Tadalafil (Cialis) for Duchenne muscular dystrophy

LAY SUMMARY

Duchenne muscular dystrophy (DMD) is a life-limiting condition that mainly affects boys. There are around 2,500 people in the UK living with the condition. It is an inherited disease caused by a fault (or mutation) on a gene called the dystrophin gene, which is very important for healthy muscles. Parents of children with Duchenne muscular dystrophy often begin to notice the signs of muscle weakness (such as difficulties in getting up off the floor) when their children are aged 2-3 years old. In boys with Duchenne muscular dystrophy, muscle weakness slowly gets worse and most patients will need to use a wheelchair by the time they are 10-12 years old.

There is no cure for Duchenne muscular dystrophy and most drug treatments that are available for patients now, aim to stop the muscles getting weaker and allow patients to walk for as long as possible, but they are not fully effective and can have unpleasant side effects. Tadalafil is a new drug for the treatment of Duchenne muscular dystrophy that is given once a day as a tablet. Some studies have suggested tadalafil may be helpful for boys with Duchenne muscular dystrophy who are still able to walk and more studies are now aiming to show how well it works and that it is safe to use.

If tadalafil is licenced for use in the UK, it could be a new treatment option for boys with Duchenne muscular dystrophy who are still able to walk. Tadalafil may slow the rate of muscle decline and allow patients to walk for longer.
TARGET GROUP

- Duchenne muscular dystrophy (DMD): ambulatory male adolescents and children; to slow the decline in walking ability – first line; in combination with corticosteroids.

TECHNOLOGY

DESCRIPTION

Tadalafil (Cialis, LY450190) is a phosphodiesterase 5 (PDE5) inhibitor. The regulation of PDE5 has been suggested as a potential therapeutic target in the treatment of DMD as this enzyme is essential to maintain the balance between synthesis and degradation of cyclic guanosine monophosphate (cGMP), a critical player downstream to the nitric oxide (NO) pathway. In a phase III clinical trial, tadalafil was administered orally at 0.3mg/kg or 0.6mg/kg once daily.

Tadalafil is currently licensed (as Adcirca) for the treatment of pulmonary arterial hypertension (PAH) in adults classified as WHO functional class II and III, to improve exercise capacity. Tadalafil is also currently licenced (as Cialis) for the treatment of erectile dysfunction and benign prostatic hyperplasia in adult males. Very common (>10%) adverse effects of tadalafil as Cialis when used for its licenced indications include headaches, flushing, nasal congestion, dyspepsia, gastro-oesophageal reflux myalgia, back pain, and pain in extremities. Tadalafil is currently in phase IV clinical trials for Becker muscular dystrophy and phase III clinical trials for pulmonary arterial hypertension in paediatric subjects.

INNOVATION and/or ADVANTAGES

If licensed, tadalafil will offer the first treatment option which is not mutation-specific to slow the decline in walking of male adolescents and children with Duchenne muscular dystrophy (DMD), who currently have few effective therapies available.

DEVELOPER

Eli Lilly & Co Limited.

AVAILABILITY, LAUNCH OR MARKETING

Tadalafil is a designated orphan drug in the USA and is in a phase III clinical trial.

PATIENT GROUP

BACKGROUND

Duchenne muscular dystrophy is a disabling inherited X-linked recessive disorder that is caused by mutations in the dystrophin gene, and is the most common muscular dystrophy of childhood. In individuals with DMD, dystrophin is absent or present at very low levels due to mutations at locus Xp21.2 of the X-chromosome. Such mutations are due to deletions (in about 65% of patients), duplications (in about 10% of patients), point mutations (in about...
10% of patients), or nonsense mutations (in about 10-15% of patients)\(^5\). Dystrophin has a structural role in linking the muscle cytoskeleton to the extracellular matrix; it is also involved in cell signalling and regulating muscle response to oxidative stress\(^6\). In patients with DMD, an absence of dystrophin disrupts the muscle's ability to tolerate conformational changes caused by contraction; this causes muscle degeneration and an inflammatory response that produces a cellular environment in which adipocytes and fibroblasts proliferate and impair the regenerative capacity of muscle precursor cells\(^6\).

The severe reduction or complete absence of dystrophin in skeletal and cardiac muscle leads to mechanically induced sarcolemmal damage, loss of intra-cytoplasmic calcium homeostasis, and muscle fibre degeneration\(^7\). Sarcolemmal damage leads to the common early signs of delayed and abnormal motor development in affected boys, with approximately 50% not walking independently at the age of 18 months\(^8\). Children with DMD typically never run properly and have difficulty climbing stairs, with only around 10% managing to jump with both feet together\(^8\). Boys with DMD also display the classical sign of proximal muscle weakness — the Gowers manoeuvre; where children need to turn onto their front and rise to standing from the floor using a broad-based stance, usually with the support of their hands on their thighs\(^8\). Additional common features of DMD include muscle hypertrophy, usually of the calves but also of other muscle groups and, frequently, global developmental delay with delayed speech\(^8\).

Signs and symptoms of DMD such as developmental delay or an inability to keep up with friends or siblings, are typically spotted between the ages of 2-3 years old, usually by parents and early years' professionals\(^a\). In a child aged five years old with DMD, around 30-40% of muscle mass will already have been lost\(^a\). Progressive muscle degeneration in affected children results in loss of ambulation at a mean age of 9.5 years\(^9,10\). After the age of 12 years most children will need to use a wheelchair\(^11\). In the second decade of life, most patients are dependent on others for their daily activities\(^12\). During advanced stages of the disease, progressive cardiomyopathy and respiratory failure occurs secondary to respiratory muscle weakness\(^10\). In 90% of cases, death is the result of respiratory failure, while in the remaining 10% it is the result of cardiac involvement\(^10\). Several dystrophin isoforms are also expressed in the brain, and their deficiency is responsible for the learning difficulties which complicates the course of the disease in approximately one third of cases\(^7\).

DMD places a heavy emotional and financial burden on families, and a diagnosis is often devastating for families who are often forced to make a number of changes their family’s lives\(^a\). For example families may need to move to a larger more accessible home, buy a new vehicle, or give up work to fulfill increasing caring responsibilities\(^a\). Research suggests that in the UK, that nearly half (49%) of caregivers reduced their working hours or stopped working completely owing to their relative’s DMD\(^a\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Improving quality of life for people with long term conditions (2013).

\(^a\) Patient group personal communication.
Horizon Scanning Research & Intelligence Centre

CLINICAL NEED and BURDEN OF DISEASE

As DMD is caused by mutations on the X-chromosome in the gene for dystrophin, it generally only affects males\(^1\). However an estimated 8-10\% of female carriers will have some manifestations of DMD, although these are usually minor, and cases presenting with muscle weakness as severe as that seen in boys are very rare\(^2\). DMD incidence is estimated to be 1 in 3,500 births\(^3\). The Muscular Dystrophy Campaign estimates that there are approximately 100 boys born with DMD in the UK every year, and there are approximately 2,500 boys with the condition in the UK at any one time\(^4,5\). In 2013-14, there were 965 admissions for muscular dystrophy (ICD-10 G71.0) in England, which includes DMD along with other muscular dystrophies, resulting in 2,296 bed days and 1,048 finished consultant episodes\(^6\). In 2013 there were 128 deaths (93 men, 35 women) from muscular dystrophy registered in England and Wales (ICD-10 G71.0)\(^7\). Without intervention for the respiratory, orthopaedic, and cardiac complications that emerge in boys with DMD, the mean age at death is around 19 years\(^8\). In the last two decades, non-invasive positive-pressure ventilation (NIPPV) has increased the median survival of patients with DMD by several years, and it is currently more than 25 years, however the average lifespan is still less than 30 years\(^9,10\). The population likely to be eligible to receive tadalafil could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

- Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. 2010\(^11\).
- Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care\(^12\).

CURRENT TREATMENT OPTIONS

There are currently no curative treatments available for DMD and therefore management focuses on four keys areas:

- improvement, maintenance and support of muscle strength and function,
- prevention and management of spinal deformity,
- management of respiratory complications,
- prevention and treatment of cardiomyopathy.

There are three phases of motor function described in DMD: making progress, plateau, and decline\(^13\). The plateau phase may last only a few months and can be identified when there is no longer any progress in motor skills\(^14\). The decline phase can be identified when the child takes longer in timed testing, loses a skill (such as climbing stairs), shows less endurance, or

\(^{b}\) Patient group personal communication.
has more falls\textsuperscript{16}. Glucocorticoids are the only pharmacological treatments that have been shown to improve skeletal muscle strength and function in reproducible randomised controlled trials\textsuperscript{16}; they also reduce the risk of scoliosis, stabilise pulmonary function, and may also improve cardiac function\textsuperscript{16}. Current guidelines recommend initiation of glucocorticoids (such as prednisolone or deflazacort) once the plateau phase has been clearly identified, generally at age 4–8 years\textsuperscript{16}. Starting glucocorticoids when the patient is in the full decline phase is still recommended, but the benefits may be more limited\textsuperscript{16}. Ataluren is a pharmacological treatment with conditional Marketing Authorisation in the UK for the treatment of patients with DMD caused by a nonsense mutation in the dystrophin gene (in ambulatory patients aged 5 years and older).

Other pharmacologic therapies for DMD are primarily used in the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure\textsuperscript{6}. For those patients with cardiomyopathy, angiotensin-converting-enzyme inhibitors are first-line therapy, while β blockers and diuretics may also be appropriate treatments for such patients\textsuperscript{17}. An increased frequency of fractures has been observed in patients with DMD receiving glucocorticoids, and supplementation with calcium and vitamin D may be considered in order to maintain bone health\textsuperscript{17}. For patients with vertebral fractures, intravenous bisphosphonates are recommended\textsuperscript{17}. Pain of varying intensity occurs in patients with DMD; treatment to address pain may include physical therapy, postural correction, appropriate and individualised orthoses, wheelchair and bed enhancements, and pharmacological treatments (such as muscle relaxants and anti-inflammatory medications)\textsuperscript{17}.

Supportive care for DMD may involve physical therapy, occupational therapy, orthopaedic surgery, genetic counselling, invasive and non-invasive mechanical ventilation, and in some cases, the use of implanted cardiac devices\textsuperscript{6}. In both the ambulatory and non-ambulatory patients, regular stretching at the ankle, knee, and hip is necessary\textsuperscript{17}. The use of resting ankle-foot orthoses (AFOs) may help to prevent or minimise progressive equinus contractures in all patients\textsuperscript{17}. For non-ambulatory patients, regular stretching of the long finger flexors and wrist, elbow, and shoulder joints also becomes necessary\textsuperscript{17}. Early non-ambulatory patients require the use of a passive standing device (for those with either no or mild hip, knee, or ankle contractures)\textsuperscript{17}. Surgery may be considered if lower-limb contractures are present despite range-of-motion exercises and splinting\textsuperscript{17}. The ankles, and to a lesser extent, the knees, are the joints most amenable to surgical correction, and even subsequent bracing\textsuperscript{17}. In the time after loss of independent ambulation, pulmonary care is especially important\textsuperscript{17}. Interventions for patients with respiratory complications are dependent on assessment of pulmonary function and may include\textsuperscript{17}:

- volume recruitment/deep lung inflation technique (by self-inflating manual ventilation bag or mechanical insufflation-exsufflation)
- manual and mechanically assisted cough techniques
- nocturnal ventilation - non-invasive ventilation with pressure cycled bi-level devices, volume cycled ventilators, or combination volume-pressure ventilators
- daytime ventilation - non-invasive ventilation with portable volume cycled or volume-pressure ventilators; bi-level devices are an alternative
- tracheostomy where use of cough assistance or non-invasive ventilation is not possible, although input from patient groups suggests that a person with a tracheostomy may continue to use mechanical cough assist daily\textsuperscript{c}.

\textsuperscript{c} Patient group personal communication.
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01865084; tadalafil vs placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Eli Lilly and Company.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry™, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=306 (planned); aged 7-14 years; ambulant males with DMD; receiving systemic corticosteroids ≥6 months immediately prior to screening, no significant change in total daily dosage or dosing regimen (except adjusting for weight changes) for ≥3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen will not change significantly (except adjustments for weight) for the duration of the study; able to complete the six minute walk distance (6MWD) test with results within 20% at a minimum of 2 pre-randomisation assessments; left ventricular ejection fraction (LVEF) ≥50%; no symptomatic cardiomyopathy or heart failure; no change in prophylactic treatment for heart failure within 3 months; no cardiac rhythm disorder; no history of participation in gene or cell-based therapy, antisense oligonucleotide stop codon read-through therapy; no use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength within 3 months prior to the start of study treatment; no surgery that might have an effect on muscle strength or function within 3 months before study entry or planned surgery at any time during the study; no evidence of a lower limb injury that may affect performance on the 6MWD; no severe behavioural problems, including severe autism or attention deficit disorders, that may interfere with completion of the 6MWD; no history of significant renal insufficiency or clinical evidence of cirrhosis; no PDE5 inhibitor therapy or treatment within 6 months.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to: tadalafil 0.3mg/kg orally once daily; tadalafil 0.6mg/kg orally once daily; or placebo orally once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for 48 weeks, thereafter tadalafil is provided to all patients in an open label extension period of 48 weeks. Participants that complete this 48 week open label extension period may continue into another open label extension period of 48 weeks.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Change from baseline in 6MWD.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Change from baseline in the North Star Ambulatory Assessment (NSAA) global score; change from baseline in timed function tests; time to persistent 10% worsening in 6MWD; time to persistent 10% worsening in timed function tests; quality of life as assessed by change from baseline in Paediatric Outcomes Data Collection Instrument (PODCI) scores; pharmacokinetics.</td>
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<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as December 2015</td>
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## ESTIMATED COST and IMPACT

### COST

Tadalafil (as Cialis) is already marketed in the UK for the treatment of benign prostatic hyperplasia, erectile dysfunction, and pulmonary hypertension; a pack of 28 x 2.5mg or 5mg tablets costs £54.99.19
### IMPACT - SPECULATIVE

#### Impact on Patients and Carers
- **☑ Reduced mortality/increased length of survival:** *any drug with the ability to slow the decline in DMD could potentially have an effect on long term ambulation, and thereby potentially survival also*.  
- **☑ Other:** *improved quality of life for carers.*
- **☐ Reduced symptoms or disability**
- **☐ 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**
- **☐ None identified**

#### Impact on Costs and Other Resource Use
- **☑ Increased drug treatment costs**
- **☐ Reduced drug treatment costs**
- **☐ Other reduction in costs:** *If tadalafil is shown to slow the decline in DMD, other costs related to the disease and its complications might be delayed.*
- **☐ Other increase in costs:**
- **☐ None identified**

#### Other Issues
- **☑ Clinical uncertainty or other research question identified:** *there may be a need to conduct some research in the area of co-prescription of tadalafil with other new drugs such as those aiming to restore dystrophin production (e.g. Ataluren and the exon skipping drugs currently in trial).*
- **☐ None identified**

### REFERENCES


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*d Expert personal opinion.*