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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Edasalonexent for Duchene muscular dystrophy

NIHRIO ID	11385	**NICE ID**	10246
Developer/Company	Catabasis Pharmaceuticals Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Edasalonexent is currently in clinical development for the treatment of male paediatric patients with Duchenne muscular dystrophy (DMD). DMD is a rare genetic condition caused by a mistake or abnormality in a gene called dystrophin, located on the X chromosome (one of the two sex chromosomes). Chromosomes are tiny structures inside cells made from deoxyribonucleic acid (DNA) and proteins. Males have one X chromosome, while females have two X chromosomes. As males have one X chromosome, DMD is much more common in males. DMD is 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. Current treatment options only target a particular mistake or abnormality and focus on slowing progression of the disease.

Edasalonexent is administered orally. It works by reducing the NF-κB activity, a protein that causes inflammation leading to muscle damage and prevention of muscle regeneration seen in patients with DMD. Edasalonexent is expected to reduce the muscle damage seen in DMD and enable muscle regeneration. If licensed, edasalonexent will provide a treatment option for male paediatric patients with DMD.

PROPOSED INDICATION

Treatment of male paediatric patients with a genetically confirmed duchenne muscular dystrophy (DMD).[1-3]

TECHNOLOGY

DESCRIPTION

Edasalonexent (CAT-1004) is a novel oral investigational drug designed to inhibit NF-kB, a protein which causes inflammation leading to muscle damage and prevention of muscle regeneration in patients with DMD, regardless of their underlying mutation.[4-6] In DMD the loss of dystrophin leads to chronic activation of NF-kB, which is a key driver of skeletal and cardiac muscle disease progression.[6] By inhibiting NF-kB, edasalonexent has the potential to decrease inflammation and fibrosis, promote muscle regeneration, and slow disease progression. Edasalonexent was designed as a stand-alone therapy and may also enhance the efficacy of dystrophin upregulation therapies.[7]

Edasalonexent is currently in clinical development for the treatment of paediatric patients with DMD. In the phase I/II (NCT02439216) and III clinical trials (NCT03703882, NCT03917719) patients will receive edasalonexent via oral administration. The dosing and administration schedules vary between trials / study arms and are detailed in the clinical trial tables of this briefing. [1-3]

INNOVATION AND/OR ADVANTAGES

Edasalonexent has a novel mechanism of action designed to inhibit NF-kB protein in patients with DMD. Current treatments only target a particular mutation, whereas edasalonexent is designed to target DMD with any mutation.[4,6] Results from a phase II study suggested that edasalonexent preserved muscle function, substantially slowed disease progression compared to rates of change in the off-treatment control period, significantly improved biomarkers of muscle health and inflammation and was safe and well-tolerated. In more than 55 cumulative patient years of exposure, the majority of adverse events were mild in nature, and the most common treatment-related adverse event was diarrhoea, which was generally mild and transient. There were no serious adverse events observed on treatment, and no adverse trends in chemistry, hematology, or measures of adrenal function.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Edasalonexent does not currently have Marketing Authorisation in the EU/UK for any indication.

In October 2015, edasalonexent received orphan designation (EU/3/15/1560) by the European Commission for the treatment of DMD.[5]

PATIENT GROUP

DISEASE BACKGROUND

Duchenne muscular dystrophy (DMD) is a rare genetic condition that affects the muscles, leading to muscle wasting that gets worse over time. DMD occurs primarily in males, though in

rare cases may affects females.[8] DMD progresses rapidly and is caused by the presence of different types of gene abnormalities on the X-chromosome in the gene for dystrophin, a protein that is important for normal muscle structure and function. The main gene abnormalities include, deletions (where part of the gene is deleted), insertions (an additional piece of DNA is inserted into the gene), duplications (when part of gene is repeated), or point mutations (when coding of genetic material is altered). These changes cause muscle fragility that progressively leads to weakness and loss of walking ability during childhood and adolescence.[9]

The risk factors for DMD include a family history of the condition, but the condition may pass down without a known family history. This means that a family member can carry a copy of the defective gene, but it does not cause DMD in that person. Sometimes, the gene can pass down for generations before affecting a child. Males are more likely to have DMD than females.[10] Males only have one X chromosome, and thus one single copy of the dystrophin gene, hence they have a much higher probability of developing DMD than females. A very small number of females develop DMD. [9]

Initial symptoms usually becomes apparent early during childhood between the ages 1 and 3 years.[9,11] Affected children may appear weaker than other children, and have difficulty walking, standing, or climbing stairs, and may have behavioural or learning difficulties. After the age of 12 most children will need to use a wheelchair.[9] Breathing problems occur due to weakness of the diaphragm and the other muscles around the lungs. Scoliosis and tight joints (contractures) may develop as muscle loss progresses.[8] The average lifespan is less than 30 years.[9] The most common symptoms may include delayed motor development, enlarged calf muscles, muscle weakness that gets worse over time, toe walking or waddling gait, using hands to get up off the floor, breathing problems, and progressive enlargement of the heart.[8]

CLINICAL NEED AND BURDEN OF DISEASE

DMD affects approximately 1 in every 3,500 newborn males and is rarely found in girls. In the UK there are around 2,500 males and young men living with the condition.[12]

In England in 2018-2019, there were 1,999 finished consultant episodes (FCEs) for muscular dystrophy (ICD-10 code G71.0) and 1,877 admissions resulting in 3,553 bed days and 1,245 day cases.[13] These data are unavailable specifically for DMD.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A multi-disciplinary approach, with the input of specialists such as physiotherapists and occupational therapists, is the best way to manage DMD and to ensure patients receive complete care. This means that in a single visit to a specialist neuromuscular centre, patients can get input from respiratory, cardiac and physiotherapy professionals who are able to provide better support when working within a multi-disciplinary team.[14] To prevent problems, regular check-ups are important with a specialist doctor and specialist physiotherapist in order to make decisions about treatment and any intervention (such as stretching exercise).[14]

Treatments are aimed at the specific symptoms present in each individual. Treatment options should include physical therapy and active and passive exercise to build muscle strength and prevent contractures. Surgery may be recommended in some patients to treat contractures or scoliosis. Braces may be used to prevent the development of contractures. The use of mechanical aids (e.g., canes, braces, and wheelchairs) may become necessary to aid walking.[11]

To slow the decline in muscle strength and mobility over a certain period of time and prevent or postpone the development of complications glucocorticoids, more precisely prednisone and deflazacort are commonly used.[14,15] Pharmacological treatments are used to slow down the progression of symptoms in boys with DMD. However, current pharmacological treatments work only for a small group of boys who carry a particular mutation in the dystrophin gene.[14]

CURRENT TREATMENT OPTIONS

Pharmacological treatment recommended by NICE for treating DMD is ataluren according to the following criteria:[16]

Ataluren for treating DMD resulting from 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
- the conditions under which ataluren is made available are set out in the managed access agreement between the company and NHS England

PLACE OF TECHNOLOGY

If licensed, edasalonexent will provide a treatment option for male paediatric patients with duchenne muscular dystrophy.[1-3]

CLINICAL TRIAL INFORMATION

Trial	**PolarisDMD,** NCT03703882; A Randomized, Double-Blind, Placebo-Controlled, Global Phase 3 Study of Edasalonexent in Pediatric Patients With Duchenne Muscular Dystrophy **Trial phase III** – Active, not recruiting **Location(s):** EU (including UK), USA, Canada and other countries **Primary completion date:** September 2020	**GalaxyDMD,** NCT03917719; An Open-Label Extension Study of Edasalonexent in Pediatric Patients With Duchenne Muscular Dystrophy **Trial phase** III- Enrolling by invitation **Location(s):** EU (including UK), USA, Canada and Australia **Primary completion date:** September 2022
Trial design	Randomised, parallel assignment, triple blinded	Single group assignment, open label
Population	N= 131; males; aged 4-7 years; diagnosis of DMD, able to perform stand from supine with assistance in ≤ 10 seconds, able to perform the 10MWT and 4-stair climb	N=140; males; aged 4-12 years; patients who completed CAT-1004-201 or CAT-1004-301;
Intervention(s)	Edasalonexent 100 mg/kg/day. Capsules taken by mouth three times per day	Edasalonexent 100mg/kg/day. Capsules taken by mouth three times per day
Comparator(s)	Matching placebo	No comparator

Outcome(s)	Change from baseline in North Star Ambulatory Assessment (NSAA) (Time frame: 52 weeks) See trial record for full list of outcomes.	Safety and tolerability of long-term treatment with edasalonexent measured by number of treatment-emergent adverse events and serious adverse events (Time frame: 104 weeks) See trial record for full list of outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Trial	**MoveDMD,** NCT02439216; A Phase 1/2 Study of Edasalonexent (CAT-1004) in Pediatric Patients With Duchenne Muscular Dystrophy **Trial phase I/II** – Completed **Location(s):** USA **Study Completion Date:** August 2019
Trial design	Randomised, crossover assignment, triple blinded
Population	N=31; males; aged 4-7 years; diagnosis of DMD, ability to walk independently, immunization for influenza and varicella
Intervention(s)	Dose 1- edasalonexent 67 mg/kg/day. Capsules taken by mouth two times per day Dose 2- edasalonexent 100 mg/kg/day. Capsules taken by mouth three times per day
Comparator(s)	Matching placebo
Outcome(s)	• Safety and tolerability (adverse events) (Time Frame: 12 weeks) • Muscle composition and inflammation as measured by MRI (Time frame: 12 weeks) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of edasalonexent is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development (GID-TA10310). Idebenone for treating Duchenne muscular dystrophy. Expected publication date: May 2021.
- NICE highly specialised technologies guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- Duchenne Muscular Dystrophy Care Consideration Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management.2018.[17]
- Duchenne Muscular Dystrophy Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. 2018.[18]
- Duchenne Muscular Dystrophy 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. 2018.[19]

ADDITIONAL INFORMATION

Catabasis Pharmaceuticals Inc, 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.

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