NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

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

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

Definitions:

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

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

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

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

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PTC Therapeutics	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	Comments noted. The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations of Study 007 and Study 020. The Committee concluded that there was not a meaningful improvement in the rate of decline in 6MWD with ataluren compared with best supportive care in the intention-to-treat populations of Study 007 and Study 020 (see FED section 5.6). The Committee considered the company's results of a pre-specified subgroup analysis of patients in Study 020 with a baseline 6MWD of 300–400 m and a meta-analysis of the results from Study 007 and Study 020 for this subgroup. The Committee noted that both sets of results for this subgroup showed statistically significant differences in the 6MWD at 48 weeks between ataluren and best supportive care. The Committee expressed concerns about the uncertainty and generalisability of the results to the broader ambulant population (see FED sections 5.7 and 5.8). The Committee considered the company's updated cost–consequence model. It should be noted that the assumptions used in this model and the associated results have been superseded by those in a third model that was subsequently submitted by the company.

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	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: **Page** Response 1 – Robustness of the clinical benefit of ataluren 3 Response 2 – Quality of life and patient impact 5 Response 3 – ERG required changes to the model 9 Response 4 – Demonstrating benefit in QALYs 10 Response 5 – QALY versus cost 10 Response 6 – Predictability of budget impact 13 Appendix 1 – Clinical data update 15 Appendix 2 – Revised economic modelling 31 Appendix 3 – North Star Ambulatory Assessment 38 Appendix 4 – Caregiver and Family Quality of Life Survey 40 ** The full company's response to the Committee's request in the evaluation consultation document is not reproduced here but is included in the Committee papers.*	The Committee considered the company's response to consultation in detail as described below.
Action Duchenne	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	Comments noted. Ataluren's conditional marketing authorisation is dependent on the results of Study 020 being provided to the EMA. 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. The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It considered the size and duration of ataluren's

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	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.	treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED section 5.2).
	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.	Comments noted.

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	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 [redacted] 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.	Comments noted. The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee also noted comments from patient organisations on the evaluation consultation document stating that the original model presented by the company did not appropriately reflect and capture the impact of the condition and ataluren on the patient and caregivers' quality of life, as well as the additional costs associated with each health state. The Committee considered that this was partially addressed by the company in its third model (for example, including costs associated with ventilation assistance and increasing the disutility faced by caregivers). The Committee considered that the condition was distinct, there was unmet need and some of the potential quality-of-life benefits of ataluren still might not be not fully captured in the model. However, it remained concerned that the overall health benefits of ataluren had not been shown in the population for which it would be used in clinical practice. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED sections 5.2, 5.18 and 5.23).
	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	Comments noted. The Committee noted comments from patient organisations on the evaluation consultation

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	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 Natural History and Outcome Measures validates such an approach in Duchenne Muscular Dystrophy. There appears to be no reference to this paper.	document stating that the original model presented by the company did not appropriately reflect and capture the impact of the condition and ataluren on the patient and caregivers' quality of life, as well as the additional costs associated with each health state. The Committee considered that this was partially addressed by the company in its third model (for example, including costs associated with ventilation assistance and increasing the disutility faced by caregivers). The Committee considered that the condition was distinct, there was unmet need and some of the potential quality-of-life benefits of ataluren still might not be not fully captured in the model. However, it remained concerned that the overall health benefits of ataluren had not been shown in the population for which it would be used in clinical practice. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED sections 5.2 and 5.18). Some information included in the Committee papers has been redacted because it was provided by the company as commercial in confidence. This was aligned with principles described in the Interim process and methods of the highly specialised technologies programme (2013) and the Guide to the processes of technology appraisal (2013). The Committee acknowledged the potential wider

[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

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	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. 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	societal benefits of ataluren treatment proposed by the company and patient experts, including the ability to contribute to society, continue education and spend more time with friends and family, as well as the potential cost savings associated with ataluren (see FED section 5.25). 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. The Committee noted that patient experts highlighted the importance to parents of seeing their children grow and develop in line with their peers for as long as possible (see FED sections 5.1 and 5.2). Number of falls was included as an outcome in the final NICE scope. Data were provided in the company submission and considered by the Committee in its evaluation of ataluren's clinical effectiveness. The importance of prolonging ambulation to patients, their carers and families is described in sections 5.1 and 5.2 of the FED. The Committee heard from the patient experts that, because ataluren is expected to delay the loss of walking, it will enable people with DMD to maintain

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

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	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.	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 delaying moving house or making home modifications (see FED section 5.25).
	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".	The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. It considered the findings of the company's survey on the quality of life of caregivers, and noted that this showed that DMD had a serious impact on multiple aspects of caregivers' lives. It also heard from the clinical and patient experts about the severe impact that the condition has on the person with the condition, family and carers' quality of life (see FED section 5.2).
	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.	The Committee discussed the nature of nonsense mutation DMD and its impact on people with the condition. 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 (see FED section 5.1).
	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 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**	The Committee heard from the patient experts explained that the impact of the condition is even

[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

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	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.	more crucial at the point when the disease progresses and the ability to walk is lost, (that is, around adolescence). The clinical and patient experts noted that, in general, this is a difficult time for every child and that the impact of the condition at this time makes it even more difficult. The Committee also heard from the patient experts that, if the time to loss of walking could be delayed, patients would have the opportunity to have a normal adolescence and to enter adulthood with a better understanding of their condition (see FED section 5.1).
	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) 4.2 A 1.6 second difference in decline over 48 weeks within the context of a 10	Comments noted. The Committee considered the secondary outcomes in the trials 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 noted that the results from the timed function tests and the North Star Ambulatory Assessment were consistent with the 6MWD results (see FED sections 5.5 and 5.8).

[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.

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	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] ([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. *[Tables have not been reproduced here but are included in the Committee papers]* 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], 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 Kate Bushby 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	

[9] McDonald, Henricson, Abresch, Florence, Eagle, Gappmaier, Glanzman; *PTC124-GD-007-DMD Study Group,* 2013
[10] http://www.nmd-journal.com/article/S0960-8966(14)00637-3/pdf

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	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 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	The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations and subgroups of Study 007 and Study 020 in full (see FED sections 5.4–5.11). The Committee noted that there was no statistically significant difference in 6MWD at 48 weeks between ataluren and best supportive care in the intention-to-treat population in Study 020, even though the enrolment criteria for this confirmatory study had been intended to enrich the population in the decline phase of DMD (that is, to obtain a group of patients with very similar baseline patient and disease characteristics based on a subgroup in Study 007) (see FED section 5.6). The Committee concluded that it was likely that the quality-of-life data collected during Study 007 and Study 020 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 (see FED section 5.10). The Committee asked the clinical experts when they would consider starting treatment with ataluren in clinical practice. It heard that they would ideally start treatment early, with the expectation of delaying loss of walking before the decline phase starts. The Committee understood that a statistically significant benefit with ataluren compared with best

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	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.	supportive care had not been shown in the population in which it was intended to be used in clinical practice (that is, in line with its marketing authorisation for ambulatory patients aged 5 years and older) (see FED section 5.9).
	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 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	Comments noted. The Committee noted NICE's position statement about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of ataluren. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by ataluren (see FED section 5.24). The Committee noted that, compared with the other

[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
[13] Ibid.
[14] Sheehan, Mark: *Highly Specialised Technology Evaluation Committee. First Meeting*, Sept 2015.

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	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 Policy16 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 multiple treatments for Duchenne in the research pipeline, the fact that numerous nations17 have already approved Ataluren will not be lost on the pharmaceutical industry.	highly specialised technologies it had previously evaluated, ataluren was associated with substantially lower incremental QALYs. However, the Committee considered that the nature of DMD meant that it might be appropriate to view the QALYs gained differently because of the time in a child's life when the QALYs are predominantly gained compared with best supportive care (see FED section 5.23). The Committee concluded that there were no specific safety concerns associated with ataluren (see FED section 5.11). No costs or disutilities for adverse events were included in the company's cost-consequence model because the company said there were no significant differences in the incidence of adverse events between the ataluren and placebo arms of Study 007. 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 (see section 5.4 of the FED). When evaluating cost to the NHS and PSS, the Committee will take into account the total budget for specialised services, and how it is allocated, as well as the scale of investment in comparable areas of medicine. The Committee will also take into account what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and development costs from sales to a limited number of patients (see section 41 in the

[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/
[17] Germany, Austria, Spain, France, Italy, Denmark, Greece & Norway.

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		Interim methods and process of the highly specialised technologies programme).
	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. 6.5 It could further be considered discriminatory to refuse access to treatment on the	Comments noted. No equality issues that needed to be taken into consideration by the Committee were identified (see summary table in the FED and the Equality Impact Assessment form). The Interim methods and process of the highly specialised technologies programme states that it is the role of the Evaluation Committee to recommend against the use of a technology if the benefits to patients are unproven or costs of technology are unreasonable. It also specifies that given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their research and development investment because of the very small populations treated (see section 36 in the Interim methods and process of the highly specialised technologies programme).

[18] http://www.musculardystrophyuk.org/app/uploads/2015/02/Access-to-high-cost-drugs-report-FINAL.pdf

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	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.	The Evaluation Committee is an independent advisory body. Members include people who work in the NHS, patient and carer organisations, relevant academic disciplines, and pharmaceutical and medical devices industries. Specific evidence submissions are sought from individual consultees, particularly patient/carer groups, where appropriate, and patient experts are invited to the Committee meeting which enables the Evaluation Committee to hear directly from people with the condition and their carers. The Evaluation Committee takes into account advice from the Institute on the appropriate approach to making scientific and social value judgements, including 'Social value judgements: principles for development of NICE guidance, second edition' (see sections 31 and 33 in the Interim methods and process of the highly specialised technologies programme).
Muscular Dystrophy UK	**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*	Comments noted. After considering further evidence that included an improved patient access scheme and a proposed managed access agreement (which include other confidential financial components), the Committee recommended ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the

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	and a suitable basis for guidance on the use of ataluren in the context of national commissioning by NHS England.	dystrophin gene in people aged 5 years and older who can walk, only when the company provides ataluren with the discount agreed in the patient access scheme and the conditions under which ataluren is made available are set out in a managed access agreement between the company and NHS England that includes the committee's considerations (see FED section 1.1 and 5.12–5.15).
	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.	Comments noted. The Committee noted that there was no statistically significant difference in 6MWD at 48 weeks between ataluren and best supportive care in the intention-to-treat population in Study 020, even though the enrolment criteria for this confirmatory study had been intended to enrich the population in the decline phase of DMD (that is, to obtain a group of patients with very similar baseline patient and disease characteristics based on a subgroup in Study 007). The Committee agreed to consider the 48 week clinical trial data from a subgroup of patients with a baseline 6MWD of 300–400 m but expressed concerns about the uncertainty and generalisability of the results to the broader ambulant population (see FED sections 5.6 and 5.7).
	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	Comments noted. The Committee considered that the proposed managed access agreement offered an opportunity to allow patients access to ataluren in the NHS while collecting both longer-term data and data from the full population with nonsense mutation DMD covered in the marketing authorisation, and to limit the financial risk associated with introducing ataluren in the NHS given the uncertainty around its benefits (see FED section 5.27).

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	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,	Comments noted. The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee also noted comments from patient organisations on the evaluation consultation document stating that the original model presented by the company did not appropriately reflect and capture the impact of the condition and ataluren on the patient and caregivers' quality of life, as well as the additional costs associated with each health state. The Committee considered that this was partially addressed by the company in its updated model (for example, including costs associated with ventilation assistance and increasing the disutility faced by caregivers). The Committee considered that the condition was distinct, there was unmet need and some of the potential quality-of-life benefits of ataluren still might not be not fully captured in the model. However, it remained concerned that the overall health benefits of ataluren had not been shown in the population for which it would be used in clinical practice. The Committee noted that ataluren is considered an

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	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] *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] 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	important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED sections 5.2, 5.18 and 5.23).

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	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	

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	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.	Comments noted. The Committee concluded that, because of the uncertainty of the clinical benefits in the relevant population in clinical practice, ataluren would represent acceptable value for money to the NHS only when it was given in the context of a managed access agreement at a price that incorporated the patient access scheme and included other financial components that reduced the total costs to the NHS (see FED section 5.27).
	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.	Comments noted. No equality issues that needed to be taken into consideration by the Committee were identified (see summary table in the FED and the Equality Impact Assessment form).
	Patient and family participation in NICE Evaluation Process We understand that the next meeting of the Committee will take place on 17	Comments noted. A list of the organisations that accepted the

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	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.	invitation to participate in this evaluation as consultees and commentators and who nominated experts to attend the Committee meeting can be found in section 9 of the FED.
The Royal College of Pathologists	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	Comment noted.
	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	Comments noted. The Committee noted that, in response to the evaluation consultation document, a professional group highlighted that additional diagnostic laboratory tests may be needed and that currently only 1 laboratory in the UK offers this analysis for DMD. The Committee considered that, apart from these possible additional diagnostic needs, no significant additional staffing and infrastructure would be needed to offer ataluren in centres where patients with nonsense mutation DMD currently have treatment (see FED section 5.26).

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	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. 4) 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	

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	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 and notes have not been reproduced here but are included in the Committee papers]*	
NHS England	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.	Comment noted. The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations of Study 007 and Study 020. The Committee concluded that there was not a meaningful improvement in the rate of decline in 6MWD with ataluren compared with best supportive care in the intention-to-treat populations of Study 007 and Study 020. It further concluded that the results of the clinical primary and secondary outcomes in Study 020 showed a benefit at 48 weeks of ataluren compared with best supportive care in patients with a baseline 6MWD of 300–400 m (see FED sections 5.6 and 5.8).
	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.	Comment noted.
	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.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
Carer	General	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.	Comment noted. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown. The committee considered that the proposed managed access agreement offered an opportunity to allow patients access to ataluren in the NHS while collecting both longer-term data and data from the full population with nonsense mutation DMD covered in the marketing authorisation, and to limit the financial risk associated with introducing ataluren in the NHS given the uncertainty around its benefits. Therefore, the committee recommended ataluren for treating nonsense mutation DMD (see FED section 5.27).
Carer	General	**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.	Comments noted.

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

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		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.	
		1. Summary 1.1 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[19]), 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. 1.2 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. 1.3 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,	Comments noted. This topic was referred to NICE for evaluation in March 2015, the technology has been available since July 2014 and stakeholders emphasised the urgency of guidance to the NHS. The topic was scheduled into the HST work programme following referral. Invitation to participate followed referral of this topic to NICE from the Department of Health. Submissions from the company and other stakeholders were due in June 2015 following the timelines described in the Interim methods and process of the highly specialised technologies programme (see section 20 of the Interim methods

[19] See Hansard, 8 July 2015, Column 315 and Hansard, 14 October 2015, Column 313

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		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. 1.4 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. 1.5 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 "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*".[20] 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	and process of the highly specialised technologies programme). The Evaluation Committee makes recommendations to the Institute regarding the benefits and costs of highly specialised technologies for national commissioning by NHS England. It is also the role of the Evaluation Committee to recommend against the use of a technology if the benefits to patients are unproven or costs of technology are unreasonable (see section 31 of the Interim methods and process of the highly specialised technologies programme). The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD.

[20] www.actionduchenne.org/clarity-required-from-the-prime-minister-over-translarna/

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		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[21]: "…***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)[22]	The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED sections 5.2 and 5.27).
		2. Specific questions asked by the Evaluation Committee **Has all of the relevant evidence been taken into account?** 2.1 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.	Comments noted. Redacted information was designated by the company as commercial in confidence. The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of

[21] www.chroniclelive.co.uk/news/health/newcastle-expert-who-helped-pioneer-8213815

[22] All Party Parliamentary Group for Muscular Dystrophy, Impact of NHS reforms on access to neuromuscular services, March 2015

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		2.2 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. 2.3 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. 2.4 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*." 2.5 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. 2.6 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	patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED section 5.27). The Committee heard from the patient experts that, because ataluren is expected to delay the loss of walking, 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 delaying moving house or making home modifications (see FED section 5.25). The Evaluation Committee reviewed the data available on the benefits and costs of ataluren, having considered evidence on the nature of DMD

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		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. 2.7 Natural history data can be gauged from other online registries including the DuchenneConnect registry in America. A paper published in PLOS Currents[23] 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	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 (see FED section 5).
		Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence? 2.8 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. 2.9 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.	Comments noted. The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations and subgroups of Study 007 and Study 020 in full (see FED sections 5.4–5.11).

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

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		2.10 The Frequently Asked Questions published by PTC Therapeutics[24] at the time of the trial included a question asking why patients with BMD were 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) .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*	

[24] http://www.parentprojectmd.org/site/DocServer/FAQ_Phase_2b_DMD-BMD_trial_-__0508.pdf

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		muscle weakness, waddling gait, and Gowers' maneuver) by 9 years of age, an elevated serum creatinine kinase level, and ongoing difficulty with walking."[25] .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. 2.13 The ERG have referenced that Professor Kate Bushby has indicated that those living with Becker Muscular Dystrophy ought not to have been 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*	

[25] Clinicaltrials.gov

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		drugs which have been approved by the EMA have a mechanism to be available on the NHS."[26] 2.14 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) .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 recognised on page 98 of the submission from PTC Therapeutics which states that	The Committee considered the secondary outcomes in the trials 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 noted that the results from the timed function tests and the North Star Ambulatory Assessment were consistent with the 6MWD results (see FED sections 5.5 and 5.8).

[26] Muscular dystrophy expert's disappointment at drug refusal. Newcastle University press release, 3rd July 2015

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		"*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. *[Tables have not been reproduced here but are included in the Committee Papers]* 2.16 The PTC submission highlights the work of Diane Escolar which is itself referenced in the published findings of the study[27] 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	

[27] Ataluren treatment of patients with nonsense mutation dystrophinopathy, Muscle Nerve. 2014 Oct; 50(4): 477–487.

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		showing benefits over placebo for TFTs carried out in the current confirmatory trial, in the announcement made by PTC Therapeutics[28].	
		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	Comments noted. The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations and subgroups of Study 007 and Study 020 in full (see FED sections 5.4–5.11). The Committee considered the secondary outcomes in the trials 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 noted that the results from the timed function tests and the North Star Ambulatory Assessment were consistent with the 6MWD results (see FED sections 5.5 and 5.8). When evaluating cost to the NHS and PSS, the Committee will take into account the total budget for specialised services, and how it is allocated, as well as the scale of investment in comparable areas of medicine. The Committee will also take into account what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and development costs from sales to a limited number of patients (see section 41 in the Interim methods and process of the highly specialised technologies programme). The Committee was disappointed that results from the intention-to-treat population of Study 020 had

[28] 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

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		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.	not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD (see FED section 5.27).
		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.	The Committee considered that the proposed managed access agreement offered an opportunity to allow patients access to ataluren in the NHS while collecting both longer-term data and data from the full population with nonsense mutation DMD covered in the marketing authorisation, and to limit the financial risk associated with introducing ataluren in the NHS given the uncertainty around its benefits. Therefore, the Committee recommended ataluren for treating nonsense mutation DMD (see FED sections 1.1 and 5.27). The Committee noted NICE's position statement about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines' (see FED section 5.24).
		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? Ataluren has been made available across a number of other EU	Comments noted. No equality issues that needed to be taken into consideration by the Committee were identified (see summary table in the FED and the Equality Impact Assessment form).

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		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 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. 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.* 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.	
Carer	General	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 Regulations Scheme (PPRS), and implore you to ensure these resources are factored into the committee's considerations concerning the proposed cost of treatment.	Comments noted. The Committee noted NICE's position statement about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this

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		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". 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". 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". We therefore ask you to direct the evaluation committee to "disengage from cost-containment measures", and consider the clinically meaningful benefit of a treatment that, by their own admission, "makes a very strong claim for NHS resources". 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)". 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, we 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 to an alternative date that reflects the severe, irreversible and degenerative nature of Duchenne muscular dystrophy. Whilst it is imperative for all the relevant information to be fastidiously factored into the committee's analysis, it is equally crucial that any delay in preparing a FED is minimised.	evaluation of ataluren. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by ataluren (see FED section 5.24). The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown. The Committee was aware of its need to consider the extent to which the cost to the NHS of providing ataluren was reasonable. The Committee concluded that, because of the uncertainty of the clinical benefits in the relevant population in clinical practice, ataluren would represent acceptable value for money to the NHS only when it was given in the context of a managed access agreement at a price that incorporated the patient access scheme and included other financial components that reduced the total costs to the NHS and recommended ataluren for treating nonsense mutation DMD (see FED section 5.27). The Committee considered the clinical effectiveness of ataluren in the intention-to-treat populations of Study 007 and Study 020. It noted that, in the intention-to-treat analysis in Study 007 and Study 020, there was no statistically significant difference in change in 6MWD at 48 weeks between the ataluren and best supportive care groups. The Committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It

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		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 and 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 the commissioning by NHS England.	considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown (see FED sections 5.6 and 5.27).
Carer	General	Our Member of Parliament [redacted], recently wrote to you in connection with the above in relation to our two dear grandsons, [redacted], 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.	Comments noted. Ataluren is an important development in treating Duchenne muscular dystrophy (DMD) with a nonsense mutation in the dystrophin gene. The Committee recognised the distinctiveness of the condition. It also recognised that the potential benefit of ataluren to prolong walking in children is very important to people with DMD and their families. The Evaluation Committee recommended ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only when the company provides ataluren with the discount agreed in the patient access scheme and the conditions under which ataluren is made available are set out in a managed access agreement between the company and NHS England that includes the committee's

Role*	Section	Comment	Response
		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 the boys with DMD is critical, as the advice is that the drug cannot repair dead muscles. 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.	considerations (see FED sections 1.1 and 5.12–5.15).
Carer	General	I am writing to you regarding access to Translama, 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 licenced 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 the 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 adaptions 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	Comments noted. The Committee discussed the nature of nonsense mutation DMD and its impact on the quality of life of people with the condition, and their parents and siblings. The Committee was disappointed that results from the intention-to-treat population of Study 020 had not provided the expected evidence of a treatment benefit in a broader group of patients in the decline phase, and considered that there was still uncertainty about long-term benefits. It considered the size and duration of ataluren's treatment benefit to be highly uncertain, and was unsure if the positive results from the subgroup of patients with a baseline 6MWD of 300–400 m could be generalised to the broader population of ambulatory people with nonsense mutation DMD. The Committee noted that ataluren is considered an important treatment by patients with nonsense mutation DMD and their caregivers, and recognised the distinctiveness of the condition, particularly because of the time in the patient's life in which the potential benefits of ataluren could be shown. . The Evaluation Committee recommended ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only

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		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 licenced treatment for Duchenne muscular dystrophy and would make a significant and meaningful impact on the physical, emotional and financial burdens of the disease. It is only right that NICE produces guidance recommending Translarna for use on the NHS.	when the company provides ataluren with the discount agreed in the patient access scheme and the conditions under which ataluren is made available are set out in a managed access agreement between the company and NHS England that includes the Committee's considerations (see FED sections 1.1 and 5.12–5.15).

The following consultees/commentators indicated that they had no comments

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