifth year, at an average of approximately [redacted] million per year. Including the patient access scheme discount of [redacted], the budget required for the first year is approximately [redacted] million and is estimated to be approximately [redacted] million in the fifth year, at an average of approximately [redacted] million per year.

ERG exploratory scenario analyses of budget impact analysis

We have undertaken scenario analyses to explore the impact on the annual budget required should ataluren be adopted. These analyses are based on the Company's budget impact model, and are presented in Tables 27-30 for comparative purposes:

Scenario 1: using the percentages of the level of identification and market uptake presented in the original model

Scenario 2: changing the average weight for people being treated with ataluren

- Average weight (39kg) derived from the best supportive care group
- Average weight (53kg) derived from the ataluren group

Scenario 3: using the percentages of the level of identification and market uptake presented in the original model (include date here), and the average weight of 39kg used in Scenario 2

ERG budget impact analysis summary

The results from Scenarios 1-3 are presented in Tables 27-30. Results from Scenario 1 shows that the average annual budget required is approximately [redacted] million and [redacted] million, respectively with and without the patient access scheme, compared to approximately [redacted] million and approximately [redacted] million in the updated budget impact model.

Table 27: Summary of the original and Scenario 1

Year	Updated budget impact model		Scenario 1	
	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]

Based on an average weight of 39kg, and using the updated information on level of patient identification and market uptake, the results show that the average annual budget required is approximately [redacted] million and [redacted] million with and without the patient access scheme, respectively, compared to approximately [redacted] million and approximately [redacted] million, respectively in the updated budget impact model.

Table 28: Summary of the original and Scenario 2a

Year	Updated budget impact model		Scenario 2a	
	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]

Using an average weight of 53kg, and the updated information on level of patient identification and market uptake, average annual cost without the patient access scheme was approximately [redacted] million compared to [redacted] million in the updated model. With the patient access scheme, average

annual cost is approximately [redacted] million compared to [redacted] million in the updated budget impact model.

Table 29: Summary of the original and Scenario 2b

Year	Updated budget impact model		Scenario 2b	
	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]

Using the percentages of the level of identification and market uptake presented in the original model, and the average weight of 39kg used in Scenario 2, the average annual cost without the patient access scheme was approximately [redacted] million compared to the [redacted] million in the updated model. Average annual cost with the patient access scheme was approximately [redacted] million compared to [redacted] million per year in the updated model.

Table 30: Summary of the original and Scenario 3

Year	Updated budget impact model		Scenario 3	
	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)	Total annual cost without patient access scheme (£)	Total annual cost with patient access scheme (£)
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]

The contents of this document have been omitted as they are confidential

The contents of this document have been omitted as they are confidential

Revised cost-consequence model results implementing the financial aspects of the MAA as presented to NHS England

The ERG made the following changes to the model in their analysis.

We have accepted the following changes:

- Different parametric survival models for scoliosis and ventilation assistance
- Discount rates of 3.5%
- Decline in ataluren >400m group after 2 years was midpoint of >400m and 300-400m decline

We have not accepted the following changes:

- Allowing patients to develop scoliosis post puberty
- Number of equivalent primary caregivers affected reduced from 3 to 2
- Non-ambulatory utilities set to be the same for both arms of the model
- No treatment effect in <300m group

We have compromised on the following changes:

- Disutility of scoliosis assumed to be 0.2

This model with the five aforementioned changes is referred to below as the PTC revised cost-consequence model.

Base case: PTC revised model with capped price per patient for the duration of the MAA

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	4.087	-0.914	5.001	2.977	-0.914	3.891
ICER		[redacted]			[redacted]	

Scenario analysis: PTC revised model with capped price per patient for lifetime treatment

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	7.647	-0.914	8.562	3.647	-0.914	4.561
ICER		[redacted]			[redacted]	

Scenario analysis: ERG revised model with capped price per patient for the duration of the MAA

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	3.694	0.803	2.890	2.716	0.803	1.913
ICER		[redacted]			[redacted]	

Scenario analysis: ERG revised model with capped price per patient for lifetime treatment

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	7.212	0.803	6.409	3.192	0.803	2.389
ICER		[redacted]			[redacted]	

DETAILED DESCRIPTION OF ERG CHANGES AND WHAT WE ACCEPT / DO NOT ACCEPT

ERG amendment 1 - accepted

The ERG disagreed with some of our choices regarding updated parametric curves for deriving non-ambulatory events, such as scoliosis, ventilation assistance and death. The ERG prefer the use of curves that are statistically the best fitting, whereas we were also addressing clinical plausibility. Although we believe that the scenarios preferred by the ERG are less clinically plausible, we have incorporated their amendments.

ERG amendment 2 – not accepted

Based on clinical opinion and published literature, a restriction was added to transition to scoliosis, such that patients do not develop scoliosis after puberty. The ERG acknowledged that scoliosis rates would be expected to be lower for patients who lose ambulation at a later age. However, they felt that the effect of the restriction, which meant a negligible number of patients in the ataluren arm developed scoliosis, was uncertain. They thought that the incidence should be lower, but not zero. They therefore imposed no restriction on the age at which patients developed scoliosis.

The ERG's assumption leads to the prediction that 75% ataluren and 80% of placebo patients develop scoliosis, which is completely unrealistic in light of the fact that currently around 20% UK patients develop scoliosis.

ERG amendment 3 - accepted

Following discussion with NICE and the ERG, we understand why they believe the applicability of the 1.5% discount rate to this evaluation is uncertain and we have therefore incorporated 3.5% into the revised model.

ERG amendment 4 - compromise

In our original submission a 0.1 disutility for scoliosis was used but based on further research and clinical opinion this was increased to 0.3. ERG preferred the original disutility of 0.1. Scoliosis is hugely detrimental to patients' function and therefore quality of life; even after corrective surgery, patients have very little physical function to the point that they are unable to self-feed. We believe that the disutility is 0.3 and the ERG prefers a more conservative assumption of 0.1 so in the absence of further data we propose a midway point of 0.2.

ERG amendment 5 - not accepted

Caregiver disutilities were increased from one primary caregiver to two primary caregivers and 2 secondary caregivers with half the disutility of a primary caregiver each. At the first Committee meeting, the Committee noted that the model had not captured the full burden of DMD on patients and their families. In an attempt to address this between the first and second Committee meetings we undertook a small survey to try and capture this extended impact. What was clear from the albeit small number of responses received was that this condition affects the parents, siblings and extended family due to the level of disability that occurs at an early age. In addition, the Committee acknowledged that the EQ-5D is unlikely to be a good measure of caregiver burden in this scenario so using value of 0.11 for each full-time caregiver is likely to be an underestimate of the true burden. We have therefore kept a carer disutility at 0.33 in our revised model.

ERG amendment 6 – not accepted

To account for the possibility that patients may have a higher quality of life post loss of ambulation with ataluren, due to being in a better state at loss of ambulation, we included differential utilities for the post loss of ambulation state of ataluren and BSC. BSC patients had a utility of 0.12 and ataluren patients had a utility of 0.25 in the non-ambulatory states. The ERG preferred the original assumption of using 0.12 in both arms. It is essential to capture to better state of quality of life that is associated with delayed loss of ambulation. An adult losing ambulation in their 20s is going to be in a better state of health, both physically and mentally, than a boy that loses ambulation in early teenage years. This was supported in the Committee meeting by the clinical experts.

ERG amendment 7 – partly accept

In our model, we used the observed decline in the placebo arm of the >400m group for the first two years only after which we used an average of the >400m and 300-400m groups for placebo. This was used until patients reached 400m, after which only the 300-400m decline was applied. Once patients reached 300m, the decline was further increased based on the observations of the <300m group. This non-linear decline over time lead to an age of loss of ambulation of 14 years, which is consistent with current best standard of care.

In the ataluren arm, we did not make these adjustments to the >400m group i.e. we used the >400m observed data until patients reached 400m, after which we used the 300-400m data until patients reached 300m, after which we used the <300m data.

The ERG provided one scenario in which only the trial data was used, with no adjustment to either placebo or ataluren. This resulted in a mean age at loss of ambulation of 19.2 years for placebo, which is not compatible with actual clinical evidence and published literature.

Two alternative approaches were also suggested by the ERG:

1. Make the same adjustment for ataluren as placebo (i.e. after two years take the average of the >400m and 300-400m groups and use that for the >400m group.)

2. Take the [redacted] increase in 48 week decline used for the placebo arm after two years, and applying this same adjustment to the ataluren arm.

A treatment effect measured by the 6MWD would not be visible over a 48-week study in patients that are not declining in their ability to perform this test over the same period. It is therefore not surprising that the Phase III studies have not demonstrated a significant change in the 6MWD in these patients over 48 weeks. However, based on the mode of action of ataluren and the myometry data from Study 007, as well as clinical opinion, it is expected that ataluren will be most effective in the long-term when started early. Therefore, the ERG's Approach 1 is highly likely to understate the long-term effectiveness of ataluren in the >400m group. While PTC disagrees with the approach, we appreciate the concerns raised by the committee in terms of the long-term data for the >400m group and as such, at this point in time and with the intention of avoiding further delays, we accept this amendment.

Approach 2 is entirely inappropriate because it applies a mean decline in the ataluren arm of [redacted] per 48 weeks then reducing to [redacted] as the patients lose ambulation – this is the wrong way around, decline should be increasing over time rather than increasing - see plot below.

[redacted]

ERG amendment 8 – not accepted

We stated that "as the 6MWD is not a sufficiently sensitive tool to measure treatment effect in the <300m group but that the NSAA and TFTs showed ataluren had a treatment effect of approximately [redacted] on average, a conservative [redacted] treatment effect of ataluren on 6MWD decline in the <300m group was applied." The ERG rejected this scenario and just used the trial observed 6MWD data therefore assuming no treatment effect in the <300m subgroup.

The 6MWD is not an appropriate measure of declining function in patients with a <300m difference

- If boys have very low function, they are unlikely to be able to face even taking the 6MWT test (a physically demanding test) and the clinician may feel it is not appropriate to subject such boys to a test. Therefore, the decline in 6MWD is artificially high.
- Timed functions tests and the NSAA have shown that ataluren has a substantial difference compared to placebo in the <300m group and therefore has a clear treatment effect. We are trying to simulate the time to loss of ambulation and it is therefore important that the effect of ataluren in this subgroup is factored into the model.
- There is published evidence of a correlation between NSAA and 6MWD (Mazzone et al) and this was used as the basis of the proxy adjustment to the 6MWD in the model for the <300m patients as the model was not built to use NSAA results.

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene- ERG critique of 'Revised cost-consequence model results implementing the financial aspects of the MAA as presented to NHS England'

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Please note that: Sections highlighted in yellow and underlined are [redacted]
Sections highlighted in aqua and underlined are [redacted]

Cost-effectiveness models (16th February 2016)

The Company has submitted updated cost-effectiveness models, which incorporate [redacted], whilst also applying a patient access scheme (PAS) at a [redacted] discount rate. [redacted].

These analyses undertaken by the Company incorporate some changes recommended by the ERG:

- *Different parametric survival models for scoliosis and ventilation assistance*
- *Discount rates of 3.5%*
- *For the intervention (ataluren) group with a 6MWD >400m the decline was estimated to be at the midpoint of the >400m and the 300-400m decline after two years*
- *Disutility of scoliosis assumed to be 0.2*

Other changes proposed by the ERG which were not accepted by the Company:

- *Allowing patients to develop scoliosis post puberty*
- *Number of equivalent primary caregivers affected reduced from 3 to 2*
- *Non-ambulatory utilities set to the same for both arms of the model*
- *No treatment effect in <300m*

The Company has presented results on:

1. Base case: PTC revised model with capped price per patient for the duration of the MAA
2. Scenario analysis: PTC revised model with capped price per patient for lifetime treatment
3. Scenario analysis: ERG revised model with capped price per patient for the duration of the MAA
4. Scenario analysis: ERG revised model with capped price per patient for lifetime treatment

1. Base case: PTC revised model with capped price per patient for the duration of the MAA

   The ERG is happy with this model, and the results for the linear and stepped analyses. (Table 1).

Table 1: Base case: PTC revised model with capped price per patient for the duration of the MAA

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	4.087	-0.914	5.001	2.977	-0.914	3.891
ICER		[redacted]			[redacted]	

2. Scenario analysis: PTC revised model with capped price per patient for lifetime treatment

   A model for these analyses was not submitted, however, the ERG has cross checked the findings, making equivalent changes to the model as submitted for point 1, and the results are the same as those reported by the Company. (Table 2).

Table 2: Scenario analysis: PTC revised model with capped price per patient for lifetime treatment

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	7.647	-0.914	8.562	3.647	-0.914	4.561
ICER		[redacted]			[redacted]	

3. Scenario analysis: ERG revised model with capped price per patient for the duration of the MAA.

   The ERG notes that this includes the following:

   - Different parametric survival models for scoliosis and ventilation assistance
   - Discount rates of 3.5%
   - For the intervention (ataluren) group with a 6MWD >400m the decline was estimated to be at the midpoint of the >400m and the 300-400m decline after two years
   - Disutility of scoliosis assumed to be 0.2
   - Allowing patients to develop scoliosis post puberty
   - Number of equivalent primary caregivers affected reduced from 3 to 2
   - Non-ambulatory utilities set to the same for both arms of the model
   - No treatment effect in <300m

   The ERG is happy with this model, and the results for the linear and stepped analyses. (Table 3).

Table 3: Scenario analysis: ERG revised model with capped price per patient for the duration of the MAA

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	3.694	0.803	2.890	2.716	0.803	1.913
ICER		[redacted]			[redacted]	

4. Scenario analysis: ERG revised model with capped price per patient for lifetime treatment

   Again, a model for these analyses was not submitted, however, the ERG cross checked the findings, again making equivalent changes to the model as submitted for point 3, and the results are the same as those reported by the Company. (Table 4) Again the ERG notes that this model includes the following:

   - Different parametric survival models for scoliosis and ventilation assistance
   - Discount rates of 3.5%
   - For the intervention (ataluren) group with a 6MWD >400m the decline was estimated to be at the midpoint of the >400m and the 300-400m decline after two years
   - Disutility of scoliosis assumed to be 0.2
   - Allowing patients to develop scoliosis post puberty
   - Number of equivalent primary caregivers affected reduced from 3 to 2
   - Non-ambulatory utilities set to the same for both arms of the model
   - No treatment effect in <300m

Table 4: Scenario analysis: ERG revised model with capped price per patient for lifetime treatment

	Linear			Stepped		
	Ataluren	**BSC**	**Incremental**	**Ataluren**	**BSC**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	7.212	0.803	6.409	3.192	0.803	2.389
ICER		[redacted]			[redacted]	

In conclusion the revised models appear to be correct. The ERG noted that not all the recommended changes proposed by the ERG are included in the PTC model.

NICE National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

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Contents:

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

Evaluation consultation document

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

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

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

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

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

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

After consultation:

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

For further details, see the Interim Process and Methods of the Highly Specialised Technologies Programme.

The key dates for this evaluation are:

Closing date for comments: 6th November 2015

Second Evaluation Committee meeting: 17th November 2015

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

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

1 Evaluation Committee's preliminary recommendations

1.1 Ataluren is an important development in treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. However, the Evaluation Committee has not yet been presented with an adequate justification for its considerable cost, in light of the available evidence of its effect on health outcomes relevant for patients, carers and family members.

1.2 The Committee is therefore minded to not recommend ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene.

1.3 The Committee recommends that NICE requests further clarification from the company on the size of the benefit ataluren provides for patients, carers and family members, taking into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020).

1.4 The Committee also recommends that NICE requests the company to provide further justification for the cost of ataluren per patient, taking into account the size of the benefit after further clarification (see 1.3), and compared with the benefit obtained with other highly specialised technologies available to NHS patients.

2 The condition

2.1 Duchenne muscular dystrophy (DMD) is a severe, progressive X-linked recessive disorder that mainly affects males. DMD with a nonsense mutation is caused by a single base variation in a person's DNA, which leads to incomplete dystrophin production in the skeletal, smooth and cardiac muscle fibres. Dystrophin production is usually affected from birth and symptoms of DMD appear by age 3 years. The main symptom of DMD is motor dysfunction but, as the disease progresses, the gastrointestinal tract and vital organs such as the heart are affected. People with DMD have a decline in physical functioning, with subsequent respiratory and cardiac failure that leads to death, usually before age 30 years.

2.2 Current management of DMD includes treatment with corticosteroids. Other interventions include cardiac and respiratory monitoring and support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation. In addition, dietetic advice (and, in some cases, gastric feeding), prevention and treatment of bone fragility, management of the complications of long-term corticosteroid therapy and psychosocial support may be needed. Clinical care is provided by a range of healthcare professionals depending on local services, including neurologists or paediatric neurologists/neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians and primary care physicians.

3 The technology

3.1 Ataluren (Translarna, PTC Therapeutics) restores the synthesis of dystrophin by allowing ribosomes to read through premature stop codons that cause incomplete dystrophin synthesis in nonsense mutation Duchenne muscular dystrophy (DMD). Ataluren has a conditional marketing authorisation in the UK for treating DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 5 years and older. The marketing authorisation is linked to results being

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

3.2 The summary of product characteristics lists the most frequent adverse reactions as nausea, vomiting and headache (occurring in 1 in 10 people or more). For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The recommended dosage of ataluren is 40 mg/kg body weight per day. The company submission states that the list price of ataluren is £2532 per box of 30 sachets containing ataluren 125 mg. Assuming a median weight range of 24–26 kg, the total cost per person per year of treatment with ataluren is £220,256. The company has agreed a patient access scheme with the Department of Health. If ataluren had been recommended, this scheme would have provided a simple discount to the list price of ataluren with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

4 Evidence submissions

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

Nature of the condition

4.1 Evidence from patient experts and patient groups highlighted the substantial impact of Duchenne muscular dystrophy (DMD) on the quality of life of people with the condition and their families:

- People with DMD have a loss of motor function until eventually they become wheelchair dependent, making it difficult to participate in normal activities at home or at school with siblings, family and friends. Parents and carers describe the frustrations experienced by their child when they cannot take part in games with their peers. Often, younger children do not understand the implications of the disease and why it makes them different.
- As the disease progresses, people with DMD lose the ability to breathe unaided and need assisted ventilation. Scoliosis develops as the back muscles weaken, for which surgery is needed. Parents and carers of people with DMD describe the importance of maintaining their child's ability to walk for as long as possible because loss of ambulation is an indication of disease progression.
- Parents and carers of people with DMD describe the emotional impact of the short life expectancy of people with DMD. They describe the sadness, anxiety and depression of knowing their child will probably die at a young age. The devastating impact of the disease and its prognosis often leads to isolation from friends and family members.
- Parents and carers described the financial impact of looking after a person with DMD. They described giving up work to look after their child full time. In addition, out-of-pocket expenses can be very high (for example, moving house to ensure the home is wheelchair accessible).

Clinical evidence

4.2 The safety and efficacy of ataluren was investigated in a phase 2b double-blind randomised placebo-controlled trial (Study 007). Study 007 included 174 male patients with nonsense mutation DMD aged 5 years and older. Patients were recruited from 37 study sites in 11 countries and included 7 patients from the UK. They were randomised to ataluren at a total daily dosage of 40 mg/kg (n=57) or 80 mg/kg (n=60), or to placebo (n=57), all for 48 weeks. The primary outcome was change in the patient’s ability to walk on a hard, flat surface measured using the 6-minute walk distance

(6MWD). The study compared the mean change in 6MWD from baseline to week 48 measured in the placebo group with that in the ataluren group. The secondary outcomes included change in proximal muscle function measured by timed function tests, and change in force exerted during knee flexion and extension. Quality of life was assessed using the Pediatric Quality of Life Inventory, which contains 4 scales: physical, emotional, social and school functioning.

4.3 The prespecified subgroups in Study 007 were: age (less than 9 years and 9 years and older), corticosteroid use (yes or no) and baseline 6MWD (350 m or less and greater than 350 m). The company conducted a post-hoc subgroup analysis in patients who were classified as being in the decline phase. The decline phase was defined as patients aged 7–16 years with a baseline 6MWD test of 80% or more of that predicted and, to minimise heterogeneity, a baseline 6MWD of 150 m or more on a stable dose of corticosteroids. The decline phase was considered clinically important because patients younger than 7 years tend to increase their 6MWD over 48 weeks because of normal developmental improvements in walking.

4.4 The intention-to-treat analysis showed no statistically significant difference between ataluren and placebo in the change in 6MWD from baseline to 48 weeks. In the corrected intention-to-treat analysis, baseline values for 2 patients (1 taking placebo and 1 taking ataluren 80 mg/kg) were replaced by their values at screening because the patients had lower-limb injuries before the baseline test. In this analysis, there was a mean observed difference at 48 weeks of 31.3 m between ataluren 40 mg/kg and placebo (-12.9 m and -44.1 m respectively). In a mixed model for repeated measures analysis, the estimated mean difference between ataluren 40 mg/kg and placebo was 31.7 m (95% confidence interval [CI] 5.1 to 58.3, p=0.0197). No effect was seen in the ataluren 80 mg group.

4.5 In the post-hoc subgroup analysis for patients in the decline phase, patients having ataluren experienced a statistically significantly smaller reduction in 6MWD compared with patients having placebo (difference in mean change in 6MWD of 45.6 m, p=0.0096). In the pre-specified group of patients with a baseline 6MWD of less than 350 m, there was a statistically significantly smaller reduction in 6MWD in the ataluren group compared with the placebo group (difference in mean change in 6MWD of 59.8 m, p=0.0053).

4.6 There were no statistically significant differences in quality of life between the ataluren and placebo groups. The company stated there was a positive trend towards improved quality of life with ataluren 40 mg/kg daily in the physical functioning subscale. The company submission also described a positive effect on school functioning and a negative trend in emotional and social subscales.

4.7 The company reported that the number of adverse events was similar in the ataluren and placebo treatment groups in Study 007. None of the patients stopped treatment with ataluren or withdrew from the study because of a treatment-related adverse event, and there were no deaths reported. The most common treatment emergent adverse events reported were: gastrointestinal disorders (73.7% of patients in the ataluren 40 mg/kg group and 37% in the placebo group), vomiting (56.1% in the ataluren 40 mg/kg group and 45% in the placebo group) and diarrhoea (19.3% in the ataluren 40 mg/kg group and 28.3% in the placebo group).

Economic evidence

4.8 The company presented a cost–consequence analysis comparing the licensed dose of ataluren (40 mg/kg daily) with best supportive care in people aged 5 years or older who were ambulatory. The company's Markov model had 6 states, representing the progression of DMD from the ambulatory phase to the non-ambulatory phases and death. The cycle length was 3 months and the time horizon of the model was limited to the

last point when 1 or more patients were in the ambulatory state (because only patients who were ambulatory had treatment). The analysis was carried out from the perspective of the NHS and personal social services, and costs and benefits were discounted at a rate of 3.5% per year.

4.9 To inform the best supportive care transition probabilities for loss of ambulation, the company used Kaplan–Meier estimates from the literature to derive time-dependent transition probabilities based on patient age. Ricotti et al. (2013) reported long-term outcomes of boys with DMD in the UK, comparing daily and intermittent use of corticosteroids. In this study, loss of ambulation with daily corticosteroid use occurred at a median age of 14 years. The company considered it reasonable to assume that these data were representative of the placebo arm in Study 007. In its base case, the company used a Weibull function to fit the data.

4.10 To inform the transition probabilities for ataluren compared with placebo, a linear regression of the values of 6MWD from week 24 to week 48 of Study 007 against time was done. The regression analysis was performed on the data from week 24 to week 48 because the company deemed it to be more representative of the long-term treatment effect of ataluren. The company suggested that this was a conservative assumption because ataluren had a greater benefit compared with best supportive care in improving 6MWD in the first 24 weeks of the study. The linear extrapolation suggested that loss of ambulation would occur in the best supportive care group at week 313 (6.0 years) and at week 733 (14.1 years) in the ataluren group, which equated to a difference of 420 weeks (8.1 years). The company fitted a Weibull curve and shifted the best supportive care curve to the right so that the difference in median time to loss of ambulation between ataluren and best supportive care was 8.1 years (that is, the same as that predicted by linearly extrapolating Study 007 data). In its response to clarification, the company explored fitting alternative parametric models.

4.11 The company model included health-related quality-of-life data from the literature to inform the utility values in the cost–consequence analysis (Landfeldt et al. 2014) for patients and carers. It explained that it did not use the paediatric quality-of-life inventory data from Study 007 because the algorithm used to map the data to EQ-5D was adapted from a study by Khan et al. (2014), which was conducted in a healthy population. The company said that no loss of utility for adverse events had been included in the company model because there were no significant differences in the incidence of adverse events between the ataluren and placebo arms in Study 007.

4.12 The company estimated that the total cost per year of treatment with ataluren for an average 8-year-old child weighing 26 kg is £246,448. To calculate the cost per patient in the cost–consequence analysis, an age–weight curve from the Royal College of Paediatrics and Child Health was used to estimate the annual increase in weight for the cohort, with a starting age of 8.5 years. The company assumed no additional costs for monitoring. Health-state costs were taken from a published study (Landfeldt et al. 2014) and were converted using the UK 2012 purchasing power parity (OECD, 2015) and then inflated to 2014 costs using the consumer price index for health (ONS, 2015). For patients in the ambulatory health state, the total costs were £9605. For patients in a non-ambulatory health state, the total costs were £23,600. In the non-ambulatory and ventilation-assisted health state, the total costs were also £23,600. In the non-ambulatory with scoliosis (with or without assisted ventilation) health states, the total costs ranged from £25,058 to £46,043.

4.13 In the company's base case, best supportive care was associated with £235,207 in costs and 2.39 quality-adjusted life years (QALYs) over the lifetime of the model. Ataluren, at list price, was associated with £5,092,540 in costs and 6.15 QALYs, amounting to an incremental cost of £4,857,333 and an additional 3.77 QALYs compared with best supportive

care. The incremental costs when applying the patient access scheme price for ataluren are confidential.

4.14 The deterministic sensitivity analysis indicated that the results were most sensitive to the discount rate for benefits and costs; changing this parameter changed the total QALYs by −21% to 41%. Apart from the discount rate, the results were most sensitive to ambulatory patient utility; changing this parameter changed the total QALYs by −19% to 19%. No probabilistic sensitivity analysis was presented.

4.15 The company presented a budget impact analysis to predict the cost of ataluren to the NHS and personal social services. The company estimated that, in year 1, a total of 35 people would have treatment, rising to 65 in year 5. The budget impact in year 1 (using the ataluren list price) was estimated to be about £8,625,680, rising to £16,019,120 in year 5. The results of the budget impact analysis that incorporate the patient access scheme are confidential.

Evidence Review Group review

Clinical effectiveness

4.16 The ERG noted that the submitted evidence reflected the decision problem and considered most of the analyses to be appropriate. The ERG noted several limitations in the clinical-effectiveness evidence presented by the company, including the following:

- The company's methods used in the systematic review were not clearly described, providing the opportunity for error and bias.
- There were inconsistencies in the reported p values for the change in 6MWD between the company submission and the European Medicines Assessment agency report.
- The follow-up time in Study 007 (48 weeks) was potentially too short to measure important outcomes (for example, mortality).

- A summary of serious adverse events from 4 ongoing and 5 completed company-sponsored clinical trials suggested that several of these, including femur fractures, were more common with ataluren than with placebo. However, the ERG was unclear if this was because of longer exposure in the ataluren group.

Cost effectiveness

4.17 The ERG noted the lack of evidence available on the long-term follow-up of people with DMD and considered that the company's use of external studies to inform model transition probabilities was valid. However, the ERG considered that there were issues with the methods used to extrapolate the data for the model, which it investigated in its exploratory analyses. In addition, the ERG noted that the model assumed that the treatment benefit of ataluren over best supportive care remained the same over time, which may not be clinically plausible.

4.18 The ERG noted that the company had not used the Pediatric Quality of Life Inventory data collected during Study 007 in its economic model. It disagreed with the company's view that it was inappropriate to map the data onto the EQ-5D scale using an algorithm adapted from a study conducted in a healthy population. The ERG believed that, in principle, the utility data derived from the clinical trial should be preferred to values from the literature.

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

ERG exploratory analyses

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

fits. Flexible parametric models were selected for all transitions other than for the ambulatory to non-ambulatory state. For transitions to the non-ambulatory state, a log-normal model was used: although a flexible parametric model gave the best statistical fit, the ERG stated that its predictions may not be clinically plausible.

4.21 The ERG produced several additional sets of analyses. The ERG's preferred scenario used a lifetime horizon and included the costs for continuing treatment with ataluren 6 months after loss of ambulation. The ERG included this assumption because, although the company submission said that people would continue to have treatment for up to 6 months following loss of ambulation, these costs were not included in the company's base-case analysis. The ERG's preferred scenario also included the best-fitting parametric curves discussed in section 4.20).

4.22 In the ERG's preferred scenario analysis, best supportive care was associated with £199,194 in costs and 3.80 QALYs over the lifetime of the model. Ataluren, at list price, was associated with £5,744,175 in costs and 6.86 QALYs, amounting to an incremental cost of £5,544,981 and an additional 3.05 QALYs compared with best supportive care.

4.23 The ERG also presented exploratory analyses to explore the effects of key assumptions on the company's budget impact estimates. The ERG explored changing the average weight of people having treatment to the average weight of people occupying the ambulatory health state in the cost–consequence model (39 kg in the best supportive care group and 53 kg in the ataluren group). Using the list price and an average weight of 39 kg, the budget impact in year 1 was estimated to be about £13,456,065, rising to ££24,989,835 in year 5. The corresponding results using an average weight of 53 kg were £18,286,450 and £33,960,550 respectively. The results incorporating the patient access scheme are confidential and may not be presented.

4.24 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the Evaluation report.

5 Consideration of the evidence

The Evaluation Committee reviewed the data available on the benefits and costs of ataluren, having considered evidence on the nature of Duchenne muscular dystrophy (DMD) and the value placed on the benefits of ataluren by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that ataluren represents and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The Committee discussed the nature of nonsense mutation DMD. It understood that DMD is a serious, progressive condition that reduces life expectancy and causes debilitating symptoms associated with loss of muscle strength that severely affect the quality of life of people with the condition, and their parents and siblings. The Committee heard from the patient experts that one of the most important aspects of managing DMD is maintaining their child's ability to walk. It heard that this means their child can continue to lead a more rounded life, for example, going to school on the bus independently, participating more fully with their friends and siblings in social and sporting activities, and spending more time with family and friends. It also heard that a loss in ambulation is followed by a greater deterioration in functioning that usually means people need constant care to perform routine daily activities such as getting out of bed, eating and going to the toilet. The Committee concluded that DMD is a serious life-threatening condition that progressively affects quality of life, with the greatest impact after loss of ambulation.

5.2 The Committee considered the current treatment options for nonsense mutation DMD. It heard from the clinical experts that the mainstay of

treatment is corticosteroid therapy, which can slow the decline in muscle strength and function. This, in turn, may help to prolong ambulation. It also heard, however, that corticosteroids can cause unwanted effects such as growth retardation, bone thinning, mood swings and weight gain. It further heard from the clinical experts that new treatments are desired that prolong the time a person is able to walk by addressing the underlying cause of disease and with a more favourable adverse-event profile. The Committee concluded that further treatment options are needed to extend the time to loss of ambulation and thus maintain quality of life.

Impact of the new technology

5.3 The Committee heard from the clinical experts that, because ataluren potentially addresses the nonsense mutation that causes DMD to develop, they considered it to be a step change in the management of DMD.

5.4 The Committee discussed how treatment benefit was assessed in the clinical trial. It was aware that the primary end point in Study 007 was the 6-minute walk distance (6MWD). It heard from the clinical experts that the 6MWD is a well-validated tool used in clinical trials to assess functioning in DMD. The Committee considered the secondary endpoints in the trial and heard from the clinical experts that some of these measures, such as time to get up and stand or time to run 10 m, are used more often in clinical practice but are not as clinically informative as the 6MWD. The Committee concluded that the 6MWD was an appropriate primary endpoint to assess the benefits of treatment with ataluren in the clinical trial.

5.5 The Committee considered the robustness of the results of Study 007. It noted that, in the intention-to-treat analysis, there was no statistically significant difference in change in 6MWD between the ataluren and best supportive care groups but that, in the corrected intention-to-treat analysis, there was a statistically significant difference of 31.7 m favouring

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

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

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

5.7 The Committee considered whether all the possible treatment benefits associated with ataluren had been captured in Study 007. It noted that there was no statistically significant difference in quality of life reported in the ataluren group compared with the best supportive care group (see section 4.6). However, the Committee considered that the results of the Paediatric Quality of Life Inventory questionnaire did not reflect the statements received by the patient experts. The Committee heard from the patient experts that they had seen meaningful stabilisation or improvements in their child's walking ability after having ataluren, which meant their child could continue daily activities unaided, such as getting out of bed, getting in the car and going to school. The Committee further noted that the duration of Study 007 was 48 weeks, and considered that this was too short to determine any long-term benefits of treatment with ataluren (for example, an effect on mortality). This was important because the company had assumed in its submission that the loss of ambulation was correlated to mortality and, by delaying the loss of ambulation, ataluren has the potential to improve survival. The Committee concluded that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren, and that there was uncertainty about the longer-term benefits of ataluren treatment because of the limitations in the evidence base.

5.8 The Committee considered the evidence on adverse events reported in Study 007. It noted that there was no significant difference in adverse events reported in Study 007. It heard from the clinical experts that, in their experience, ataluren is well tolerated and treatment has not been stopped because of adverse events. The Committee understood that

regulatory requirements around the risks associated with ataluren treatment are outlined in the summary of products characteristics and the European public assessment report for ataluren. The Committee concluded that there were no specific safety concerns associated with ataluren.

Cost to the NHS and Personal Social Services

5.9 The Committee considered the results of the company's budget impact model. It noted that, at list price, the total cost per person per year of treatment with ataluren is £220,256 (assuming a median weight range of 24–26 kg). It further noted that the company had estimated that, in year 1, the total cost of treating nonsense mutation DMD with ataluren (at list price) is £8.6 million, rising to £16 million in year 5 (see section 4.15). The Committee acknowledged that these costs would be lower when using the price incorporating the patient access scheme.

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

5.11 The Committee considered the cost of ataluren in the context of the costs incurred by the company for research, development and manufacturing, and asked the company for an explanation for the cost of the drug. It heard from the company that the cost of ataluren is driven by the need to recoup the high costs of research and development (and to fund future investment in other therapy areas), as well as manufacturing and marketing a treatment that can only be used by a small number of patients. The Committee acknowledged that developing orphan and ultra-orphan treatments was associated with challenges that were different from treatments with bigger patient populations; however, it was not convinced that the high cost per patient of ataluren was justified compared with other treatments for rare conditions. The Committee was unsure if there were any clinical or safety needs during clinical development that might justify the development cost of ataluren being materially greater than for other treatments for small populations. Furthermore, the Committee was not satisfied that there was an explanation of the relationship between the development costs of ataluren and the price being proposed for the NHS. Based on the information with which it had been presented, the Committee concluded that it was uncertain if the proposed cost of ataluren was justified by the incremental therapeutic improvement over standard therapy.

Value for money

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

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

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

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

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

5.16 The Committee discussed the results of the company's cost–consequence model. It noted that the results of the company's base-case analysis showed that best supportive care was associated with £235,207 in costs and 2.39 quality-adjusted life years (QALYs) over the lifetime of the model. Ataluren, at list price, was associated with £5,092,540 in costs and 6.15 QALYs, amounting to an incremental cost of £4,857,333 and an additional 3.77 QALYs compared with best supportive care. Total costs and incremental costs for ataluren compared with best supportive care that incorporated the patient access scheme were considered commercial in confidence and cannot be reported. However, after considering its discussions in sections 5.10–5.15, the Committee concluded that the assumptions used in the ERG's exploratory analysis were more plausible. In the ERG's exploratory analysis, best supportive care was associated with £199,194 in costs and 3.80 QALYS over the lifetime of the model. Ataluren, at list price, was associated with £5,744,175 in costs and 6.86 QALYs, amounting to an incremental cost of £5,544,981 and an additional 3.05 QALYs compared with best supportive care. The total cost of ataluren and incremental costs incorporating the patient access scheme were considered commercial in confidence and cannot be reported here. The Committee concluded that it was likely that treatment with ataluren generated around 3 additional QALYs compared with best supportive care.

5.17 The Committee considered the overall value for money provided by ataluren. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. The Committee noted that the company had estimated the total budget impact (list price) for 35 patients in year 1 to be £8.6 million, meaning that the estimated cost of ataluren per patient for year 1 (list price) would be £245,714. The Committee acknowledged that the cost per patient per year and total budget impact would be lower when using the price incorporating the patient access scheme. The Committee considered the overall value of ataluren, taking into account both its health

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

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

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

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

5.18 The Committee acknowledged the potential wider societal benefits of ataluren treatment proposed by the company and patient experts, including the ability to contribute to society and continue education. It heard from the patient experts that, because ataluren is expected to delay the loss of ambulation, it will enable people with DMD to maintain their independence for longer and this will lead to cost savings. The Committee heard that potential cost savings include parents and carers staying in work for longer, a reduction in out-of-pocket expenses for travel to appointments, and more time spent with friends and family. The Committee acknowledged the expected cost savings but considered that, because ataluren was not a curative treatment, some costs may only be delayed until the disease progressed. However, on balance, the Committee was persuaded that the non-health effects of ataluren were likely to be of value in the short term.

5.19 The Committee considered the impact of ataluren on the delivery of the highly specialised service, and acknowledged statements from NHS England showing that treatment with ataluren is unlikely to involve additional services or monitoring costs. It heard from the clinical experts that services are already in place to monitor and treat people with DMD and, if ataluren were to be recommended for use, additional funding would not be needed. The Committee was therefore satisfied that no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment.

Conclusion

5.20 The Committee discussed the appropriate recommendations for ataluren for nonsense mutation DMD. It appreciated that DMD is a serious condition that has severe effects on the lives of people with the condition, as well as their families and carers. After considering all available

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

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

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

Summary of Evaluation Committee's key conclusions

	Evaluation title: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	Section
Key conclusion		
Ataluren is an important development in treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. However, the Evaluation Committee has not yet been presented with an adequate justification for its considerable cost, in light of the available evidence of its effect on health outcomes relevant for patients, carers and family members. The Committee is therefore minded to not recommend ataluren for treating Duchenne muscular dystrophy (DMD) with a nonsense mutation in the dystrophin gene. The Committee recommends that NICE requests further clarification from the company on: • the size of the benefit ataluren provides for patients, carers and family members, taking into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020). • further justification for the cost of ataluren per patient, taking into account the size of the benefit after further clarification, and compared with the benefit obtained with other highly specialised technologies available to NHS patients.		1.1–1.4
Current practice		
Nature of the condition, including availability of other treatment options	The Committee heard from the patient experts that DMD is a serious, progressive condition that reduces life expectancy and causes debilitating symptoms associated with loss of muscle strength that severely affect the quality of life of people with the condition, and their parents and siblings. The Committee heard from the clinical experts that the mainstay of treatment is corticosteroid therapy, which can slow the decline in muscle strength and function. This, in turn, may help to prolong ambulation. It also heard, however, that corticosteroids can cause unwanted effects such as growth retardation, bone thinning, mood swings and weight gain.	5.1, 5.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical experts that, because ataluren potentially addresses the nonsense mutation that causes DMD to develop, they considered it to be a step change in the management of DMD.	5.3
Adverse reactions	The Committee concluded that there were no specific safety concerns associated with ataluren.	5.8
Clinical evidence		
Availability, nature and quality of evidence	The Committee concluded that the 6-minute walk distance (6MWD) was an appropriate primary endpoint to assess the benefits of treatment with ataluren in the clinical trial. The Committee concluded that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren, and that there was uncertainty about the longer-term benefits of ataluren treatment because of limitations in the evidence base.	5.4, 5.7
Uncertainties generated by the evidence	The Committee noted that in Study 007 there was no statistically significant difference in change in 6MWD between the ataluren and best supportive care groups in the intention-to-treat analysis but that there was in the corrected intention-to-treat analysis. It accepted that the company's post-hoc adjustment could be justified but questioned whether the study had been sufficiently powered. The Committee was aware that a phase III confirmatory trial, Study 020, is examining the effect of ataluren compared with best supportive care in patients in the decline phase. The Committee considered that the results of Study 020 (due at the end of 2015) would provide valuable information that could reduce the uncertainty around Study 007 results.	5.5, 5.6
Impact of the technology	The Committee concluded that it was reasonable to use the post-hoc subgroup analysis of patients in the decline phase in its decision-making. It further concluded that the results of Study 007 suggested ataluren is associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care; however, there is considerable uncertainty in the robustness of the results.	5.5, 5.6
Cost evidence		

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

Cost to the NHS and Personal Social Services	The Committee considered the results of the company's budget impact model. It noted that, at list price, the total cost per person per year of treatment with ataluren is £220,256 (assuming a median weight range of 24–26 kg). It further noted that the company had estimated that, in year 1, the total cost of treating nonsense mutation DMD with ataluren (at list price) is £8.6 million, rising to £16 million in year 5. The Committee concluded that the company's calculations, whether using the list price or the price incorporating the patient access scheme, had likely underestimated the total budget impact of ataluren for treating nonsense mutation DMD.	5.9, 5.10
Value for money	The Committee concluded that the assumptions used in the ERG's exploratory analysis were more plausible than those in the company's base case. In the ERG's exploratory analysis, best supportive care was associated with £199,194 in costs and 3.80 QALYS over the lifetime of the model. Ataluren, at list price, was associated with £5,744,175 in costs and 6.86 QALYs, amounting to an incremental cost of £5,544,981 and an additional 3.05 QALYs compared with best supportive care. The total cost of ataluren and incremental costs incorporating the patient access scheme were considered commercial in confidence and cannot be reported here. Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model, the Committee remained concerned that the health benefits associated with ataluren treatment were not great enough to justify its high cost. In the absence of clear evidence explaining the reasons for ataluren's high cost and its lower incremental QALY gains than other highly specialised technologies that that have been evaluated by NICE, the Committee was unconvinced that ataluren represented overall good value for money to the NHS.	5.16, 5.17

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

6 Related NICE guidance

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

There is no related guidance for this technology.

7 Proposed date for review of guidance

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

Peter Jackson
Chair, Highly Specialised Technologies Evaluation Committee
October 2015

8 Evaluation Committee members, guideline representatives and NICE project team

Evaluation Committee members

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

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

The minutes of each Evaluation Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Peter Jackson (chair)
Consultant Physician and Honorary Reader in Clinical Pharmacology

Ron Akehurst
Health Service Researcher, Strategic Director

Steve Brennan
Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

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

Sarah Davis
Senior Lecturer in Health Economics, the University of Sheffield

Jonathan Howell
Public Health Physician – Consultant in Public Health

Vincent Kirkbride

Consultant Paediatrician, Sheffield NHS Foundation Trust

Jeremy Manuel

Lay member

Linn Phipps

Lay member

Mark Sheehan

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

Lesley Stewart

Director, Centre for Reviews and Dissemination, York

Sheela Upadhyaya (non-voting member)

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

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the Highly Specialised Technologies Programme.

Vicky Kelly

Technical Lead

Linda Landells

Technical Adviser

Leanne Wakefield

Project Manager

Meindert Boysen

Programme Director

9 Sources of evidence considered by the Committee

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

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

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

I. Company:

- PTC Therapeutics

II. Professional/specialist and patient/carer groups:

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

III. Other consultees:

- Department of Health
- NHS England

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

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

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

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

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

- Edmund Jessop selected by NHS England

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

- PTC Therapeutics

Highly Specialised Technology Evaluation

Duchenne muscular dystrophy (nonsense mutation) - ataluren [ID428]

Manufacturer's Response to the Evaluation Consultation Document (ECD)

Summary

NICE requested that further analyses from the company should be made available to the Evaluation Committee, including:

- *Further information on the size of the benefit with ataluren for patients, carers and family members, taking into account the results of Study 020*
- *Further justification for the cost of ataluren per patient, taking into account the size of the benefit of ataluren compared with the benefit obtained with other highly specialised technologies available to NHS patients*

We present results of Study 020 as requested by the Committee, which importantly include pre-specified subgroup and meta-analyses which, together with the results from Study 007, confirms the efficacy of ataluren.

The Committee concluded at the first appraisal committee meeting that it was reasonable to use the subgroup analysis of patients in the decline phase in its decision-making, as it was in this subgroup that the treatment effect of ataluren would be detected most readily. The results from Study 020 show consistent evidence of the clinical benefit of ataluren for individuals with nmDMD, its impact on the course of the condition, and the impact on quality of life for these boys and young men. The totality of the data for ataluren, as reflected in the pre-specified meta-analysis of the whole study populations as well as the 300-400m subgroup, consistently demonstrate clinical benefit across primary and secondary endpoints and confirm that ataluren positively impacts the course of disease progression.

The health economic model has been updated using the pooled data from the decline phase and shows the significant QALY gains that are achieved with ataluren. In addition we have incorporated suggestions from the ERG to improve the robustness and clinical validity of the modelling. The resulting analysis shows gains of 8-12 incremental QALYs with consistent relative incremental costs. This represents value for money that is comparable with other treatments for rare diseases already funded by the NHS, including those recently reviewed by the Committee.

In addition, we present further justification regarding the cost of ataluren and have addressed concerns regarding budget predictability.

The manufacturer's response is divided into the following areas:

Abbreviations

Term	Definition
ADL	Activities of Daily Living
cITT	Corrected intention to treat
CSR	Clinical study report
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	Food and Drug Administration
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LoA	Loss of ambulation
MRS	Magnetic resonance spectroscopy
NA	Non-ambulatory
nmDMD	Nonsense mutation Duchenne muscular dystrophy
NSAA	North Star Ambulatory Assessment
PedsQL	Paediatric Quality of Life Inventory
PODCI	Pediatric Outcomes Data Collection Instrument
QALY	Quality-adjusted life year
QoL	Quality of Life
SAP	Statistical analysis plan
SMC	Scottish Medicines Consortium
TFTs	Timed function tests
6MWD	6 minute walk distance
6MWT	6 minute walk test

Response 1 – Robustness of the clinical benefit of ataluren

ECD Section 1.3: Clarification on the size of the benefit ataluren provides for patients, carers and family members, taking into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020)

ECD Section 5.5: Committee concluded that the results of Study 007 suggested ataluren is associated with a meaningful improvement in the rate of decline in 6MWD compared with best supportive care; however, there is considerable uncertainty in the robustness of the results.

ECD Section 5.6: Committee discussed which was the most appropriate patient population to inform its decision-making. … It noted that a phase III trial, Study 020, is examining the effect of ataluren compared with best supportive care in patients in the decline phase and that study results are due at the end of 2015. The Committee considered that Study 020 would provide valuable information that could reduce the uncertainty around the results of Study 007. The Committee concluded that it was reasonable to use the subgroup analysis of patients in the decline phase in its decision-making, even though the results for this subgroup, in which effects should be detected most readily, remained uncertain because of the post-hoc nature of the analyses.

The Committee concluded at the first appraisal committee meeting that it was reasonable to use the subgroup analysis of patients in the decline phase in its decision-making, as it was in this subgroup that the treatment effect of ataluren would be detected most readily. The Committee was however uncertain of the robustness of the results from Study 007 because of the post-hoc nature of the analyses. PTC believes these concerns have been fully addressed by the results of Study 020, which importantly include pre-specified subgroup and meta-analyses and these confirm the efficacy seen in Study 007.

Moreover, the Duchenne Muscular Dystrophy (DMD) clinical and patient communities have welcomed the results of Study 020 (ACT-DMD), which confirm the clinical benefit of ataluren and further refines the optimum patient group in which it is possible to measure a significant therapeutic effect within the confines of a 48-week study.

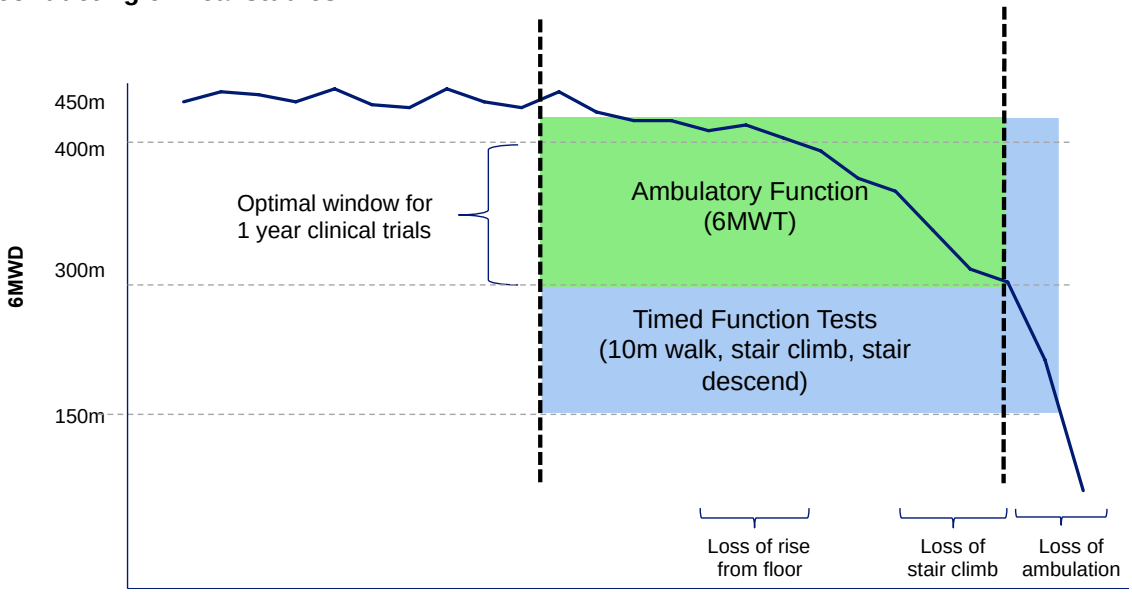
In the overall study population for Study 020, ataluren showed a 15m benefit over placebo in 6MWD ($p = 0.2$). Although Study 020 was designed with the intent of enriching for patients in the decline phase (6MWD at baseline of 150m-400m), in fact, the inclusion criteria of 6MWD <80% predicted and > 150m were too broad to capture only the decline phase population. Thus, the patients actually enrolled in Study 020 had a baseline range from [redacted]. This higher than anticipated upper value was attributed to patients achieving a higher than predicted 80% 6MWD at baseline, likely due to the wide variability of age and height when the study is performed in this age group. The lesser than anticipated lower value was attributed to differences in 6MWD between screening and baseline. Although the result for the primary endpoint was not statistically significant, this study has confirmed the clinical benefit of ataluren in nmDMD. It has also contributed to our evolved understanding of the natural history of DMD and has confirmed that for a clinical trial in DMD designed to show a treatment effect on the 6MWD over a 48-week period the optimum range for baseline 6MWD is 300-400m.

The results from the pre-specified subgroup analysis of 300-400m baseline 6MWD, along with the pre-specified meta-analyses, have conclusively demonstrated the treatment effect of ataluren in ambulatory patients with nmDMD. This aligns with the Committee's conclusion that it was reasonable to use the results and analyses of patients in the decline phase for decision-making and is supported by the FDA and EMA guidance, which provide for the use of meta-analyses and pre-specified sub-groups to demonstrate a treatment effect.

Patients with a baseline 6MWD of 300-400m have a demonstrable loss of ambulation but still have sufficient lower-limb muscle mass to detect a drug effect over a 48-week period using the 6MWT. Patients with baseline 6MWD >400m and <300m are too stable or have too

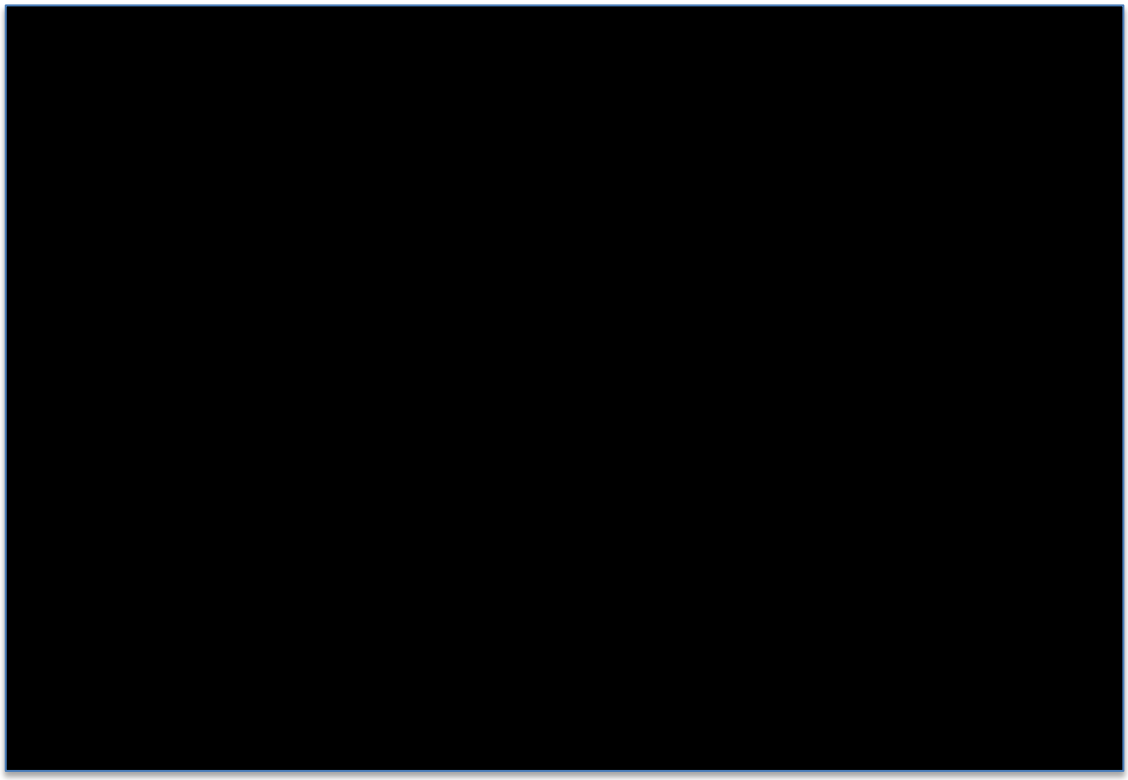
severe muscle loss (respectively) to be able to detect a statistically significant treatment effect in the 6MWT over a 48-week time period. Due to the nature of the 6MWD as an endurance test and considering the progressive nature of the patients with <300m, it has been suggested that shorter tests for burst effects are less burdensome for the patient (e.g., 10m walk/run and other TFTs). These tests show a more linear decline over the entire spectrum of the DMD continuum and might be more sensitive to detect differences in a 48-week clinical trial. This is illustrated diagrammatically in Figure 1.

Figure 1: Progressive loss of function highlights the complexities associated with conducting clinical studies in DMD



In Study 020, ataluren demonstrated a statistically significant benefit in the pre-specified 300-400m 6MWD baseline subgroup, with 47m less decline than placebo (p=0.007). This is highly consistent with the results seen in Study 007 where, in the 300-400m group, there was 49m less decline than placebo (p=0.026). In the pre-specified meta-analysis of the 300-400m groups from Study 007 and Study 020, ataluren patients had 45m less decline than placebo (p<0.001). These results demonstrate a robust and significantly consistent treatment effect of ataluren (Figure 2).

Figure 2: Clinical benefit of ataluren across primary and secondary endpoints in Study 007 (ambulatory decline phase), Study 020 (ACT-DMD) and the pre-specified meta-analysis in the optimal baseline 6MWD 300-400m population



Maintaining ambulation is key to boys with nmDMD and their families as it is not only a significant event from a healthcare and societal standpoint, but also a milestone for multiple complications for DMD patients as described in the original submission. [redacted]. In the 300-400m baseline 6MWD group, none of the 47 (0%) ataluren-treated patients lost ambulation during the 48 weeks of Study 020, which is the same as Study 007, while 4 of 52 (8%) placebo patients in this group became non-ambulatory. This observation confirms the ability of ataluren to prolong ambulation in boys with nmDMD.

Studies 007 and 020 are the two largest randomised placebo controlled trials ever conducted in DMD, with over 400 patients treated. The totality of the efficacy data for ataluren consistently demonstrates a clinical benefit across primary and secondary endpoints [timed function tests (TFTs) and North Star Ambulatory Assessment (NSAA)] (see Appendix 1).

These data confirm that ataluren changes the course of disease progression and provides clinically meaningful benefit. PTC recently met with the EMA and Rapporteurs to discuss the data from Studies 020 and 007 and confirmed our intention to submit these by the end of 2015 in order to satisfy the condition of the marketing authorisation.

Response 2 – Quality of life and patient impact

ECD Section 5.7: The Committee considered whether all the possible treatment benefits associated with ataluren had been captured in Study 007. It noted that there was no statistically significant difference in quality of life reported in the ataluren group compared with the best supportive care group. However, the Committee considered that the results of the Paediatric Quality of Life Inventory questionnaire did not reflect the statements received by the patient experts. The Committee heard from the patient experts that they had seen meaningful stabilisation or improvements in their child's walking ability after having ataluren, which meant their child could

continue daily activities unaided, such as getting out of bed, getting in the car and going to school... The Committee concluded that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren.

ECD Section 5.14: Committee recalled that it was likely that the quality-of-life data collected during Study 007 had not fully captured the short-term benefits experienced by patients having ataluren (see section 5.7) and concluded that the values taken from the literature should be used in its decision-making.

ECD Section 5.17: Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model, the Committee remained concerned that the health benefits associated with ataluren treatment were not great enough to justify its high cost.

In the ECD the Committee recognised that the QoL impact of having DMD, as well as the benefits seen with ataluren treatment, were not fully captured in Study 007 and did not fully reflect the experience of patients and clinical experts. With the availability of results from Study 020 we can demonstrate more completely the wider benefits of ataluren that reflect the impact that treatment has on individuals with nmDMD and their families.

The Committee also recognised that is can be very difficult to capture all of the benefits for patients and their families within the clinical trial setting, particularly in a very rare multi-system condition which has such a wide-reaching and devastating impact on patients, their families and carers as DMD. In this respect the patient testimonies have provided invaluable evidence of the real impact that ataluren has on aspects of patients' and their families' lives that are unquantifiable in trial settings. As noted by the ERG in their review of our submission, the patient and clinician submissions testify to a reduction in emotional and psychological burden of the condition with ataluren treatment.

In Study 007 and Study 020, clinically meaningful differences in TFTs, which reflect ability to carry out day-to-day activities such as climbing and descending stairs, were observed in ataluren treated patients compared to placebo (see Figure 2 in Response 1 and Appendix 1).

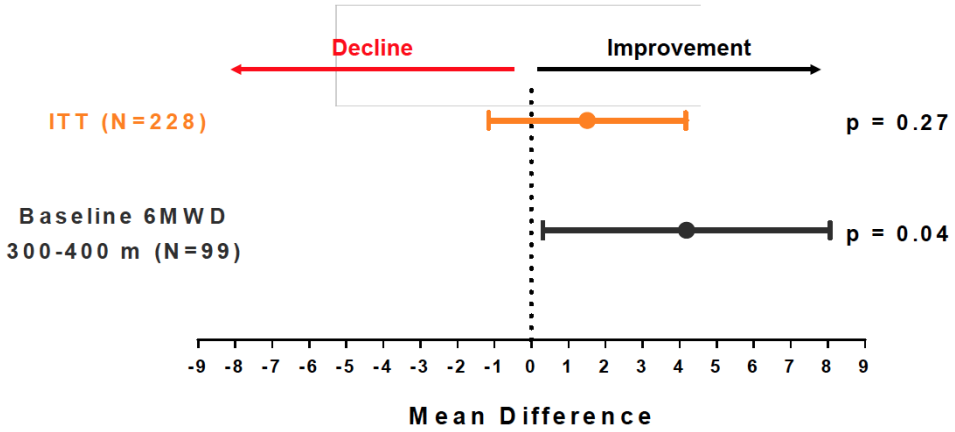
Study 020 included additional outcome measures, the NSAA, the PODCI (Pediatric Outcomes Data Collection Instrument) and Activities of Daily Living (ADL), which demonstrated the benefit of ataluren in a wider range of ambulatory functions important in everyday life and are presented below.

The North Star Ambulatory Assessment (NSAA)

- The NSAA is an important instrument to measure ambulatory function and complements the 6MWT by providing information on a wider spectrum of functions that are important in everyday life, especially in boys at school age (Mazzone 2013). See Appendix 3 for further details about the instrument.
- The NSAA has been specifically designed for ambulant DMD patients. The scale has been developed in the United Kingdom by the North Star Clinical Network for Paediatric Neuromuscular Disease Management with good intra- and inter-observer reliability.
- The scale includes items assessing abilities that are necessary to remain functionally ambulant, i.e., ability to rise from the floor, ability to get from lying to sitting and sitting to standing, and that are known to progressively deteriorate in untreated patients. The scale also includes items assessing head raise and standing on heels that can be partly present in the early stages of the disease and a number of activities such as hopping, jumping, and running. Hence is a useful tool for monitoring disease progression. NSAA scores directly correlate with upper-limb muscle function as well as lung function (Ekici 2011), suggesting that a treatment effect on the NSAA in ambulatory patients with DMD may offer clinical benefit to non-ambulatory patients at a later stage of the disease.
- In this assessment, a benefit was seen for ataluren over placebo in the ITT population (p=0.268) and in the 300-400m subgroup a statistically significant benefit was seen for

ataluren over placebo (p=0.041) – Figure 3.

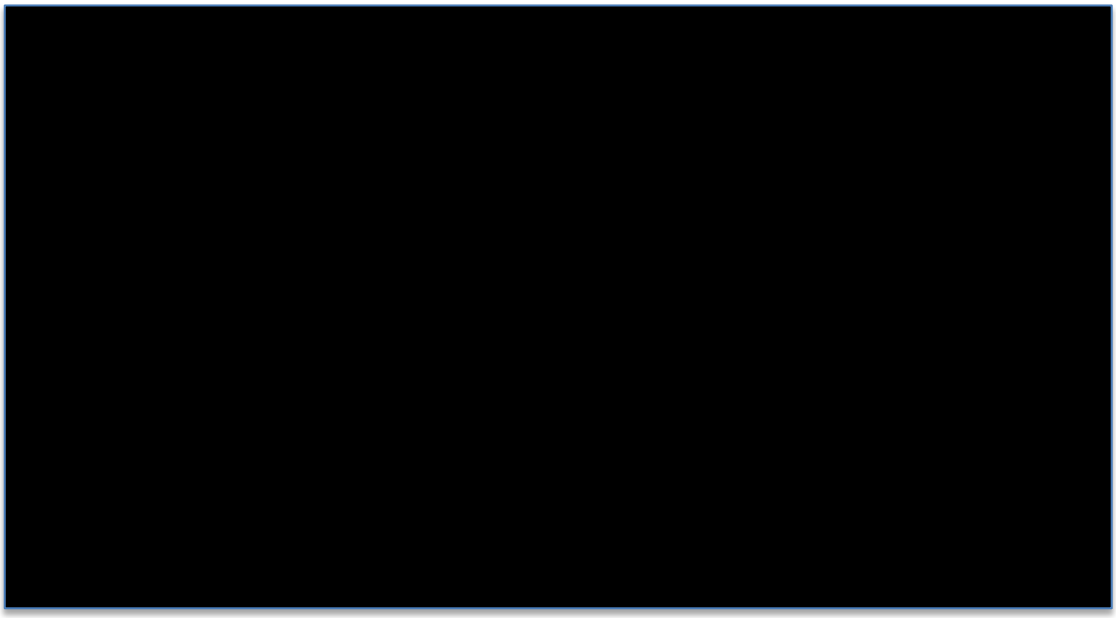
Figure 3: North Star Ambulatory Assessment in Study 020



The Pediatric Outcomes Data Collection Instrument (PODCI)

- The PODCI has emerged as the patient reported outcome quality of life measure of choice in DMD (McDonald 2010, Henricson 2012). It has previously also been used in other disease settings (e.g. cerebral palsy).
- The PODCI 'transfers/basic mobility' and 'sports/physical function' domain scores are significantly associated with disease progression in patients with DMD (McDonald 2013).
- Changes in patient-reported health-related quality of life, as assessed by the PODCI domain scores (transfers/basic mobility and sports/physical functioning), consistently favoured ataluren over placebo in the Study 020 ITT population and the 300-400m subgroup (Figure 4). As a patient-reported outcome measure, the PODCI results numerically favouring ataluren reflect direct patient perception of treatment benefit.

Figure 4: QoL Assessment (PODCI) in the ITT population and baseline 6MWD 300-400m group in Study 020



- *Transfers/Basic Mobility Domain: assesses difficulty in performing routine motor activities*
- *Sports/Physical Functioning Domain: assesses difficulty in more active recreational activities*

Unfortunately, there are no published mappings of the PODCI to a generic measure of quality of life (EQ-5D / HUI / SF-36) so utilities cannot be generated for the cost-consequence model. As a result the values taken from the literature have continued to be used in the cost-consequence model as supported by the Committee (ECD Section 5.14).

Activities of Daily Living (ADLs)

Anecdotal reports from parents and teachers of boys participating in prior studies of ataluren in nmDMD suggested that boys have experienced psychological, social and behavioural benefits (e.g. less frustration with physical tasks, improved ability to play with other children) in association with improved endurance and reduced fatigue while receiving ataluren. Due to the progressive nature of DMD, maintaining stability is an important outcome as frequently expressed by the patient and clinical community.

A disease symptom survey was used in Study 020 to capture individualised patient and parent/caregiver-reported changes in activities of daily living and disease symptoms that are specific to dystrophinopathy and are not assessed in standardised questionnaires. This survey has been developed by PTC Therapeutics based upon reports from participants in previous ataluren studies

The results for ADLs in Study 020 showed that more ataluren-treated patients reported either improvement in or lack of progression in walking than placebo-treated patients (Figure 5). The same pattern of changes was observed for stair-climbing and upper extremity activities of self-care.

Figure 5: Activities of Daily Living

These results for NSAA and ADL are consistent with the primary and secondary endpoint results, described in Response 1 and Appendix 1. The 6MWD outcome is a measure of ataluren's ability to maintain muscle function. Whilst 6MWD may be relatively stable in patients with a higher level of functional ability there is a strong rationale for treatment of patients at an early age because drugs that preserve muscle, in particular, may have the greatest effect on prognosis before muscle health has deteriorated. Ambulatory outcome measures are not expected to be sufficiently sensitive to demonstrate response to dystrophin restoration therapy in patients with little intact lower-limb skeletal muscle. Nonetheless, a drug effect on upper-limb skeletal, respiratory, and cardiac muscle are expected and this is strongly supported from a mechanistic perspective. As a dystrophin restoration therapy ataluren is expected to change the course of disease in all patients.

Impact of ataluren on families

Ataluren has been shown to reduce the amount of occasional wheelchair use (Study 007 CSR). Increased dependence on wheelchair use results in markedly reduced quality of life and a greater need of informal care (Hendriksz 2014), therefore reductions in wheelchair dependency would be expected to improve the quality of life for patients treated with ataluren. Delaying occasional wheelchair has further positive impact such as delaying visits to wheelchair services and the need for home modifications.

The quality of life benefit resulting from a lessening dependence on wheelchair use was considered in the recent NICE appraisal of elosulfase alfa and it was agreed that a significant utility decrement for patients sometimes using a wheelchair was appropriate but significantly less impactful in comparison to total wheelchair use (NICE, 2015).

In order to gather further impact on the quality of life of caregivers of patients with DMD and help inform the Committee a brief survey was conducted on behalf of PTC among carers of people with DMD. A copy of the survey can be found in Appendix 4. Carers reported that caring for a person with DMD has a serious impact on multiple aspects of their life including, in particular, emotional wellbeing and mental health, personal care, and the ability to maintain relationships (n=6). All respondents reported that as a result of caring for someone with DMD they felt tired, depressed or hopeless and stressed or anxious. Most also had trouble sleeping or experienced problems with their own health. In all cases at least one other family member were involved in giving care, with care being provided by both parents and in some cases support from grandparents or respite childminders. The impact on other caregivers was high with all respondents rating the impact on their spouse or partner as serious (see Appendix 2) and that the availability of a treatment such as ataluren would have significant impact on their quality of life. For example, based on the following question – "*Please describe what the availability of a treatment that could extend the time to loss of ambulation (ability to walk), for the person with DMD that you care for, would mean to you*?" responses received were as follows:

"Ataluren would mean delaying visits to wheelchair services, maintain DLA allowance at a lower level and prevent respiratory intervention and heart medication. It would mean that my wife and I could maintain the full-time employment we currently have and delay or prevent further house adaptions and specialist equipment such as self-turning beds."

"Massive impact on quality of life and care giving time. Currently XXXXX can move independently to go to the toilet etc. If he was to lose this that would massively impact on my ability to work and my quality of life. As soon as independence is lost there is a major decrease in mobility and the dependence increases exponentially"

"The loss of independence needs is compensated for by additional time and cost spent of carers teachers, occupational therapist, wheelchair services, councils, GP's and nurses. Homes need to be adapted as well as schools. Equipment needs to be provided. Extending the time for ambulation would have a significant impact on decreasing all of these annual and reoccurring costs. Those are all costs that can be quantified. In addition there are the qualitative costs which include the individual's ability to participate fully in obtaining an education, working and social activities."

Response 3 – ERG Required Changes to the Model

ECD Section 5.12: Committee noted that the company had not included a lifetime time horizon in its base-case analysis. It concluded that it was more appropriate to use a lifetime time horizon, as the ERG had done in its exploratory analyses, to adequately capture the total costs and benefits of treatment.

This has now been included into the model – see Appendix 2.

ECD Section 5.13: Committee concluded that the ERG's preferred approach to extrapolating data to inform the transition probabilities should be used in its decision-

making, although it noted that differences between the scenarios considered were not overwhelming.

As detailed in Appendix 2, the manufacturer does not have access to the ERG model thus the ERG preferred approach to extrapolating the data cannot be applied directly in the revised analysis. Furthermore, some of the ERGs assumptions were clinically unrealistic (e.g. 25% best supportive care patients alive at the age of 70) thus are not appropriate. The manufacturer has used the updated extrapolations as submitted to NICE during ERG clarification questions. As stated in the ECD, the difference between the ERG and manufacturer extrapolations is minimal.

ECD Section 5.15: Committee was aware that the ERG had included these additional [6 months post-becoming fully non-ambulatory] costs in its exploratory analysis and concluded that the ERG's approach was appropriate.

This has now been included into the model – see Appendix 2.

Response 4 – Demonstrating Benefit in QALYs

ECD Section 5.17: Committee considered the overall value of ataluren, taking into account both its health benefits (around 3 additional QALYs) and associated costs in the context of other highly specialised technologies. … Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model

PTC is in agreement that many of the benefits of ataluren for patients, and subsequently the benefits conferred on carers and other family members, were not fully captured in the model submitted.

Based on an evolved understanding of DMD and its impact on boys and their carers, as well as clinical expert feedback and the data from Study 020, we have made improvements to the model which include:

- Incorporation of the quality of life impact of scoliosis
- The impact of loss of ambulation (LoA) on carers
- The indirect quality of life impact of ataluren on delaying LoA

This has resulted in incremental QALYs for ataluren of 11.748, which is comparable to other products recently recommended by the Committee as well as other rare disease drugs currently funded through NHS England (see Table 2).

Response 5 – QALY versus Cost

ECD Section 1.4: Further justification for the cost of ataluren per patient, taking into account the size of the benefit after further clarification (see 1.3), and compared with the benefit obtained with other highly specialised technologies available to NHS patients.

ECD Section 5.11: Committee acknowledged that developing orphan and ultra-orphan treatments was associated with challenges that were different from treatments with bigger patient populations; however, it was not convinced that the high cost per patient of ataluren was justified compared with other treatments for rare conditions. … [The] Committee concluded that it was uncertain if the proposed cost of ataluren was justified by the incremental therapeutic improvement over standard therapy.

ECD Section 5.17: Committee considered the overall value of ataluren, taking into account both its health benefits (around 3 additional QALYs) and associated costs in the context of other highly specialised technologies. … Although it had considered the evidence of improved outcomes from clinical trials and the patient testimonies, and considered that the benefits were distinct and likely to be not fully captured in the model, the Committee remained concerned that the health benefits associated with ataluren treatment were not great enough to justify its high cost. In the absence of clear evidence explaining the reasons for ataluren's high cost and its lower incremental QALY gains than other highly specialised technologies that that have been evaluated by NICE, the Committee was unconvinced that ataluren represented overall good value for money to the NHS.

Investment

Much like other treatments for very rare disorders, the price of ataluren is driven by the high cost of developing a drug for a very small patient population. Specifically, a high level of investment in research and development, regulatory, manufacturing, pharmacovigilance and medical information requirements as well as all of the additional departments and functions needed to run an organisation (human resources, finances, legal etc.). Manufacturers need sufficient revenues that allow them to recoup these costs from a very small number of patients during the limited period of market exclusivity as well as continuing to invest in new research so as to develop further innovative therapies for untreated rare diseases. This challenge inevitably results in high acquisition costs for these products on a per patient basis.

To date, PTC Therapeutics Inc. has invested over $500 million on the discovery, development and commercialisation of Translarna. This research has been pioneering and has taken over 17 years with the possibility of failure at each step. As with other very rare diseases, which are often neglected in terms of research, at the time that PTC initiated their studies in nmDMD, the level of scientific knowledge was low and as such the risks in clinical research much higher. Thus all of this research and development investment has been at considerable risk with no guarantee of success. For example, the preclinical development involved high throughput screening of ~800,000 compounds, ex vivo synthesising and testing of over 3,500 selected compounds for protein/ function, with subsequent in vivo testing of selected compounds in mouse models of DMD and then phase 1, 2 and 3 studies of ataluren in patients with nmDMD.

DMD was a previously untreated condition in terms of addressing the underlying cause and prior to the initiation of the PTC studies there was very limited natural history data. Translarna is a drug with a new mode of action and all of this innovation as well as the drive to address the high unmet need in treating Duchenne muscular dystrophy, were recognised by the EMA in granting early approval.

In addition to the investment to date, we anticipate we will spend at least an additional $75 to 100 million in ongoing clinical research and registry commitments in nmDMD. The long-term efficacy, tolerability and safety outcomes will continue to be monitored and evaluated via the Translarna STRIVE registry, a joint research initiative in co-operation with TREAT-NMD; a group of international clinical experts with a considerable lead coming from experts based in Newcastle. The idea is to create an integrated database, bringing together natural history data, as well as clinical and other patient-reported outcomes.

In order to develop Translarna, PTC has built a team of more than 120 scientists and clinically trained experts (40% of employees) based in New Jersey in the US and across Europe and indeed 30% of our staff have a PhD or medical degree. In addition to the work to develop ataluren, some of these scientists are also researching existing and new compounds as potential treatments for other rare diseases. Indeed, we have spent over $100 million on the discovery and development of a robust early stage pipeline however only ataluren for the treatment of cystic fibrosis has a near-term expectation for commercialisation. Investment in research not only provides a benefit to society by leading the development of new medicines, but also provides for the long-term future of the company. Again such investment is high risk and an acceptable return on this investment is therefore ethically justified.

Based on the most up to date incidence and prevalence data there are around 65 patients in England with nmDMD aged 5 and over and ambulatory. [redacted] This is a very small number of patients from which to recoup all investment costs and it is therefore very difficult to predict exactly when PTC will "break even". On the basis of our projections it is many years away and it will be even longer before we earn a return on the investment to date.

It is also important to consider that the patent system is designed to allow those companies taking the high risk to develop products to make an adequate return and to continue to invest in R&D, but then essentially to give the product to society after patent expiry freeing up budget to fund the next round of innovative products.

Investment in England

A considerable amount of our research effort has been conducted in England. We have recruited (and continue to recruit) English patients into clinical trials in a number of rare diseases. In total [redacted] nmDMD patients have been treated in clinical trials in the UK (of which [redacted] were from England), with the majority continuing on extension studies. Also, reflecting the value we place on conducting clinical research in England, Professor Kate Bushby from Newcastle was chosen as the lead author of Study 007 published last year in the Lancet.

Treatment cost

Ataluren falls well with within the price range of comparable orphan drugs used to treat similar sized populations (Table 1). In addition, as this submission includes a stopping criterion, ataluren is not being given as a lifetime treatment and therefore the treatment benefit reflects the duration and related cost over a specific treatment period.

Table 1: Products for rare/ ultra-rare disease funded by NHS

Drug name	Condition	Patient Population (England)	Annual Cost (list price) based on average weight	Publication(s)
Ataluren (Translarna)	nmDMD	Approx. 65	24-26kg: £246K	NICE ID428
Elosulfase (Vimizim)	Morquio (MPS IV)	Approx. 74-77	25.3kg: £394K	NICE ID744
Idursulfase (Elaprase)	Hunter syndrome (MPS II)	Approx. 60	36kg: £309K	SMC advice (Jul 2007
Ivacaftor (Kalydeco)	Cystic fibrosis (G551 D mutation)	Approx. 300	Not weight based. £182K	NIHR (Mar 2014)
Alglucosidase alfa (Myozyme)	Pompe (early and late onset)	Approx. 1,350	10kg child: £38K 60kg adult: £230K	Ausems 1999; Martiniuk 1998; SMC (Mar 2007)
Eculizumab (Soliris)	aHUS	Approx. 170	Adult: £327K - £340K	NICE HST1 (Jan 2015); NICE ID 428

PTC recognises that the committee need to try to make comparisons. If a comparison of incremental costs and QALYs across diseases and technologies is being considered by the committee as it appears to be, then it becomes important for the committee to consider a relative measure, such as the ICER, and thus review ataluren in the context of other therapies shown in the table above. Ataluren is not a lifetime treatment; it is only indicated for ambulatory patients. Consequently, the lifetime treatment costs of ataluren are lower than other highly specialized technologies evaluated by NICE. Comparisons of incremental cost per QALY can be made based on existing publications and submissions. These comparisons are presented in Table 2.

Table 2: Cost per QALY for products to treat rare/ ultra rare diseases

Drug name	Condition	QALY gain	Cost/QALY	Publication
Translarna	nmDMD	8.2-11.7	£715,043 (list price) £[redacted] (with PAS)	See Appendix 2
Vimizim	Morquio (MPS IV)	9.91	£829,870 (with PAS)	SMC (Sept 2015)
Elaprase	Hunter syndrome (MPS II)	NA	£564,692. Sensitivity analysis £601,059 - £1,174,342	SMC advice (Aug 2007)
Kalydeco	Cystic fibrosis (G551 D)	2.16-4.27	£607,699 and £1.05M	NIHR (Mar 2014)
Myozyme	Pompe	N/A	Infant: £244,450 - £318,283 per QALY Late onset: £819,806	SMC (Mar 2007)
Soliris	PNH	N/A	£348,000 - £521,000	NHS England (Sept 2013)
Agalsidase alfa and beta (Fabrazyme and Replagal)	Fabry disease	1.6 – 10.56	£241,000 - £2,342,494	Connock et al (2006); Rombach et al (2013)

Response 6 – Predictability of Budget Impact

ECD Section 5.10: Committee considered it unlikely that the average weight of the expected patient population over the first 5 years would be 24–26 kg and that it was therefore not representative of the anticipated patient population. …The Committee concluded that the company's calculations, whether using the list price or the price incorporating the patient access scheme, had likely underestimated the total budget impact of ataluren for treating nonsense mutation DMD.

As stated in our submission, the median weight of patients used in the budget impact calculation is assumed to be between 24-26 kg. Using this bodyweight for a daily dose of 1,000 mg from the table D13.5 of the Manufacturer's Submission, the number of patients identified in section 13.1 and uptake in section 13.2, the budget impact in year 1 is estimated to be approximately £8.6M rising to around £16M in Year 5 assuming uptake by this time is high at [redacted]. The median figure was based on the population of patients in study 007 who had an age range of 5-20 years which we consider to be representative of the age range, and therefore the weight range, of patients that would be treated in any given year under the current label i.e. aged 5 and over and ambulatory. In Study 020 the median body weight of patients was [redacted] kg and [redacted] kg in the placebo and ataluren arms respectively where the median age was 9 years (7-14 years). PTC still believes that in clinical practice the median body weight of patients will in the range of 24-26 kg as a greater proportion of patients will be initiated on ataluren at the age of 5 years in line with the marketing authorisation of ataluren.

[redacted]

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Appendix 1: Clinical Data Update

Summary

The Translarna (ataluren) conditional marketing authorisation (CMA) for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD) was granted based on efficacy and safety data from a single Phase 2b trial (PTC124-GD-007-DMD, Study 007) and is subject to the Specific Obligation to complete a confirmatory Phase 3 study (PTC124-GD-020-DMD, Study 020), the top line results of which are presented here.

The data presented in this document are best understood within the context of the pathogenesis, natural history, and evolving treatment paradigms. Based on the Study 007 data and available natural history data at the time of design of Study 020, an optimal target patient population using baseline 6 minute walk distance (6MWD) of >150m to <80% predicted for age and height was defined (called the ambulatory decline phase population). This population was further stratified by baseline 6MWD >350m which represents a more stable population and <350m representing a more rapid decline population.

Since then, a deeper understanding of the natural history of DMD has evolved, which has demonstrated that the originally proposed population (baseline 6MWD of >150 metres [m] and <80% predicted) still represents a fairly heterogeneous population and that patients with a baseline 6MWD of 300-400m is the best target population to demonstrate a drug effect over a 48-week period. This range represents patients who have a significant loss of ambulation but still have sufficient lower-limb muscle mass to detect a drug effect over a 48-week period using the 6 minute walk test (6MWT). Patients with baseline 6MWD >400 and <300m are either too stable or have too severe muscle loss (respectively) to be able to demonstrate a statistically significant drug effect over this time period. For this reason, and as per FDA and EMA guidance, a pre-specified analysis was included for the 300-400m subgroup as was a pre-specified meta-analysis of Studies 007 and 020.

Data from Studies 007, 020 and the meta-analysis of Studies 020 and 007 confirm ataluren's treatment benefit for patients with nmDMD

- **Efficacy was confirmed in Study 020 in nmDMD patients**
  - Ataluren demonstrated clinical benefit in the 6MWT and key secondary endpoints:
    - 15 metre benefit in 6MWD for ataluren over placebo in the intent-to-treat (ITT) population (p=0.213)
    - Timed function tests (TFTs; 10 metre walk/run, stair climb, stair descend), North Star Ambulatory Assessment (NSAA), and Pediatric Outcomes Data Collection Instrument (PODCI) all favoured ataluren
  - Most importantly, ataluren demonstrated benefit in the pre-specified 300-400 metre subgroup, which has emerged as the optimal window to detect a clinical effect in a 48-week trial using the 6MWT
    - 47 metre benefit for ataluren over placebo (p=0.007)
    - Timed function tests (10 metre walk/run, Δ -2.1 seconds, p=0.066; 4 stair climb, Δ -3.6 seconds, p=0.003; 4 stair descend, Δ -4.3 seconds, p<0.001)
  - NSAA linear total score trended in favour of ataluren in the ITT population, and showed a significant difference in favour of ataluren in the 300-400 metre subgroup (in which the 95% confidence interval excluded zero)
  - PODCI domain scores trended in favour of ataluren in the ITT population and in the 300-400 metres subgroup, all favoured ataluren
  - Pre-specified meta-analysis of Studies 020 and 007 shows 6MWD benefit of 22 metres (p=0.015) for ataluren compared to placebo
    - In the 300-400 metre subgroup, ataluren was associated with a 45m reduced decline in 6MWD (p<0.001) compared to placebo

        - Timed function tests (10 metre walk/run, Δ -1.4 seconds, p=0.025; 4 stair climb, Δ -1.6 seconds, p=0.018; 4 stair descend, Δ -2.0 seconds, p=0.004) all showed statistically significant benefit for ataluren over placebo
        - Results provide evidence of consistency of response across studies in primary and key secondary efficacy endpoints
    - No ataluren-treated patient with baseline 6MWD of 300-400 metres lost ambulation in Study 020
        - In Study 020, 0/47 (0%) ataluren patients vs. 4/52 (8%) placebo patients lost ambulation
        - Across Studies 007 and 020, in the 300-400 metre combined subgroup, none of the 69 ataluren-treated patients lost ambulation, while 6 of 72 placebo patients became non-ambulatory (8%)

- **Ataluren was generally well tolerated in patients with nmDMD.**
    - Approximately 900 subjects, including healthy volunteers and patients with nonsense mutation genetic disorders, have been exposed to ataluren as of 30 September 2015
    - Treatment was generally well tolerated with very few drug-related study discontinuations
    - No new safety signals have been identified
- **Benefit vs. risk is favourable, in nmDMD patients.**
    - nmDMD is a serious, life-threatening, ultimately fatal genetic disorder with high unmet medical need
    - Ataluren is a first-in-class treatment intended to treat the underlying cause of nmDMD
    - Ataluren demonstrates a favourable risk-benefit profile in patients with nmDMD

1.1. Confirmatory Phase 3 Study

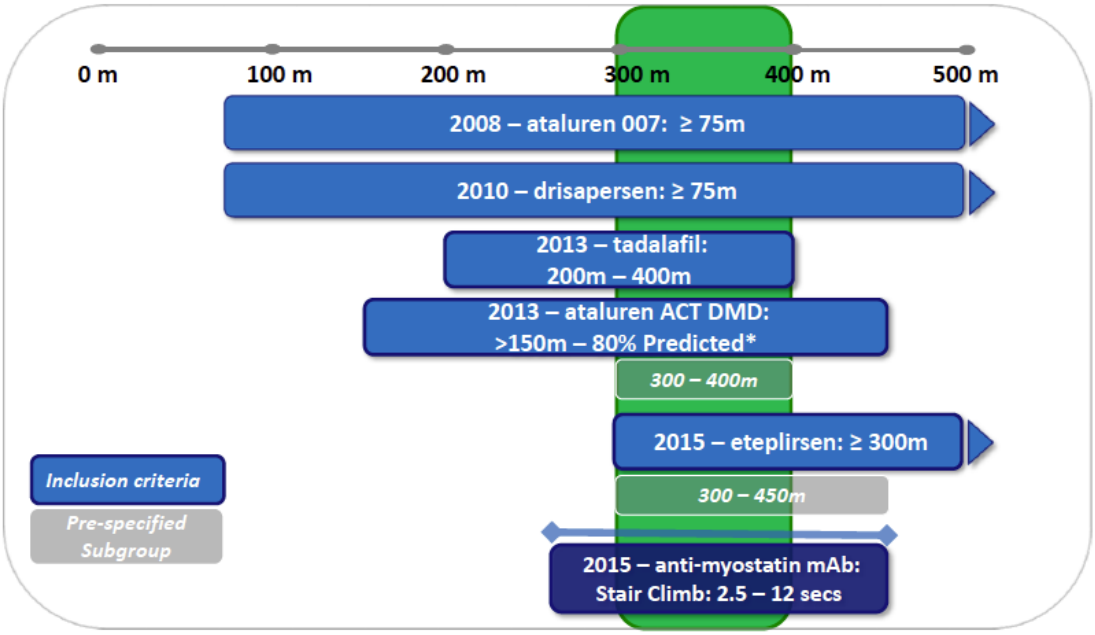
A randomised, double-blind, placebo-controlled Phase 3 trial (Study 020) was designed and conducted to confirm the clinical benefit for ataluren demonstrated in the Phase 2b, randomised, double-blind, placebo-controlled trial (Study 007). Study 020 was an international multi-centre trial undertaken to evaluate the efficacy and safety of ataluren in ambulatory nmDMD patients 7 to 16 years old. The study design took into account feedback from the EMA and FDA.

1.2. Natural History Data

Based on the Study 007 data and available natural history data at the time of design of Study 020, an optimum target patient population was determined for the purpose of stratification in order to best demonstrate a drug effect. The intent of this patient population was to include nmDMD patients who were not so advanced in the condition that it would prove difficult to show a drug effect through measures of ambulation or who were too early in the development of the condition such that loss of function would not be evident over a one year period.

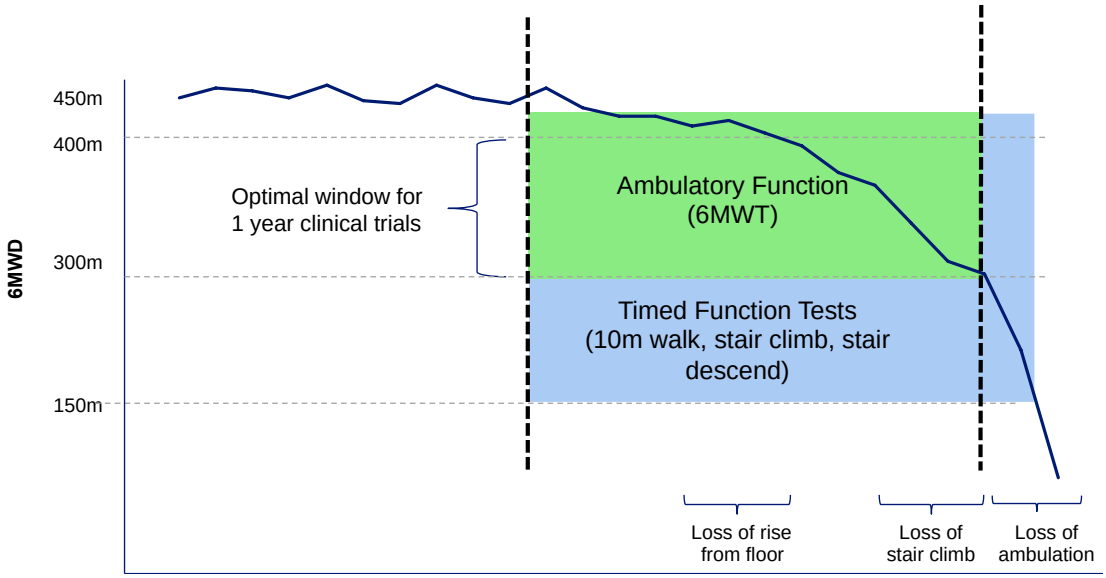
In addition, from a post hoc analysis of Study 007, a patient population which had a 6MWD of >150 to <420m (80% predicted for age and height) was defined as an optimum population and referred to as the ambulatory decline phase population. Within this population, those patients walking >350m were thought to be more stable and those walking <350m were thought to be in a more rapid ambulatory decline phase. Since the design of Study 020, there has been further understanding of the natural history of the rate of decline in ambulation as measured by the 6MWT in DMD patients as represented by Figure A1.1.

Figure A1.1 Evolution of 6MWD Inclusion Criteria in Selection of the Population that can Best Demonstrate a Treatment Effect over 48 weeks



The natural history data consistently demonstrate that patients with higher baseline 6MWD remain stable and those with a lower 6MWD decline more rapidly. This has been very constant both across mutations and across DMD clinical trials. In particular, narrowing the range of patients' baseline 6MWD to approximately 300-400m is now believed to be the optimum range to best demonstrate a drug effect over a 48-week period. The rationale for defining this target population is that patients with a baseline 6MWD of 300-400m have a significant loss of ambulation but still have sufficient lower-limb muscle mass to detect a drug effect over a 48-week period using the 6MWT, as represented in Figure A1.2.

Figure A1.2 Progressive loss of function highlights the complexities associated with conducting clinical studies in DMD

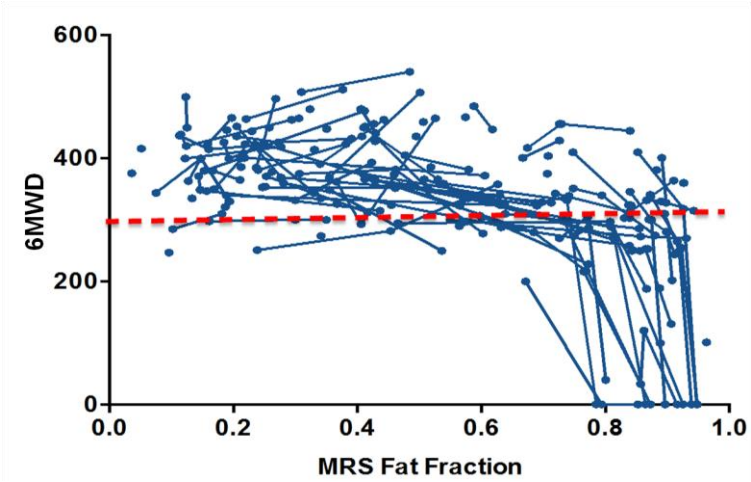


Patients with a baseline 6MWD >400m represent a more stable population, which has very little change in the 6MWT over a 48-week period, as demonstrated in Study 007 and confirmed in Study 020.

Patients with baseline 6MWD <300m have a high risk of rapidly becoming non-ambulatory. Emerging magnetic resonance spectroscopy (MRS) data reinforce this view as illustrated in Figure A1.3 comparing 6MWD as a function of muscle fat fraction as measured by MRS. The MRS measures the replacement of viable muscle tissue by fat. The results show there is a linear decline in 6MWD with disease progression until a clinical threshold value of muscle loss occurs at approximately 80% MRS fat fraction, namely the point at which 80% of the lean muscle tissue has been replaced by fat.

Due to the nature of the 6MWT as an endurance test and considering the progressive nature of DMD in patients with 6MWD <300m at baseline, it has been suggested that shorter tests of ambulation and function that are less burdensome for the patient e.g., 10m walk/run and other timed function tests, are more appropriate to show change at this end of the spectrum of the DMD continuum and might also be more sensitive to detect differences in a 48-week clinical trial. In addition, a drug effect on upper-limb skeletal, respiratory, and cardiac muscle is expected from a mechanistic perspective.

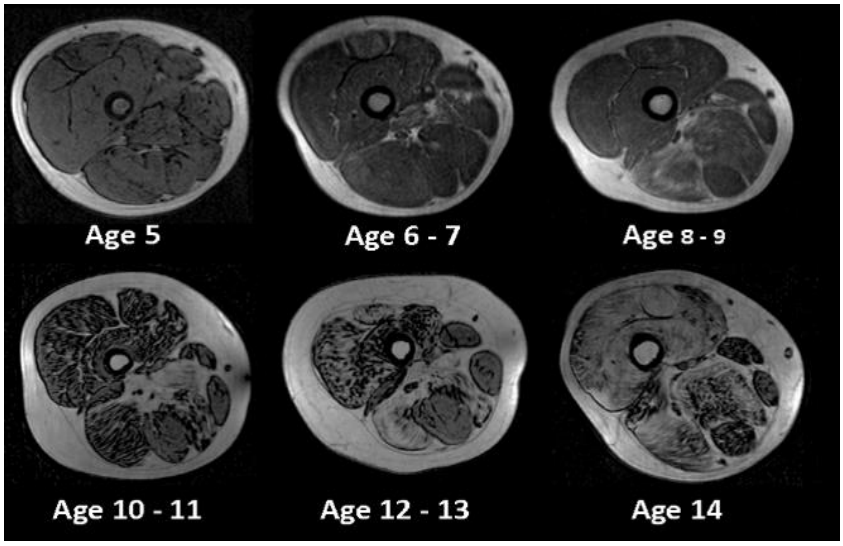
Figure A1.3 6MWD as a Function of Muscle Fat Fraction



Data provided courtesy of Professor Lee Sweeney

Figure A1.4 illustrates the progressive changes over a period of 9 years in a DMD patient as fat and fibrous tissue replace muscle tissue.

Figure A1.4 Imaging Data Illustrate Infiltration of Muscle by Fat and Fibrous Tissue



Data provided courtesy of the imaging DMD network that have previously been publicly presented by Professor Lee Sweeney.

1.3. Study Design Elements

The study design and statistical analysis plan (SAP) were developed in the context of Study 007 and the evolving understanding of the natural history data of DMD. The study comprised a 2-week screening period, a 48-week blinded treatment period, and a 6-week post-treatment follow-up period. At the completion of blinded treatment, all compliant participants were eligible to receive open-label ataluren 40 mg/kg/day in a separate extension study. Eligible patients were stratified based on age, duration of corticosteroid use, and baseline 6MWD.

1.3.1. Pre-Specified Analyses

Two key analyses were prospectively specified in the Study 020 statistical analysis plan:

1) A meta-analysis combining data from the two randomised clinical trials (Study 020 and the ambulatory decline phase subgroup of the corrected ITT (cITT) population for Study 007, [i.e., the subgroup of patients in Study 007 with characteristics that met the main entry criteria for Study 020])

2) Subgroup analysis of patients with baseline 6MWD of 300-400m

1.3.2. Patient Population

Main inclusion criteria in Study 020 were:

- Male
- Age ≥7 and ≤16 years (as compared to ≥5 years in Study 007)
- Phenotypic evidence of dystrophinopathy and documentation of the presence of a nonsense point mutation in the dystrophin gene
- Valid Screening 6MWD ≥150 metres. Valid Screening 6MWD must be ≤80% of predicted for age and height (as compared to Study 007 where included patients were able to walk ≥75 metres)
- Use of systemic corticosteroids for a minimum of 6 months immediately prior to start of study treatment

Inclusion criteria have focused on a progressively narrow range of patients in order to screen out ambulatory patients with too great a loss of lower extremity muscle tissue and whose response to treatment may not be appropriately measured by the 6MWT in a 48-week ambulatory clinical trial. These criteria also attempt to screen out higher functioning patients, those with 6MWD of approximately 420m at baseline, in whom 6MWD would not likely change much over a 48-week timeframe.

The Study 020 enrolment criteria were intended to enrich the population for the decline phase of DMD. Comparison of the patient populations enrolled in Studies 007 and 020 shows that ultimately, the Study 020 population was only modestly enriched for the ambulatory decline phase (Table A1.2). Two factors contributed to this: first, by setting the upper limit to 80% predicted, a larger number of patients with a baseline 6MWD >400 were enrolled than anticipated (i.e., 37%); second, increasing the lower limit from 75m in Study 007 to 150m in Study 020 did not adequately screen out those patients at high risk of loss of ambulation.

However, there is a competing desire in DMD trials to be as inclusive as possible given that patients have no other treatment options and also to satisfy the requests of the regulators. Thus, whilst the Study 020 entry criteria resulted in this broader than intended patient population the situation was appropriately and proactively managed by implementing pre-specified subgroup analyses (i.e., the 300-400m subgroup) and meta-analyses.

115 patients were randomised into each study arm of which 114 were included in the ITT population (Figure A1.5). Baseline demographics were well balanced across treatment arms (Table A1.1).

Figure A1.5 Patient disposition in Study 020

Table A1.1 Study 020 Baseline Characteristics

Characteristic	Treatment Arms	
	Placebo	Ataluren
	[redacted]	[redacted]
Age, years		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race, n (%)		
Caucasian	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Hispanic	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Body height, cm		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Body weight, kg		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Body mass index, kg/m^2		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Sibling pairs or triads[a], n	[redacted]	[redacted]

SD = standard deviation

Table A1.2 Study 007 and Study 020 Patient Populations

	Study 007 N = 114	**Study 020 N = 228**
Age (years)		
Mean (range)	8.5 (5 – 20)	8.9 (7 – 14)
5 – 6 year olds (n / %)	23 / 20%	NA
7 – 9 year olds (n / %)	63 / 55%	155 / 68%
10 years and older (n / %)	28 / 25%	73 / 32%
Baseline 6MWD (metres)		
Mean	356 m	364 m
<300 m (n / %)	28 / 25%	45 / 20%
300 to 400 m (n / %)	44 / 39%	99 / 43%
>400 m (n / %)	42 / 37%	84 / 37%

6MWD = 6-minute walk distance

1.3.3. Endpoints

The primary objective of Study 020 was to determine the ability of ataluren to slow disease progression as assessed by ambulatory decline. As in Study 007, the primary efficacy endpoint was the change in the 6MWD from baseline to Week 48 with ataluren compared to placebo.

Secondary endpoints were chosen to evaluate changes in skeletal muscle function through assessment of proximal muscle function and, as in Study 007, included timed function tests (TFTs). Patient or parent/caregiver perception of physical functioning were assessed using the PODCI and reported activities of daily living.

An additional secondary endpoint, the NSAA, was included in Study 020 to provide further supportive evidence for positive changes in muscle function. The NSAA is a DMD-specific measure of disease progression in the ambulatory patient population (Appendix 3) and has been suggested as an endpoint in the EMA Guideline on the clinical investigation of medicinal products for the treatment of DMD (European Medicines Agency, 2013). The scale was developed and piloted in the United Kingdom by the North Star Clinical Network for Paediatric Neuromuscular Disease Management. It has been shown to have good intra- and inter-observer reliability and has been used in other large multi-centre studies (Ricotti, 2015; Mazzone, 2011). The NSAA is a clinician-reported outcome instrument consisting of 17 items designed to measure ambulatory function in DMD including, for instance, ability to rise from the floor, ability to get from lying to sitting and sitting to standing (see Appendix 3), all of which are known to progressively deteriorate in untreated patients. The NSAA measures relevant muscle functions at different stages of the disease and hence is a useful tool for monitoring disease progression. NSAA scores directly correlate with upper-limb muscle function as well as lung function (Ekici 2011), DMD supports likely clinical benefit during the more progressive ambulatory decline phase as well as in non-ambulatory patients. The NSAA and the 6MWD are complementary assessments in that the 6MWD measures endurance whereas the NSAA provides information on a wider spectrum of functions that are important in everyday life, especially in boys of school age (Mazzone 2013).

Study 020 included the PODCI as a secondary outcome measure. The PODCI has emerged as the patient reported outcome quality of life measure of choice in most DMD trials, to date. The PODCI is a quality of life instrument previously applied in other disease settings (e.g., cerebral palsy) and recently has been validated in DMD (McDonald 2010, Henricson 2012). The PODCI ‘transfers/basic mobility’ and ‘sports/physical function’ domain scores are significantly associated with disease progression in patients with DMD (McDonald 2013). The ‘transfers/basic mobility’ domain assesses difficulty experienced in performing routine motor activities in daily life, and the ‘sports/physical functioning’ domain assesses difficulty encountered in participating in more active recreational activities. Each domain is scored from 0 to 100, with 100 representing the highest level of functioning and least pain. As a patient-

reported outcome measure, the PODCI results reflect direct patient perception of treatment outcome.

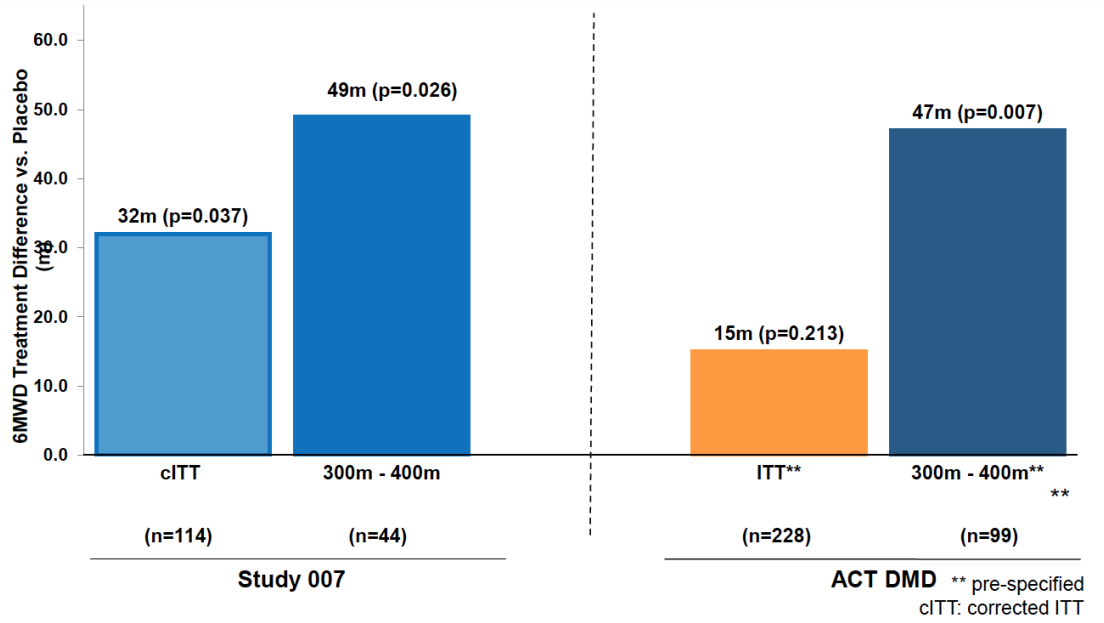
1.4. Efficacy Results

The results of Study 020 show a consistent benefit for ataluren over placebo and confirm the benefit for nmDMD patients previously observed in Study 007.

1.4.1. Primary Endpoint

In the ITT population of Study 020, there was a 15m difference favouring ataluren over placebo in the primary 6MWD endpoint, however, this was not a statistically significant change (p=0.213). In the pre-specified 300-400m subgroup, a benefit of 47m was observed, with a significant difference in favour of ataluren over placebo (p=0.007) (Figure A1.6). The pre-specified subgroup analysis is robust given the sample size of 99 randomised, placebo-controlled patients and is consistent with the benefit seen in Study 007, where a 49m difference (p=0.026) was observed in the same 300-400m subgroup.

Figure A1.6 Primary Endpoint - 6MWD Treatment Difference vs. Placebo



1.4.2. Key Secondary Endpoints

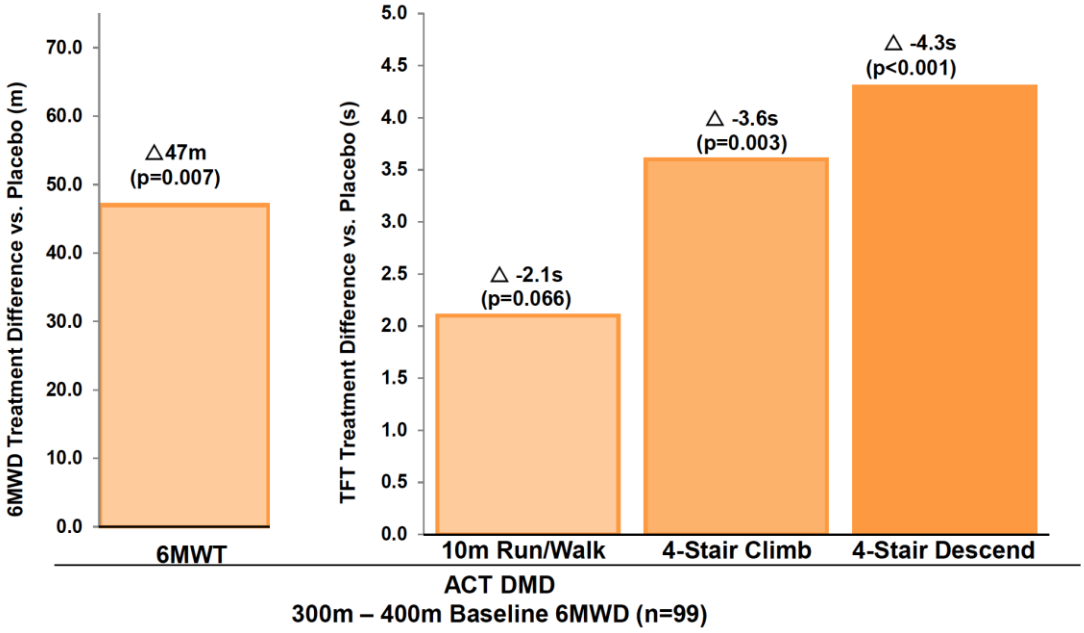
Over 48 weeks, ataluren treated patients showed less decline in muscle function, as evidenced by positive differences in the times to walk/run 10 metres, climb 4 stairs, and descend 4 stairs relative to placebo. Outcomes for each of these measures were consistent with the primary endpoint, supporting an ataluren treatment effect on disease progression. An overview of TFT results, including the ITT population and patients with baseline 6MWD 300-400m, are illustrated in Figure A1.7 and Figure A1.8, respectively.

The consistency of results with TFTs in the 300-400m subgroup confirms the treatment effect with ataluren as observed by the clinically meaningful benefit shown in each of the key TFTs (Figure A1.8).

Figure A1.7 Key Secondary Endpoints Consistent with Primary Endpoint in ITT Population

[redacted]

Figure A1.8 Key Secondary Endpoints Consistent with Primary Endpoint in 300-400m Subgroup



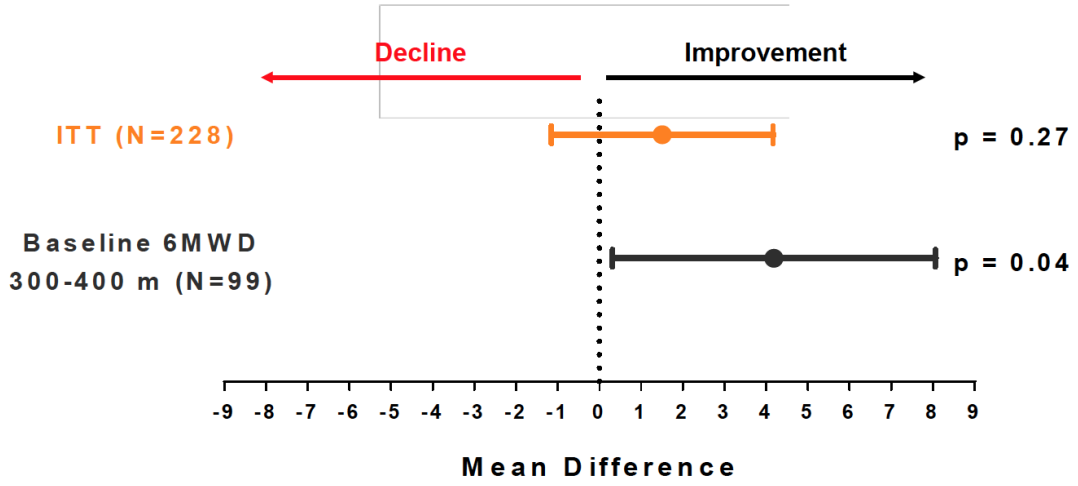
1.4.3. Maintaining Ambulation

[redacted]. The majority of these patients had baseline 6MWD <300m. During the 48 weeks of Study 020, none of the 47 ataluren-treated patients in the 300-400m subgroup lost ambulation, while 4 of 52 (8%) placebo patients in this subgroup became non-ambulatory. This observation suggests the ability of ataluren to prolong ambulation in boys with nmDMD.

1.4.4. North Star Ambulatory Assessment

As previously described, the NSAA is another important instrument to measure ambulatory function. In this assessment, a benefit was seen for ataluren over placebo in the ITT population (1.51, p=0.268) and in the 300-400m subgroup a statistically significant benefit was seen for ataluren over placebo (4.45, p=0.041) (Figure A1.9)

Figure A1.9 North Star Ambulatory Assessment Linear Total Score



1.4.5. Patient Reported Outcome

PODCI transfers/basic mobility and sports/physical function domain scores are significantly associated with disease progression in patients with DMD (McDonald, 2013). The transfers/basic mobility domain assesses difficulty experienced in performing routine motor activities in daily life. The sports/physical functioning domain assesses difficulty encountered in participating in more active recreational activities.

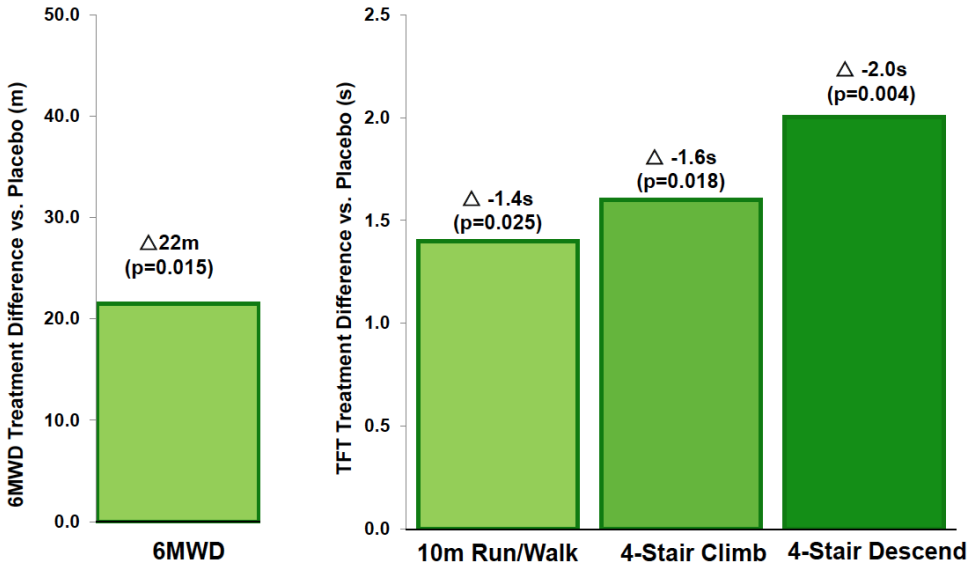
Changes in patient-reported health-related quality of life, as assessed by the PODCI domain scores (transfers/basic mobility and sports/physical functioning), consistently favoured ataluren over placebo in the Study 020 ITT population and the 300-400m subgroup (Figure A1.10). As a patient-reported outcome measure, the PODCI results numerically favouring ataluren reflect direct patient perception of treatment benefit.

Figure A1.10 Results of the Pediatric Outcomes Data Collection Instrument

1.4.6. Pre-Specified Meta-Analysis

The combined results from Study 020 and the ambulatory decline phase in Study 007 consistently demonstrate a statistically significant benefit for ataluren across the primary 6MWD endpoint and key secondary endpoints of TFTs. In this pre-specified meta-analysis, ataluren showed a 22m benefit over placebo in the primary endpoint of the 6MWD (p=0.015). The key secondary endpoints of TFTs supported this benefit; 10m walk/run (p=0.025), 4 stair climb (p=0.018), and 4 stair descend (p=0.004) (Figure A1.11).

Figure A1.11 Pre-Specified Meta-Analysis of Primary and Key Secondary Endpoints

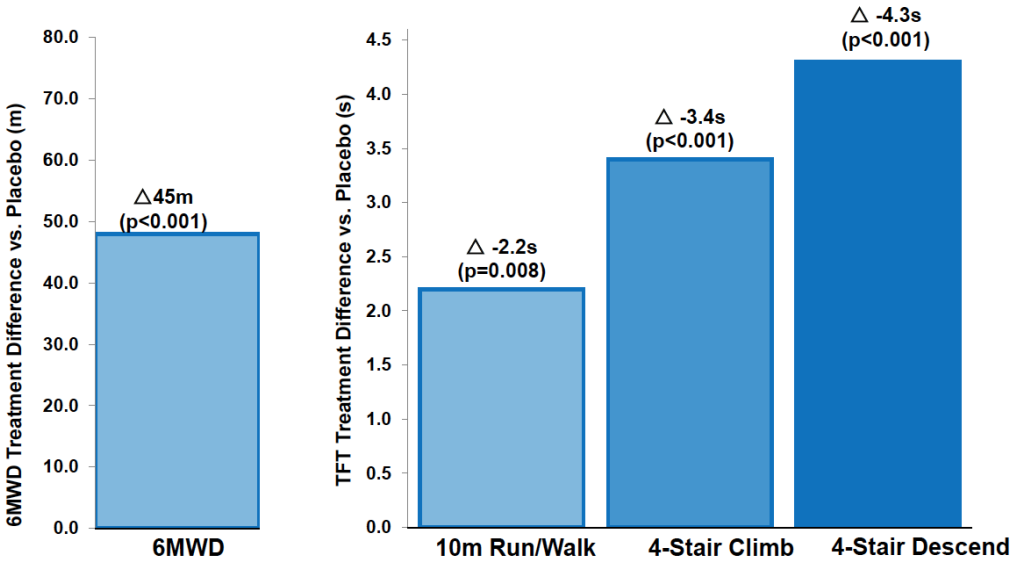


Meta-analysis: ACT DMD and ADP subgroup of Study 007 (n=291)

ADP: Ambulatory Decline Phase defined as aged 7 years to 16 years with a baseline of 6MWD ≥150 metres, and 80% of predicted 6MWD and on a stable dose of corticosteroids

In the meta-analysis of the 300-400m subgroup, the benefit was even more robust. In this analysis, ataluren showed a benefit of 45m over placebo (p<0.001), and was supported by positive results in all key secondary TFT endpoints (all p-values are below 0.01) (Figure A1.12).

Figure A1.12 Pre-Specified Meta-Analysis of Primary and Key Secondary Endpoints in 300-400m Subgroup



Meta-analysis: ACT DMD and ADP subgroup of Study 007 (n = 143)

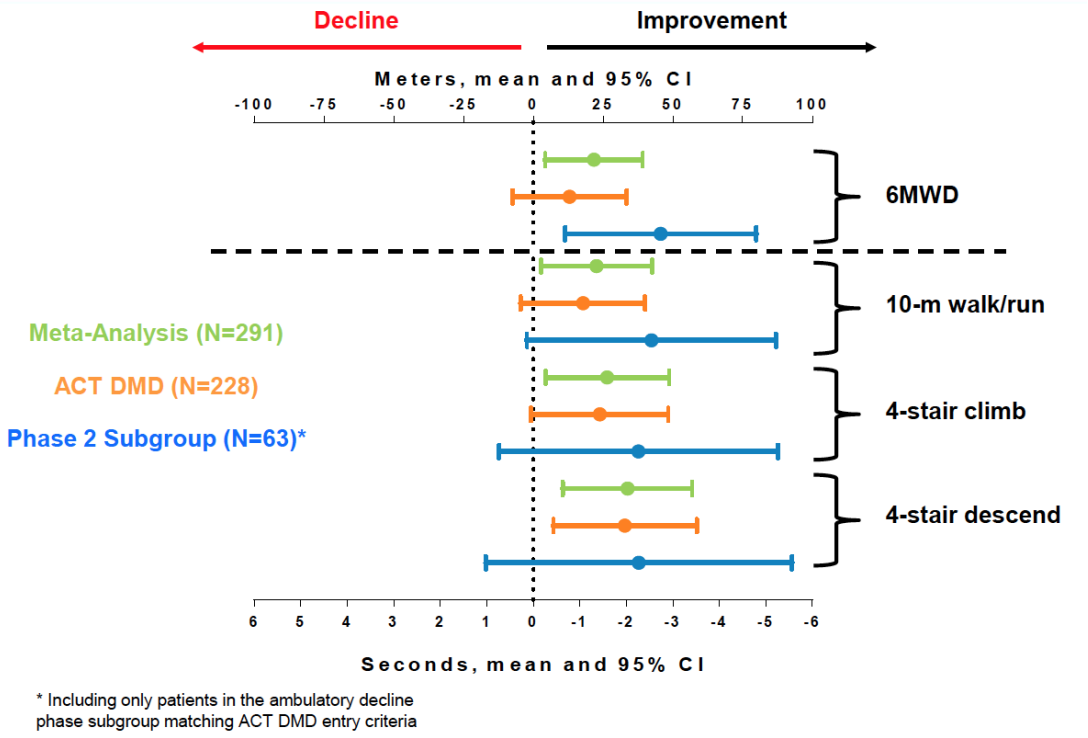
ADP: Ambulatory Decline Phase defined as aged 7 years to 16 years with a baseline of 6MWD ≥150 metres, and 80% of predicted 6MWD and on a stable dose of corticosteroids

In the combined analysis of Studies 007 and 020, the difference in loss of ambulation was also meaningful. In the 300-400m combined subgroup, none of the 69 ataluren-treated patients lost ambulation, while 6 of 72 (8%) placebo patients became non-ambulatory. Ultimately, maintaining ambulation is key to patients and their families.

1.4.7. Summary of Efficacy Results

The results from the Study 020 trial show consistent evidence of the clinical benefit of ataluren for individuals with nmDMD, its impact on the course of the disease, and the improvement in quality of life for these boys and young men. The totality of the data for ataluren as demonstrated by the pre-specified meta-analysis of the study populations as well as of the 300-400m subgroup, consistently demonstrate clinical benefit across primary and secondary endpoints (Figures A1.13 and A1.14 respectively) and confirm that ataluren stabilises the course of disease progression.

Figure A1.13 Pre-specified meta-analysis of combined study populations



* Including only patients in the ambulatory decline phase subgroup matching ACT DMD entry criteria

Figure A1.14 Meta-analysis of pre-specified subgroup (6MWD at baseline 300-400m)

1.5. Safety profile

1.5.1. Extent of Exposure

As of 30 September 2015, approximately 900 subjects have been exposed to ataluren in Phase 1 studies in healthy volunteers, Phase 2 and Phase 3 clinical trials, early access programs, and where commercially available as treatment for nmDMD. Additional safety data from ongoing nmDMD studies and studies in other indications up to a cut-off of 31 July 2015 will be provided in the Type II variation for submission to EMA in December 2015.

1.5.2. Summary of Safety Results

In Study 020, adverse event profiles were similar in the placebo and ataluren arms. . (Table A1.3). The majority of treatment-emergent adverse events were mild or moderate in degree; severe adverse events were infrequent, and the only life-threatening adverse event occurred in the placebo arm (scoliosis). Adverse events considered possibly or probably drug-related were somewhat more frequent in the ataluren arm.

Table A1.3 Overview of Treatment-emergent Adverse Events in Study 020

Parameter, n (%)	Placebo [redacted]	Ataluren [redacted]	All Patients [redacted]
Patients with adverse events	[redacted]	[redacted]	[redacted]
Adverse events by severity			
Grade 1 (mild)	[redacted]	[redacted]	[redacted]
Grade 2 (moderate)	[redacted]	[redacted]	[redacted]
Grade 3 (severe)	[redacted]	[redacted]	[redacted]
Grade 4 (life-threatening)	[redacted]	[redacted]	[redacted]
Adverse events by relatedness			
Unrelated	[redacted]	[redacted]	[redacted]
Unlikely	[redacted]	[redacted]	[redacted]
Possible	[redacted]	[redacted]	[redacted]
Probable	[redacted]	[redacted]	[redacted]
Discontinuations due to adverse events	[redacted]	[redacted]	[redacted]
Serious adverse events (SAEs)	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]

1.6. Conclusion

In summary, the totality of the efficacy data for ataluren consistently demonstrates clinical benefit across primary and secondary endpoints. The pre-specified key subgroup for analysis and the pre-specified meta-analysis, both demonstrate the statistically significant and clinically meaningful benefit of ataluren for nmDMD patients and demonstrate a favourable benefit-risk profile for ataluren in nmDMD.

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Appendix 2: Revised economic modelling

Further to the evidence submitted on the cost-benefit of ataluren by the manufacturer in June 2015, the following further evidence has come to light:

- Evolved understanding of the natural history of nmDMD by PTC and the clinical community
- Further expert opinion on the natural history of nmDMD and how ataluren may modify the course of the disease
- Results from Study 020 (ACT-DMD)
- Opinion of the NICE Highly Specialised Technology committee on choice of methods used to evaluate the cost and consequences of ataluren

Based on this additional evidence, the model submitted to NICE in June 2015 has been modified as follows:

1. Included updated parametric curves used to extrapolate time to loss of ambulation, time to scoliosis, time to ventilation-assistance and time to death

Due to limited time that we had to create the economic model, the Weibull function was used to extrapolate all clinical outcomes in the original submission. Following submission, PTC performed a comprehensive curve fitting analysis to find better fitting functions for the published data. The updated parametric curves for loss of ambulation, time to scoliosis, time to ventilation-assistance and time to death were submitted to the ERG as part of the response to their clarification questions in July. The ERG had also been running an almost identical curve fitting analysis simultaneously. We have not been provided with the ERG model that contains their preferred curves so we have used our closest approximation. Furthermore, some of the curves chosen by the ERG were clinically unrealistic (25% best supportive care patients alive at the age of 70) so are not appropriate. The difference between the ERG curves and PTCs updated curves is minimal.

2. Added restriction on transition to scoliosis health states such that patients do not develop scoliosis after puberty

A restriction on the age at which patients can transition to a health state with scoliosis was included in the model submitted to the ERG as part of the response to clarification questions during their review in July. As detailed in the response to the ERG, the clinical literature suggests that boys who walk longer are at a lower risk of developing scoliosis (Eagle, 2007; Yilmaz, 2004; Kinali, 2007; Humbertclaude, 2012). One study showed that approximately a quarter of the patients did not have any scoliosis or only had a minimal scoliosis at aged 17, when growth was completed (Kinali, 2006). As maintaining ambulation is one of the most important factors in preventing or slowing the progression of scoliosis, the longer boys can remain ambulant until growth is completed, the higher the likelihood of avoiding scoliosis. Consequently, according to data used in the model (Humbertclaude, 2012), in the revised model it is assumed that patients will not develop scoliosis after puberty i.e. that the time to event curve plateaus at 17-20 years of age.

3. Included costs of treatment for 6 months following loss of ambulation.

This is in line with the proposed stopping rule for treatment and was recommended by the ERG.

4. Included lifelong time horizon

This was recommended by the ERG. The model has been extended from a 40-year to a 50-year time horizon to capture the outcomes for every patient within the simulated cohort.

5. Amended discount rate for costs and outcomes to 1.5%

Section 6.2.19 of the NICE guidelines state that a discount rate of 1.5% may be considered where treatment restores people who would have a very severely impaired life to full or near

full health over a very long period of time (NICE, 2014). Given ataluren significantly delays loss of ambulation by 7-12 years and positively effects the entire course of the disease, and the life of the patient, and the ERG have recommended a lifelong time horizon, a 1.5% discount rate has been used. Furthermore, it is expected in the future that ataluren will be initiated in patients at the earliest possible stage of the disease (when 6MWD > 400m), where treatment may enable patients to maintain physical function further beyond the simulated trajectory such that they remain ambulant into their 30s.

6. Increased disutility due to scoliosis to 0.3

Expert opinion on the impact of scoliosis on patients and caregivers quality of life has indicated that the previous estimated disutility of 0.1 is likely to underestimate the burden of patients developing scoliosis, the surgery required, and the aftercare.

Scoliosis causes pain, discomfort and breathing difficulties. Scoliosis is particularly problematic in DMD since lung function is restricted both by spinal curvature and muscular weakness, which also affects the respiratory muscles. In contrast to idiopathic scoliosis there is a significant decrease of vital capacity even in scoliosis with only small curvature (Heller, 1997). Spinal surgery is often carried out even in mild cases as it improves sitting comfort, appearance, and quality of life (Kinali, 2006).

The estimate of 0.3 is assumed based on patients developing severe scoliosis having approximately half the utility decrement as when they became non-ambulatory (utility 0.66 to 0.12 = 0.54 utility decrement).

7. Applied caregiver disutilities for three caregivers rather than one

As reiterated by the NICE committee, it is clear that DMD has a huge impact on the friends and family of patients. Members of the committee expressed that the NICE-preferred quality of life measure, the EQ-5D, is unlike to capture the true quality of life burden of DMD on caregivers. In an attempt to quantify the impact of DMD on other family members and friends, a caregiver survey was conducted (see ECD response for further details). At least one other family member was involved in giving care, with care being provided by both parents and in some cases support from grandparents or respite childminders. The impact on other caregivers was high with all respondents rating the impact of caring for the child affected by DMD on the quality of life of their spouse or partner as 9.6 on a scale of 1 to 10, (where 0 is no impact and 10 is serious). The impact on the quality of life of grandparents was also significant (rated as 5.3).

Siblings of boys with DMD also provide care for their brothers and are negatively impacted by the restrictions having a family member with DMD imposes on family life. In a UK study that included 35 siblings (aged 11-18 years) of boys with DMD (aged 5 -22 years, 93% using a wheelchair), the majority assisted with all aspects of routine care, including personal hygiene, nutritional needs and hoisting the wheelchair, as well as facilitating leisure activities (Read, 2011). Some older male siblings felt that caring responsibilities had increased over time and others that balancing home demands with their own needs and interests was difficult:

"If he's in bed it means your hands and feet are his, you do whatever he wants, you don't have much of a choice really but you get through it. If his arm drops off his wheelchair he hasn't got the strength or mobility to lift it back up, so you've got to do it for him"

Some spoke of their annoyance, frustration and ambivalence towards these responsibilities, or cited fatigue at always being 'on duty'. It is difficult to quantify the impact on siblings as they have adapted to it whilst growing up and it is all they have ever known. However, there is clearly an impact with siblings reporting lack of attention from parents and feeling excluded as well as having to balance their own needs against those of their affected sibling and their parents (Read, 2011).

In the original analysis, a disutility of 0.11 was applied based on the findings of Landfeldt et al (2014), in which the primary caregiver disutility was explored. In the absence of any more

data on the specific impact per family member or friend, we applied the 0.11 disutility for two adult caregivers (equating to 0.22) in line with the feedback from the caregiver survey. Furthermore, based on the significant impact of nmDMD on grandparents, other family members and friends in the caregiver survey, disutilities of half the amount for parents was applied for one sibling and a secondary caregivers (equating to 0.11) thus a disutility of 0.33 was applied in total.

8. Applied early non-ambulatory utilities for ataluren patients

Since ataluren prolongs ambulation until after puberty, patients are in a better state of wellbeing once they become non-ambulatory than a patient that turned non-ambulatory at a younger age. Patients that lose ambulation after puberty have better lung function and a delayed loss of upper arm strength, which means they can continue with daily activities for longer, including carrying out important tasks such as eating, cleaning and transferring, even when they are wheelchair bound. This leads to prolonged independence thus increased quality of life.

This change is important because we have not been able to consider the indirect longer-term effects of ataluren prolonging ambulation and altering the course of the disease in the original model. The early non-ambulatory utility of 0.25 from Landfeldt (2014) is applied to ataluren patients, whilst best supportive care patients are assumed to have the original late-non-ambulatory utility of 0.12.

9. Included costs for ventilation assistance

The ERG and committee noted that no costs of ventilation-assistance had been incorporated into the model for the patients that developed respiratory failure. To address this concern, costs for ventilation assessment, a ventilator, equipment and consumables were sourced from the NICE guideline on Motor Neurone disease (CG105) and NHS reference costs (Department of Health, 2015).

10.Remove the assumption that ambulatory patients can die from DMD

In the original model, it was assumed that all patients could die from nmDMD regardless of their health status. To more realistically reflect the natural history of the disease, patients are assumed to only be able to die due to non-Duchenne causes whilst they are ambulatory.

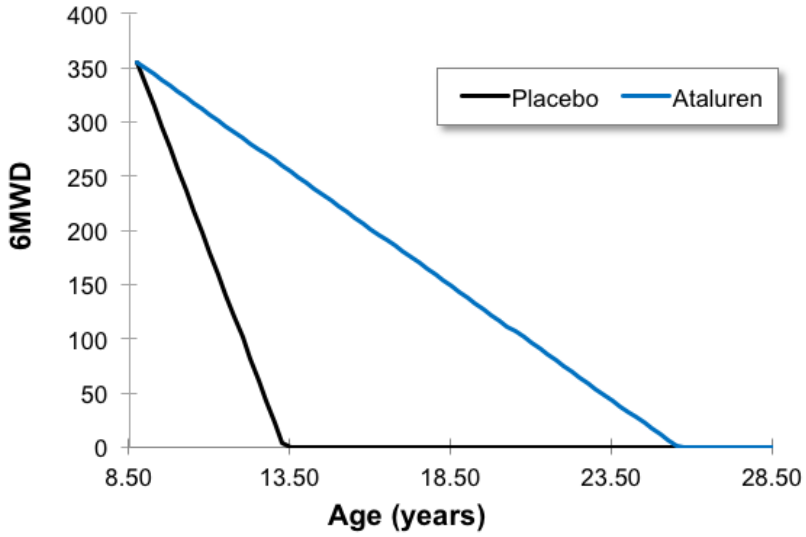
11.Inclusion of data from ACT-DMD (Study 020)

Two methods were used to extrapolate the data from the meta-analysis of ACT-DMD and Study 007. The first method is a linear extrapolation of the observed 48-week decline. This is consistent with the original model, in which declines in 6MWD for ataluren and placebo were extrapolated from the mean baseline of Study 007 until patients reached a 6MWD = 0m (non-ambulatory). The second method of extrapolation is the stratification of patients into 3 groups of 6MWD (>400m, 300-400m, <300m) and simulation of stepped 6MWD decline with placebo and ataluren based on observations for the 3 groups, such that the decline in 6MWD is non-linear.

11a. Linear extrapolation of 6MWD

The mean extrapolated 6MWD decline for the meta-analysis decline phase subgroup (Study 007 and 020) is presented in Figure A2.1. The decline phase subgroup is used to estimate the mean effect of ataluren because it is the best group of patients in which to demonstrate the effects of treatment (see ECD response). The validity of this approach is evident when the extrapolated placebo data gives mean time to LoA of 13.3 years which is consistent the mean UK age at LoA based on Ricotti et al (2013) (13.5 years). The mean age at LoA for ataluren patients is expected to be 25.6 years old, equal to a delay in loss of ambulation of 12.2 years.

Figure A2.1 Extrapolated linear decline in 6MWD for decline phase subgroup



11b. Extrapolated stepped decline in 6MWD

The second approach is considered for three reasons:

1. It is expected that many patients will be initiated on treatment at an earlier stage in their disease when they have a higher 6MWD. The patient population in the clinical studies were enriched to demonstrate a treatment effect and therefore had a relatively low 6MWD of ~360m. Natural history studies have included patients with 6MWD of over 500m (McDonald, 2013; Mazzone, 2010). The weighted average baseline 6MWD of the patients with a >400m 6MWD at baseline in Study 007 and Study 020 was [redacted].

2. There is clear evidence within the clinical data for ataluren and published natural history data that patients with a high 6MWD at baseline typically have a very different trajectory in 6MWD over time, compared to a patient with lower 6MWD. This method of extrapolation captures the variation in expected 6MWD over the 6MWD threshold of 300m and 400m.

3. Patients initiated on treatment with ataluren early in the disease, when their 6MWD is high, will have the most potential to benefit from ataluren as the ambulatory decline in patients with a 6MWD >400m is extremely low. For this reason, clinical experts have expressed a preference to start treat with ataluren early, before the decline phase begins (ECD section 5.6). This extrapolation method enables us to simulate the benefits of starting treatment early.

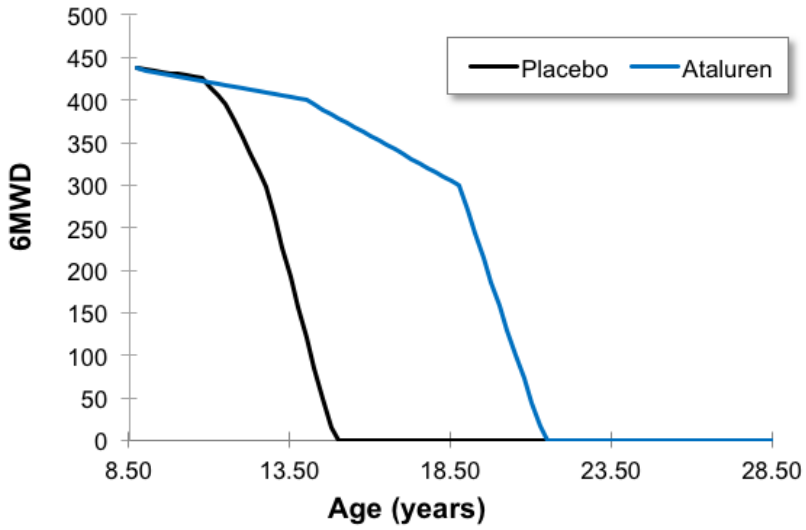
To approximate the 48-week decline for the pooled data from Study 020 and the ambulatory decline phase patients from Study 007 [those that met the Study 020 inclusion criteria], a weighted average of 020 and 007 data for the >400m, 300-400m and <300m groups was used. Given that the 6MWD is not sufficiently sensitive tool to measure treatment effect in the <300m group but that the NSAA and TFTs showed ataluren had a treatment effect of approximately [redacted], on average, a conservative 20% treatment effect of ataluren on 6MWD decline in the <300m group was applied, to account for the improved function with ataluren in the rapidly declining group.

The weighted mean decline in the >400m baseline groups was applied from the baseline of [redacted] until patients reached 400m, at which point the mean decline in the 300-400m baseline group was applied. Once patients reached 300m, the weighted average of the decline in the <300m patients from Study 007 and 020 was applied.

[redacted] Therefore, rather than extrapolating this observation, the observed 48-week decline for placebo patients was only applied for the first two years, after which a [redacted] decline was applied. This value of [redacted] was derived from an average of the 48-week decline in the >400m group ([redacted]) and 300-400m group ([redacted]) so that the mean age at loss of ambulation with placebo (14.2 years) was comparable to the UK mean age at LoA of 13.5 years (Ricotti, 2013).

The resulting simulated 6MWD for best supportive care and ataluren patients is presented in Figure A2.2. Using this approach, the mean age at LoA for ataluren patients is expected to be 21.3 years old, equal to a delay in loss of ambulation of 7.1 years.

Figure A2.2 Extrapolated stepped decline in 6MWD



Results

The results of the revised analysis, combining scenarios from 1-10 above, are presented in Table A2.1, with key analyses highlighted in blue. The base case analysis results in 11.7 incremental QALYs and a list price incremental cost of £8.4m and a PAS incremental cost of [redacted]. The alternative scenario results in incremental QALYs of 8.2 and a list price incremental cost of £5.5m and a PAS incremental cost of [redacted]. Therefore, although the number of incremental QALYs varies depending on the method of extrapolating the data, the relative costs also vary accordingly, such that the relative value for money is similar [redacted].

Table A2.1 Results of revised economic model scenarios

Scenario	Incremental QALYs	Incremental costs at list price	ICER at list price	ICER at PAS price
Model with Study 007 data only, incorporating the ERGs preferred scenario and enhancements to further capture the benefit of ataluren (change 1-10)	8.972	£6,128,102	£683,057	[redacted]
Linear extrapolation of 6MWD decline from meta-analysis of decline phase population (Change 1-10, 11a)	11.748	£8,400,164	£715,043	[redacted]
Extrapolation of 6MWD decline stratified by patients with >400m, 300-400m and <300m (Change 1-10, 11b)	8.194	£5,532,819	£675,241	[redacted]
Extrapolation of 6MWD decline stratified by patients with >400m, 300-400m and <300m starting at 450m baseline (Change 1-10, 11b)	9.666	£6,619,256	£684,776	[redacted]
Extrapolation of 6MWD decline stratified by patients with >400m, 300-400m and <300m starting at 500m baseline (Change 1-10, 11b)	13.685	£10,260,287	£749,758	[redacted]
Extrapolation of 6MWD decline stratified by patients with >400m, 300-400m and <300m starting at 550m baseline (Change 1-10, 11b)	16.564	£13,177,004	£795,524	[redacted]

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Appendix 3: North Star Ambulatory Assessment

The North Star Ambulatory Assessment (NSAA) is a clinician-reported outcome instrument consisting of 17 items (Table A3.1) designed to measure ambulatory function in DMD.

Table A3.1 Items in the North Star Ambulatory Assessment

Activity	Instructions to patient	Start position/test detail
1. Stand	Can you stand up tall for me for as long as you can and as still as you can	Feet should be close together and heels on the ground if possible. Arms by sides. NO shoes should be worn.
2. Walk	Can you walk from A to B (state to and where from) for me.	Walk without shoes/socks on. Should be enough of a distance to observe 'normal gait' for that subject
3. Stand up from chair	Stand up from the chair keeping your arms folded if you can	Starting position 90o hips and knees, feet on floor/supported on a box step.
4. Stand on one leg - Right	Can you stand on your right leg for as long as you can?	Minimum count of 3 seconds to score 2. NO shoes should be worn.
5. Stand on one leg - Left	Can you stand on your left leg for as long as you can?	Minimum count of 3 seconds to score 2. NO shoes should be worn.
6. Climb box step - right	Can you step onto the top of the box using your right leg first?	Stands facing the box step. Step should be approximately 15cm high
7. Climb box step - left	Can you step onto the top of the box using your left leg first?	Stands facing the box step. Step should be approximately 15cm high
8. Descend box step - Right	Can you step down from the box using your right leg first?	Stands on top of the box step facing forwards. Step should be approximately 15cm high
9. Descend box step - Left	Can you step down from the box using your left leg first?	Stands on top of the box step facing forwards. Step should be approximately 15cm high
10. Gets to sitting	Can you get from lying to sitting?	Starting position supine on a mat. No pillow should be used under head
11. Rise from floor	Get up from the floor using as little support as possible and as fast as you can (from supine)	Starting position supine with arms by sides, legs straight. No pillow to be used
12. Lifts head	Lift your head to look at your toes keeping your arms folded	Supine on a mat. No pillow should be used.
13. Stands on heels	Can you stand on your heels?	Standing on the floor. No shoes to be worn.
14. Jump	How high can you jump?	Standing on the floor, feet fairly close together.
15. Hop right leg	Can you hop on your right leg?	Starting position standing on floor on right leg. No shoes should be worn.
16. Hop left leg	Can you hop on your left leg?	Starting position standing on floor on right leg. No shoes should be worn.

17. Run (10m)	Run as fast you can to.....(give point)	A straight 10m walkway should be clearly marked in a quiet department or corridor. A stopwatch should be used to time the walk. Be consistent as to whether shoes are worn or not. Ensure safety of patient. They should self select speed after being asked to go 'as fast as they can'.

Source: North Star Clinical Network, Available at: http://www.musculardystrophyuk.org/assets/0000/6388/NorthStar.pdf

Appendix 4: Caregiver and Family Quality of Life Survey in Duchenne Muscular Dystrophy

Anyone living with or supporting a person with DMD is invited to complete a brief five-page survey, which should take about 15 minutes of your time to complete.

It is designed to provide information to assist PTC Therapeutics in their submission for the medicine ataluren to NICE (National Institute for Care Excellence and Health) for funding on the National Health Service in England and Wales.

Your replies will be anonymous; so do not put your name anywhere on the form. Participation is completely voluntary. You may choose to not answer any question by simply leaving it blank.

The anonymous answers you provide will be shared with PTC Therapeutics and NICE to inform them on the impact of DMD on the quality of life of caregivers and families.

Please complete the following questions to reflect your opinions as accurately as possible. Thank you for your participation in completing this questionnaire.

Background details

Q1. Please indicate your gender (please put an 'X' in one of the boxes below)

☐ Male ☐ Female

Q2. Please give your age within the ranges below? (please put an 'X' in one of the boxes below)

☐ < 18 years old
☐ 18-24 years old
☐ 25-34 years old
☐ 35-44 years old
☐ 45-54 years old
☐ 55-64 years old
☐ 65-74 years old
☐ 75 years or older

Q3. Marital Status: What is your marital status? (please put an 'X' in one of the boxes below)

☐ Single, never married
☐ Married or domestic partnership
☐ Divorced
☐ Separated
☐ Widowed
☐ Prefer not to say

Q4. What is your relationship to the person with DMD? (please put an 'X' in one of the boxes below)

☐ Father/ Mother
☐ Spouse/ partner
☐ Grandparent
☐ Other relative
☐ Friend
☐ Other

Please go onto next page

Q5. Please tell us which of the following also applies to you (please put an 'X' in one of the boxes below)

☐ In paid work full time	☐ In paid work part-time (less than 30 hours)	☐ Retired
☐ Self Employed	☐ Student (Full time education or training)	☐ Voluntary (unpaid work)
☐ Not in work	☐ Looking after home/ family full time	☐ Other

Q6. How many people do you currently provide care for who have DMD? (please put an 'X' in one of the boxes below)

One person	☐
Two People	☐
Three or more people	☐

Q7. Is the person(s) with DMD you support able to walk (<u>take any steps unaided</u>)? (please put an 'X' in the relevant boxes below where applicable)

Person 1	Person 2
☐ Yes	☐ Yes
☐ No	☐ No

Q8. Does the DMD person(s) you are caring for currently receive the medicine ataluren (for instance within a clinical trial)? (please put an 'X' in the relevant boxes below where applicable)

Person 1	Person 2
☐ Yes	☐ Yes
☐ No	☐ No

<u>Please go onto next page</u>

How looking after a person with DMD affects health, well-being and quality of life

Q9. To what extent does caring for the person with DMD impact on the following aspects of your life?

	Rate on the scale below by marking an 'X' by the relevant number where 0 means no impact and 10 means serious impact										
	0	1	2	3	4	5	6	7	8	9	10
a) Physical health and wellbeing											
b) Ability to have a good nights sleep											
c) Emotional well being and mental health											
d) Choice and control over daily life / spending time how you want											
e) Personal Care/ domestic routines											
f) Opportunities to take part in work, education or learning											
g) Ability to have time to yourself or to socialise / do things you value and enjoy											
h) Ability to take holidays											
i) Ability to maintain relationships with family and friends											
j) Your financial situation											

Q10. Please indicate the ways your health has been affected by caring for the person with DMD in any of the ways listed below? (please put an 'X' in any of the boxes below that apply)

Feeling tired	
Feeling depressed or hopeless	
Gained or lost weight	
Disturbed sleep/ trouble sleeping	
General feelings of stress/ anxiety	
Physical Strain (e.g. back pain)	
Short tempered/ irritable	
Had to see own GP	
Had any new or worsening health problems attributed to caregiving	
Low self esteem	
Started or increased a bad habit such as smoking, drinking or prescription drugs to cope	

Other (please give details in this section)

Please go onto next page

Q11. Others who provide support for the person(s) with DMD

Please let us know if the person with DMD that you care for gets support from anyone else, for example partner, family, friends, neighbours etc.

Who also provides support?	**Put 'X' in any box that applies**	**How many people are involved? e.g. 3 grandparents**	**If possible, please estimate in <u>your own view</u>, to what extent you think that caring for the person with DMD impacts on the quality of life for other carers/family members <u>on a scale of 0 to 10</u> where 0 is no impact and 10 is serious impact?**
Father/ Mother			
Spouse/ partner			
Grandparent			
Other relative			
Friend/ neighbour			
Other			

Q12. For the above people involved in providing support for the person with DMD you identified in the previous question, can you briefly describe in the box below the things they do for the person with DMD you care for?

<u>Time devoted to care of a person with DMD</u>

Q13. On average, how many hours of your time is spent looking after the person(s) with DMD over a week? (please put an 'X' in one of the boxes below)

24 hours a day, 7 days a week	
50+ hours a week	
31-50 hours per week	
21-30 hours per week	
11-20 hours per week	
1-10 hours per week	

Q14. How long have you been a carer for someone with DMD?

☐ years

<u>Please go onto next page</u>

Impact on work and education

Q15. On average how many hours per week do you work/ attend school or college? (please put an 'X' in one of the boxes below)

Less than 20 hours	☐
20 to 24 hours	☐
25 to 29 hours	☐
30 to 34 hours	☐
35 to 40 hours	☐
41 to 45 hours	☐
More than 45 hours	☐

Q16. How has caring for the person with DMD affected your work status or schooling? (please put an 'X' in any of the boxes below that apply)

Used sick/ carer's leave hours to care	☐
Taken additional job or increased hours	☐
Left one job for a different one	☐
Taken unpaid leave	☐
Cut back on hours or quit work	☐
Had to cut back on study time or quit full time education	☐

Q17. During the past seven days, how many hours did you miss from work because of caring for the person with DMD? Include hours you missed on sick days, times you went in late, left early, etc.

☐ hours

Q18. Please describe what the availability of a treatment that could extend the time to loss of ambulation (ability to walk), for the person with DMD that you care for, would mean to you?

Thank you very much for your participation in completing this questionnaire.

ERG critique of additional evidence (Company's Response to the Evaluation Consultation Document)

Study design

The company provided top line results from the phase 3 Study 020, described as an international multi-centre randomised double-blind placebo controlled trial. The study protocol was provided by the company at the request of the ERG. There is some evidence of selective reporting bias based on observation of the reported results and analyses (see below under 'Outcome measures').

Population

The main inclusion criteria in Study 020 are described and justified. The company states that although Study 020 enrolment criteria were intended to enrich the population for the decline phase of DMD, comparison of the patient populations enrolled in the phase 2 Study 007 and Study 020 shows the Study 020 population was only modestly enriched for the ambulatory decline phase. This was demonstrated by a comparison of age and baseline 6MWD in Studies 007 and 020. Baseline characteristics for Study 020 are provided; the groups appear similar based on observation of the data.

Outcome measures

The primary endpoint was the change in 6MWD from baseline to week 48. Secondary outcomes are stated as changes in skeletal muscle function through assessment of proximal function, measured by timed function tests. Four timed function test were reported in the phase 2 Study 007 (time to run/walk 10 m, time to climb 4 stairs, time to descend 4 stairs and time to stand from a supine position), however data are reported for only [redacted] of these in Study 020. The ERG notes that according to the study protocol [redacted] was measured in Study 020, although it wasn't specified as a secondary endpoint.
[redacted] were also measured in Study 020, but data are not reported.

Additional outcome measures (not included in Study 007) were the North Star Ambulatory Assessment (NSAA) the PODCI (Pediatric Outcomes Data Collection Instrument) and Activities of Daily Living (ADLs). The NSAA is a clinician-reported outcome instrument designed to measure ambulatory function in DMD. It is described as having good-intra- and inter-observer reliability, however the minimum clinically important difference (MCID) is not discussed. The PODCI quality of life measure has been validated in DMD. Two of eight PODCI scales are reported by the company: 'transfers/basic mobility' and 'sports/physical function'; it is stated that these are significantly associated with disease progression in DMD. According to the study protocol, [redacted] ADLs were measured by a disease symptom survey developed by PTC Therapeutics based upon reports from participants in previous ataluren studies. The validity and reliability of the survey are unclear. The MCIDs for PODCI and ADLs are not discussed. The clinical significance of the patient reported outcomes is therefore unclear.

Statistical analyses

[redacted]

Two pre-specified analyses are described by the company:

1) A meta-analysis combining data from the two randomised clinical trials (Study 020 and the ambulatory decline phase subgroup of the corrected ITT (cITT) population for Study 007, [i.e., the subgroup of patients in Study 007 with characteristics that met the main entry criteria for Study 020])
2) Subgroup analysis of patients with baseline 6MWD of 300-400m

A meta-analysis combining data from the 300-400m subgroups of Studies 007 and 020 is also presented, although it is not clear whether this was pre-specified.

[redacted] These data are not provided.

Data were initially reported for the ITT population and 300-400m subgroup only. Data for subgroups <300m and >400m (6MWD and timed function tests only) were provided by the company at the request of the ERG, however the information did not include numbers, P values or 95% confidence intervals. A statistical test for subgroup treatment effect interaction is not reported.

Results are presented as the mean treatment difference versus placebo and P value (where reported). Measures of variance, such as 95% confidence intervals, are not reported for the primary and secondary outcomes (other than for NSAA and the meta-analyses, which are displayed in figures). The proportion of participants who lost ambulation is presented, but the statistical significance is not reported. Data for PODCI and ADLs are presented in a figure only with no exact numerical data, and the statistical significance of the differences is not reported. ADLs data are not presented according to subgroup.

Results from Study 020 are summarised in the Appendix.

New cost-effectiveness modelling

The company has submitted a new cost-effectiveness model, with a number of changes in assumptions from both of the previous models submitted. They supply two sets of analyses that could be considered base-case analyses of the trial data. The first uses the same methodology of linearly extrapolating 6MWD reductions as in the original submission, with the values from the 300-400m baseline 6MWD group used for the entire extrapolation. The second uses a stepped approach, with 6MWD divided into bands of >400m, 300-400m and <300m, and different rates of decline, based on the trial data, used as patients move through each of the states. The base-case results provided by the company for these two modelling approaches are as follows:

Base-case results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	8.512	11.747

Base-case results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	4.959	8.194

A commentary on each of the changes made by the company, together with the impact this change has on the results for both modelling approaches is presented below.

1) Updated parametric curves – This submission, like that submitted following ERG clarification questions, involves full parametric curve fitting, and is thus an improvement over the initial submission which used Weibull distributions for everything. However, as in that submission, the company has not made use of the best-fitting curves from its own exercise. The ERG therefore made the following changes to the survival functions used, based on the models supplied by the company (results of these changes are presented below):

- Time to scoliosis (LoA>11y): Changed from log-logistic to generalised gamma.
- Time to ventilation-assistance (8y<LoA<11y): Changed from log-logistic to generalised gamma.
- Time to ventilation-assistance (LoA>11y): Changed from log-logistic to generalised gamma.

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£356,734	[redacted]	[redacted]
QALYs	-2.868	8.564	11.432

Results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£356,734	[redacted]	[redacted]
QALYs	-2.868	5.194	8.062

Incremental QALYs were reduced by 0.315 and 0.132 in these scenarios, respectively.

2) Restriction added to transition to scoliosis, such that patients do not develop scoliosis after puberty – The net effect of this change is the virtual elimination of scoliosis in the ataluren arm of

the model (see figures 1 and 2 below), as most patients in the ataluren arm do not lose ambulation until puberty, and hence never have the opportunity to develop scoliosis.

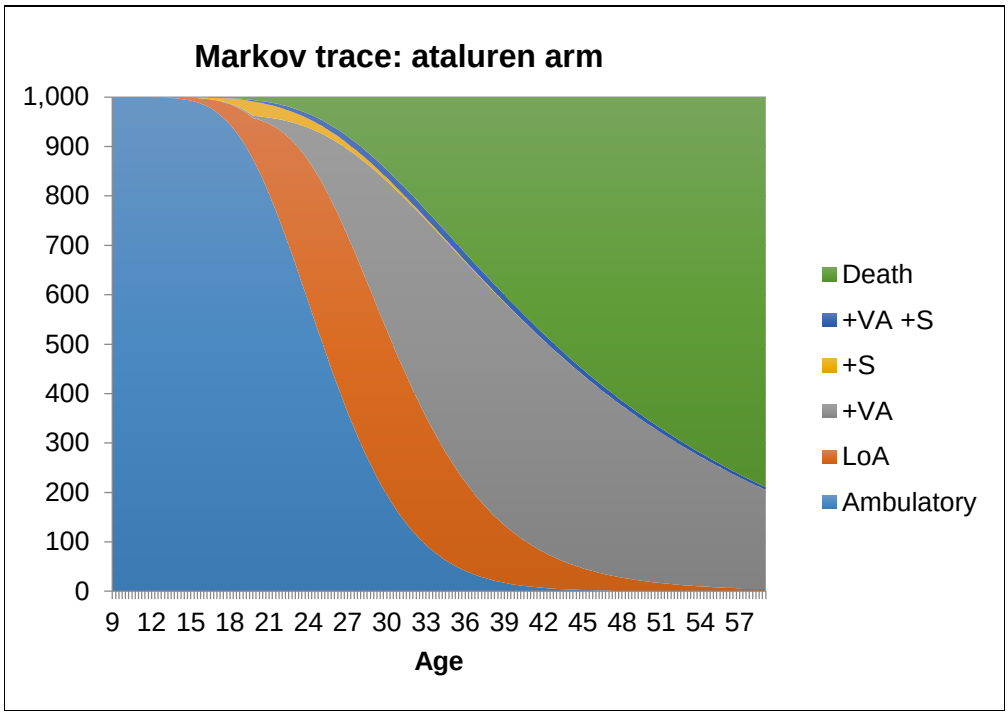


Figure 1: Markov trace plot for the ataluren arm

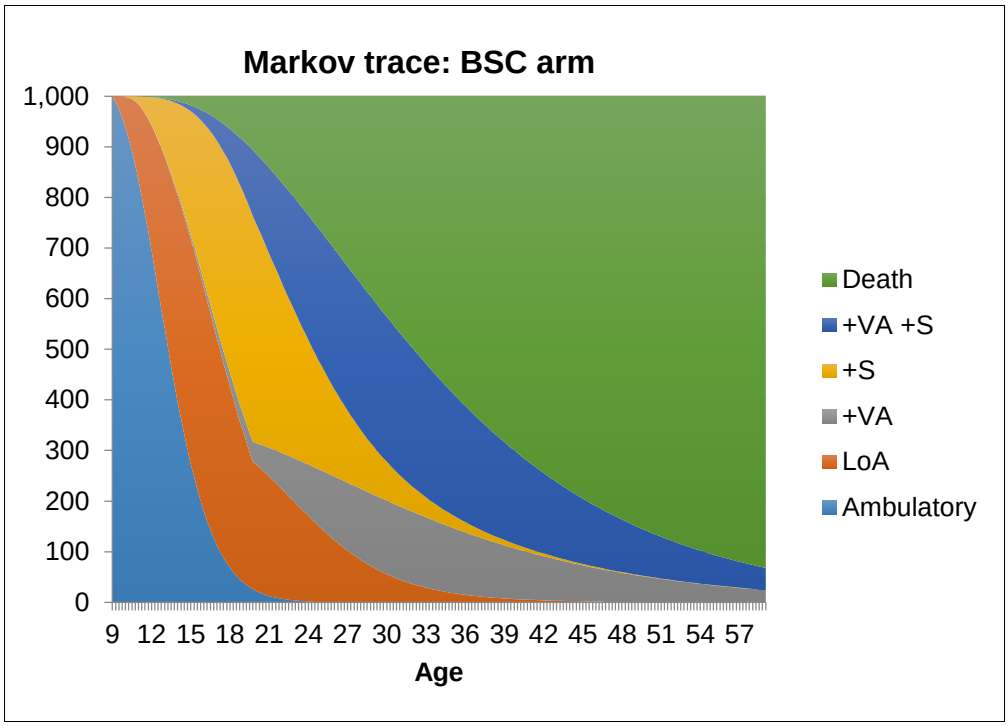


Figure 2: Markov trace plot for the best supportive care arm

However, it is unclear if this restriction is fully justified as, whilst scoliosis rates might well be expected to be lower for patients who lose ambulation at a later age, it is not certain it would entirely eliminate such events (we do know the risk for scoliosis in adults, whilst lower, is not zero).

Returning to the assumptions of the original model, where it was possible to continue developing scoliosis post-puberty, makes the following changes to the results.

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£386,292	[redacted]	[redacted]
QALYs	-4.054	6.150	10.204

Results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£386,292	[redacted]	[redacted]
QALYs	-4.054	2.561	6.615

Incremental QALYs were reduced by 1.543 and 1.579 in these scenarios, respectively.

3) Inclusion of treatment costs for 6 months post loss of ambulation – The ERG is entirely happy with the changes made by the company.

4) Increase in the time horizon of the analysis from 40 years to 50 years – The ERG is entirely happy with the changes made by the company.

5) Discount rates changed from 3.5% to 1.5%, on the basis of NICE technology appraisal guidance on treatments which significantly improve health over a long-period of time. For completeness, the full quote from the NICE methods document is reproduced below:

"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."

Thus the following barriers need to be crossed for the use of 1.5% discount rates to be appropriate:

- Ataluren restores nmDMD patients to full or near full health.
- These benefits are sustained over a very long period (normally at least 30 years).
- The long-term benefits are very likely to be achieved (we need to be highly confident results from these 1 year trials will be sustained for at least 30 years.)
- No significant irrecoverable costs from introduction.

If the discount rates from the original submission (3.5% for both costs and outcomes) were to be preferred, this would make the following changes to the results:

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£277,150	[redacted]	[redacted]
QALYs	-1.743	7.590	9.334

Results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£277,150	[redacted]	[redacted]
QALYs	-1.743	4.914	6.657

Incremental QALYs were reduced by 2.413 and 1.537 in these scenarios, respectively.

6) Increased disutility due to scoliosis – The new submission includes a tripling of the utility decrement associated with scoliosis, from 0.1 to 0.3. This is however, based on expert opinion rather than any data, and the justification given for the particular number (just over half the utility decrement associated with being non-ambulatory), does not appear to be directly related to scoliosis. Returning to the original decrement of 0.1 (over and above the decrements associated with being non-ambulatory), makes the following changes to the results:

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.408	8.614	10.021

Results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.408	5.493	6.901

Incremental QALYs were reduced by 1.726 and 1.293 in these scenarios, respectively.

7) Increased caregiver disutilities for – Caregiver disutilities were increased from one primary caregiver to the equivalent of 3 full time primary caregivers (actually justified as two primary caregivers and 2 secondary caregivers with half the disutility of a primary caregiver each). A justification is given for why considering more than one caregiver might be appropriate, but it is not clear were the choice of four significantly affected people has come from, nor why more than one of them should be assigned the decrement of a primary caregiver. Alternative assumptions include a return the initial model value of one primary caregiver, or including the equivalent of two primary caregivers rather than three.

Results (Linear extrapolation) – 2 primary caregivers

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.479	9.826	11.305

Results (Stepped-decline) – 2 primary caregivers

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-1.479	6.541	8.021

Incremental QALYs were reduced by 0.442 and 0.173 in these scenarios, respectively.

Results (Linear extrapolation) – 1 primary caregiver

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	0.277	11.140	10.863

Results (Stepped-decline) – 1 primary caregiver

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	0.277	8.124	7.847

Incremental QALYs were reduced by 0.884 and 0.347 in these scenarios, respectively.

8) Non-ambulatory utilities – To account for the possibility that patients may have a higher quality of life post loss of ambulation with ataluren, due to being in a better state at loss of ambulation, the company included differential utilities for the post loss of ambulation state of ataluren and BSC. However, it is unclear if the source for the numbers chosen can be justified. The data used are from Landfeldt et al, and refer to people in an early non-ambulatory (12-15 years) and late non-ambulatory state (16+ years). These definitions are very different to how the data has been used by the company. The Landfeldt health states are defined by current age (i.e. patients would move from being early non-ambulatory to late non-ambulatory as they age) whilst the company uses age at loss of ambulation, and it is not at all clear these definitions are interchangeable. Secondly, the company applied the utility from the early non-ambulatory state (i.e. the younger population) to the ataluren arm of the model (where people become non-ambulatory at a higher age), and conversely the later non-ambulatory utility (older patients) to the BSC arm (younger loss of ambulation). Finally, the model assumed this improved quality of life is sustained for the entire time the person is in the loss of ambulation state, and it is not clear if this can be justified based on data mainly from patients soon after loss of ambulation.

Returning, to the original model assumptions, where utility is based on ambulation state alone (not ambulation status and treatment) makes the following change to the results:

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	6.959	10.195

Results (Stepped-decline)

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	3.088	6.323

Incremental QALYs were reduced by 1.552 and 1.871 in these scenarios, respectively.

9) Inclusion of costs for ventilation assistance – The ERG is entirely happy with the changes made by the company.

10) DMD deaths in ambulatory patients – The Company altered the model so that patients in the ambulatory health state could not die from DMD, only non-Duchenne causes. The ERG did not explore alternative assumptions here, but it should be noted that this is quite a strong assumption as, whilst patients might be expected to pass through the non-ambulatory state before death directly as a result of DMD, it is reasonable that the presence of DMD could result in increased mortality rates from co-morbidities, something which is now excluded from the model for ambulatory patients.

11) The inclusion of the new data from study 020 provides useful additional evidence, and appears to have been appropriately combined with data from study 007.

11a) Linear extrapolation of 6MWD. The linear extrapolation model presented is similar to that used in earlier submissions. Importantly, it makes use of the rates of decline in 6MWD for the two arms of the model from the 300-400m subgroup, and then applies those to the whole population (even though the evidence suggests the treatment benefit from ataluren is less in the <300m group. For this reason, the ERG prefers the stepped-decline model, which makes use of the data collected on the differences in ataluren treatment benefit across the different 6MWD ranges. To show the sensitivity of the model to the changes made by the Company in the new submission, the ERG undertook a new sensitivity analysis, making the following changes:

- Different survival models for scoliosis and ventilation assistance (see section 1)
- Allowing patients to develop scoliosis post puberty
- Discount rates of 3.5%/3.5%
- Disutility of scoliosis returned to the original value of 0.1
- Number of equivalent primary caregivers affected reduced from 3 to 2.
- Non-ambulatory utilities set to be the same for both arms of the model.

Results (Linear extrapolation)

	BSC	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	7.212	6.409

Incremental QALYs are reduced by 5.338 in this scenario (45.4%)

11b) As stated above, the ERG believes the stepped decline model represents a better approach to long-term extrapolation, as it takes into account what appear to be very different trajectories based on baseline 6MWD. However, there are some specific technical issues with the way the stepped decline model has been implemented, in particular where data from the trials has been replaced by assumed values, and these assumptions have been much more favourable to ataluren than the data from the trial. There are two key issues, to address, which are dealt with sequentially below:

The >400m subgroup

The pooled data from the studies suggests a [redacted]m 48 week decline with placebo for patients in the >400m group at baseline, and an equivalent decline of [redacted]m with ataluren. The company has, quite reasonably, suggested these numbers may not be representative of the long-term decline, and hence after two years has replaced this with the average decline from the 300-400m subgroup and the >400m subgroup. However, no such adjustment has been made to the ataluren arm (meaning patients are expected to continue plateauing in this state, but not the placebo state), which means a bias in favour of the ataluren group has been introduced. To show the important of this effect, the table below shows the values used in the model, and what values would be used if data for the trial were used for he >400m subgroup in the same way as the other subgroups.

Post-hoc adjustment to placebo arm

	Model data		Trial data	
	Placebo	**Ataluren**	**Placebo**	**Ataluren**
Baseline 6MWD	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline first 2 years	[redacted]	[redacted]	[redacted]	[redacted]
48 week decline >400m baseline after 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Annual decline 300-400m baseline	[redacted]	[redacted]	[redacted]	[redacted]

Annual decline <300m baseline				
Years to LoA				
Difference in LoA	7.1			
Age at LoA				

Two alternative approaches, which still account for the expected faster decline over time in the >400m group, but do not introduce such an optimistic assumption for ataluren, would be:

1. Making the same adjustment for ataluren as placebo (i.e. after two taking the average of the >400m and 300-400m groups and using that for the >400m group.
2. Taking the [redacted] increase in 48 week decline used for the placebo arm after two years, and applying this same adjustment to the ataluren arm (this assumes the increase in decline rate is related solely to the disease, and is thus treatment independent).

Using these two different assumptions in the modelling gives the results below:

Post-hoc adjustment to placebo and ataluren arms

	Approach 1		**Approach 2**	
	Placebo	**Ataluren**	**Placebo**	**Ataluren**
Baseline 6MWD				
48 week decline >400m baseline first 2 years				
48 week decline >400m baseline after 2 years				
Annual decline 300-400m baseline				
Annual decline <300m baseline				
Years to LoA				
Difference in LoA				
Age at LoA				

Results (Stepped-decline) – Approach 1

	BSC	**Ataluren**	**Incremental**
Costs	£366,043		
QALYs	-3.235	2.740	5.975

Results (Stepped-decline) – Approach 2

	BSC	**Ataluren**	**Incremental**
Costs	£366,043		
QALYs	-3.235	2.153	5.388

Incremental QALYs were reduced by 2.219 and 2.806 by these approaches, respectively.

The <300m subgroup

The company states that "as the 6MWD is not a sufficiently sensitive tool to measure treatment effect in the <300m group but that the NSAA and TFTs showed ataluren had a treatment effect of approximately [redacted] on average, a conservative 20% treatment effect of ataluren on 6MWD decline in the <300m group was applied." Firstly, it is not clear that treatment effects are transferable between different measures, and it is unclear how it can be regarded as conservative to replace trial data with assumptions more favourable to ataluren. Secondly, even if the 6MWD is not sufficiently sensitive for effects measured to be statistically significant, it does not follow that data from the trial for this

measure should simply be ignored, particularly when it is the primary outcome used in the model. Making use of actual trial data rather than these post-hoc assumptions makes the following changes to the results above.

Results (Stepped-decline) – Approach 1 and trial data for <300m subgroup

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	2.412	5.647

Results (Stepped-decline) – Approach 2 and trial data for <300m subgroup

	BSC	Ataluren	Incremental
Costs	£366,043	[redacted]	[redacted]
QALYs	-3.235	1.827	5.062

Incremental QALYs were reduced by 0.328 and 0.326 from the previous scenarios, respectively.

It should be noted that, since the ERG did not know the exact numbers of patients randomised to each arm across the trials, this analysis involved the simplifying assumption that patient numbers were exactly balanced between the arms of the studies.

Combined changes

In its last analysis, the ERG included the impact of these changes, together with the model adjustments from section 11a, specifically:

- Different survival models for scoliosis and ventilation assistance (see section 1)
- Allowing patients to develop scoliosis post puberty
- Discount rates of 3.5%/3.5%
- Disutility of scoliosis returned to the original value of 0.1
- Number of equivalent primary caregivers affected reduced from 3 to 2.
- Non-ambulatory utilities set to be the same for both arms of the model.

The results from these final models produced were as follows:

Results (Stepped-decline) – Approach 1, trial data for <300m subgroup and other changes

	BSC	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	3.186	2.383

Results (Stepped-decline) – Approach 2, trial data for <300m subgroup and other changes

	BSC	Ataluren	Incremental
Costs	£283,303	[redacted]	[redacted]
QALYs	0.803	2.831	2.028

These represent reductions of 5.811 (70.9%) and 6.166 (75.3%) QALYs from the base-case values for the stepped-decline model.

Conclusion

In conclusion, it is relevant to note that model is highly sensitive to a number of assumptions, both in the structure of the model and the parameter values chosen, and that alternative assumptions can result in considerably different estimates of both costs and QALYs. There is also quite a high

correlation between costs and QALYs, meaning reductions in QALYs (often driven by reductions in time in the ambulatory health state) are accompanied by reductions in costs (the lower treatment costs for a smaller number of people still being on ataluren).

Finally, it should be noted that here the ERG only considered the impact of changes to the model based on the new submission made by the company. Other comments on the model made in the original ERG report (e.g. the initial cohort used in the model are older than the likely starting age in clinical practice, the model assumes the treatment benefit with ataluren persist beyond the time horizon of the trials) remain valid for the new data and model submitted.

ERG comments on Action Duchenne's Response to the Evaluation Consultation Document

Paragraph 4

Action Duchenne expressed enthusiasm for ataluren and an understandable desire for introduction of a new drug which could alleviate the symptoms and improve the lives of people with Duchenne. The ERG had sympathy with the Action Duchenne interpretation of results which suggested that even very small changes in outcomes or reductions in decline would be welcomed and might represent improvements, although some of these were not statistically significant.

The ERG notes that the data for 'run/walk 10 m' (1.6 s) and 'descend 4 stairs' (1.5 s) in the text and in their Table under paragraph 4.3 have been transposed for the two outcomes.

Appendix: ERG summary of results from Study 020

Results are summarised in Table 1. There was no statistically significant difference between ataluren and placebo in the primary endpoint, change in 6MWD (mean difference (MD) 15m, p=0.213, ITT population). The ataluren group had less decline on the three timed function tests compared with placebo,
[redacted]. There was no statistically significant difference in change in NSAA score (mean difference 1.51, p=0.268). PODCI and ADL data were presented in a figure only with no statistical analyses.
[redacted]

Pre-specified subgroup analyses for the 300-400 m subgroup are summarised in Table 1. A statistically significant difference was seen in favour of ataluren for change in 6MWD (MD 47m, p=0.007), two of the three timed function tests (4-stair climb: MD -3.6 s, p=0.003; 4-stair descend: MD -4.3 s, p<0.001) and NSAA score (MD 4.45, p=0.041). Fewer participants in the ataluren arm lost ambulation compared with placebo (0% vs 8%, P value not reported).

Data for the <300 m and >400 m subgroups were provided by the company at the request of the ERG (difference in change values between groups presented in Table 1; baseline and endpoint values presented in Table 2). Participants in the >400 m subgroup appear to have [redacted] with ataluren compared with placebo. There is [redacted] in 6MWD between ataluren and placebo in the <300m subgroup, [redacted] the effects on the timed function tests [redacted] in this subgroup than in the ITT population. Statistical analyses are not reported.

Pre-specified meta-analysis combining Study 020 with the ambulatory decline phase subgroup of 007 found a statically significant benefit of ataluren on 6MWD and the three timed function tests (Table 3). Meta-analysis of the 300-400 m subgroups from studies 020 and 007 showed even greater benefit with ataluren (Table 3).

[redacted] Adverse events considered possibly or probably related drug-related were more frequent in the ataluren arm
[redacted]

Table 1 Summary of results

Study and outcome	Treatment difference		P value
6 MWD (primary outcome), metres			
Study 007 (cITT), n=114	32 m		0.037
Study 007 (subgroup 300m-400m),[a] n=44	49 m		0.026
Study 020 (ITT), n=228	15 m		0.213
Study 020 (subgroup 300m-400m), n=99	47 m		0.007
Study 020 (subgroup <300m), n=45 [d]	[redacted]		Not reported
Study 020 (subgroup >400m), n=84 [d]	[redacted]		Not reported
Timed function tests, seconds			
Study 020 (ITT), n=288			
[redacted]	[redacted]		[redacted]
Study 020 (subgroup 300m-400m), n=99			
10 m run/walk	-2.1 s		0.066
4-stair climb	-3.6 s		0.003
4-stair descend	-4.3 s		<0.001
Study 020 (subgroup <300m), n=45			
10 m run/walk	[redacted]		Not reported
4-stair climb	[redacted]		Not reported
4-stair descend	[redacted]		Not reported
Study 020 (subgroup >400m), n=84			
10 m run/walk	[redacted]		Not reported
4-stair climb	[redacted]		Not reported
4-stair descend	[redacted]		Not reported
NSAA score			
Study 020 (ITT), n=288	1.51		0.268
Study 020 (subgroup 300m-400m), n=99	4.45		0.041
PODCI, change in score	**Ataluren**	**Placebo**	**P value**
Study 020 (ITT), n=288			
transfers/basic mobility	[redacted]	[redacted]	Not reported
sports/physical function	[redacted]	[redacted]	Not reported
Study 020 (subgroup 300m-400m), n=99			
transfers/basic mobility	[redacted]	[redacted]	Not reported
sports/physical function	[redacted]	[redacted]	Not reported
ADLs			
Study 020 (ITT), n=288	[c]	[c]	Not reported
Study 020 (subgroup 300m-400m), n=99	[c]	[c]	Not reported
Proportion who lost ambulation	**Ataluren**	**Placebo**	**P value**
Study 020 (ITT), n=288	[redacted]	[redacted]	Not reported
Study 020 (subgroup 300m-400m), n=99	0/47 (0%)	4/52 (8%)	Not reported

[a] Not previously reported in Company Submission. [b] Estimated from figure A1.10. [c] Not possible to accurately estimate values from Figure 5. [d] Numbers in subgroups taken from Table A1.2, but numbers in analysis uncertain, as additional data provided by the company at the ERG's request (Table 2) differ from those in their 'Response to ECD' document for 6MWD 300-400m subgroup and total group.

Table 2 Subgroup data: baseline and endpoint values

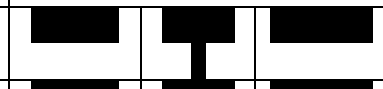
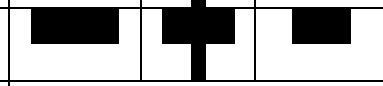
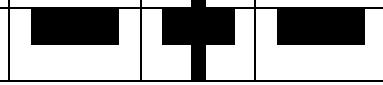
Subgroups	6MWD			10-metre walk/run			4 stair climb			4 stair descend		
	Baseline	Wk 48	Change	Baseline	Wk 48	Change	Baseline	Wk 48	Change	Baseline	Wk 48	Change
<300 m												
Ataluren												
Placebo												
300-400 m												
Ataluren												
Placebo												
>400 m												
Ataluren												
Placebo												
Total of above												
Ataluren												
Placebo												

Table 3 Summary of meta-analyses

Study and outcome	Treatment difference	P value
Study 020 (n=228) and Study 007 ADP subgroup (n=63), n=291		
6MWT (primary outcome)	22 m	0.015
10 m run/walk	-1.4 s	0.025
4-stair climb	-1.6 s	0.018
4-stair descend	-2.0 s	0.004
300-400m subgroups of Study 020 (n=99) and Study 007 (n=44), n=143		
6MWT (primary outcome)	45 m	<0.001
10 m run/walk	-2.2 s	0.008
4-stair climb	-3.4 s	<0.001
4-stair descend	-4.3 s	<0.001

ADP: Ambulatory Decline Phase defined as aged 7 years to 16 years with a baseline of 6MWD ≥150 metres, and 80% of predicted 6MWD and on a stable do

Response to NICE Evaluation consultation document

Ataluren for treating Duchenne Muscular Dystrophy with a nonsense mutation in the dystrophin gene

Prepared by Action Duchenne

October 2015

Please find enclosed Action Duchenne's feedback to the National Institute for Health and Care Excellence's evaluation consultation document on the draft guidance offered by the committee on the use of Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. Within this response we have sought to address the specific questions directed to us in the ECD. However, in this forward, we are additionally eager to emphasise the concerns of families and patients affected by Duchenne muscular dystrophy and the difficulties encountered in the evaluation processes which have assessed Ataluren.

In 2014, the European Medicines Agency accepted the published evidence and submissions made in respect of the associated opinion of the Committee for Medicinal Products for Human Use (CHMP), and granted regulatory approval in May of the same year. Since that date, many nations (including Germany, France, Spain, Italy, Denmark, Austria, Greece, Norway & Turkey) have already funded the treatment. These decisions were made on the basis of PTC Therapeutics' phase 2b trial, a placebo controlled randomised double blinded study which ran for 48 weeks and was deemed to have demonstrated clinically meaningful benefit. The Phase 2b trial was the largest and longest study of an investigational drug in patients with Duchenne/Becker Muscular Dystrophy. That NICE should consider the evidence submitted to date to be insufficient, effectively challenging the opinion of the CHMP and recommendation of the EMA, is disappointing. We are further discouraged by the fact that this draft decision, requesting additional data, appears to rest on the inclusion of 2 patients with Becker Muscular Dystrophy out of a total 174 boys and young men.

Furthermore, we are mindful to emphasise the inadequacies within the appraisal processes to which Ataluren has been subject in the UK. NHS England's specialised commissioning process was subject to legal challenge after being deemed discriminatory towards drugs for rare, ultra-rare and orphan conditions. After a ninety day consultation on the prioritisation principles underpinning decision making, NHS England's own Patent and Public Voice Assurance Group refused to assure the organisations response to inequities within their process. The inability of NHS England to render a fair decision on the use of Ataluren was ultimately illustrated in their decision to defer responsibility for the treatment's evaluation to the NICE's HST process. These failings had serious repercussions for NICE's evaluation of Ataluren. PTC Therapeutics were underprepared for this process and were subsequently afforded insufficient time to undertake the requisite modelling. The economic model used within this evaluation is resultantly incapable of covering all the complex disease states that exist for Duchenne. Whilst we have attempted to provide additionally relevant evidence for the consideration of the committee we would like to highlight the limitations of this evaluation.

The eighteen month wait for a final and determinative decision on the use of Ataluren for the treatment of Duchenne has undeniably had a significant impact upon the well-being of eligible patients. The condition of patients is one of unremitting decline. Put simply, we do not have any more time to wait. We implore the committee to take "into account the results of the multi-centre, randomised double-blind, placebo controlled confirmatory study (PTC 124-GD-020-DMD)", as quickly as possible, and are encouraged to see the results of this study are now published. Whilst we recognise the importance for all relevant information to be fastidiously factored into the committee's analysis, the severe, irreversible and degenerative nature of Duchenne necessitates the minimisation of delay in the preparation of a final evaluation determination.

Thank you for taking the time to consider our feedback to this consultation.

1. Background

1.1 Action Duchenne was the first organisation in the UK dedicated exclusively to Duchenne and Becker Muscular Dystrophy. We now fund cutting edge research into the condition whilst campaigning to improve the lives of everyone affected. We also oversee the UK DMD Registry, linking patients to clinical trials, and have published the only Duchenne research strategy of its kind in the UK.

1.2 This consultation has been completed by a partnership of existing trustees and staff. We would also like to thank Action Duchenne founder, [redacted], and parent Bernie Mooney for their contributions.

2. Summary of Key Points.

2.1 The true savings for families and the health service, quality of life benefits, in addition to the impacts upon morbidity and mortality, which are likely to be influenced by the routine commissioning of Ataluren for treating nmDMD, have been severely underestimated.

2.2 In recognition of the unremitting decline experienced by patients living with Duchenne and their resultant short life expectancy, more weight should be applied to any quality of life benefit or health benefit in comparison with conditions which are not severely debilitating and life limiting.

2.3 Due to the nature of the condition and the downstream effects, a cocktail approach to treatment is needed. It is likely that many of the treatments in clinical trial development will combine with Ataluren and have an incremental effect.

2.4 The draft decision of NICE, in requesting further data and calling into question the findings of the Phase 2b trial, focused on the inclusion of 2 patients with Becker Muscular Dystrophy. These individuals comprised 1% of the cohort for this trial and should therefore not invalidate the other findings of this study.

2.5 National commissioning decisions must be understood within the context of UK Life Sciences Policy and its express intention to boost innovation, health and wealth through the rapid development and adoption of innovative medicine.

Specific questions asked by the Evaluation Committee

3. Has all of the relevant evidence been taken into account?

3.1 The economic model used within this evaluation is incapable of covering all the complex disease states that exist for Duchenne. Subsequently, the true costs, quality of life benefits, in addition to the impacts upon morbidity and mortality, which are likely to be influenced by the routine commissioning of Ataluren for treating nmDMD, have been severely underestimated.

3.2 The disease states that the company's model was able to present were crudely defined, despite the attempt made by PTC Therapeutics. Due to the late decision by NHS England to remove Ataluren from its clinical commissioning process, this definition is reflective of the limited time the company were afforded to undertake the modelling.

3.2.1 To use one indicative example, the existing model has considered the conventional costs of spinal surgery, but has overlooked that the procedure involves a significantly larger team to manage the risks of the surgery and anaesthesia in the case of Duchenne patients. As a consequence, the impact upon the quality of life of parents has been left unobserved. Any surgery and anaesthesia carries a much higher risk of death in the case of Duchenne patients. Spinal surgery is therefore not a decision that is taken lightly, and causes significant stress and anguish to families facing this choice. Downstream costs for the health service are also much higher. Patients cannot be sent home to recover as a normal ambulatory patient would. The care required in terms of hoisting, toileting, and bathing is too severe for parent carers to manage after surgery, meaning patients tend to remain in hospital until recovery is complete. It should further be noted that significant costs are incurred by parents following surgery. After surgery patients often require new wheelchairs, leaving families in need of wheelchair accessible vehicles and homes. This example irrefutably illustrates that significant and relevant evidence has been overlooked.

3.3 Whilst a noteworthy amount of evidence is contained in the committee papers published by NICE, parts of this have been redacted. It is important that all available natural history data be used. For example, it is not known how much data was taken from the North Star database although it is included in the list of published references contained in the committee papers. Natural history data can be gauged from other online registries including the DuchenneConnect registry in America; a paper published in PLOS Currents[1] in 2014 on

[1] Online Self-Report Data for Duchenne Muscular Dystrophy Confirms Natural History and Can Be Used to Assess for Therapeutic Benefits, PLOS Currents, October 2014

Natural History and Outcome Measures validates such an approach in Duchenne Muscular Dystrophy. There appears to be no reference to this paper.

3.4 Whilst the committee's willingness to consider the downstream savings the NHS may realise through the routine commissioning of Ataluren is acknowledged and appreciated, the magnitude of these savings is insufficiently considered. For example, whilst we accept the committee's contention that, "because Ataluren [is] not a curative treatment, some costs may only be delayed until the disease progress[es]", the scale of savings accompanying reduced palliative treatment and minimised unplanned admissions through a reduction in falls and fractures is neither analysed or acknowledged. According to the most recent figures, a lack of proactive and pre-emptive care for Duchenne patients costs the NHS approximately £81.5m in emergency admissions per annum[2]. In significantly delaying the rapidity of patient decline, Ataluren has the ability to diminish these costs.

3.5 Furthermore, the above statement, made by the committee, overlooks the significance of delaying disease progression, even if Ataluren is not a curative treatment. As [redacted], (mother to [redacted], aged 11 and in receipt of Ataluren) puts it, this delay means, "my son can do things other 11 year olds take for granted: like managing a week at school, going to after school clubs and go swimming. He can get out and enjoy life and have opportunities to learn skills and make friends as every young person should". Considered within the context of limited life expectancy, every moment a child can spend in a better state of health is of more value than it would be to those with a normal life expectancy.

3.6 In its findings, the submission and review takes little consideration of the significance of falls. In addition to encumbering the health service with significant costs, falls have a very significant impact upon physical and psychological impact upon boys and parents. Fear of falling makes boys with Duchenne cautious and self restrictive. If they fall, they often do not have the strength to get up, and therefore require constant supervision. The quality of life of parents is therefore affected in turn. Falls can furthermore lead to instant loss of ambulation much earlier than expected by causing severe fractures. In the worst cases, falls and minor traumas can be fatal owing to the frequency of Fat Embolism Syndrome[3] in patients with Duchenne muscular dystrophy.

[2] Landfeldt, Lindgren, Bell: *The Burden of Duchenne Muscular Dystrophy. An International Cross-Sectional Study*, 2014.
[3] McAdam: *Neuromuscular Disorders*, 2012.

3.7 A failure to acknowledge the scale of the financial burden accompanying Duchenne can be further witnessed in the committee's analysis of costs faced by families living with the condition. Indeed, whilst we approve the committee's readiness to consider those costs which are not reimbursed by the NHS; (moving home or paying for modifications for accessibility purposes, giving up work to meet outstanding care needs, travel appointments and payment for additional help such as physiotherapy), the size of this expense, encumbered by families is not analysed. Latest estimates (in 2012 international dollars) put the average annual per-patient household burden at $63,600[4]. We request the committee to afford the existing costs faced by families as well as the health service appropriate analytical gravity.

3.8 The committee must further acknowledge the full emotional impact of Duchenne upon those affected. Duchenne is a severe, irreversible, and currently, untreatable condition with a predictable trajectory. The effect this has upon the emotional well being of entire families cannot be understated. A recent comprehensive study of parents to boys and men living with Duchenne showed 84% of parents measuring above the clinical threshold for anxiety and depression. This is high even in relation to other studies of parents of disabled children and young people[5]. Moreover, this impact is not limited to parents, as the statement of Bernie Mooney, parent to [redacted], aged 15, living with Duchenne, testifies, "the emotional impact it is having on his brother is only just becoming apparent. Last year he had a breakdown at school after googling his brother's condition".

3.9 The neurobehavioral impact upon patients living with the condition is also profound. Research shows that nearly half of men living with Duchenne or Becker muscular dystrophy have mental health concerns. Mental well-being is furthermore inextricably linked to the ability to walk independently. As recent study confirmed that, "males 1-29 years of age with Duchenne or Becker Muscular Dystrophy, who were losing their ability to walk, were more likely to have behavioural concerns, and more than three times and likely to have depressed moods as those who were still able to walk independently"[6]. Given the ability of Ataluren to delay loss of ambulation, the committee needs to appreciate the significant benefit routine commission may have upon the mental health of Duchenne patients.

3.10 These benefits will furthermore extend to the alleviating anxiety and depression amongst family members of those living with Duchenne. For families, the most precious

[4] Landfeldt, Lindgren, Bell: *The Burden of Duchenne Muscular Dystrophy. An International Cross-Sectional Study*, 2014.
[5] Bushby: *Transition to Adulthood for Young Men with Duchenne Muscular Dystrophy and their Families*, 2009.
[6] http://www.cdc.gov/ncbddd/musculardystrophy/features/mental-health-and-dbmd.html

benefit that this treatment affords is extra time. Example: **"Time for us to enjoy being with him and for him to enjoy just being himself. Time for us to make those special memories which we will need to keep us going through the darkest days to come"**[7]. In failing to sufficiently measure the emotional impact of Duchenne, the committee fails to appreciate the importance of 'extra time' for families. This is largely distinctive from other treatments and owes its significance to the inevitable decline associated with the condition. In recognition of the unremitting decline experienced by patients living with nmDMD, and the short life expectancy of boys, more weight should be applied to any quality of life benefit or health benefit.

3.11 Parent Project Muscular Dystrophy recently released a landmark qualitative study measuring Benefit Risk Assessment's in Rare Disorders. This surveyed parents and patients affected by Duchenne, and proposed that, "new approaches for regulatory benefit risk assessments are considered for [...] rare progressive, fatal disease(s) for which no current therapy is approved"[8]. We further believe that this should be applied to the assessment processes which go beyond the regulatory framework. As such, we ask the committee to heed this advice and afford patients views on benefit expectations and risk tolerance urgent consideration.

4. Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?

4.1The secondary outpoints in Study 007 and in particular Timed Function Tests (TFT), provided an important measure of efficacy. The ERG took the view, in respect of the EMA's Scientific Advisory Group that "There was little supportive evidence of effect from the data on the secondary endpoints." but this is a generalisation and does not reflect the actual change demonstrated in the Timed Function Tests in the Phase 2b trial (and as now reported from the Phase 3 data). There are concerns that the ERG report states that:

"Smaller increases between baseline and 48 weeks in the time required to climb four stairs were found with Ataluren compared with placebo [2.4 seconds (SD 4.6) versus 4.8 seconds (SD 7.9), p=0.0207 cITT analysis set]. No statistically significant differences were found for descending four stairs, run/walk 10 metres, or supine to stand time." (Page 61, para 4.2.6.1) (emphasis added)

[7] Sheehan: *Highly Specialised Technology Evaluation Committee First Meeting. Patient Perspective*, 2015.
[8] Franson, Paey: *PPMD Benefit Risk Assessments in Rare Disorders. The case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for new approaches*, 2015.

4.2 A 1.6 second difference in decline over 48 weeks within the context of a 10 metre run/walk is significant, as is a 1.5 second difference for climbing four stairs, reported as representing a 45.1% and 39.9% difference from the mean. By way of personal context, [redacted]'s (son of Action Duchenne trustee, [redacted]) Act 10 metre test, as part of the 6 monthly North Star assessment at his 6 monthly clinic, declined slightly from 4.4 seconds to 4.6 seconds over the six months to September 2015.

4.3 The difference in decline between what has been reported in the placebo group previously and in the Ataluren 40mg/kg/day group is significant within the context of a test which typically lasts less than 10 seconds. When the Timed Function Tests are presented in terms of the % decline from the baseline time, the differences between are significant.

	Decline based on TFT change recorded after 48 weeks Placebo	Decline based on TFT change recorded after 48 weeks Ataluren 40mg/kg/day
Climb four stairs	48%	23%
Descend four stairs	75%	39%
Run/walk 10 metres	80%	30%

4.4 The conclusion of the ERG that the changes in descending four stairs and running 10 metres, in the Ataluren 40mg/kg/day group, are not 'statistically significant differences' is contested. TFTs are an established part of the North Star assessments carried out every 6 months in neuromuscular clinics for Duchenne patients and as a valid secondary endpoint in this trial, there is scope to assess them against the natural history data available from the North Star database.

4.5 Whilst, "the 6MWD is an optimal primary endpoint for Duchenne clinical trials that are focused therapeutically on preservation of ambulation and slowing of disease progression"[9],

[9] McDonald, Henricson, Abresch, Florence, Eagle, Gappmaier, Glanzman; *PTC124-GD-007-DMD Study Group,* 2013

the precipitous declines in patients with greater disease severity has the potential to produce variability. Not only may longer duration studies be necessary to demonstrate benefit, but measures should be expanded to include increased dystrophin levels. Indeed, the improved understanding of the natural history of dystrophin deficiency and the wealth of recently collective outcome measure data forms a very good foundation to inform new trials and drug development programmes[10].

4.6 The draft decision of NICE, in requesting further data and calling into question the findings of the Phase 2b trial, focused on the inclusion of 2 patients with Becker Muscular Dystrophy out of a total of 174 boys and young men. It is acknowledged that Professor [redacted] is reported to have indicated that those living with Becker Muscular Dystrophy ought not to have been included in the trial. These individuals comprised 1% of the cohort for this trial and should therefore not invalidate the other findings of this study.

4.7 The committee fails to acknowledge the importance of delaying the loss of ambulation as a significant and distinct outcome, independently of the prospect of life extension. This is witnessed in the committee's willingness to accept and deem justifiable the company's post hoc adjustment and sub group analysis of patients in the decline phase. Despite this evidencing a delay of 8.1 years in the loss of ambulation with the use of Ataluren versus best standards of care, the conclusion is reached that this study was too short to yield any long term benefits of treatment with Ataluren, namely, "an effect on mortality". The distinct importance of delaying loss of ambulation is supported by the statements of patient experts submitted to the committee. For example: "Work isn't your main focus when you are wondering whether your child will stop walking today".

4.8 The committee appears to contradict themselves over the reliability of a 48 week trial to yield conclusions surrounding the long term benefit of Ataluren. Despite defending the company's decision to use utility values from supporting literature rather than Study 007 as justifiable (owing the short nature of the trial), the fact that "there was no statistically significant differences in quality of life between Ataluren and placebo groups" in Study 007 seems to be a major concern for the committee and contributes towards their "uncertainty over the longer term benefits of Ataluren".

4.9 However, whereas the paucity of evidence has led to quality of life benefits being severely underestimated, the lack of statistically significant differences between Ataluren

[10] http://www.nmd-journal.com/article/S0960-8966(14)00637-3/pdf

and placebo groups does at least show that it is not doing any harm. This is reflected in the reality that in the largest ever study in DMD, no patients discontinued treatment or withdrew from the study.

4.10 It appears the limited importance which has been placed on the TFTs by the ERG has underpinned the relative scepticism about the efficacy of Ataluren. This needs to be revisited.

4.11 Ataluren (or indeed any genetic fix for DMD) will not immediately and instantly reverse the severe damage to muscle. Dystrophin takes time to produce (albeit truncated by one base) in all muscle fibres across the body. The genetic fix stabilises the muscle fibres but it also takes considerable time to allow the body's own satellite or stem cell mechanisms to begin repairing existing damage. It also takes time to start to clear out scar and fatty tissues to produce good functioning stable muscle. With data accrued over 48 weeks, it is hard to show benefits and even harder to predict the likely improvement in length of life and sustained quality of life.

4.12 With Duchenne, "multiple and combined strategies are required to accelerate therapeutic developments for neuromuscular disorders. This should include disease-specific and -sensitive outcome measures, which advance hand in hand with the evolving natural history of the condition; clinical trial design, which takes into account the variables and dynamics of the disorder; and finally integrate through intelligent use of registries/databases the collection of broad-based evidence to strengthen knowledge building and modernise clinical care"[11]. Due to the nature of the condition and the downstream effects; a cocktail approach is needed. It is likely that many of the treatments in clinical trial development will combine with Ataluren and have an incremental effect.

5. Are the provisional recommendations sound and suitable basis for guidance on the use of Ataluren in the context of national commissioning by NHS England?

5.1 The unwillingness of the committee to recommend the use of Ataluren, given the current evidence, on the basis of its "considerable cost" contradicts assurances within NHS guidelines that, "commissioners have received the expected level of funding to cope with the growth in cost of branded medicines"[12]. NHS England has received £796 million in PPRS

[11] Ricotti, Muntoni, Voit: *Challenges of Clinical Trial Design for DMD*, 2015.
[12] https://www.england.nhs.uk/wp-content/uploads/2014/05/pharm-price-reg-qa.pdf

payments for 2015/16, theoretically allowing commissioners to "shift from cost-saving onto securing better patient outcomes" and allowing commissioners to "disengage from cost-containment measures"[13] . These statements are clearly not reflected in the committee's guidance for a treatment that, by their own admission, "makes a very strong claim for NHS resources"[14].

5.2 The unwillingness of the committee to recommend the use of Ataluren on the basis of "the benefit obtained [compared] with other highly specialised technologies available to NHS patients" is an unsound and unsuitable basis for guidance. This is insensitive to both the absence of alternative treatments addressing the underlying causes of Duchenne, and the fact that Ataluren was never supposed to be subjected to a HST appraisal. This statement further fails to consider the willingness of patients and parents affected by Duchenne to accept moderate side effects and risks then they, "could be compensated for by a treatment that stops the progression of muscle weakness"[15].

5.3 This recommendation is further based upon an erroneous comparison of Ataluren with eculizumab (for treating atypical haemolytic uraemic syndrome) and elosulfase alfa (for treating mucopolysaccharidosis type Iva). These are very different conditions to Duchenne, requiring much less complex prognosis. They furthermore have divergent treatment pathways to the genetic treatment of Duchenne. The treatments in question have the potential to reverse these conditions and have very immediate benefits, whilst also benefitting from more evidence and a reasonably simple method of action. For Duchenne, the process of gene therapy is one of gradual stability and significant downstream longer term benefits to length and quality of life.

5.4 National commissioning decisions must be understood within the context of UK Life Sciences Policy[16] and its express intention to boost innovation, health and wealth through the rapid development and adoption of innovative medicine. UK processes have consistently proved themselves unsuitable and unresponsive to innovative treatments for orphan, rare and ultra rare conditions. If this continues, companies will be forced to seek out alternative and more auspicious environments for investment, thereby undermining this agenda. With

[13] Ibid.
[14] Sheehan, Mark: *Highly Specialised Technology Evaluation Committee. First Meeting*, Sept 2015.
[15] Franson, Paey: *PPMD Benefit Risk Assessments in Rare Disorders. The case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for new approaches*, 2015.
[16] http://www.actionduchenne.org/interim-report-on-the-accelerated-access-review-published/

multiple treatments for Duchenne in the research pipeline, the fact that numerous nations[17] have already approved Ataluren will not be lost on the pharmaceutical industry.

6. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

6.1 The recommendations could be deemed discriminatory on the basis of Ataluren's regulatory approval in the EU. The treatment is already available to patients in Germany, Austria, Spain, France, Italy, Denmark, Greece and Norway. Whilst none of these nations follow a health technology assessment process, we are mindful that British patients and families could be discriminated against.

6.2 The committee's recommendations made on the basis of cost are divergent to other commissioning bodies within the UK. The SMC is currently granting individual patient funding requests on the basis of the current information on benefits and existing cost. We are mindful to emphasise this disparity in patient access.

6.3 It is imperative that the UK has a fair, transparent and equitable process of evaluating treatments for rare, ultra-rare and orphan conditions. NHS England's specialised commissioning process was suspended and subjected to public consultation for putting said treatments on an unequal footing. There is a danger that the NICE HST process will prove itself as equally discriminatory and unresponsive to the needs of rare disease patients.

6.4 As a community we have long been recommending that NICE places rare disease patients are at the heart of the decision making processes, and ensures that, "vulnerable patients with very rare conditions are not denied treatment on the grounds of cost following an inappropriate cost benefit analysis"[18]. We recognise that the HST process should theoretically do this. However, our experiences thus far validate our concerns that there appears to be no coherent strategy to rapidly develop and fund these new drugs.

[17] Germany, Austria, Spain, France, Italy, Denmark, Greece & Norway.
[18] http://www.musculardystrophyuk.org/app/uploads/2015/02/Access-to-high-cost-drugs-report-FINAL.pdf

6.5 It could further be considered discriminatory to refuse access to treatment on the grounds of cost for a currently untreatable condition which causes short life expectancy. As previously mentioned, the quality of life and health benefits of those with a short life expectancy should be weighed more heavily. The inevitable decline associated with Duchenne, the absence of other treatments which directly tackle the underlying causes of the disease and the distinctive importance of 'extra time' for both patients and families need to be considered in the committee's recommendation.

6.6 We are additionally concerned that NICE has no disabled people on its equality panels. Therefore, these panels necessarily have a lack of understanding about the impact of profound disabilities. This lack of insight is not helpful.

Muscular Dystrophy UK

Fighting muscle-wasting conditions

Introductory statement

1.1. Muscular Dystrophy UK is deeply disappointed that the draft guidance produced by NICE on 16th October is 'minded not to approve' *ataluren* for the treatment of Duchenne muscular dystrophy (DMD) caused by a nonsense mutation in the dystrophin gene.

1.2. As the first licensed drug to target an underlying genetic cause of DMD, *ataluren* has been shown to have a clinically significant effect in clinical trials, slows down the progression of what is a devastating condition and has a profound impact on the health and quality of life of eligible boys and their families.

1.3. We therefore do not believe that the provisional recommendations are *'sound and a suitable basis for guidance on the use of ataluren in the context of national commissioning by NHS England.*

Study 020

2.1. We note that the Evaluation Committee requested data from PTC124-GD-020-DMD;Study020 and we are pleased that the results of this study have now been published.

2.2. These results reinforce evidence that *ataluren* slows down the progression of DMD, and we are particularly encouraged that a 47 metre benefit was observed in 6MWD in the pre-specified subgroup of 300 - 400 metre at baseline.

2.3. We believe this underlines the importance of administering treatment at the earliest possible stage for maximum benefit in accordance with the licence, a situation that is at sharp odds with the increasing length of time it is taking for the product to receive reimbursement in the UK.

Long-term benefits and Managed Access Programme

3.1. We note that the Committee states *'there was uncertainty about the longer-term benefits of ataluren treatment because of the limitations in the evidence base'.*

3.2. It is clear current limitations on evidence of long-term benefit are difficult to avoid without a managed access or similar programme in place, given that this evidence would need to be gathered over a longer period of time than has been available to the company. Steps are being taken through the STRIDE database to monitor boys currently on treatment in Europe, so there is now a sound infrastructure to enable the gathering of evidence on a long term basis. We believe that concerns around the long-term evidence base risk discriminating unfairly against newly licensed drugs for rare conditions such as Duchenne, where the evidence base will almost certainly be more limited in the absence of a managed access or similar programme put in place within the terms of licence.

3.3. The committee's statement in 3.1 must also be balanced against both the evidence from clinical trials that *ataluren* slows the progression of DMD and the high unmet medical need for the condition.

3.4. In highlighting its concerns around availability of evidence on long-term benefit, the Committee itself makes a strong case for *ataluren* being made available through a Managed Access Programme. This would enable evidence on long-term impact to be gathered whilst allowing patients access to the drug. Muscular Dystrophy UK believes this option should be strongly considered at NICE's Evaluation Committee meeting on 17 November. Ataluren may also represent a suitable candidate to be introduced via the NHS England Commissioning through Evaluation process.

Impact of the condition

4.1. We strong believe that the Committee has failed to understand or capture both the long term progression of DMD, and the impact the condition has on those affected, their families and society in terms of quality of life, health, costs, morbidity and mortality.

4.2. We are concerned that the company itself, the ERG and the Committee have significantly underestimated the severity of the condition. The economic modelling was over-simplistic in the choice of states, and then does not adequately represent the quality of life of patients and carers or the costs associated with each state. We acknowledge that published evidence is sparse, again due to the rare nature of the

condition, but there are patient experiences which are very relevant and have not been incorporated.

4.3. Taking the assisted ventilation state as an example, the Committee states that 'people with DMD lose the ability to breathe unaided and need assisted ventilation', but this does not come near to capturing the impact this has on an individual. Assisted ventilation means an individual will need overnight care, which at a stroke significantly increases the care, quality of life and cost burdens. Ventilated patients may need assistance up to 10 times a night. Further, a simple power cut is potentially life threatening, evidenced by a tragic recent case where two young men with DMD died in a power failure which cut power to their ventilation equipment.

4.4. Social opportunities become more and more limited as the disease progresses, and young men and their families are extremely restricted in what they can do. The progression of Duchenne and the need for ventilation also exposes individuals and their families to further societal prejudices around disability. One young man in Surrey was thrown out of the cinema by staff after complaints from other cinema goers his ventilator was "too noisy". The emotional and psychological impact this kind of incident has on an individual and their family is profound, and unfortunately is encountered all too frequently.

4.5. Added to this is the consideration that once serious respiratory difficulties are encountered – which is one of the primary causes of death in DMD – individuals and families must begin to engage with and face what many find to be the truly frightening aspects of the condition. One mother with whom Muscular Dystrophy UK works closely was called out to her son's residential home at 2am at a weekend in September due to an emergency incident. Whilst her son was not hospitalised long term, he is experiencing increasing difficulties and his mother told us that *'he is very aware of his own mortality'.*

4.6. Other young men are hospitalised frequently and often for long periods of time due to chest infections, which are very difficult to shift and which are life threatening. The current time of year is a frightening time for young men and their families affected by DMD, with colds and chest infections much more likely.

4.7. Inability to clear mucus and secretions also places patients at risk of respiratory failure and hospitalisation. One young man, [redacted] was hospitalised due to hypoxia, which he described as a terrifying and 'out of body' experience. Although he was discharged from hospital, [redacted] tragically died at the age of 21. His mum, [redacted] said: '[redacted]*'s last few weeks were awful as he was completely dependent*

on a ventilator we had at home. He had no energy or appetite. He had no quality of life at all."

4.8. [redacted]'s case also highlights that whilst life expectancy today is now reaching on average into the late 20s, it is sadly still not uncommon for boys to die in their teens and early twenties due to the complications and underlying health difficulties associated with the condition. This unpredictability and danger of sudden death at an earlier age should be recognised.

4.9. The condition also places severe emotional and psychological strain on younger patients. The Committee describes the 'frustrations' experienced by boys who cannot participate in games and thereby keep up to socialise with their peers. Whilst true, this statement makes no attempt to acknowledge the serious psychosocial effects this will have on a child, leading to challenging behaviour and social isolation which impacts upon the whole family.

4.10. For these younger ambulant patients, parents need to keep a watch at all times, even during something as simple as playing in the garden. This is due to an increased risk of falling and fractures. The use of steroids leading to bone thinning as a side effect are a contributory factor to the increased risk of fractures. When a fracture occurs, loss of ambulation is highly likely to follow.

4.11. The Committee recognises that 'scoliosis develops as the back muscles weaken, for which surgery is needed'. Against, whilst true, no consideration is given to the severe risks associated with such surgery for patients whose respiratory function is compromised. A 2-3 week stay in hospital is necessary, and in some cases boys have to be cared for outside of the home for a time after discharge, as their needs cannot be accommodated in their family home.

4.12. As the condition progresses, each unplanned visit to hospital carries its own risks. A fracture or body trauma can induce rapid breathing and/or neurologic deterioration. Anaesthetic precautions must be taken and inhaled anaesthetics should not be used. Muscular Dystrophy UK is aware of cases where a patient has died in emergency admission due to the inappropriate administering of treatment.

4.13. In the absence of long-term data, the Committee must take fully into account that loss of ambulation is associated with a faster progression of the disease, the later stages of which are frightening and absolutely devastating. In a short life, the main goal is to spend as much of that life in the best state of health and quality of life possible. We therefore believe that more weight should be applied to any benefits

that can be obtained through the use of Translarna, in the context of that short and limited life.

4.14. A delay in any of the devastating consequences of the disease, no matter how short, contributes. Whilst ataluren is not yet licensed for use as an 'end of life' medicine (it is still to be tested in clinical trials with older patients), the existing trials evidence shows it delays the progression of the disease during a very significant stage of a boy's life and as a proxy measure also indicates it is likely to delay the end of a life.

4.15. We strongly believe that special consideration has to be given to the limited life expectancy of these boys. The current draft guidance simply does not reflect this sufficiently.

Cost

5.1. We note that the Committee has requested further information from PTC Therapeutics on the costs of the drug. Muscular Dystrophy UK understands that the price of treatments such as ataluren to the NHS are often seen as high for patients with rare diseases like DMD, given the small numbers of patients eligible and who benefit from the treatment.

5.2. However, it is vital to ensure that the relatively high price involved for drugs with 'orphan status' are not an insurmountable barrier to these drugs being funded by the NHS and reaching patients in this country. It must be borne in mind that the granting of orphan status by the EMA reflects the statutory recognition that drugs for patients with rare diseases and high unmet medical needs should be allowed access to emerging treatments as much as those with more common diseases.

5.3. We urge NICE and the company to discuss the costs of ataluren as a matter of urgency, so that considerations on pricing do not prevent the drug reaching boys and their families, who have endured a long, anxious and upsetting wait since ataluren received its conditional licence approval from the EMA in August 2014.

Discrimination

6.1. We believe the draft guidance as it stands discriminates against patients with nonsense mutation DMD for the following reasons:

- It asks for a long-term evidence base to an extent that is clearly discriminatory against rare disease drugs for patients with high unmet medical needs
- It fails by a significant extent to recognise the severity of DMD and the benefits of ataluren in the context of a short life

- It risks discriminating against families in lower socio-economic groups, who may need re-housing after loss of ambulation, who cannot afford adaptations and are at greater risk of being in unsuitable housing and non-specialist schools
- By denying access to ataluren, patients' conditions will progress at an otherwise faster rate and they will be exposed to the societal prejudice that is all too often aimed at patients with later stage DMD.

Patient and family participation in NICE Evaluation Process

We understand that the next meeting of the Committee will take place on 17 November. Muscular Dystrophy UK has been told that a decision has not yet been taken on whether patient and clinical experts will be invited to participate.

We make our view clear to NICE that it is essential that patients and families are able to be represented at the meeting, especially in light of the Committee's failure to fully recognise the severity of DMD and the burden and costs associated with each state. This will also ensure that patients and families are involved as fully as possible in a process and decision which will primarily affect them.

6 November 2015

NHS England response to:

Evaluation consultation document - Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

1. NHS England recognises that Duchenne muscular dystrophy is a devastating disease with profound consequences for patients and for their families and carers. NHS England believes that the relevant information, both in the company submission and in expert testimony from patients and parents, has been taken into account. NHS England agrees that important information will be provided by the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC124-GD-020-DMD; Study 020), which will need to be considered in the final evaluation.

2. NHS England believes that the summaries of the criteria considered by the Committee, and the clinical and economic considerations are reasonable interpretations of the evidence. NHS England also agrees that the Evaluation Committee has not yet been presented with an adequate justification for its considerable cost, in light of the available evidence of its effect on health outcomes relevant for patients, carers and family members.

3. NHS England is not able to comment, until the results of the confirmatory study have been fully evaluated, on whether the provisional recommendations sound and a suitable basis for guidance on the use of ataluren in the context of national commissioning by NHS England.

The Royal College of Pathologists
Pathology: the science behind the cure

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

Comments

1. After reviewing the document, I can understand the need to ask for more supportive evidence to support the cost benefits, however, I hope this can be provided as Ataluren has considerable promise as a treatment for Duchenne muscular dystrophy.

2. I would like highlight one issue that was stated in the document in Section 5.19.

   "5.19 The Committee considered the impact of ataluren on the delivery of the highly specialised service, and acknowledged statements from NHS England showing that treatment with ataluren is unlikely to involve additional services or monitoring costs. It heard from the clinical experts that services are already in place to monitor and treat people with DMD and, if ataluren were to be recommended for use, additional funding would not be needed. The Committee was therefore satisfied that no significant additional staffing and infrastructure would be needed in centres where patients with nonsense mutation DMD currently have treatment."

   However, I feel that this statement maybe inaccurate in that it does not take into the account of the additional laboratory tests such as RNA analysis that maybe required to ensure that the patients are suitable for this treatment. In 2010, Abbs *et al*. published the current best practice for Duchenne/Becker muscular dystrophy diagnostic testing. At present most diagnostic laboratories that perform D/BMD diagnostic testing use these guidelines. However, following a recent meeting (Leiden 2nd Nov 2015 - sponsored by Biomarin) I and other colleagues (including Profs Ferlini, Sejersen and Mueller who were co-authors of the originally guidelines) feel that these guidelines need to be updated due to the rapid improvements with mutation detection technology and availability of new potential treatments (gene, therapy, exon skipping and read-through of nonsense mutations –see Lu, 2014). At this meeting it was agreed that there should be two recommended Tiers of Testing – one for Therapeutic and one for Diagnostic testing. The second Tier is to take into account the lack of Governmental Public Health financial support in some countries such as Brazil and Argentina.

   Tier One (Therapeutic):

   1) NGS DMD panel (and/or DMD HD aCGH/MLPA for CNV confirmations) + RNA sequencing
   2) DMD HD aCGH (with MLPA for CNV confirmations) + DNA sequencing + RNA sequencing

   Tier Two (Diagnostic)

   1) DMD HD aCGH + DNA sequencing
   2) MLPA + DNA sequencing

3) mPCR + DNA sequencing

Everyone was in agreement that all patients that are enrolled for Therapeutic trials should undergo as comprehensive a DNA-based screen as possible, being tested for deletions, duplications and point mutations. Even patients with a detected deletion or duplication should still undergo testing for a point mutation to ensure that there no second mutation (Soltanzadeh *et al*. 2010). RNA sequence analysis of dystrophin transcripts from muscle biopsy is also recommended to be mandatory. For any pathogenic mutation that have been detected using DNA based tests, RNA analysis is needed to determine the effect of these mutations on the RNA splicing of patient's dystrophin muscle transcripts. For example, in a BMD patient we have identified the following nucleotide change, c.3430C>T which is predicted to result in the substation of a Glutamine amino acid by a nonsense codon [p.(Gln1144Ter)]. However, RNA analysis showed that the c.3430C>T causes aberrant splicing of the in-frame exon 25 in the patient's dystrophin mRNA transcripts explaining his milder BMD phenotype. Without RNA analysis, we cannot be sure if a nonsense mutation could potentially have the same effect.

However, over the years, since the availability of cheap DNA tests such as MLPA analysis, fewer patients with a suspected X-linked dystrophinopathy have had a muscle biopsy. Unfortunately, there are no alternatives to muscle biopsy material for RNA testing, although a needle biopsy is sufficient to generate sufficient material. This may be an issue as RNA analysis is a laborious manual technique and at present our laboratory is the only one in the UK that is offering RNA analysis for D/BMD as a clinical diagnostic service.

References:

1. Abbs S, Tuffery-Giraud S, Bakker E, Ferlini A, Sejersen T, Mueller CR. Best Practice Guidelines on molecular diagnostics in Duchenne/Becker Muscular dystrophies. Neuromuscul Disord 2010;20:422–427.

2. Lu. Q, Cirak. S, Partridge. T. What Can We Learn From Clinical Trials of Exon Skipping for DMD? *Mol Ther Nucleic Acids* 2014;3:e152.

3. Soltanzadeh P, Friez MJ, Dunn D, von Niederhausern A, Gurvich OL, Swoboda KJ, *et al*. Clinical and Genetic Characterization of Manifesting Carriers of DMD Mutations. *Neuromuscul Disord.* 2010;20:499–504.

Typos in document

Section 4.23
Extra "£" sign i.e. ££24,989,835, line 8

Abbrevations:
D/BMD = Duchenne/Becker muscular dystrophy
NGS = Next Generation Sequencing
HD aCGH = High Density array Comparative Genomic Hybridisation
MLPA = Multiplex Ligation Probe Analysis
mPCR = multiple PCR analysis
CNV = copy number variation
DNA = deoxyribonucleic acid
RNA = ribonucleic acid

Comments by:
Dr S C Yau
Research and Development Manager and Principal Clinical Scientist, Viapath

Dear Mr Fallon

Within this newsletter is an update regarding the funding of Translarna. I am so bitterly disappointed that words fail me. NICE continuously put off making a definitive decision which I, along with others, find unacceptable. During the time NICE have dithered I have to watch my grandsons ability to walk deteriorate. Of course, he is not alone and as there are others boys in the same boat. If there is anything that you feel you are able to do in order to bring some sanity to the matter I would naturally be very grateful.

Regards

[redacted]

Comment from a member of the public via MP (received 05 November 2015)

Response to NICE Evaluation consultation document

Ataluren for treating Duchenne Muscular Dystrophy with a nonsense mutation in the dystrophin gene

Prepared by [redacted]

Parent and Trustee, Action Duchenne and
Member of Action Duchenne Research Sub-Committee

November 2015

1. Background

1.1 My name is [redacted] and I am the father of a 10 year old child with Duchenne Muscular Dystrophy. Since 2008, I have been a trustee of Action Duchenne, where I sit on the research sub-committee, evaluating a wide range of research proposals submitted to the charity. I also contributed to the development of the Action Duchenne research strategy which remains the only published research strategy of its kind within the United Kingdom or the wider, international Duchenne community.

1.2 My son [redacted] is participating in the ongoing PTC124-GD-020-DMD trial where he receives Ataluren/Translarna on a daily basis. Since being enrolled onto the open label extension of the trial in late 2014, his 6 minute walk distances have remained constant.

1.3 Given my considerable involvement in assessing research proposals and potential treatments for Duchenne Muscular Dystrophy, I am familiar with reading technical papers of some complexity. I have read both the 620 page Committee Papers published by NICE, as well as the consultation document, prior to responding.

2. Summary

2.1 Although I will respond to the specific questions asked by NICE in its consultation, I would first like to emphasise that the regulatory process for assessing Ataluren, involving NHS England and now NICE, has generated serious concerns amongst families living with Duchenne Muscular Dystrophy. The highly protracted nature of this process, the conflicting and at times incorrect information provided by officials and politicians (including the Prime Minister on two occasions[1]), mean that 18 months have passed since conditional marketing approval for Ataluren was granted by the European Medicines Agency (EMA) in May 2014. There are still children in England who do not have access to Ataluren who would otherwise be eligible for this treatment and this is simply unacceptable.

2.2 In 2014, the EMA accepted the published evidence and submissions made in respect of Ataluren and the associated opinion of the Committee for Medicinal Products for Human Use (CHMP). It was originally intended that NHS England would determine whether Ataluren would be routinely funded. This remained the case up until NHS England eventually decided in July 2015 not to make such a determination but to announce that a final funding decision should instead be made by NICE.

2.3 This in itself meant that PTC Therapeutics had a very limited period in which to prepare a complete and robust submission ahead of the NICE evaluation committee in September. The consequence of this and NICE's subsequent draft recommendation in September is that of a wholly negative impact on children living with a life-limiting disability, a protected characteristic under the Equalities Act 2010. Therefore, there are concerns that the recommendations to date and the way in which they have been made, potentially breach the provisions of the Act in discriminating against those living with Duchenne.

2.4 Notwithstanding these valid concerns, in light of the EMA decision in 2014, it is unclear why NICE should be calling into question the findings of the phase 2b trial. The EMA decision was based on the findings of this trial, a 2b placebo controlled randomised double-blinded study which ran for 48 weeks and which was deemed to have demonstrated sufficient efficacy upon which to base a condition marketing approval.

2.5 As a conditional approval, there was a requirement for a further confirmatory trial to be undertaken and initial data from that trial has now been released, within a few months of the 48 week Phase 3 trial (020) being completed. The draft decision of NICE, in requesting further data and calling into question the findings of the Phase 2b trial, appeared to highlight the inclusion of two patients with Becker Muscular Dystrophy out of a total of 174 boys and young men. In this respect and in stating that

[1] See Hansard, 8 July 2015, Column 315 and Hansard, 14 October 2015, Column 313

"The Committee considered, therefore, that the results of Study 007 were uncertain." (paragraph 5.5 of evaluation consultation document) NICE have simply contradicted the opinion of the CHMP and recommendation of the EMA.

2.5 The Phase 2b trial was the largest and longest study of an investigational drug in patients with Duchenne/Becker Muscular Dystrophy yet it is noted that the Prime Minister recently stated:

> "*the NHS should not use Translarna until further information becomes available on how well the drug works".*[2]

2.6 This advice, given to a family living with Duchenne in August 2015 prior to the draft recommendation issued by NICE, appeared to conflict with the valid expectations which exist around the scope and considerations of NICE's ongoing appraisal. The Prime Minister has subsequently sought to clarify that he was not seeking to pre-empt NICE's conclusions but the fact that NICE subsequently requested further information on how well the drug works raises real concerns about the way in which the entire process has been approached.

2.7 Finally, it is worth considering what Professor Kate Bushby – one of the leading international Duchenne experts - stated in her submission to the All Party Parliamentary Group for Muscular Dystrophy in March 2015[3]:

> *"…**the process of approving rare disease drugs like Translarna, which can treat some boys with Duchenne muscular dystrophy, has been shambolic.** The process seems to be too complicated and protracted. One potential solution to this could be for the European Medicines Agency procedures, with reviews and questions and responses, to be made available **rather than going through endless re-reviews of the same information**."* (emphasis added)[4]

[2] www.actionduchenne.org/clarity-required-from-the-prime-minister-over-translarna/

[3] www.chroniclelive.co.uk/news/health/newcastle-expert-who-helped-pioneer-8213815

[4] All Party Parliamentary Group for Muscular Dystrophy, Impact of NHS reforms on access to neuromuscular services, March 2015

3. Specific questions asked by the Evaluation Committee

Has all of the relevant evidence been taken into account?

3.1 A significant amount of evidence is contained in the committee papers published by NICE although parts of this have been redacted. It is obviously not known which data or other content has been redacted but a primary concern is that NICE have failed to adequately understand the complex nature of this rare condition and the even rarer subgroup with the nonsense mutation for whom Ataluren is targeted. In doing so, the actual cost of managing Duchenne have been significantly underestimated. Similarly, benefits associated with improvements to quality of life, given that this is a life limiting condition affecting children **and** this is currently the only treatment available are simply given insufficient weight throughout. There is a much greater for NICE to recognise how Ataluren can buy urgently needed time for children while other Duchenne drugs are trialled.

3.2 There are many interventions required as a result of a diagnosis with Duchenne Muscular Dystrophy. These are not always obvious and are certainly not always reflected in NICE's assessment which is simplistic in its approach. For example, my son, as well as being monitored by a local dentist, is also reviewed by the Dental department at Great Ormond Street. This is because any more complex treatments cannot be undertaken locally in children with Duchenne due to the risks associated with anaesthesia. Whilst this would not in itself be addressed through treatment with Ataluren, it illustrates that the additional costs and larger teams required for surgery and other interventions are not adequately reflected in the NICE evaluation.

3.3 Similarly the savings from delaying loss of ambulation, in terms of psychosocial improvements are not properly reflected, including the costs for local authorities, families (we have to privately fund a psychologist who visits the school) and charities (we rely heavily on a local charity to provide respite care). Moving Duchenne from an untreatable, terminal condition into a chronic, but relatively manageable one in the paediatric population, would greatly reduce the burden on schools and local education authorities.

3.4 In the longer term and through the long term use of Ataluren, there is also the increased likelihood that young adults living with Duchenne will be able to work, pay taxes and claim fewer benefits. The ERG noted in respect of savings to government bodies, on Page 152, that

> "*cost estimates for these savings were not presented in the CS…it would have been useful for the Company to include scenario analyses based on the uptake of ataluren treatment on these costs savings*."

3.5 Given that the company would have had insufficient time to prepare a complete submission, due to the protracted nature of NHS England's 'non-decision', this is unsurprising.

3.6 Finally, in terms of evidence, it is important that all available natural history data be used. The long term efficacy of a treatment cannot be judged alone through a 48 week trial and that should not be used as a reason to avoid making a positive conditional recommendation and deviate from the basis for the conditional marketing approval given by the EMA. It is not known how much data was taken from the North Star database although it is included in the list of published references contained in the committee papers.

3.7 Natural history data can be gauged from other online registries including the DuchenneConnect registry in America. A paper published in PLOS Currents[5] in 2014 on Natural History and Outcome Measures validates such an approach in Duchenne Muscular Dystrophy and followed a comprehensive data mining exercise from over 1,000 male Duchenne patients, led by Stanley Nelson. There appears to be no reference to this paper in the documents published by NICE.

Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?

3.8 This response focuses on two areas where it is considered the Committee made neither a reasonable or rational interpretation of the evidence. These relate to (1) the inclusion of two boys with Becker Muscular Dystrophy in the Phase 2b trial and (2) the results of the Timed Function Tests.

3.9 Undue significance is attached by the ERG to the inclusion of two patients with Becker Muscular Dystrophy (BMD) out of a total of 174 boys and young men and the influence or bias this 'may have introduced' into PTC Therapeutics' submission (page 15 of the ERG paper). These two patients comprised 1% of the total number of patients enrolled yet paragraph 5.5 of the evaluation consultation documents states that "The Committee considered, therefore, that the results of Study 007 were uncertain." This is a disproportionate response, not simply because of the wider findings of the Phase 2b trial, but because it fails to take account of the fact that patients with milder or later onset of BMD – who might have introduced some bias into the data - would simply not have been enrolled onto the trial in the first place.

3.10 The Frequently Asked Questions published by PTC Therapeutics[6] at the time of the trial included a question asking why patients with BMD were

[5] Online Self-Report Data for Duchenne Muscular Dystrophy Confirms Natural History and Can Be Used to Assess for Therapeutic Benefits, PLOS Currents, October 2014

[6] http://www.parentprojectmd.org/site/DocServer/FAQ_Phase_2b_DMD-BMD_trial_-__0508.pdf

included in the Phase 2b trial when they hadn't been included in the earlier clinical trials. The answer provided stated:

> "*DMD and BMD, rather than being distinct diseases, represent a continuum of the same disease. A mutation in the dystrophin gene is the cause for both DMD and BMD; however, the types of mutation in patients with BMD appear to cause less rapid loss of muscle function. Because changes in muscle function vary among patients, it is not always clear whether a particular patient should be defined as having DMD or BMD…*
>
> *…In order to be able to show improved functioning in trial participants,* ***enrollment is limited to those patients with BMD who had medically documented signs of their disease, such as elevated creatine kinase, muscle weakness, waddling gait, and Gowers' maneuver*** *[sic]* ***by age 9, and are having problems with walking.*** *These criteria indicate that they have problems due to their BMD/DMD that make it appropriate for them to consider an investigational drug like PTC124*." (emphasis added)

3.11 BMD is often not diagnosed in patients until adulthood with ambulation sometimes continuing into a patient's 40s and 50s. Conversely, in patients with earlier onset of Becker symptoms, it can be difficult to differentiate between Becker and Duchenne Muscular Dystrophy, hence the assertion in the company submission that the number of Becker patients 'was estimated to be ~2 patients'. Nevertheless, the published inclusion criteria for the Phase 2b trial clearly state:

> "*Phenotypic evidence of DMD/BMD based on the onset of characteristic clinical symptoms or signs (ie., proximal muscle weakness, waddling gait, and Gowers' maneuver) by 9 years of age, an elevated serum creatinine kinase level, and ongoing difficulty with walking.*"[7]

3.12 BMD patients identified as meeting these criteria by the age of 9 would be expected to be much closer to Duchenne patients, in terms of manifestation of symptoms, than those with later onset of BMD. The inclusion of two patients with the above clinical symptoms identified at age 9 or under, would not be capable of influencing the result of Study 007 to the extent that it could be considered 'uncertain'. In fact, it is likely that the 6MWD of those patients would not differ significantly from those at the higher performing end of the 6MWD of Duchenne patients, who typically can walk in excess of 450 or 500 metres.

3.13 The ERG have referenced that Professor Kate Bushby has indicated that those living with Becker Muscular Dystrophy ought not to have been

[7] Clinicaltrials.gov

included in the trial. However, Professor Bushby has never questioned the overall benefits which Ataluren offers and in a statement issued in July 2015, following the announcement that NHS England would not made a decision on funding, stated:

> *"It is very disappointing for the Duchenne muscular dystrophy community that the NHS has decided not to fund Translarna at this juncture. The drug is already available in several European countries following EMA conditional approval last year including Germany, Greece, Italy and France...*
>
> *…Drugs for rare diseases are very expensive, but this is a function of the development pipeline and should not disadvantage the patients who suffer from these conditions. If we are to have a constructive pipeline for rare disease drug development then there needs to be a way to ensure that drugs which have been approved by the EMA have a mechanism to be available on the NHS."*[8]

3.14 A second area where the ERG has made an unreasonable interpretation of the evidence, is that of the secondary outpoints in Study 007 and in particular Timed Function Tests (TFT). TFTs provided important, additional indicators of efficacy but the ERG took the view, in relation to the earlier observations of the EMA's Scientific Advisory Group, that "There was little supportive evidence of effect from the data on the secondary endpoints." This broadbrush generalisation simply fails to reflect the actual change demonstrated in the Timed Function Tests in the Phase 2b trial (and as now reported from the Phase 3 data). Specifically, there are concerns that the ERG report states that:

> "*Smaller increases between baseline and 48 weeks in the time required to climb four stairs were found with ataluren compared with placebo [2.4 seconds (SD 4.6) versus 4.8 seconds (SD 7.9), p=0.0207 cITT analysis set].* ***No statistically significant differences were found for descending four stairs,run/walk 10 metres, or supine to stand time*****.**" (Page 61, para 4.2.6.1) (emphasis added)

3.15 A 1.6 second difference in decline, over 48 weeks, within the context of a 10 metre run/walk is significant, as is a 1.5 second difference for climbing four stairs, reported as representing a 45.1% and 39.9% difference from the mean. The 'smaller increases' in the time to climb four stairs of 2.4 seconds in the Ataluren group are significant within the context of a test which has a duration of less than 10. Moreover, when the TFTs are presented in terms of the % decline from the baseline time, the differences between the placebo and Ataluren groups are significant and this is

[8] Muscular dystrophy expert's disappointment at drug refusal. Newcastle University press release, 3rd July 2015

recognised on page 98 of the submission from PTC Therapeutics which states that

"*Considering that these tests are performed at baseline in 6 to 8 seconds, the magnitudes of the treatment differences are large on a percentage basis*."

In percentage terms, this is illustrated in the treatment differences over 48 weeks as set out in the table below.

	Decline based on TFT change recorded after 48 weeks **Placebo**	Decline based on TFT change recorded after 48 weeks **Ataluren 40mg/kg/day**
Climb four stairs	48%	23%
Descend four stairs	75%	39%
Run/walk 10 metres	80%	30%

3.16 The PTC submission highlights the work of Diane Escolar which is itself referenced in the published findings of the study[9] in defining the threshold for a statistical difference in TFTs. This is reported as being 0.4 in (natural log) seconds and in the context of the ataluren 40mg/kg/day Phase 2b results, "this was back transformed to ~1.5 seconds." (page 120, PTC Therapeutics submission). The Phase 2b trial yielded differences of 2.4 seconds, 1.6 and 1.5 seconds and so there can be no valid basis for stating that there was no statistically significant differences between the groups. Moreover, the differences between placebo and Ataluren are even greater in the decline phase sub-group and <350 metres subgroup.

3.14 The conclusion of the ERG that the changes in descending four stairs and running 10 metres, in the Ataluren 40mg/kg/day group, are not 'statistically significant differences' needs to be challenged. TFTs are an established part of the North Star assessments carried out every 6 months in neuromuscular clinics for Duchenne patients and as a valid secondary endpoint in this trial, there is also scope to assess them against the natural history data available from the North Star database.

3.15 The limited significance placed on the TFTs by the ERG has underpinned its reservations about the efficacy of Ataluren and this is reflected in the evaluation consultation document which attaches no importance to them. This must be revisited, particularly in light of any Phase 3 data now available given that Ataluren has been reported as showing benefits over

[9] Ataluren treatment of patients with nonsense mutation dystrophinopathy, Muscle Nerve. 2014 Oct; 50(4): 477–487.

placebo for TFTs carried out in the current confirmatory trial, in the announcement made by PTC Therapeutics[10].

Are the provisional recommendations sound and a suitable basis for guidance on the use of ataluren in the context of national commissioning by NHS England?

3.16 The provisional recommendations are **not** considered to provide a sound and suitable basis for guidance on the use Ataluren. This is due to:

i) the reasons set out above in this response and in particular, (a) the underestimation of the medical and social/welfare savings and the quality of life benefits (b) the committee's view of the results of Study 007 'being uncertain' due to the influence of two Becker MD patients and (c) the disregard and lack of weight attached to the statistical significance of the TFTs.

ii) the fact that the provisional recommendations compare Ataluren to 'other highly specialised technologies available' fails to reflect the complete absence of any other alternative treatments available to address the underlying cause of Duchenne Muscular Dystrophy, a fatal genetic condition which is only ever diagnosed in a paediatric population in England.

iii) the failure to recognise that the conditional marketing approval granted by the EMA recognises that there is sufficient evidence to make Ataluren available on an interim basis, pending the outcome of the confirmatory trial.

iv) a disproportionate emphasis on the cost of Ataluren particularly in light of the very small sub-population eligible for the drug and the availability of funding for such treatments, including almost £800m made available through the Pharmaceutical Price Regulation Scheme in 2015/16 alone.

6. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

3.17 Ataluren has been made available across a number of other EU countries following the EMA decision in 2014. The EMA decision applies across the EU and so denying access to Ataluren to a paediatric population with a rare and life-limiting disability may well constitute unlawful discrimination

[10] PTC Announces Results from Phase 3 ACT DMD Clinical Trial of Translarna™ (ataluren) in Patients with Duchenne Muscular Dystrophy, PTC Therapeutics press release, October 2015

against a patient group with two protected characteristics – disability and age. It is also completely unethical to allow children to have access to a drug with proven efficacy as part of a clinical trial, only for those children to be denied treatment following the completion of a trial.

3.18 Further to this, the draft recommendation Professor Bushby, in responding to Equality issues in Table 23 (page 93 of the ERG report), states:

> *It is to me discriminatory that for drugs for rare diseases the high cost of drugs means that inevitably they have a very high threshold to reach. That is not these patients' fault and we have to find a way to square this difficult balance without the patients losing out.*

3.19 The Public Sector Equality Duty applies to NICE in carrying out its functions. NICE must ensure that it complies with the associated requirements of that Duty and eliminate any form of discrimination against vulnerable children living with a rare and life-limiting condition in its decision making. As such, it is imperative that NICE reverse its decision in light of both the submissions made by myself and others and the additional evidence provided by PTC Therapeutics.

05 NOV 2015

Sir Andrew Dillon
National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

15 September 2015

Dear Sir Andrew,

I am writing to you regarding access to Translarna, a new treatment for Duchenne muscular dystrophy, which is currently going through a NICE Highly Specialised Technologies Evaluation.

I am writing to impress upon you the importance of an approval from NICE for this therapy, which is the only licensed treatment for Duchenne muscular dystrophy to address the underlying genetic cause of the condition.

Duchenne muscular dystrophy places a huge burden on those affected and their families. This is a burden that increases once decline in physical function becomes more profound, and children lose the ability to walk and require the full time use of a wheelchair. Loss of ambulation also heralds the onset of later devastating respiratory and cardiac compromise.

Costs of care increase once ambulation is lost and care needs become more complex. This represents a significant cost to the National Health Service and also to local authorities, who must meet the costs of increased need for social care. There is also likely to be a greater knock on effect on family life, including loss of earnings as parents cut down or give up work altogether to allow for full time caring responsibilities. The family is likely to have to move home, purchase an adapted vehicle and meet the whole myriad of costs and adaptations that occur once a child is no longer ambulant.

For the children themselves, decline in physical function is incredibly upsetting: whilst their friends are able to do more and more, they find themselves able to do less and less. This can manifest itself in mood swings, outbursts and behavioural difficulties at home and school, as the child struggles to make sense of their condition and physical limitations. Reducing the rate of disease progression in children would therefore make a significant difference to their quality of life.

Available data from clinical trials of Translarna (ataluren when in trial) indicate that there was a clinically meaningful difference in walking distance over six minutes between boys on a placebo and those on a controlled dose of the drug. This would indicate that the drug slows decline in physical function for boys affected by this devastating disease, and this evidence has been deemed robust enough to gain approval in countries including France, Italy, Denmark and Germany.

I cannot stress enough, Translarna is the only licensed treatment for Duchenne muscular dystrophy and would make a significant and meaningful impact on the physical, emotional and financial burdens for the disease.

It is only right that NICE produces guidance recommending Translarna for use on the NHS.

NOV 2015

Sir Andrew Dillon
Chief Executive
National Institute for Health and Excellence
10 Spring Gardens
London
SW1A 2BU

3rd November 2015

Dear Sir Andrew

Re: Translama and the Treatment for boys with Duchenne Muscular Dystrophy (DMD)

Our Member of Parliament for Colchester, Mr William Quince MP, recently wrote to you in connection with the above in relation to our two dear grandsons, [redacted] aged 6.0 yrs and [redacted] aged 3.8 yrs, both of whom have nonsense mutation DMD. Both boys are under Great Ormond Street Hospital (GOSH) and their parents, our son and his wife, have full knowledge that we are writing to you as part of the consultation on NICE's recent draft guidance.

As the Committee who advise NICE affirm, Translama represents an important development in the treatment of DMD as it is the first ever drug to potentially offer an actual treatment for this devastating, life-limiting condition. Reference is usually made to the relatively small number of boys with this condition in England being able to remain mobile for longer, but it is our understanding that it is also other critically important muscles that would benefit as well, particularly relating to the heart and lungs and to the physical integrity of their young bodies, particularly relating to their arms, shoulders and back.

Following the landmark decision by the NHS in Scotland for a boy with DMD to receive limited treatment with Translama, we are hoping that NHS England will become a world-leader and approve the use of this drug for this condition. We know it is extremely expensive due to its research and development costs, but any delay for boys with DMD is critical, as the advice is that the drug cannot repair dead muscle.

We would be extremely grateful if this letter could be submitted as part of the consultation, and look forward with hopeful anticipation for a positive and ground-breaking decision.

11 NOV 2015

Action Duchenne
Epicentre
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London
E11 4LJ

Sir Andrew Dillon
National Institute for Health & Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

6 November 2015

Dear Mr Dillon.

We the undersigned are writing to you concerning the National Institute for Health & Care Excellence's (NICE) ongoing Highly Specialised Technology evaluation of Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. We would be grateful if clarity could be provided on the considerations and date of the Second Evaluation Committee Meeting which acknowledges and examines all relevant information before rendering a final evaluation determination (FED) on the use of Ataluren. Additionally, we ask you to recognise the significant payments received by the health service under the Pharmaceutical Price Regulation Scheme (PPRS), and implore you to ensure these resources are factored into the committee's considerations concerning the proposed cost of the treatment.

On 16 October 2015, NICE published its draft guidance, provisionally not recommending Ataluren for the treatment of Duchenne. This decision reflected the committee's conviction that they had, "not yet been presented with an adequate justification for its considerable cost"[1]. We are concerned that this statement contradicts assurances within NHS guidelines that "commissioners have received the expected level of funding to cope with the growth in cost of branded medicines"[2]. Indeed, NHS England received £796 million in PPRS payments for 2015/16, theoretically ameliorating issues of affordability arising from price growth in branded medicine, and allowing commissioners to, "shift from cost-saving onto securing better patient outcomes"[3]. We therefore ask you to direct the evaluation committee to "disengage from cost-containment measures"[4], and consider the clinically meaningful benefit of a treatment that, by their own admission, "makes a very strong claim for NHS resources"[5].

The committee additionally refrained from recommending Ataluren for the treatment of Duchenne owing to a desire to take "into account the results of the multicentre, randomised, double-blind, placebo-controlled confirmatory study (PTC 124-GD-020-DMD; Study 020)"[6]. Whilst the Duchenne community was subsequently encouraged to see the results of this study, further demonstrating Ataluren's clinically meaningful benefit, published on the same day[7], we

[1] http://www.nice.org.uk/guidance/indevelopment/gid-duchennemusculardystrophy/consultation/html-content
[2] https://www.england.nhs.uk/wp-content/uploads/2014/05/pharm-price-reg-qa.pdf
[3] Ibid.
[4] Ibid.
[5] Sheehan, Mark: *Highly Specialised Technology Evaluation Committee. First Meeting*, Sept 2015.
[6] http://www.nice.org.uk/guidance/indevelopment/gid-duchennemusculardystrophy/consultation/html-content
[7] http://www.actionduchenne.org/ptc-therapeutics-release-phase-iii-data-for-translarna/

require reassurances that the existing timelines for NICE's evaluation will accommodate a scrupulous analysis of PTC Therapeutics' confirmatory data.

We therefore ask you to guarantee that the results of this study are appropriately considered alongside all feedback to NICE's Evaluation consultation document and are factored into the committee's analysis before a FED is reached. The current date for the Second Evaluation Committee meeting is 17 November. If a comprehensive examination of the confirmatory data cannot be undertaken and completed in advance of this time, we request the committee agree an alternative date that reflects the severe, irreversible and degenerative nature of Duchenne muscular dystrophy. Whilst it is imperative for all relevant information to be fastidiously factored into the committee's analysis, it is equally crucial that any delay in preparing a FED is minimised.

However, we are additionally mindful to emphasise that consistent and substantial evidence signifying Ataluren's clinically meaningful benefit has already been submitted. Many nations (including Germany, France, Spain, Italy, Denmark, Austria, Greece, Norway & Turkey), have already funded the treatment in advance of the evidence expounded within PTC Therapeutics' confirmatory study. If a thorough analysis of this additional data necessitates a substantial delay in the development of a FED, we implore you to follow the direction of these countries and institute an interim funding policy on the use of Ataluren, allowing the treatment to be delivered to those patients eligible to immediately benefit. The condition of these patients is one of unremitting decline. Ataluren received conditional marketing approval from the European Medicines Agency in May 2014. Put simply, we do not have any more time to wait.

In further recognition of this urgency, we moreover request that any positive recommendation, ultimately reached within the FED, be immediately used as the basis for NICE's guidance on using Ataluren in the context of national commissioning by NHS England.

Yours sincerely,

The Delegates and Attendees of the Action Duchenne International Conference 2015.