NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2022

Ataluren for Duchenne Muscular Dystrophy with nonsense mutation

Company/Developer	PTC Therapeutics International Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29937	NICE ID: 11774	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Ataluren is in clinical development for the treatment of boys aged 6 months to 2 years with Duchenne muscular dystrophy (DMD) that have a nonsense mutation (nmDMD). DMD is a rare progressive neuromuscular disorder caused by a gene mutation (change). DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. It affects mainly boys (<1% of those with DMD are girls) and symptoms often start before the age of five. The main symptom is muscular weakness, with other common symptoms including enlargement of the calves, a waddling gait, lumbar lordosis, running, jumping and walking difficulties. DMD is a fatal condition with no cure. It causes progressive muscle weakness and often leads to loss of walking ability by the age of twelve, as well as problems with the heart and lungs. Ataluren, the first drug in its class, targets nonsense mutations enabling the production of functional proteins.

Ataluren is given by oral suspension, it acts by bypassing stop signals that produce dysfunctional dystrophin proteins, allowing full-size dystrophin proteins to be made which protects the muscles from damage and weakening. There are currently no recommended treatment options for children aged 6 months to 2 years with nmDMD, so if licensed ataluren would provide the first treatment option for this age group.

Proposed Indication

For the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation (nmDMD) in the dystrophin gene, in ambulatory patients aged 6 months and older.[1]

Technology

Description

Ataluren (Translarna) restores the synthesis of dystrophin by allowing ribosomes to read through premature stop codons that cause incomplete dystrophin synthesis.[2] Patients with DMD lack normal dystrophin, a protein found in muscles. As this protein helps protect muscles from injury as they contract and relax, in patients with DMD the muscles become damaged and eventually stop working. Patients with nmDMD produce shortened dystrophin proteins that do not function properly, ataluren enables protein-making to move past the defect and for cells to produce functional dystrophin.[3]

Ataluren is currently in phase II clinical development for male patients aged ≥6 months to <2 years with nmDMD (NCT04336826). Patients receive ataluren oral suspension 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 24 weeks.[1]

Key Innovation

Ataluren, the first drug in its class, is an orally available small molecule compound that targets nonsense mutations. It appears to allow cellular machinery to read premature stop codons in mRNA, and thus enables the translation process to produce full-length, functional proteins.[4] Additionally, evidence suggests that ataluren slows the disease progression of DMD and that its safety profile is not of major concern.[3]

Regulatory & Development Status

In the EU, ataluren is licensed to treat patients aged 2 years and older with nmDMD who are able to walk.[3]

In the UK ataluren is licensed to treat patients with nmDMD aged 2 years and older who can walk.[5]

Ataluren has the following regulatory designations/awards:

- An orphan drug in EU in 2005 for the treatment of DMD.[3]
- An orphan drug in US in 2005 for the treatment of Muscular Dystrophy resulting from premature stop mutations in the dystrophin gene.[6]

Patient Group

Disease Area and Clinical Need

The muscular dystrophies are a group of inherited genetic conditions caused by changes (mutations) in the genes responsible for the structure and functioning of a person's muscles. The mutations cause changes in the muscle fibres that interfere with the muscles' ability to function. There are many different types of muscular dystrophies, one of the most common and severe forms is DMD.[7] DMD is a muscle-wasting condition caused by the lack of a protein called dystrophin.[8] The Duchenne gene is found in the X-chromosome, thus primarily affecting males (<1% of those with DMD are female).[9] Symptoms start in early childhood, generally between ages 2 and 3, first causing muscular weakness in the proximal muscles of the hips, pelvic area, thighs and shoulders, and later the distal limb muscles in the arms, legs and trunk. Other symptoms include enlargement of the calves, a waddling gait, lumbar lordosis, running, jumping and

walking difficulties.[10] Furthermore, progressive muscular damage and degeneration occurs in people with DMD, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy.[11] With medical care, most people with DMD die from heart or respiratory failure in their 20s or 30s.[9,12] DMD is also associated with a substantial cost burden to society and to affected families, and significantly impairs quality of life in both patients and caregivers.[13]

DMD is the most common fatal genetic disease diagnosed in childhood.[14] The prevalence is estimated to be 19.5 cases per 100,000 live male births in the UK and it is estimated that there are currently around 2,500 people living in the UK with DMD at any one time.[8,11] The average lifespan of a patient with DMD is 29 years.[15] In England, 2020-21, there were 1,374 finished consultant episodes (FCE) for muscular dystrophy (ICD-10 G71.0, which includes DMD), resulting in 936 day cases and 1,678 FCE bed days.[16]

Recommended Treatment Options

NICE does not currently recommend any treatment options for patients aged ≥6 months to <2 years with nonsense mutation DMD. Currently ataluren is only recommended for DMD with nonsense mutation in the dystrophin gene for people aged 2 years and older who can walk.[17,18]

Clinical Trial Information

Trial	NCT04336826; 2020-000980-21; An Open-Label Study Evaluating the Safety and Pharmacokinetics of Ataluren in Children From ≥6 Months to <2 Years of Age With Nonsense Mutation Duchenne Muscular Dystrophy **Phase II –** Recruiting **Location(s):** United States **Primary completion date:** March 2023
Trial Design	Open label, single group assignment.
Population	N=6[a]; males aged 6 months to 2 years old; diagnosis of DMD with nonsense mutation of the dystrophin gene
Intervention(s)	Ataluren oral suspension 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening each day for 24 weeks.
Comparator(s)	No comparator.
Outcome(s)	Number of Participants With Treatment-Emergent Adverse Events [Time Frame: Baseline up to Week 24]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ataluren hospital only, per 30 oral suspension sachets, list price as follows:[19]

[a] Information provided by PTC Therapeutics International Ltd

- Ataluren 125mg £2,532.00
- Ataluren 250mg £5,064.00
- Ataluren 1g £20,256.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Fordadistrogene movaparvovec for the treatment of Duchenne muscular dystrophy (TS ID 10420). Expected publication date: TBC
- NICE highly specialised technology guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) (ID1642). Expected publication date: January 2023.
- NICE highly specialised technology guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3). July 2016.

NHS England (Policy/Commissioning) Guidance

- NHS Standard Contract (2013/2014). For Diagnostic Service for Rare Neuromuscular Disorders (all ages). D04/S(HSS)/a

Other Guidance

- Scottish Medicines Consortium (SMC). Ultra-orphan initial assessment: Ataluren (Translarna). April 2021.[20]
- NHS Scotland. Paediatric guidance for management of Duchenne muscular dystrophy in Scotland. December 2015.[21]

Additional Information

PTC Therapeutics Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. *A Study to Evaluate the Safety and Pharmacokinetics of Ataluren in Participants From ≥6 Months to <2 Years of Age With Nonsense Mutation Duchenne Muscular Dystrophy (nmDMD)*. *Trial ID: NCT04336826*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04336826 [Accessed 09 Jun 2022].

2 British National Formulary (BNF). *Ataluren.* Available from: https://bnf.nice.org.uk/drugs/ataluren/ [Accessed 13 Jun 2022].

3 European Medicines Agency (EMA). *Ataluren (Translarna).* 2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/translarna [Accessed 13 Jun 2022].

4 Ryan NJ. Ataluren: First Global Approval. *Drugs*. 2014 2014/09/01;74(14):1709-14. Available from: https://doi.org/10.1007/s40265-014-0287-4.
5 European Medicines Compendium (emc). *Translarna 125 mg granules for oral suspension.* 2021. Available from: https://www.medicines.org.uk/emc/product/2576/smpc [Accessed 11 Jul 2022].
6 US FDA. *Ataluren - Treatment of Muscular Dystrophy resulting from premature stop mutations in the dystrohin gene.* Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=197204 [Accessed 13 Jun 2022].
7 NHS. *Muscular dystrophy.* 2021. Available from: https://www.nhs.uk/conditions/muscular-dystrophy/ [Accessed 13 Jun 2022].
8 Muscular Dystrophy UK. *Duchenne muscular dystrophy (DMD).* Available from: https://www.musculardystrophyuk.org/conditions/duchenne-muscular-dystrophy-dmd [Accessed 13 Jun 2022].
9 Action Duchenne. *How is Duchenne inherited?* Available from: https://www.actionduchenne.org/what-is-duchenne/duchenne-explained/what-is-duchenne/ [Accessed 13 Jun 2022].
10 Muscular Dystrophy Association. *Duchenne Muscular Dystrophy (DMD).* Available from: https://www.mda.org/disease/duchenne-muscular-dystrophy [Accessed 13 Jun 2022].
11 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. *Lancet Neurol*. 2018 Mar;17(3):251-67. Available from: https://doi.org/10.1016/s1474-4422(18)30024-3.
12 NHS. *Muscular dystrophy - Types.* Available from: https://www.nhs.uk/conditions/muscular-dystrophy/types/ [Accessed 13 Jun 2022].
13 Landfeldt E, Alfredsson L, Straub V, Lochmüller H, Bushby K, Lindgren P. Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. *PharmacoEconomics*. 2017 2017/02/01;35(2):249-58. Available from: https://doi.org/10.1007/s40273-016-0461-5.
14 Duchenne UK. *Duchenne muscular dystrophy in detail.* Available from: https://www.duchenneuk.org/duchenne-in-detail/ [Accessed 13 Jun 2022].
15 National Institute for Health and Care Excellence (NICE). *Proposed health technology appraisal: Idebenone for treating duchenne muscular dystrophy. Draft scope (pre-referral).* 2017. Available from: https://www.nice.org.uk/guidance/gid-ta10310/documents/draft-scope-pre-referral#:%7E:text=The%20average%20lifespan%20is%2029,UK%20at%20any%20one%20time [Accessed 13 Jun 2022].
16 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 13 Jun 2022].
17 National Institute for Health and Care Excellence (NICE). *Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/hst3 [Accessed 11 Jun 2022].
18 National Institute for Health and Care Excellence (NICE). *Addendum to Managed Access Agreement: Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD) in patients aged between 2 years and 5 years.* 2019. Available from: https://www.nice.org.uk/guidance/hst3/resources/addendum-to-managed-access-agreement-pdf-6779076589 [Accessed 11 Jul 2022].
19 British National Formulary (BNF). *Ataluren - Medicinal forms.* Available from: https://bnf.nice.org.uk/drugs/ataluren/medicinal-forms/ [Accessed 21 Jun 2022].

20 Scottish Medicines Consortium (SMC). *Ultra-orphan initial assessment: Ataluren (Translarna)* (*SMC2327)*. Last Update Date: Apr 2021. Available from: https://www.scottishmedicines.org.uk/medicines-advice/ataluren-translarna-uo-pathway-smc2327/ [Accessed 11 Jul 2022].

21 NHS Scotland. *Paediatric Guidance for Management of Duchenne Muscular Dystrophy in Scotland.* 2015. Available from: https://www.smn.scot.nhs.uk/wp-content/uploads/2017/12/Paediatric-guidance-for-DMD.pdf [Accessed 13 Jun 2022].

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