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# Domagrozumab (PF-6252616) for Duchenne muscular dystrophy in children and adolescents

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## LAY SUMMARY

Duchenne muscular dystrophy (DMD) is a rare progressive neuromuscular disorder caused by a gene mutation. It affects mainly boys and symptoms often start before the age of five. 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. Current treatments focus on symptom management.

Domagrozumab is a novel antibody, which is being developed as a treatment for the condition and is currently being tested in phase II clinical trials. It works by impacting myostatin, a naturally occurring protein in muscles that helps control muscle growth. Blocking the activity of myostatin is thought to be a promising treatment option for muscle wasting diseases such as DMD. Domagrozumab is delivered as a monthly intravenous injection, and if licenced, could offer a new mode of treatment for children with DMD.



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## TARGET GROUP

- Duchenne muscular dystrophy (DMD); children and adolescents

## TECHNOLOGY

### DESCRIPTION

Domagrozumab (PF-06252616) is an anti-myostatin monoclonal antibody.[1] Myostatin is a naturally occurring protein in muscles that helps control muscle growth; blocking its activity could have potential therapeutic applications in treating muscle wasting diseases such as DMD by stimulating increases in muscle mass and strength.[1] Domagrozumab is currently being tested to see if blocking myostatin will help to increase muscle strength and function in patients with DMD.

Domagrozumab is delivered as an intravenous injection, with three different dose regimens being tested in currently ongoing phase II trials.[2] The drug is not licenced or in development for any other indication.

Several other treatments are currently in trials with DMD patients. These include eteplirsen (by Sarepta) and drisapersen (by BioMarin), but these potential treatments would only be applicable to a subset (about 15%) of patients with DMD, while domagrozumab could potentially treat a higher number of DMD patients.[3]

### INNOVATION and/or ADVANTAGES

If licensed, domagrozumab could offer a novel treatment option for patients with DMD who currently have no effective, licenced therapies available to them.

### DEVELOPER

Pfizer Inc

### AVAILABILITY, LAUNCH or MARKETING

Domagrozumab is a designated orphan drug in the EU and USA for DMD.[4]

It was also granted Fast Track Designation in November 2012 by the FDA.[1]

The drug is currently in phase II clinical trials.

## PATIENT GROUP

### BACKGROUND

DMD is caused by mutations in the gene that encodes for dystrophin, the absence of which leads to easily damaged muscle cells.[5] This damage causes progressive muscle weakness and loss of strength, resulting in loss of independent ambulation as well as cardiac and respiratory issues.[5] [6] The Duchenne gene is found in the X-chromosome, thus primarily affecting boys (only ≤1% of those with DMD are female).[5]

The condition is fatal and there is no cure – without any intervention, the mean age of death with DMD is around 19 years.[7] Breathing complications and cardiomyopathy are common causes of death.[8] However, life expectancy for men with DMD has improved with some now surviving until their 30s and 40s.[5] 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.[6]

DMD can be inherited in families in an X-linked recessive fashion, but the disease also often occurs in children from families without a known history of the condition.[8] Symptoms start in early childhood, generally between ages 3 and 5, first affecting the muscles of the hips, pelvic area, thighs and shoulders, and later the skeletal muscles in the arms, legs and trunk.[1]

## CLINICAL NEED and BURDEN OF DISEASE

Duchenne muscular dystrophy is the most common fatal genetic disorder diagnosed in childhood.[5] It has been estimated as affecting approximately 1 in every 3,500 to 6,300 live male births, and around 2,500 people in the UK have DMD.[5 6]

In 2015/16, there were 1,563 hospital admissions for muscular dystrophy (ICD-10 G71.0; includes DMD along with other muscular dystrophies) in England, resulting in 1,676 finished consultant episodes and 2,786 bed days.[9]

## PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- 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]. **Suspended** June 2016.
- NICE highly specialised technologies guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene [HST3]. July 2016

### NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/A/a.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All Ages). D04/S(HSS)/a.
- NHS England. 2013/14 NHS Standard Contract for Respiratory: Complex Home Ventilation (Adult). A14/S/a.

### OTHER GUIDANCE


- Bushby, K., Finkel, R., Birnkrant, D.J., Case, L.E., Clemens, P.R., Cripe, L., Kaul, A., Kinnett, K., McDonald, C., Pandya, S. and Poysky, J., 2010. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. The Lancet Neurology, 9(1), pp.77-93.
- British Thoracic Society. (2012) Guidelines for respiratory management of children with neuromuscular weakness.

## CURRENT TREATMENT OPTIONS

No curative treatments for DMD exist and current treatments thus focus on symptom management. Corticosteroid treatment slows the progression of muscle weakness, and is associated with a delay in the loss of ambulation by 2-3 years, but comes with significant adverse effects.[10] [11] Other interventions currently used include cardiac and respiratory monitoring and support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation.[10]

Ataluren (Translarna) has a conditional Marketing Authorisation in the UK for treating a subtype of DMD resulting from a nonsense mutation in the dystrophin gene, based on an analysis by EMA.[10] [12] It has been made available in the UK through a Managed Access Agreement between the company and NHS England.[13]

Eteplirsen (Exondys 51) is another treatment for DMD, but is only aimed for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, affecting about 13 percent of the population with DMD.[11]

## EFFICACY and SAFETY

| **Trial** | DMD Myostatin trial; NCT02310763; B5161002; PF-06252616 vs placebo; phase II | DMD Myostatin trial extension trial; NCT02907619; phase II; long term safety, efficacy, pharmacodynamics and pharmacokinetics of IV dosing of PF 06252616; extension |
|---|---|---|
| **Sponsor** | Pfizer | Pfizer |
| **Status** | ongoing | ongoing |
| **Source of Information** | Trial registry,[2] trial website[14] | Trial registry[15] |
| **Location** | EU (incl UK), USA, Canada, Japan, Australia | US, Japan |
| **Design** | Randomised, placebo-controlled, crossover trial | Open-label extension trial |
| **Participants** | N=108 already enrolled (enrolment will close by May 2017); male; aged 6 to 15 years, ambulatory; diagnosed with DMD. | Subjects with Duchenne muscular dystrophy who enrolled and completed study B5161002. |
| **Schedule** | Two-hour monthly IV infusion. Three dose levels (5mg/kg, 20mg/kg and 40 mg/kg) investigated in a within-subject dose escalating fashion (dose may increase every 4 months).<br><br>Randomisation to 1 of 3 sequence groups for 2 periods of 48 weeks each.<br><br>In period 1, two of the sequence groups will receive PF-06252616 and one group will receive placebo. In | Monthly individualized maximum tolerated dose based on tolerability profile/data from B5161002. |

| | | |
|---|---|---|
| | period 2, the placebo group will switch to PF-06252616 and the two remaining sequence groups will either receive placebo or PF-06252616. | |
| **Follow-up** | 97 weeks | |
| **Primary Outcomes** | Mean change from baseline on the 4 Stair Climb (4SC) as compared to placebo in seconds, from baseline to 49 weeks; adverse events. | Adverse events; abnormal laboratory findings; abnormal and clinically relevant changes in liver MRI and physical examinations. |
| **Secondary Outcomes** | Forced Vital Capacity; NSAA score; ankle range of motion; PUL score; 6MWD; handheld myometry; thigh muscle volume (MRI) | Functional capacity assessments; pulmonary function tests; muscle strength measured by myometry |
| **Key Results** | - | - |
| **Adverse effects (AEs)** | - | - |
| **Expected reporting date** | Primary completion date reported as April 2018. | Primary completion date reported as March 2021. |

# ESTIMATED COST and IMPACT

## COST

The cost of domagrozumab is not yet known.

According to a 2017 modelling study (to inform DMD HTAs), the lifetime direct medical costs associated with DMD range between £217,510 and £284,640, with total costs of between £624,240 and £713,840.[6]

There are no direct comparators for this treatment, but costs for ataluren which is applicable to a subset of DMD patients are detailed in the table below:

| Drug | Dose | Annual cost[10] |
|---|---|---|
| Ataluren | 40 mg/kg body weight per day | Assuming a median weight range of 24-26kg, the total cost per person per year is £220,256. A confidential discount has been agreed with the company. |

## IMPACT – SPECULATIVE

## IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival ☒ Reduced symptoms or disability

☐ Other ☐ No impact identified

## IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services ☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

## IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: *new treatment option for this population cohort*

☐ Other reduction in costs

☐ Other

☐ None identified

## OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

## REFERENCES


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[15] ClinicalTrials.gov. *An Open-label Extension Study To Evaluate Safety Of PF-06252616 In Boys With Duchenne Muscular Dystrophy.* Available from: https://clinicaltrials.gov/show/NCT02907619 [Accessed 11 April 2017]