Health Technology Briefing
February 2022

Fordadistrogene movaparvovec for Duchenne muscular dystrophy

Company/Developer	Pfizer Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 24048	NICE ID: 10420	UKPS ID: 651937

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Fordadistrogene movaparvovec is a medicinal product in clinical development for the treatment of ambulatory boys greater than or equal to 4 years of age to 7 years with a confirmed genetic diagnosis of Duchenne muscular dystrophy (DMD). DMD is a severe and rare progressive neuromuscular disorder caused by a gene mutation (change). DMD is caused by an absence of functional dystrophin, a protein that helps keep muscle cells intact. It affects mainly boys and symptoms often start before the age of five. 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. 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. There is no cure for DMD, and treatment is mainly supportive, with mortality primarily due to cardiac and/or respiratory complications in their 20s or 30s.

Fordadistrogene movaparvovec is a gene therapy, which delivers a functional version of the dystrophin gene via a single intravenous injection. Fordadistrogene movaparvovec is based on a viral carrier to deliver a shorter version of the DMD gene, called mini-dystrophin. This shorter gene contains enough information to produce a protein that restores the function of dystrophin, this subsequently promotes muscle development in target muscle tissue. If licenced fordadistrogene movaparvovec would provide a novel (new) treatment option for boys with DMD.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

For the treatment of Duchenne muscular dystrophy (DMD).[1]

Technology

Description

Fordadistrogene movaparvovec (PF-06939926) is an investigational recombinant adeno-associated virus serotype 9 (rAAV9) capsid carrying a shortened version of the human dystrophin gene (mini-dystrophin) under the control of a human muscle-specific promotor. The rAAV9 capsid was chosen as the delivery mechanism because of its potential to target muscle tissue.[2,3]

Fordadistrogene movaparvovec is currently in a phase III clinical trial (NCT04281485). Fordadistrogene movaparvovec is given to male patients aged 4-7 years old as a single IV infusion.[4] The proposed dose for fordadistrogene movaparvovec is a single intravenous (IV) infusion of 2E14 vg/kg.[a] In the phase Ib clinical trial (NCT03362502) for the treatment of males aged 4 years and older,[1] fordadistrogene movaparvovec is given as a single IV infusion at either a "low" dose of 1E14 vector genomes per kilogram (vg/kg) or a "high" dose of 3E14 vg/kg.[5]

Key Innovation

Fordadistrogene movaparvovec is a gene therapy which aims to restore function to dystrophin. It does this by encoding for mini-dystrophin gene, an altered version of dystrophin gene which has been shortened to allow incorporation into an adenovirus capsid. Mini-dystrophin was suggested as a potential approach for DMD treatment through preclinical testing. If fordadistrogene movaparvovec is approved, its mini-dystrophin-based mechanism of action would represent a novel method of treatment for patients with DMD.[6] Additionally, current treatments either focus on disease management or are only available for specific mutations. If approved fordadistrogene movaparvovec could provide a new treatment option for a wider range of mutations.[7]

Regulatory & Development Status

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

Fordadistrogene movaparvovec was granted orphan drug status by EMA in 2016 for treatment of DMD.[7] It has also received US FDA fast track designation 2020 for the treatment of DMD.[8]

Fordadistrogene movaparvovec is not currently in phase II or III development for any other indications.[9]

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.[10] DMD is a muscle-wasting

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condition caused by the lack of a protein called dystrophin.[11] The Duchenne gene is found in the X-chromosome, thus primarily affecting males (<1% of those with DMD are female).[12] 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.[13] 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.[14] With medical care, most people with DMD die from heart or respiratory failure in their 20s or 30s.[12,15] Unfortunately, diagnosis may involve several referrals before confirmation.[16] DMD is also associated with a substantial direct and indirect cost burden to society and to affected families and significantly impairs quality of life in both patients and caregivers.[17]

DMD is the most common fatal genetic disease diagnosed in childhood.[18] 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.[16,19] Out of the estimated people living with DMD in the UK, there are a smaller percentage that are ambulatory, the population likely to be eligible to receive fordadistrogene movaparvovec could not be estimated from available published sources. The average lifespan of a patient with DMD is 29 years.[20] 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.[15] In addition to direct medical costs, there is also a significant indirect cost burden associated with DMD and the economic cost of DMD climb dramatically with disease progression.[21]

Recommended Treatment Options

Currently there is no cure for DMD but treatments and therapies aim to ease the symptoms and amongst the ambulant patient population (those who are able to walk), increasing the time a patient is able to walk is one of the major aims of treatment.[20,22] Steroids are often prescribed to slow progression of muscle weakness, reduce the development of scoliosis and delay the onset of breathing and heart problems, with commonly prescribed steroid including prednisolone and deflazacort.[22] Physiotherapy and orthotics (splints) are also used to help delay contractures and maintain mobility.[13]

NICE currently recommends ataluren for treating DMD resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk.[23]

Clinical Trial Information

Trial	NCT04281485; 2019-002921-31; A Phase 3, multicenter, randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of PF 06939926 for the treatment of Duchenne muscular dystrophy **Phase III –** Active, not recruiting **Location(s):** 4 EU countries, UK, Canada and other countries **Primary completion date:** September 2023
Trial Design	Randomised, quadruple masked, parallel assignment.
Population	N=99 (estimated); ambulant boys aged 4 to 7 years old; male; confirmed diagnosis of DMD by prior genetic testing.

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Intervention(s)	Fordadistrogene movaparvovec will be administered as a single intravenous (IV) infusion of 2E14 vg/kg.[b]
Comparator(s)	Matched placebo.
Outcome(s)	Change from Baseline in North Star Ambulatory Assessment (NSAA) [Time Frame: Week 52] The NSAA is a 17-item test that measures gross motor function in children with Duchenne. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	Study currently active – Three serious adverse events of muscle weakness, two of which involved myocarditis (inflammation of the heart tissue) have been reported.[24]

Trial	NCT03362502; A phase 1B multicenter, open-label, single ascending dose study to evaluate the safety and tolerability of PF-06939926 in ambulatory and non-ambulatory subjects with Duchenne muscular dystrophy **Phase IB –** Active, not recruiting **Location(s):** United States **Primary completion date:** March 2022
Trial Design	Open label, non-randomised sequential assignment.
Population	N=23 (actual); aged 4 years and older; male; diagnosis of DMD confirmed by medical history and genetic testing.
Intervention(s)	• Low dose: Single IV infusion of fordadistrogene movaparvovec at 1E14 vector genomes per kilogram (vg/kg).[5] • High dose: Single IV of fordadistrogene movaparvovec at 3E14 vg/kg.[5]
Comparator(s)	No comparator.
Outcome(s)	Incidence of dose-limiting safety or intolerability, as measured by treatment-related adverse events [Time Frame: through 1 year post-treatment] See trial record for full list of other outcomes.
Results (efficacy)	The median change from baseline to one year in ambulatory function as measured by NSAA total score was a 1-point improvement for participants who received gene therapy vs. a 4-point decline in the external control. At one year, the majority (74%; N=14/19) of study participants that received gene therapy maintained or increased an NSAA total score vs. 30% of participants in the external control (P < 0.002). At one-year post-treatment, there was a mean 5.6-point improvement in NSAA from baseline among participants that received gene therapy compared to the external control. The study also showed dystrophin/mini-dystrophin expression increasing on average from 2 to 12 months after gene therapy. Mean of 22% normal (2 months) and 40% normal (12

[b] Information provided by Pfizer Inc.

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	months) dystrophin levels via liquid chromatography mass spectrometry. Mean of 39% positive fibres (2 months) and 62% positive fibres (12 months) via immunofluorescence.[25]
Results (safety)	Three treatment-related serious adverse events (SAE) occurred (dehydration, acute kidney injury, thrombocytopenia); all resolved within 15 days.[25] On 20th December 2021, Pfizer announced that a patient participating in the non-ambulatory cohort of the phase Ib gene therapy trial passed away. This SAE is still under investigation by the external data review committee and there is not yet a final outcome.[26]

Estimated Cost

The cost of fordadistrogene movaparvovec is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Idebenone for treating Duchenne muscular dystrophy (ID1092). Expected publication date: TBC.
- NICE highly specialised technologies guidance in development. Eteplirsen for treating Duchenne muscular dystrophy (ID1003). Expected publication date: TBC.
- NICE highly specialised technologies guidance in development. Drisapersen for the first-line treatment of Duchenne's muscular dystrophy (ID911). Expected publication date: TBC.
- NICE highly specialised technologies guidance in development. 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 technologies 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

- NHS Scotland. Paediatric guidance for management of Duchenne muscular dystrophy in Scotland. December 2015.[27]

Additional Information

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