Clinical Commissioning Policy: Ataluren for the treatment of nmDMD

Reference: NHS ENGLAND XXX/X/X

England NHS England

Clinical Commissioning Policy: Ataluren for the treatment of nmDMD

Prepared by NHS England Clinical Reference Group for Paediatric Neurosciences

First published Month Year

Published by NHS England, in electronic format only.

Contents

Policy Statement

Ataluren (Translarna™ will be routinely commissioned for the treatment of Duchenne Muscular Dystrophy (DMD) resulting from a nonsense mutation in patients aged 5 years and above who are ambulatory. A nonsense mutation results in a premature stop codon in the gene for the protein dystrophin.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing. In accordance with the SmPC, treatment with ataluren should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy.

The commissioning of ataluren will be in accordance with the criteria outlined in this document and with the manufacturer's agreed discount scheme.

Equality Statement

Throughout the production of this document due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

There are many different types of muscular dystrophy, and each affects different muscles. The severity of conditions and how they affect individuals varies greatly from person to person. Most conditions are progressive, causing the muscles gradually to weaken over time, and can either be inherited or occur out of the blue where there is no family history.

Duchenne muscular dystrophy (DMD) is a neuromuscular condition caused by the lack of a protein called dystrophin. Patients with DMD have a continual and relentless decline in physical function followed by a decline in lung and heart function. They develop progressive muscle weakness from early childhood, losing lower and then upper body function. This loss of physical function continues to progress and wheelchair use is normally required from around 12 years of age. Full loss of physical function occurs from around age 20 years and patients become dependent on carers for all aspects of living, including feeding and personal care.

Loss of walking ability (ambulation) in patients with DMD is a key milestone; this impacts quality of life significantly Loss of ambulation is one of the most upsetting and devastating points of disease progression for children and families affected by Duchenne muscular dystrophy. Consequently, any treatment that can prolong walking life would relieve some of the stress and burden that the disease places on those affected. Loss of ambulation is also correlated with a faster rate of loss of upper-limb mobility and loss of self-feeding, as well as the need for breathing assistance. The subsequent heart and lung complications of DMD usually lead to death before the age of 25 years (see figure 1).

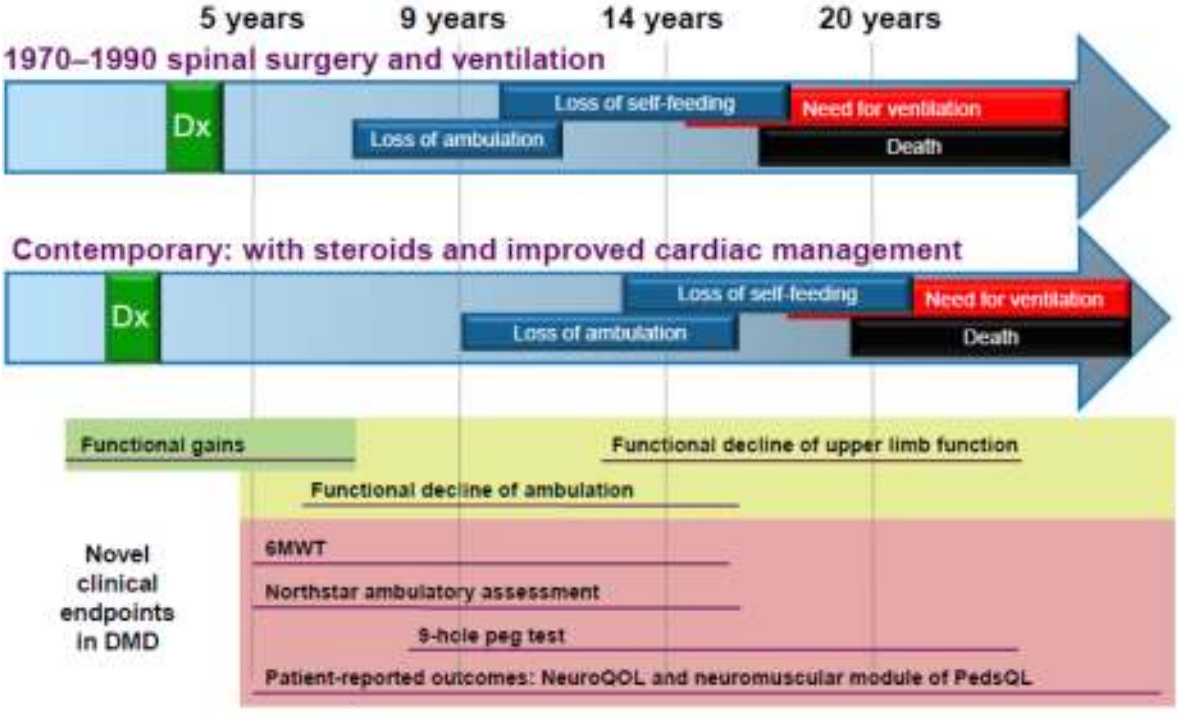
About 100 boys with Duchenne muscular dystrophy are born in the United Kingdom each year of which around 11% will have been caused by a nonsense mutation. DMD is typically diagnosed at around 5 years of age, although the diagnosis might be suspected earlier if there are delays in the attainment of developmental milestones such as independent walking or speaking.

Ataluren is the first licensed treatment for DMD that addresses the underlying cause of the disorder: that is the loss of dystrophin. Ataluren is indicated for patients with DMD resulting from a nonsense mutation (nmDMD) who are aged 5 years and older and who are assessed as still having a level of ambulatory (walking) ability.

In a well-conducted international research study of ataluren versus placebo in patients with nmDMD, treatment with ataluren for 48 weeks was associated with a clinically meaningful reduction in the decline in the distance patients could walk during 6 minutes (6 minute walk distance; 6MWD), a recognised predictor for the timing of loss of ambulation. Additionally, ataluren was well tolerated with a safety profile similar to that of placebo.

There is no therapy that treats the underlying causes of DMD and current treatment options are limited and palliative.

Figure 1. Changing the natural history of DMD and the application of novel clinical endpoints in 2012 (McDonald, 2013).



1. Introduction

DMD is a severe, progressive and rare genetic childhood muscle wasting disease characterised by a rapid decline in physical functioning with subsequent respiratory and cardiac failure, leading to early death. In England, DMD affects 8.29 per 100 000 males (Norwood 2009), which equates to approximately 2200 patients in England in 2013 (Office for National Statistics 2014).

DMD is caused by mutations in the gene encoding dystrophin, a structural protein that stabilises muscle cell membranes. This has a direct effect on the ability of the muscles to function, and over time the absence of functional dystrophin causes progressive muscle damage and weakness, leading to loss of ambulation, cardiac and respiratory complications, and early death. Based on data from the Swedish Cause of Death Registry, the mean age of death in Swedish patients with DMD between 2000 and 2010 was estimated to be 25 years old (range 10 years to 46 years), and death was most commonly caused by cardiac (40%) or respiratory (35%) failure (Stromberg 2012). This compares closely with the mean age of death recorded for UK patients with DMD (25.3 years old) who have received ventilator support (Eagle 2002).

In nmDMD the absence of dystrophin is due to a premature stop codon (also called a nonsense mutation) in the mRNA. This premature stop codon halts the ribosome and stops translation, resulting in a truncated protein that is too short and often too unstable to function properly.

There is no existing therapy for nmDMD that treats the underlying cause of the disease. Current palliative treatments, which aim to alleviate symptoms and manage complications, are restricted to glucocorticoids, orthopaedic devices and surgery, wheelchairs, and artificial ventilation.

Current interventions can be summarised as follows:

• Early childhood: treatment with steroids; cardiac and respiratory monitoring; occasional inpatient orthopaedic intervention

• Later childhood and teenage years: inpatient spinal surgery and rehabilitation for some patients (this is less common for those on steroids than steroid-naïve patients); increased need for inpatient orthopaedic intervention; continued cardiac and respiratory intervention; inpatient episodes for treatment of respiratory complications.

In addition, dietetic advice and, in some cases, gastrostomy feeding, prevention and treatment of bone fragility and management of complications of long-term steroid therapy are all required, as well as psychosocial support. Genetic counselling and testing with antenatal diagnosis are offered to all families with affected children.

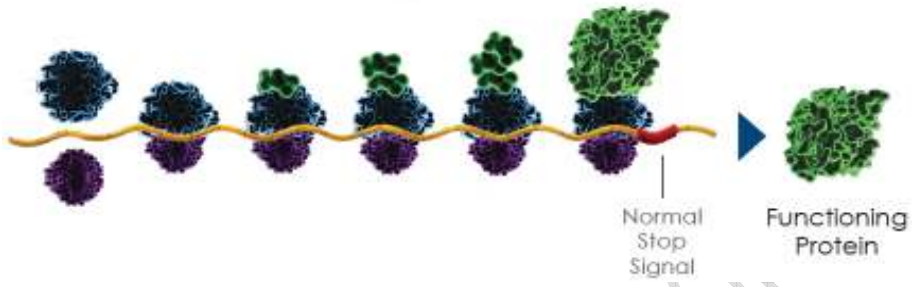
As nmDMD is associated with a high burden of disability and early mortality, and given the relentless progression of the condition, one of the most important treatment objectives according to patients, caregivers and clinicians, is to slow the progression of the disease.

2. Definitions

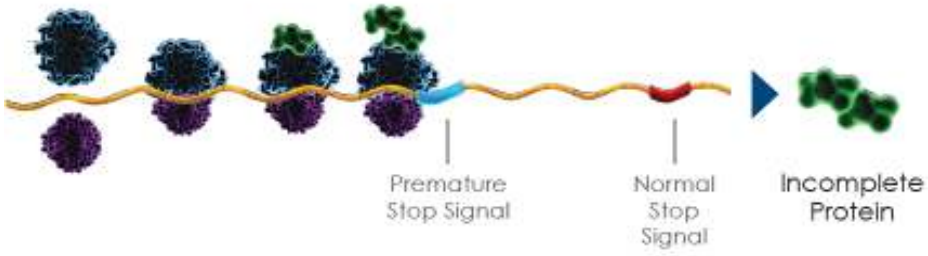
Ataluren belongs to a new class of drugs that target the underlying cause of nmDMD and is the first treatment to be licensed for use specifically in nmDMD. Ataluren allows the ribosomes to read through the premature stop codon, whilst respecting the normal stop codon, to restore the synthesis of functional dystrophin protein (Figure 2).

Figure 2: Translation of mRNA into protein: comparison of normal translation (A), premature termination (B), and treatment with ataluren (C)

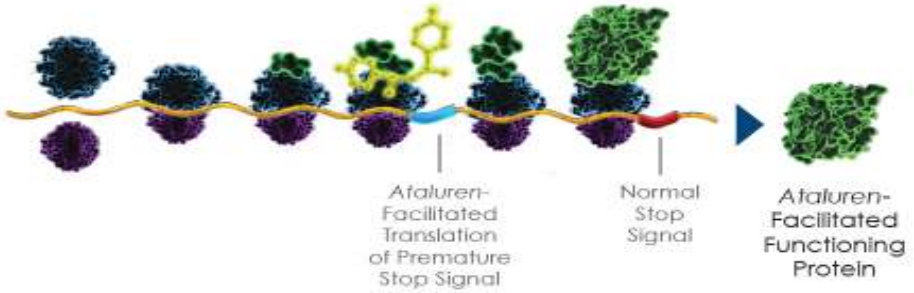
(A) Complete functioning protein



(B) Incomplete protein



(C) Ataluren-facilitated functioning protein



Ataluren is provided as granules for oral suspension and is administered three times a day. The recommended dose is 10 mg/kg bodyweight/day in the morning, 10 mg/kg bodyweight/day at midday, and 20 mg/kg bodyweight/day in the evening (for a total daily dose of 40 mg/kg bodyweight/day). For ease of reference in this document the daily dose and three times/day dosing schedule (10mg/kg/day, 10mg/kg/day and 20mg/kg/day) will be referred to as ataluren 40mg/kg/day.

3. Aim and objectives

This policy aims to assess the clinical and budget impact of ataluren when used within its marketing authorisation and to determine the circumstances under which it will be funded by NHS England.

4. Epidemiology and needs assessment

DMD is considered an orphan disease as its frequency is less than 5 per 10 000 in the general population. It affects mainly boys because it is a recessive X-linked genetic disorder. Girls carrying the mutation typically do not have any phenotypic consequences except in very rare cases (8%) of female carriers who show progressive muscle weakness in adult life (Barkhaus 1989).

The exact global incidence of DMD is unknown; it has been estimated to be between 1 in 3500 to 1 in 6000 live male births, with considerable differences in the prevalence rate across different geographic regions (Emery 1991; Merlini 1992; Rodino-Klapac 2007; van Essen 1992; Bushby 2010a; Bushby 2010b). The incidence in the England is estimated to be 1 in 5868 live male births with a prevalence of 4.2 per 100 000 (8.29 per 100 000 males) (Norwood 2009; Parsons 2002).

Although European population-based studies are lacking, it is established that about 11.5% of French male patients with DMD have a nonsense mutation (UMD-DMD France 2014). This is in line with US estimates suggesting that approximately 13% of patients with DMD have a nonsense mutation (Prior 1995). Based on these estimates, the incidence of nmDMD would represent about 10 new cases per year in the England with a total nmDMD population of approximately 250 patients.

The proportion of patients who are ambulatory varies according to age. Up to age 9 years around 95% or patients will be ambulatory whereas after age 20 around 95% of patients will be non-ambulatory (Henricson 2013; Ricotti 2011).

The estimated number of patients in England meeting the criteria for treatment with ataluren (DMD resulting from a nonsense mutation aged 5 years and over and ambulatory) is approximately 80. [There are currently 16 ambulatory patients receiving ataluren either through the extension to the phase 2b study or in the ongoing ACT-DMD study].

There is no existing therapy for nmDMD that treats the underlying cause of the disease. Current palliative treatments, which aim to alleviate symptoms and manage complications, are restricted to glucocorticoids, orthopaedic devices and surgery, wheelchairs and artificial ventilation. Given the relentless progression of the condition, one of the most important treatment objectives according to patients, caregivers and clinicians, is to slow the progression of the disease.

In boys with DMD, walking abnormalities are a major disease manifestation of great importance for patients and families. Ambulation is a prerequisite for normal physical functioning in humans; a major goal of medical and physical therapy intervention during the ambulatory phase of DMD is to maintain ambulation for as long as possible. The distance walked in 6 minutes (6MWD), a well-established outcome measure in a variety of diseases, is accurate and reproducible, simple to administer, and well tolerated (ATS 2002). The 6-minute walk test (6MWT), from

which the 6MWD is derived (McDonald 2013; ATS 2002), was originally developed as an integrated global assessment of cardiac, respiratory, circulatory and muscular capacity. More recently, it has been used to evaluate functional capacity in neuromuscular diseases, and has been the basis for regulatory registration of several drugs. Importantly, the 6MWT assesses function and endurance, which are important aspects of the disease status of patients with DMD. The 6MWT is a robust assessment tool for use in clinical trials given its ability to quantitatively evaluate ambulation in a controlled environment (McDonald 2010).

In addition, boys with DMD encounter considerable ambulatory challenges in their daily life that are clinically important. Being able to walk a distance of 30 metres may have real-world significance in terms of keeping up with peers, a distance that may be required to get from the car park into school, walk to a bus stop, or walk independently to the toilet/bathroom (McDonald 2013).

5. Evidence base

The evidence for treatment with ataluren in this patient population is primarily informed by PTC Therapeutics' Study 007 (Bushby 2014). This study was a Phase 2b, international, multicentre, randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of ataluren in ambulatory male patients with nonsense mutation dystrophinopathy (referred to as nmDMD) aged 5 years and over. The study enrolled 174 patients who were then randomised in a 1:1:1 ratio to receive study drug three times per day at morning, midday, and evening, according to one of the regimens shown below:

- Placebo
- Ataluren 10, 10, and 20 mg/kg/day (referred to as "40 mg/kg/day") (licensed dose)
- Ataluren 20, 20, and 40 mg/kg/day (referred to as "80 mg/kg/day")

All patients continued to receive the best supportive care they were on when they entered the study including, in many cases, corticosteroid treatment.

Patients were assessed every 6 weeks over a 48-week treatment period and a 6-week post-treatment follow-up period. Efficacy measures included the primary endpoint (change from baseline to week 48 in 6MWD) as well as secondary endpoints of physical function including timed function tests, frequency of accidental falls, upper and lower extremity myometry, step activity monitoring and physical function-related quality of life.

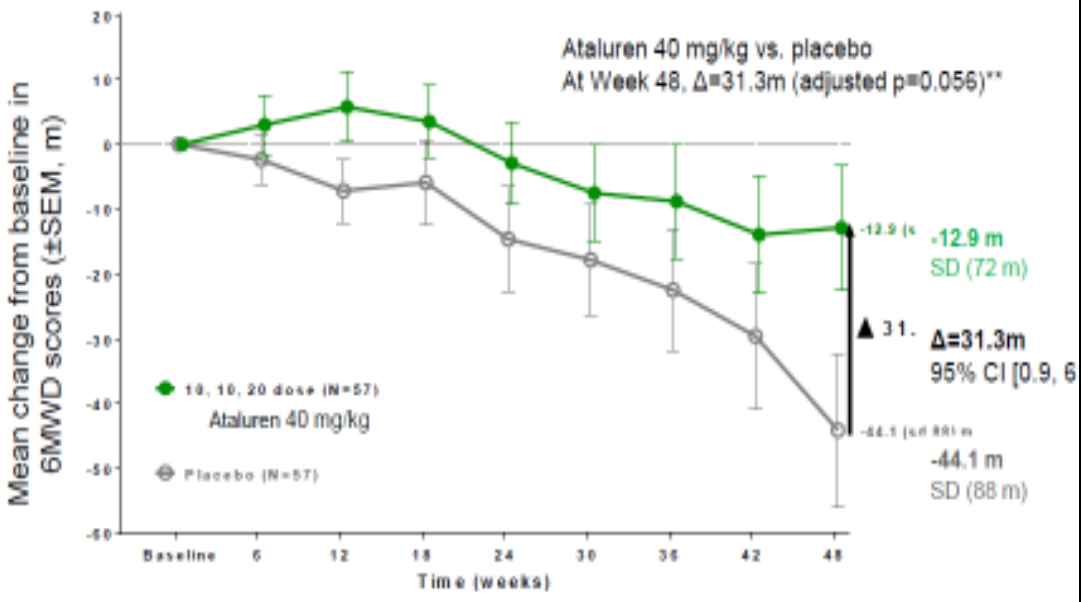
It was noted after data collection that two patients had suffered acute lower limb injuries within 1 day or 2 days of screening but prior to their baseline measurements, which impaired their walking ability. They subsequently recovered from these injuries during the course of the trial. As the study protocol had stipulated that a valid 6MWD value available at baseline and at least one post-baseline visit were required for inclusion into the ITT population, these two patients' baseline 6MWD values were replaced with their screening 6MWD values and the updated dataset was referred to as the "corrected ITT population" (cITT). The data presented here are taken from this analysis set unless stated otherwise.

There was no difference in treatment effect between ataluren 80 mg/kg/day and

placebo. The evidence of an effect in patients receiving ataluren 40 mg/kg/day, but not in patients receiving ataluren 80 mg/kg/day, is further supported by results in non-clinical studies that provide support of the inverse dose-response observed in Study 007. Overall, patients receiving ataluren 40 mg/kg/day achieved plasma concentrations associated with a treatment effect.

Treatment with ataluren 40 mg/kg/day resulted in a mean decline from baseline to week 48 in 6MWD of 12.9 metres (SD=72 metres) compared to a decline of 44.1 metres (SD=88 metres) for patients receiving placebo; a mean difference between treatment arms of 31.3 metres (95% CI: 0.9 to 61.7 metres) indicating a slower decline of ambulation in patients receiving this dose of ataluren (nominal p=0.0281; adjusted p=0.056), as shown in Figure 3.

Figure 3. Mean change in observed 6MWD from baseline over 48 weeks, cITT analysis set



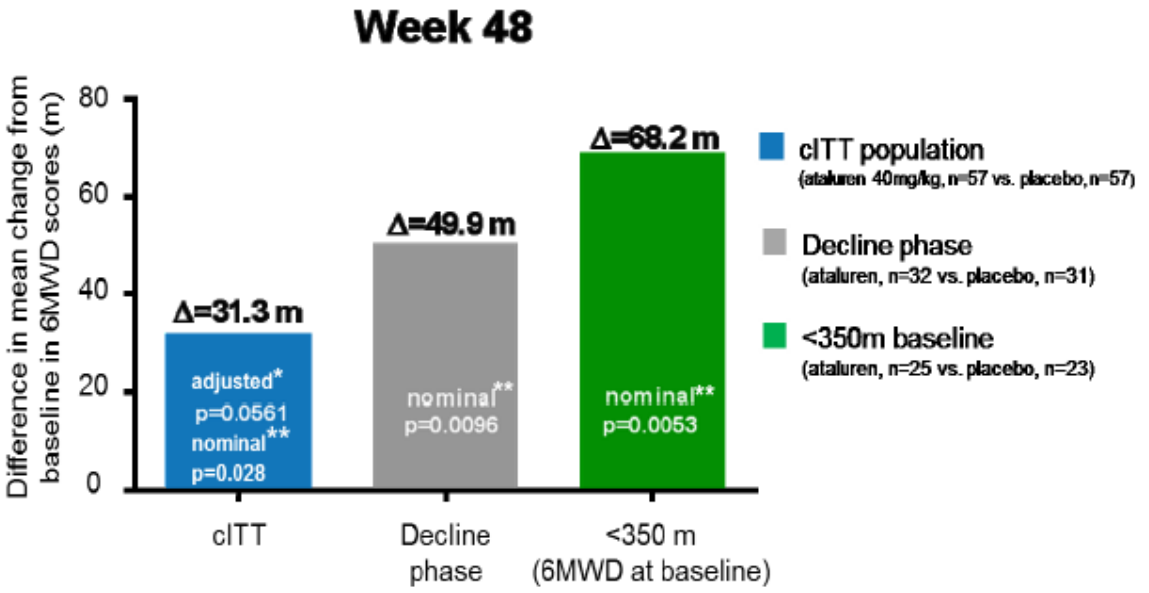
*Patients treated with placebo and with ataluren continued to receive the best supportive care on which they entered the study, includ corticosteroid treatment; **The adjusted p value relates to statistical analyses carried out on data from both the 40 mg/kg and the 80 ataluren arms; the nominal p-value refers to statistical analysis from only the 40 mg/kg treatment arm

A reduction of 6MWD greater than 30 metres is considered clinically meaningful and is predictive for loss of ambulation, which is correlated with a faster progression of disease (McDonald 2013a).

Patients with more advanced nmDMD (i.e. those in the decline phase[1] or those with a baseline 6MWD <350 metres) demonstrated larger changes in the mean difference from baseline to 48 weeks in 6MWD compared to patients treated with placebo (49.9 metres [nominal p=0.0096) and 68.2 metres [nominal p=0.0053], respectively), as shown in Figure 4.

[1] The ambulatory decline phase subgroup comprises patients who are 7 to 16 years of age, receiving concomitant treatment with corticosteroids, have ≤80% predicted healthy walking ability of normal 6MWD (predicted based on age and height), and a ≥150m baseline 6MWD.

Figure 4. Mean difference in change in observed 6MWD from baseline to 48 weeks for patients treated with 40mg/kg/day of ataluren compared to placebo, for the cITT analysis set, decline phase subgroup, and <350 metres subgroup

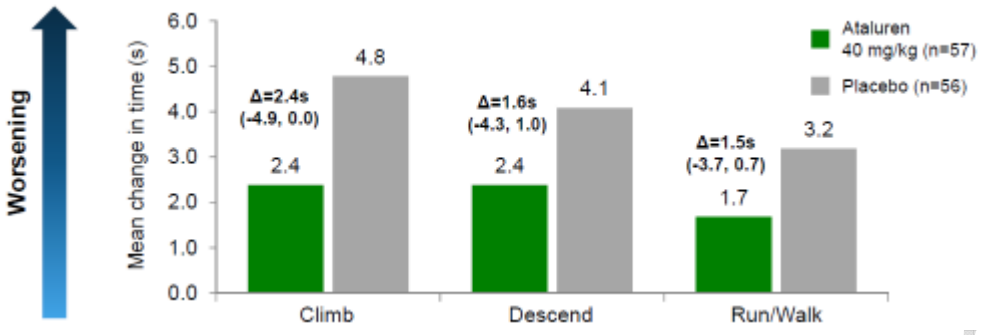


*The adjusted p value relates to statistical analyses carried out on data from both the 40 mg/kg and the 80 mg/kg ataluren
**Nominal p-values are calculated from only the 40 mg/kg treatment arm vs. placebo
Decline phase subgroup evaluated *post hoc*; Ambulatory decline phase and <350m patient subpopulations defined *a priori*

An analysis of time to persistent 10% worsening in 6MWD showed that 26% of patients receiving ataluren 40 mg/kg/day progressed at Week 48 compared to 44% in the placebo group (p=0.0652). These results indicate that fewer patients receiving ataluren 40 mg/kg/day worsened in 6MWD over 48 weeks.

A reduction in the rate of decline in physical functioning is further supported by a clinically meaningful difference (at least a 1.5-second difference; (Escolar 2011) in the mean values of three timed function tests over 48 weeks in patients treated with ataluren 40mg/kg/day when compared to placebo (Figure 5). Consistent with the 6MWD data, larger treatment effects were observed in the ambulatory decline phase and baseline 6MWD <350 m subgroups. Mean differences, in seconds, for stair climbing, stair descending, and walking/running 10 metres were: 2.9, 2.9, and 2.8 in the ambulatory decline subgroup; and 6.4, 5.0, and 3.5 in the baseline 6MWD <350 metres subgroup.

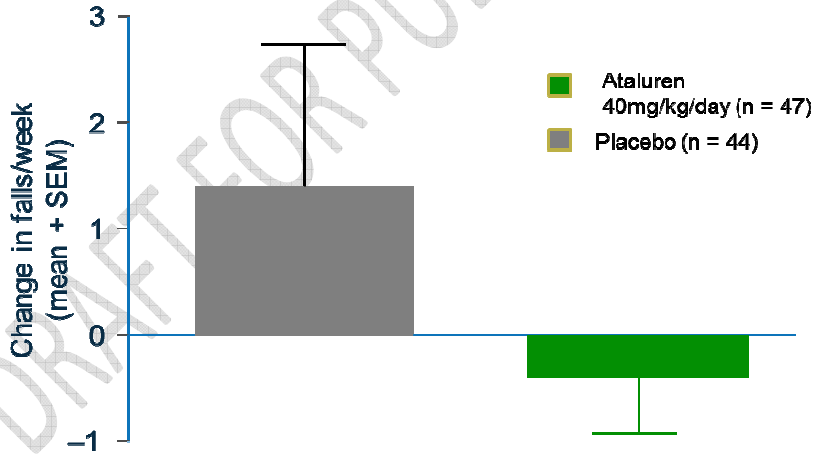
Figure 5. Mean change in time across three different timed function tests from baseline to 48 weeks, cITT analysis set



Treatment with ataluren 40 mg/kg/day was also associated with positive trends in physical functioning in the PedsQL, reduction in the number of falls, and reduction in wheelchair use versus placebo over 48 weeks, thus allowing patients the possibility to remain self-sufficient for a longer period of time:

- The difference in the mean change in physical functioning score was 3.4 (95%CI: -5.5 to 12.2) at Week 48. This was more pronounced in the ambulatory decline phase subgroup, with a difference of 6.1 in the mean change in physical functioning score, favouring ataluren 40 mg/kg/day over placebo at Week 48.
- The accidental fall rate at Week 48 favoured treatment with ataluren 40mg/kg/day compared with placebo; the relative ratio of the estimated fall rates at Week 48 was 0.38 (95% CI = 0.16, 0.94) for ataluren 40 mg/kg/day versus placebo (Figure 6).

Figure 6. Mean change in patient-reported accidental falls from baseline to 48 weeks, cITT analysis set



- At baseline, the mean percentage of days of patient-reported wheelchair use was 13.2% for patients in both the placebo and ataluren 40 mg/kg/day treatment groups. The mean percentage of days of wheelchair use increased from baseline to Week 48 by 11.5% for placebo compared to 4.0% for ataluren 40 mg/kg/day, resulting in a difference of 7.5% favouring ataluren.
- Patients aged 5 and 6 years of age treated with ataluren 40 mg/kg/day also showed an improvement across all myometry measures compared to patients dosed with placebo.

Treatment with ataluren 40 mg/kg/day was generally well tolerated. The number of adverse events reported was similar between the treatment groups in Study 007. No patients discontinued treatment due to adverse events and there were no deaths reported. Only 3.4% of ataluren patients (both doses) reported a serious adverse event compared to 5.3% in the placebo arm treatment group. Importantly, none of these events was considered to be related to treatment with ataluren by the investigator.

Furthermore, treatment with ataluren has been evaluated in several clinical studies that enrolled both healthy participants and patients (total n=588). The manufacturer has pooled these data available as of 1 September 2013.

This combined safety dataset for nmDMD included patients ranging in age from 5 years to 22 years with a median age of 9 years. In these patients, ataluren was generally well tolerated and the most common adverse events (those reported in ≥20% of patients) included headache (40.7%), diarrhoea (27.3%), nasopharyngitis (26.4%), cough (25.0%), upper abdominal pain (21.8%), pyrexia (21.8%), fall (20.8%) and upper respiratory tract infection (20.8%).

As of 1 September 2013, no deaths were associated with treatment and serious adverse events were only observed in a small number of patients. Similarly, discontinuation of ataluren treatment due to an adverse event was rare. Long-term ataluren exposure (≥48 weeks) occurred in 179 patients with nmDMD who received ataluren.

Overall, these data suggest a positive benefit-risk assessment in favour of treatment with ataluren.

Cost impact

The number of patients in England meeting the criteria for treatment with ataluren (DMD resulting from a nonsense mutation aged 5 and over and ambulatory) is approximately 80.

The list price of ataluren is shown in the Table 1 together with the recommended dose and cost for the median patient weight range of 24 kg to 26 kg (age 7 years to 9 years). Ataluren will be made available in accordance with an agreed discount scheme.

Table 1: List price of Ataluren and recommended dose and cost for the median patient weight range of 24 kg to 26 kg (age 7 years to 9 years).

Drug name	Price*	Dose	Dose for 24 kg to 26 kg person	Cost for 24 kg to 26 kg person
Ataluren	Box of 30 sachets: • 125 mg: £2,532 • 250 mg: £5,064 • 1000 mg: £20,256	40 mg/kg/day body weight per day given as 3 divided doses: • 10 mg/kg/day morning • 10 mg/kg/day midday	1000 mg daily given as follows: • 1 x 250 mg morning • 1 x 250 mg midday • 2 x 250 mg	Per month: £18,355 Per year: £220,256

		*Submitted to DH on 23rd July 2014	• 20 mg/kg/day evening	evening	

6. Rationale behind the policy statement

There is good evidence that ataluren is clinically effective for patients with DMD resulting from a nonsense mutation, although long-term safety and effectiveness data beyond 48 weeks are not yet available. Evidence for the clinical effectiveness of ataluren is based on the results from PTC Therapeutics' Phase IIb clinical study (Study 007), as well as the recent granting of conditional marketing authorisation. The positive recommendation by the Committee for Medicinal Products for Human Use (CHMP) was received in May and the European Commission ratification was confirmed on 31st July 2014. Conditional approval is one of the Agency's mechanisms to provide patients with early access to medicines that fulfil high unmet medical need or address life-threatening diseases. The conditional approval of a medicine is made on the basis of a less mature or complete clinical data package than is normally required to support a marketing authorisation. To gain conditional approval, the available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.

As the first new drug targeting the underlying cause of nmDMD, ataluren offers promise as a treatment for this orphan genetic disorder with high unmet medical need.

7. Criteria for commissioning

Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation (determined by genetic testing) in the dystrophin gene in ambulatory patients aged 5 years and older.

Definitions of ambulatory and non-ambulatory status vary and currently there is no clinical consensus. For the purposes of this policy, an "ambulatory" patient is defined as one who can take any steps unaided. "Non-ambulatory" is defined as patients who have continuous indoor and outdoor wheelchair use (Bello 2014; Pettygrove 2013). Concomitant use of intravenous aminoglycosides is contraindicated.

The underlying mechanism of ataluren means that it should stabilise or delay the decline in function of other muscles, including those in the upper body. While such outcomes have not been fully studied, myometry results in patients with nmDMD aged <7 years treated with ataluren 40mg/kg/day showed stabilisation of their muscle function.

Stopping criteria

If a patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to consider

stopping ataluren treatment. Treatment should not be stopped while the patient has any degree of ambulatory ability as it has been shown with other treatments (corticosteroids) that withdrawal of medication at this time can have negative consequences. Patients should stop treatment no later than 6 months after becoming fully non-ambulant.

8. Patient pathway

Ataluren will be considered as a treatment option for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation. It will be added to existing standard treatment, including use of corticosteroids. Treatment will continue unless the patient meets the stopping criteria described above.

9. Governance arrangements

Standards of Care Guidelines that are NICE accredited:

- Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management.
- Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.

Paediatric Neurosciences – Neurology (E09/S/b): http://www.england.nhs.uk/wp-content/uploads/2013/06/e09-paedi-neurology.pdf

10. Mechanism for funding

Ataluren is a high cost drug excluded from PbR tariff. It will be funded by pass through payment against invoices received from provider Trusts, subject to the terms of the manufacturer's discount.

11. Audit requirements

Use of ataluren within the guidance of this policy will be audited by NHS England. In addition, the manufacturer, PTC Therapeutics, will be putting in place a product registry

12. Documents which have informed this policy

Bushby K, Finkel R, Birnkrant D, Case L, Clemens P, Cripe L, Kaul A, Kinnet K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezko J, Constantin C. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *The Lancet.* Published online November 30, 2009.

Bushby et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *The Lancet*. Published online February

2010

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of IFR.

14. Date of review

This policy will be reviewed in April 2018 unless information is received that indicates that the proposed review date should be brought forward or delayed.

References

ATS. (2002) ATS statement: Guideline for the six-minute walk test. American Journal of Respiratory Critical Care Medicine. 116, 111-117.

Barkhaus PE, Gilchrist JM. (1989) Duchenne muscular dystrophy manifesting carriers. Arch Neurol. 46(6): 673-675.

Bello L, Kesari A, Gordish-Dressman H, Punetha J, Henricson E, et al. Loss of ambulation in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS) is synergistically influenced by glucocorticoid corticosteroid treatment, patient ethnicity, and SPP1/LTBP4 polymorphisms.

Bushby K, Finkel R, Wong B, Barohn R, Campbell C, et al. (2014) Ataluren Treatment of Patients with Nonsense Mutation Dystrophinopathy. Muscle Nerve. 'Accepted Article', doi: 10.1002/mus.24332

Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, et al. (2010a) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 9(1): 77-93.

Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, et al. (2010b) Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 9(2): 177-189.

Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, et al. (2002) Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 12(10): 926-929.

Emery AE. (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord. 1(1): 19-29.

Escolar DM, Hache LP, Clemens PR, Cnaan A, McDonald CM, et al. (2011) Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology. 77(5): 444-452.

Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, et al. (2013) The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle Nerve. 48(1): 55-67.

McDonald CM, Henricson EK, Abresch RT, Florence J, Eagle M, et al. (2013) The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve. 48(3): 357-368.

McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, et al. (2010) The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve. 41(4): 500-510.

Merlini L, Stagni SB, Marri E, Granata C. (1992) Epidemiology of neuromuscular disorders in the under-20 population in Bologna Province, Italy. Neuromuscul Disord. 2(3): 197-200.

Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, et al. (2009) Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 132(Pt 11): 3175-3186.

Office for National Statistics. (2014) Population Estimates for UK, England, Wales, Scotland and N. Ireland - mid 2013. http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population#tab-data-tables,

Parsons EP, Clarke AJ, Hood K, Lycett E, Bradley DM. (2002) Newborn screening for Duchenne muscular dystrophy: a psychosocial study. Arch Dis Child Fetal Neonatal Ed. 86(2): F91-F95.

Pettygrove S, Zhenqiang L, Andrews J, Meaney FJ, Sheehan D, Price E, et al. (2013) Sibling concordance for clinical features of Duchenne and Becker muscular dystrophies. Muscle and Nerve. DOI 10.1002/mus.24078

Prior TW, Bartolo C, Pearl DK, Papp AC, Snyder PJ, et al. (1995) Spectrum of small mutations in the dystrophin coding region. Am J Hum Genet. 57(1): 22-33.

Ricotti V, Roberts RG, Muntoni F. (2011) Dystrophin and the brain. Dev Med Child Neurol. 53(1): 12.

Rodino-Klapac LR, Chicoine LG, Kaspar BK, Mendell JR. (2007) Gene therapy for duchenne muscular dystrophy: expectations and challenges. Arch Neurol. 64(9): 1236-1241.

Stromberg A, Darin N, Kroksmark AK, Tulinius M. (2012) What was the age and cause of death in patients with Duchenne muscular dystrophy in Sweden during 2000-2010? Neuromuscular disorders : NMD 22(9), 880-881.

UMD-DMD France. (2014) http://www.umd.be/DMD/4DACTION/WSEARCH,

van Essen AJ, Busch HF, te Meerman GJ, ten Kate LP. (1992) Birth and population prevalence of Duchenne muscular dystrophy in The Netherlands. Hum Genet. 88(3): 258-266.