ataluren 125mg, 250mg, and 1,000mg granules for oral suspension (Translarna®)

PTC Therapeutics Ltd

05 March 2021

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

Key points:

- Duchenne muscular dystrophy is a devastating condition resulting in a decline in function, loss of ambulation and early death due to respiratory or cardiac failure. The caring burden impacts on the whole family.
- In the clinical trials programme, the difference in 6-minute walking distance (6MWD) favoured ataluren over placebo however the differences were generally not statistically significant. Further clinical trial data are awaited.
- Observational data from registries generally favoured ataluren plus standard of care over standard of care alone for most outcomes relevant to disease progression, including age at loss of ambulation and measures of pulmonary function.
- Quality of life data are limited but may suggest some improvements favouring ataluren over placebo.
- There were a number of outstanding uncertainties in the economic analysis provided by the company relating to the method of inclusion of utilities for patients and caregivers in the model that suggest the cost-effectiveness may be substantially above that presented by the submitting company.
- Despite a Patient Access Scheme (PAS), the treatment's cost in relation to its health benefits remains high.

Chairman
Scottish Medicines Consortium

Indication

Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

Dosing Information

Ataluren should be administered orally every day in three doses. The recommended dose is 10mg/kg body weight in the morning, 10mg/kg body weight at midday, and 20mg/kg body weight in the evening (for a total daily dose of 40mg/kg body weight). Ataluren should be administered orally after mixing it to a suspension in liquid or in semi-solid food.

Treatment with ataluren should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy.

Further details are included in the Summary of product characteristics.[1]

Product availability date

August 2018.

Ataluren has conditional marketing authorisation from the EMA.

SMC ultra-orphan designation

Ataluren has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of Duchenne muscular dystrophy is less than 1 in 50,000 of the population in Scotland.
- Ataluren has EMA orphan designation for the treatment of Duchenne muscular dystrophy (EU/3/05/278) and this was maintained at the time of marketing authorisation.
- Duchenne muscular dystrophy is a rare genetic muscle wasting disease that is chronic and severely disabling due to rapid decline in physical functioning with subsequent respiratory and cardiac failure.
- This condition requires highly specialised management.

Nature of condition

Duchenne muscular dystrophy is a rare X-linked genetic condition caused by mutations in the gene for dystrophin. This protein is essential to the structural stability of myofibres in skeletal, diaphragmatic and cardiac muscle and is also of importance for the central nervous system and smooth muscles. Approximately 13% of patients with Duchenne muscular dystrophy will have the nonsense mutation. A nonsense mutation is a change in the nucleotide sequence of DNA that is transcribed into a premature stop codon in the messenger RNA (mRNA) for dystrophin. This stop codon causes the ribosome complex to terminate translation prematurely and results in a truncated, non-functional protein.[2-4]

Duchenne muscular dystrophy is a devastating condition resulting in a decline in function, loss of ambulation and early death due to respiratory or cardiac failure. Symptoms also include muscle weakness, pain, and fatigue. Patients have significant care needs and, as the disease progresses, they rely on parents and carers for all aspects of daily living. Loss of ambulation and dependence on a wheelchair usually occurs before they become teenagers and eventually even the ability to operate an electric wheelchair or use a mobile phone, for example, is lost. Patients will usually require ventilatory assistance by their late teens. Duchenne muscular dystrophy significantly affects patients' quality of life and children with this condition are unable to participate in normal physical activities, for example, playing sports with their friends or riding a bike. In addition, parents may be unable to work due to caring responsibilities.

There are currently no curative treatments available for Duchenne muscular dystrophy. Management is based on prevention and management of complications and includes the use of physiotherapy and corticosteroids. Corticosteroids are the only treatment that has been demonstrated to temporarily reduce motor function decline in patients with Duchenne muscular dystrophy. Some patients may not be able to take corticosteroids due to adverse effects or lack of response. The EMA concluded that Duchenne muscular dystrophy is a life-threatening and chronically debilitating condition where no satisfactory treatments exist.[2]

New technology

Ataluren promotes ribosomal read-through of a premature stop codon in the dystrophin gene, enabling formation of full-length functional dystrophin protein in patients with Duchenne muscular dystrophy who have a nonsense mutation.[1, 2] Ataluren is the first medicine to be licensed in the UK for this indication.

Impact of new technology

Comparative efficacy

The submitting company presented a propensity score matched comparison comparing the efficacy of ataluren plus standard of care (observational data from Strategic Targeting of Registries and International Database of Excellence; STRIDE Registry) with standard of care

(observational data from The Cooperative International Neuromuscular Research Group; CINRG, Duchenne Natural History Study; DNHS) in patients with Duchenne muscular dystrophy. The company provided results for the most recent data-cut off however SMC is unable to present these due to commercial confidentiality issues.

Patients included in the STRIDE Registry had Duchenne muscular dystrophy and a nonsense mutation.[5] It was not specified that Duchenne muscular dystrophy had to be due to a nonsense mutation in the CINRG-DNHS.[6] Both registries included ambulatory and non-ambulatory patients. Commonly, standard of care includes treatment with corticosteroids and these were received at any time by most patients.[6] The outcomes assessed included age at loss of ambulation; age at time to stand from supine ≥10 seconds; age at time to climb four stairs ≥10 seconds and pulmonary function (measured as age at predicted forced vital capacity (FVC) <60%, FVC <50% and age at FVC <1L). Results favoured ataluren plus standard of care for the majority of outcomes including age at loss of ambulation and measures of pulmonary function.[5]

Studies 007, 020 (and extension study 020e) and 030 provide efficacy data from clinical trials for ataluren:

Study 007 was a randomised, double-blind, placebo-controlled phase IIb study conducted in ambulatory males aged ≥5 years old with Duchenne muscular dystrophy resulting from nonsense mutation in the dystrophin gene (n=174). Stable use of concomitant corticosteroids was permitted. Patients were randomised equally to oral treatment with ataluren 40mg/kg/day (administered in three divided doses: 10mg/kg, 10mg/kg, 20mg/kg) (licensed dose) (n=57); ataluren 80mg/kg/day (as three doses: 20mg/kg, 20mg/kg, 40mg/kg) (n=60); or placebo (n=57) for 48 weeks, stratified prospectively by age (<9 or ≥9 years), use of glucocorticoids (yes or no), and baseline 6-minute walking distance (6MWD) (≥350m or <350m).[7] The primary outcome was change from baseline to week 48 in the 6MWD analysed in the intent-to-treat (ITT) population, which included all randomised patients with a valid 6MWD available at baseline and at least one post-baseline visit.

Results are only presented here for the licensed dose of ataluren (40mg/kg/day). In the ITT population, mean declines in 6MWD at Week 48 of 12.9m and 42.6m were observed for ataluren and placebo, respectively, the difference of 29.7m was not statistically significant. A greater effect over 48 weeks was seen in patients in the "ambulatory decline" phase, that is patients between 7 and 16 years of age, with baseline 6MWD ≥150m and ≤80% of predicted value.[2] Secondary outcomes included time function tests (ascend four stairs, descend four stairs, 10m run/walk, and supine to stand), none were significantly different. Patients in the ataluren group had a higher mean change in the Pediatric quality of life inventory (PedsQL) physical and school functioning score than the placebo group but not in the emotional and social functioning score.[2, 8]

Study 020 was a randomised, double-blind, placebo controlled, phase III study that recruited ambulatory males aged ≥7 to ≤16 years with Duchenne muscular dystrophy due to a nonsense

mutation in in the dystrophin gene (n=230) on stable doses of corticosteroids. Patients were randomised equally to receive ataluren orally three times daily (total dose 40mg/kg per day) (n=115) or placebo (n=115) for 48 weeks. Randomisation was stratified by age (<9 years vs ≥9 years), duration of previous corticosteroid use (6 months to <12 months vs ≥12 months), and baseline 6MWD (<350m vs ≥350m). The primary outcome was the change in 6MWD from baseline to week 48.

In the ITT population, the least-squares mean change in 6MWD from baseline to week 48 was -47.7m in the ataluren group and -60.7m in the placebo group, the difference of 13.0m was not statistically significant. The secondary efficacy outcome was the effect of ataluren on proximal muscle function, as assessed by timed function tests (10m run or walk, four-stair climb, four-stair descend). Only the four-stair descend was statistically significant.[3, 9] Quality of life, as assessed by the Pediatric Outcomes Data Collection Instrument (PODCI) transfers/basic mobility and sports/physical functioning domain scores, favoured ataluren over placebo.[10] Study 020e was an international, open-label, single group, extension of Study 020. The study enrolled 218 patients who had successfully completed the double-blind, placebo-controlled Study 020. A total of 68 patients completed 144 weeks of treatment. There appears to be a gradual decline in the performance of the 6MWD. Patients with higher baseline values remained longer in the study.[11]

A meta-analysis using data from Study 007 (n=114) and Study 020 (n=228) was conducted to assess the total efficacy of ataluren 40mg/kg/day (given orally in three doses: 10, 10 and 20mg/kg for morning, midday and evening doses, respectively) or placebo for 48 weeks. The primary outcome, in the intention-to-treat (ITT) population, least-squares (LS) mean difference in change in 6MWD from baseline to week 48 was statistically significant in favour of ataluren over placebo (LS mean difference 17.2m [95% CI: 0.2 to 34, p=0.047]). There were significant differences in favour of ataluren over placebo in the secondary outcomes, time to climb four stairs and descend four stairs. However, there was no difference between treatments in time to run/walk 10m. Patients who received ataluren versus placebo also had a significantly reduced risk of persistent 10% 6MWD worsening.[12]

Study 030 was a single-arm, open-label, phase II study. This study recruited males aged ≥2 to <5 years of age with a diagnosis of Duchenne muscular dystrophy due to a nonsense mutation in in the dystrophin gene (n=14). Stable use of concomitant corticosteroids was permitted (43% of patients were on corticosteroids at baseline). Patients received ataluren 10mg/kg in the morning and at midday and 20mg/kg in the evening for 4 weeks during the pharmacokinetic analysis, and for 48 weeks during the extension period. The primary outcome was to evaluate the safety of ataluren in this younger patient population. Secondary outcomes included assessment of the impact of ataluren therapy on proximal muscle function using timed function tests (including time to climb 4 stairs, descend 4 stairs, run or walk 10m, and stand from a supine position) and change in physical function, assessed using the North Star Ambulatory Assessment (NSAA) 16-Item Scale, as well as 8-and 3-item NSAAs (these two scales

are adapted for use in younger children). The assessment of timed function tests and NSAA shows an improvement following treatment with ataluren.[13]

*Other data were also assessed but remain confidential.**

Comparative safety

At the time of the initial marketing authorisation the EMA concluded that ataluren was generally well tolerated and that the safety profile could be considered acceptable, although it was based on a rather limited patient exposure.[2]

The safety profile of ataluren is based on pooled data from studies 007 and 020 (n=232 ataluren-treated patients). The most common adverse events recorded in these studies were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence. Adverse events were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these two studies. One patient in both the ataluren group and placebo group in study 020 discontinued treatment due to an adverse event.[1, 2]

Study 030 provided safety data in patients aged ≥2 to <5 years (n=14). Commonly reported AEs included pyrexia, ear infection, nasopharyngitis, rash, cough, and vomiting. A higher frequency of malaise, pyrexia, ear infection, and rash were reported in patients aged ≥2 to <5 years compared with patients aged ≥5 years, these may be more frequent in younger children in general. The adverse event profile in these patients was similar to older patients and consistent with the known safety profile of ataluren. No new safety signals were observed.[1, 4, 13]

Interim safety results from the STRIDE registry (global registry of patients receiving ataluren in clinical practice) appear be consistent with the known safety profile of ataluren.[5]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths:

- The primary outcome of studies 007 and 020, the change in 6MWD from baseline to week 48, showed a statistically non-significant advantage for ataluren compared to placebo (29.7m and 13m, in studies 007 and 020, respectively). The meta-analysis combining these studies identified a significant difference of 17.2m. A difference of 30m is considered by the EMA to be clinically relevant.[2]
- Results from a propensity score matched comparison using data from observational registries generally favoured ataluren plus standard of care over standard of care alone

for outcomes relevant to disease progression, including age at loss of ambulation and measures of pulmonary function.

- The safety study 030, supported the license extension to patients aged between 2 and <5 years.

Key uncertainties:

- The company states that the key evidence for this indication is from a propensity score matched comparison comparing the efficacy of ataluren plus standard of care, with standard of care in patients with Duchenne muscular dystrophy. This comparison was associated with a number of limitations: only the STRIDE registry was used to provide data for ataluren with no information from the clinical trial programme included due to the shorter follow up; marketing authorisation is for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene but it was not specified in CINRG-DNHS that Duchenne muscular dystrophy was due to a nonsense mutation; there may have been additional relevant baseline characteristics that were not matched; there was greater censoring in the STRIDE population which could potentially bias results; due to the observational data used, outcomes relating to the 6MWD, frequency of wheelchair use, NSAA, assessment of upper limb function, safety and health-related quality of life were not evaluated. Due to these limitations, the company's conclusions are uncertain.
- Most of the outcomes in studies 007 and 020 were not significantly different between the treatment groups. The difference in 6MWD between ataluren and placebo in study 020, and in the meta-analysis was less than the difference considered to be clinically relevant.[3]
- Study 030 was open-label, designed to predominately assess safety and did not include a control arm. In addition small patient numbers were included (although small numbers are expected due to the rarity of the condition).
- This is a lifelong condition and further data on long-term efficacy are awaited.

Ataluren has conditional marketing authorisation from the EMA. The marketing authorisation holder will conduct and submit the results of a multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open-label extension.[4]

*Other data were also assessed but remain confidential.**

Impact beyond direct health benefits and on specialist services

If treatment with ataluren results in a longer duration before patients lose ambulation this could have considerable benefits to both patients and carers. The patient could retain some independence, for example continuing in education and socialising with friends. Patients retaining ambulation for longer could potentially result in reduced caring requirements. If ataluren reduced the decline in pulmonary function this could have benefits not only to the patient and carer, but could potentially reduce the impact on specialist services.

Patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received a joint patient group submission from: Muscular Dystrophy UK, Action Duchenne, Duchenne Family Support Group and Duchenne UK. All four organisations are registered charities.
- Muscular Dystrophy UK has received 1.1% pharmaceutical company funding in the past two years, including from the submitting company. Action Duchenne has received 35% pharmaceutical company funding in the past two years, including from the submitting company. Duchenne Family Support Group has not received any pharmaceutical company funding in the past two years. Duchenne UK has received 9.8% pharmaceutical company funding in the past two years, including from the submitting company.
- Duchenne muscular dystrophy is a rare, progressive muscle wasting condition which mainly affects boys. Affected children lose the ability to walk independently and most become reliant on a wheelchair between the ages of 8 and 13 years. Some children never walk. As the condition progresses patients lose the ability to feed themselves or undertake any self-care. Most experience serious orthopaedic, cardiac and respiratory complications. Around 20-30% will be diagnosed with autism, anxiety or other mental health or behavioural issues. The diagnosis is devastating for the family, and caregivers often suffer from anxiety and depression and have prolonged absences from work.
- Current treatments focus on the management of symptoms, rather than addressing the underlying genetic cause. A variety of treatments are used. Patients with Duchenne muscular dystrophy are monitored by a lot of different specialists, requiring patients and carers to attend many different clinics.
- The parents of children who have been taking ataluren described how it had helped them to retain mobility for longer and as a result provided increased independence for both the patients and their families. Respiratory and cardiac functions were also reported to have improved while on treatment. Parents also highlighted improvements in behaviour that allowed greater inclusion in school and home life. In addition, they described benefits to mental health and social functioning for both children and their families.

- Ataluren is the only medicine available in the UK that targets an underlying genetic cause of Duchenne muscular dystrophy and potentially offers substantial benefits over existing treatment. It would be given in addition to current standard treatments. This will result in more management for parents but they are used to adapting their routines to help manage their children's condition.

Value for money

The submitting company presented a cost-utility model comparing ataluren with best supportive care in patients aged ≥2 years old with Duchenne muscular dystrophy resulting from a nonsense mutation, based on a propensity score matching of the STRIDE registry with historical control data from CINRG. Patients who were non-ambulatory at baseline were excluded from the analysis. Matching was based on age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of other corticosteroid use. The perspective adopted was that of NHS Scotland and social care, with the addition of caregiver QALYs; a wider societal perspective incorporating indirect costs was included among scenario analyses, which also addressed informal care costs.

A partitioned survival approach was adopted, with several health states. Patients entered the model in an ambulatory state. Subsequent states were loss of ambulation (fully wheelchair bound), predicted forced vital capacity (FVC) greater or less than 50%, FVC < 1 litre (FVC<1L), and death. Kaplan-Meier data were analysed to fit parametric functions for loss of ambulation and predicted FVC<50%. Independent functions were fitted to the time to event data from STRIDE and CINRG. For both endpoints the lognormal was selected as the better fitting of the candidate distributions based on Akaike Information Criterion (AIC). There were no discernible differences between any of the distributions fitted to the predicted FVC<50% data in terms of fit to observed KM, and the lognormal was again selected based on AIC, though there were substantial differences in extrapolation.

Due to the immaturity of the ataluren STRIDE data for FVC<1L, this milestone was not modelled as a parametric function but as a constant five-year 'shift' of the ataluren curve relative to that for best supportive care. The submitting company pointed to a 5-year improvement in median time to predicted FVC<50% in a propensity matched analysis of CINRG versus study 019 (n=16 per arm). This is similar to the median difference predicted based on the main propensity score analysis for predicted FVC<50%, and the five years difference is applied as a constant 'shift' to the FVC<1L survival curves (i.e. FVC<1L is proxied by improvement in predicted FVC<50%). Such is the degree of censoring that an estimate based on the main analysis' observed data would not be possible. At median survival both cohorts are heavily censored, and the five-year median difference is substantially greater than is seen at any point where an event occurs on either Kaplan-Meier function.

Patients are assumed to enter the model at five years of age, based on age of diagnosis in Scotland. In a scenario for earlier commencement of treatment with ataluren (two years of

age), a treatment benefit is modelled as a further one-year shift in the loss of ambulation curve. Treatment is assumed to continue until patients reach a predicted FVC<50%, by which point patients are expected largely to require night-time ventilation support. Otherwise, discontinuation is assumed to occur at a rate of approximately 3.8% per annum based on STRIDE data, irrespective of milestone reached.

The valuation of health effects addressed patient utility, caregiver utility, and bereavement due to loss of a child. For best supportive care Duchenne muscular dystrophy-specific utilities derived using the HUI-3 from Landfeldt et al (2017) were used.[14] For the non-ambulatory ataluren in combination with BSC health states, the relative reductions in utility seen in Landfeldt et al were applied. Thus, patient utilities were specific for ataluren and best supportive care throughout patients' lifetimes. The proportional decrement applied for non-ambulatory (predicted FVC>50%) resulted in higher utility for ataluren in this impaired state than for ambulatory best supportive care. The submitting company assigned utility to caregivers based on Landfeldt et al (2017), assigning full per person utility estimates to each caregiver (two caregivers assumed), rather than utility decrements, and attributed further gains to ataluren based on delayed bereavement, assuming a fixed life year gain of five, with 9% of this (0.45), taken as being the bereaved persons' QALY loss. Health state costs were taken from Landfeldt et al (2017). Direct costs increased from £6,223 per quarterly model cycle for ambulation to £14,283 for FVC<1L. Increasing indirect costs were also included for scenario analyses.

Ataluren was costed based on dosing of 10mg/kg morning and midday, and 20mg/kg in the evening (40mg/kg per day). An average weight of 35kg was assumed, with use of 1,170 sachets per three-monthly model cycle, amounting to £84,774 per cycle at list prices.

The company discounted costs at 3.5%, and health outcomes at 1.5%, rather than the standard 3.5% per annum, however a revised base case was provided by the company using a common 3.5% discount in line with SMC guidance. The results using differential discounting are presented in table 2, scenario 3.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented and are shown in table 1.

Table 1. Base case results at list price

	Ataluren + BSC	BSC	Incremental (Ataluren + BSC versus BSC)
Total LY	**21.90**	**20.53**	**1.37**
Total QALYs	**47.17**	**38.55**	**8.62**
Total costs (List)	**£5,200,244**	**£693,797**	**£4,506,447**
Incremental cost per QALY gained (List)	-	-	**£522,664**

Patients and caregivers in the ataluren arm of the model derive substantial incremental health gains. Patients' life years are modelled to increase by 1.37 (with discounting), and total QALYs by 8.62, the latter incorporating gains relating to caregiver utilities for the two assumed caregivers and the impact of bereavement. Approximately 70% of the modelled total QALYs, and approximately 25% of the modelled incremental QALY gain in the company's revised analysis is attributable to caregiver benefits.

Sensitivity analyses mainly focused on parameters of the lognormal time to event distributions and patient and caregiver utilities. Scenario analyses were performed with results as shown in Table 2 below.

Table 2. Selected scenario analyses at list price

	Scenario	ICER at list price £/QALY
1	Ataluren treatment commenced at age 2	518,319
2	Societal perspective	523,524
3	Discount rate (3.5% costs and 1.5 % benefits)	356,093
4	Common utility values for BSC and ataluren	1,080,378
5	Exclude caregiver utilities and bereavement loss	784,707
6	Inclusion of informal care cost (Landfeldt et al., 2014)	527,069
7	Weibull for time to event analyses	487,407
8	FVC<1L 1 yr shift	664,251
9	FVC<1L 3 yr shift	580,757
10	Death 1 yr shift	505,248
11	Death 3 yr shift	514,013
12	Combined 1 yr shift (i.e. 9 & 11)	660,169
13	Combined 3 yr shift (i.e. 10 & 12)	574,466
14	Utility difference by arm only in ambulatory state	608,244

Key strengths:

- Health states were relevant and while a number included in the HERCULES natural history model which the company references the model as being based on, were not included, the submission provided reasonable explanations for these omissions.
- Health state costs are based on published regression analyses of observational data.

Key uncertainties:

- The submission made use of relevant observational evidence from a propensity score matching analysis rather than using data from the key clinical trials for ataluren. The company justified this approach as being preferable to relying on very short term clinical trial data. However, as noted in the clinical effectiveness section above, the propensity score matching analysis was associated with some weaknesses, and it is also noted that the findings from studies 007 and 020 were not statistically significant.
- Due to the immaturity of the data with respect to later endpoints, a crude assumption is relied upon to 'shift' the relevant survival curves according to data from a separate small sample propensity score comparison of study 019 versus CINRG (n=16 per arm). A delay in time to event of five years with ataluren is assumed based on median time to predicted FVC<50%. This also informs assumptions around mortality following milestone FVC<1L. Uncertainties remain as to the impact of these assumptions on the ICER.
- The model assigns a substantial utility advantage to ataluren at baseline. Multiplicative adjustment of subsequent milestone health states leads to a (diminishing) permanent advantage in utility score for ataluren irrespective of disease stage. The effect of this extends to providing ataluren patients in the model with substantially greater utility in the first non-ambulatory state than for BSC patients who remain ambulatory. This utility premium for ataluren is based on naïve comparison of the sourced ataluren utilities and published historical data for best supportive care. The validity of this utility premium for ataluren is associated with uncertainty; in response to a clarification request the company alluded to a publication reporting similar differences in utility for ataluren and BSC. However, these estimates were based on a very small sample (n=6) of clinical experts' proxy HUI-3 responses and common utilities applied in scenario analyses substantially increase the ICER. The company provided additional sensitivity analysis exploring the use of utility values which did not vary by treatment. The ICERs in scenarios 4 and 14 in table 2 demonstrate the upward impact on the results of adopting a different approaches to patient utilities.
- The model incorporates caregiver utilities. Though consideration of caregiver burden is reasonable the submission models QALYs accrued by (two) caregivers over patients' lifetimes, rather than recognising decrements to carers' quality of life. The latter

approach can be expected to indicate substantially lower QALY gains for these caregivers.

- In addition to the caregiver QALYs, a further QALY gain is assigned in recognition of delayed eventual bereavement. This reflects a fixed assumption around differential life years gained for patients, with a fraction of this gain (based on application of the method in a NICE HST appraisal), taken to represent the bereaved persons' QALY gain. This gain is undiscounted. The inclusion of specific impacts on families related to bereavement is not commonly seen in economic evaluations and there are uncertainties around the appropriate methods for incorporation.
- The company amended its approach to the inclusion of utilities in sensitivity analyses to avoid logically implausible values being applied. There remained some uncertainty over the suitability of the ranges applied (e.g. including health states valued at perfect health).

The cost of ataluren in relation to its health benefits is high and there are outstanding uncertainties relating to the inclusion of utilities for patients and caregivers in the model that suggest a most realistic ICER may be substantially above that presented by the submitting company.

*Other data were also assessed but remain confidential.**

Costs to NHS and Personal Social Services

The submitting company estimated there would be approximately 5 patients eligible for treatment with ataluren in year 1 and 7 patients in year 5 and that all eligible patients would be treated with ataluren.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The North American Duchenne muscular dystrophy care considerations working group published guidance in 2010, most recently updated in 2018. The guidance notes that ataluren and eteplirsen are the first mutation-specific medicines to gain regulatory approval. Ataluren was granted conditional marketing authorisation by the European Commission in 2014 targeting approximately 11% of boys with Duchenne muscular dystrophy caused by a stop codon in the dystrophin gene. Eteplirsen was approved by the FDA in 2016, via an accelerated process, targeting approximately 13% of boys with a mutation in the dystrophin gene that is amenable to exon 51 skipping. Supportive management via a multidisciplinary approach is

recommended to achieve improvements in function, quality of life and life expectancy. Physiotherapy and treatment with glucocorticoids remain the mainstays of Duchenne muscular dystrophy treatment. Direct physical, occupational, and speech and language therapy should be provided. In addition, pain, endocrine, gastro-intestinal and nutrition, respiratory, cardiac, bone health, and orthopaedic management and psychosocial care are required.[15-17]

Additional information: comparators

Corticosteroids (patients could receive ataluren in addition to corticosteroids). Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
ataluren	10mg/kg in the morning, 10mg/kg at midday, and 20mg/kg in the evening.	123,224 to 739,344

Costs from BNF online on 11.01.21. Costs calculated using weight range 12kg to 70kg. Costs do not take any patient access schemes into consideration.

References

1. Electronic Medicines Compendium (EMC). PTC Therapeutics Ltd. Ataluren (Translarna) 125mg granules for oral suspension. Summary of product characteristics. . 2020 11/08/2020 [cited; Available from: https://www.medicines.org.uk/emc/product/2576/smpc.
2. The European Medicines Agency (EMA). Assessment report for initial marketing authorisation application. Ataluren (Translarna). EMEA/H/C/002720. 22 May 2014. Available at: https://www.ema.europa.eu/en.
3. The European Medicines Agency (EMA). Assessment report. Ataluren (Translarna). EMEA/H/C/002720/R/0022. 23 November 2016. Available at: https://www.ema.europa.eu/en.
4. The European Medicines Agency (EMA). CHMP extension of indication variation assessment report. Atauren (Translarna). EMEA/H/C/002720/II/0037. 31 May 2018. Available at: https://www.ema.europa.eu/en.
5. Mercuri E, Muntoni F, Osorio AN, Tulinius M, Buccella F, Morgenroth LP*, et al.* Safety and effectiveness of ataluren: Comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. Journal of Comparative Effectiveness Research. 2020;9(5):341-60.
6. McDonald CM, Henricson EK, Abresch RT, Joyce NC, Duong T, Hu F*, et al.* Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet The Lancet. 2018;391(10119):451-61.
7. Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP*, et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve Muscle & Nerve. 2014;50(4):477-87.
8. PTC Clinical Study Report, PTC124-GD-007-DMD. A phase 2b efficacy and safety study of PTC124 in subjects with nonsense-mutation-mediated Duchenne and Becker muscular dystrophy. 2014.
9. McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N*, et al.* Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2017;390(10101):1489-98.
10. PTC Clinical Study Report, PTC124-GD-020-DMD. A phase 3 efficacy and safety study of ataluren in patients with nonsense mutation dystrophinopathy. 2015.
11. The European Medicines Agency (EMA). Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 - Procedure no: EMEA/H/C/002720/P46/025. 2019
12. Campbell C, Barohn RJ, Bertini E, Chabrol B, Comi GP, Darras BT*, et al.* Meta-analyses of ataluren randomized controlled trials in nonsense mutation Duchenne muscular dystrophy. Journal of Comparative Effectiveness Research. 2020;9(14):973-84.
13. Tian C, Kong R, Jin F, O'Mara E, TrifiLlis P, McIntosh J*, et al.* Ataluren in patients aged >= 2 to <5 years with NMDMD: 28- week results from a phase 2 study. Journal of Neuromuscular Diseases. 2018;5 (Supplement 1):S200-S1.
14. Landfeldt, E., et al., Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics, 2017. 35(2): p. 249-258.
15. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D*, et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. The Lancet Neurology. 2018;17(3):251-67.

16. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018.
17. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, Cripe L, Herron AR, Kennedy A, Kinnett K, Naprawa J, Noritz G, Poysky J, Street N, Trout CJ, Weber DR, Ward LM; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. 2018.

This assessment is based on data submitted by the applicant company up to and including 12 February 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions

in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.