Health Technology Briefing
November 2024

Givinostat for Duchenne muscular dystrophy

Company/Developer	Italfarmaco SpA

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 8088	NICE ID: 9963	UKPS ID: 673537

Licensing and Market Availability Plans

Completed phase III clinical development.

Summary

Givinostat is in clinical development for Duchenne muscular dystrophy (DMD). DMD is a genetic disease that gradually causes weakness and atrophy (wasting) of the muscles. It mainly affects boys, and usually starts before the age of six years. Patients with DMD lack normal dystrophin, a protein found in muscles. Because this protein helps to strengthen and protect muscles from injury as muscles contract and relax, in patients with DMD, the muscles become weak and eventually stop working. DMD causes long-term disability and is life threatening because of its effects on the heart and the respiratory muscles (muscles that are used to breathe). The disease usually leads to death in adolescence or early adulthood. Treatment of DMD has been challenged by the limited number of available medicinal products and the minimal benefits associated with currently available ones.

Givinostat is administered orally, and blocks enzymes called histone deacetylases (HDACs), which are involved in turning genes on and off within cells. By blocking HDAC enzymes, givinostat counteracts DMD disease progression by reducing inflammation, scar tissue and muscle cell death, and increasing muscle fibre area alongside muscle fat replacement in patients with DMD. Givinostat is expected to delay muscle insufficiency, slow down DMD disease progression and delay the age of persistent loss of muscle function. If licensed, givinostat will offer an additional treatment option for the treatment of DMD independent of genetic mutation.

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

Duchenne muscular dystrophy (DMD) in patients aged 6 years and older.[1]

Technology

Description

Givinostat (Duvyzat, ITF2357) is a molecule that works to inhibit enzymes called histone deacetylases (HDACs), which turn off gene activity and can affect the ability of muscle cells to regenerate.[1-3] By inhibiting HDAC activity, givinostat may help to activate muscle repair mechanisms to increase muscle fibre regeneration, reduce inflammation, and reduce fibrosis.[2] Inhibiting HDAC enzymes also switches on the follistatin gene, thereby increasing the amount of the follistatin protein in muscle cells. Follistatin increases muscle mass and prevents muscle degeneration by opposing the effects of myostatin, a protein that causes fat and fibrotic tissue to build up in the muscle preventing muscle growth and regeneration.[4] Furthermore, givinostat has shown to be able to inhibit all the processes which determine muscle fibrotic substitution (inflammation, necrosis, fatty replacement and fibrosis) and to stimulate muscle regeneration with the formation of larger muscle fibres and overall more muscle tissue in animal models.[5]

Givinostat is in clinical development for the treatment of DMD in ambulant and non-ambulant male patients aged 6 years and older. In the phase III clinical trial (NCT02851797, EPIDYS), ambulant participants received givinostat oral suspension (10 mg/mL) twice daily for 18 months, and in the phase III clinical trial (NCT05933057, ULYSSES) non-ambulant participants received givinostat twice daily in a fed state according to a flexible dose regimen based on patient weight.[1,6]

Key Innovation

To date there is no standard therapy for DMD patients that is curative. DMD can be caused by several genetic abnormalities. Available treatments that target specific mutations in DMD are used to treat only children whose disease is due to these mutations targeted by these treatments.[7-9] However, only a minority of patients can benefit from these treatments.[7] The mechanism of action of givinostat has the potential to inhibit HDAC pathological overactivity in an effort to address the cascade of events leading to muscle damage, thereby counteracting the disease pathology and slowing down muscle deterioration.[10] Since givinostat acts on the pathogenetic events downstream of the genetic defects, it is potentially a treatment for the whole DMD population and also counter the disease pathogenetic events in all muscular districts.[11] This broader application positions givinostat to address the progressive muscle damage in various muscular regions, which is not achieved by mutation-specific therapies.

If licensed, givinostat will offer a treatment option, independent of the genetic mutation for the treatment of ambulant and non-ambulant DMD patients who currently have few well-tolerated effective therapies available.

Regulatory & Development Status

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

Givinostat has the following regulatory designations/awards:

- An orphan designation award in the European Union (EU) in 2012 for the treatment of DMD.[4]
- An orphan drug designation award in the United States (US) in 2013 for the treatment of DMD.[12]
- Rare paediatric disease designation in the US in 2020 for the treatment of DMD.[13]

Givinostat is currently in phase II/III clinical development for other indications including:[14]

- Chronic myeloproliferative neoplasms
- Polycythaemia vera
- Becker muscular dystrophy

Patient Group

Disease Area and Clinical Need

DMD is a rare genetic disorder characterised by progressive muscle degeneration and weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact.[15] The lack of the dystrophin protein leads to muscle fibres break down and be replaced by fibrous and/or fatty tissue, causing the muscle to weaken gradually.[16] In most cases, muscular dystrophy (MD) develops after inheriting a faulty gene from one or both parents. It is caused by mutations in the genes responsible for healthy muscle structure and function. In a few cases, the genetic mutation that causes MD can also develop as a spontaneous mutation in the family.[17] Muscle weakness is the principal symptom of DMD. It can begin as early as age 2 or 3, first affecting the proximal muscles (those close to the core of the body) and later affecting the distal limb muscles (those close to the extremities). Usually, the lower external muscles are affected before the upper external muscles. The affected child might have difficulty jumping, running, and walking. Other symptoms include enlargement of the calves, a waddling gait, and lumbar lordosis (an inward curve of the spine). As the disease progresses, the heart and respiratory muscles are affected as well. Progressive weakness and scoliosis result in impaired pulmonary function, which can eventually cause acute respiratory failure.[15]

DMD usually affects boys in early childhood and people with the condition will usually only live into their 20s or 30s.[18] About 100 boys with DMD are born in the UK each year and there are about 2,500 boys and young men known to be living with the condition in the UK at any one time. For the general population, the risk of having a child with DMD is about one in every 3,500-5,000 male births.[16] In England, 2023-2024, there were 2,066 finished consultant episodes (FCE) and 1,942 admissions for muscular dystrophy (ICD-10 G71.0, which includes DMD). This resulted in 1,414 day cases and 2,388 FCE bed days.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends ataluren for treating DMD with a nonsense mutation in the dystrophin gene in people aged 2 years and over who can walk.[20] Current treatment options are limited, with supportive care with corticosteroids being the main treatment option for DMD.[21]

Clinical Trial Information

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Trial	**ULYSSES**, NCT05933057; **EUCT** 2023-503521-19-00; Randomised, Double-blind, Placebo-controlled, Multicentre Study to Evaluate the Efficacy, Safety and Tolerability of Givinostat in Non-ambulant Patients With Duchenne Muscular Dystrophy **Phase III** – recruiting **Locations:** 5 EU countries, UK, and Canada **Primary completion date:** February 2028
Trial Design	Randomised, quadruple-masked, parallel assignment
Population	N=138 (estimated); males aged 9 to 17 years with non-ambulant DMD
Intervention(s)	Givinostat administered twice daily in a fed state according to a flexible dose regimen based on patient weight
Comparator(s)	Placebo
Outcome(s)	Primary outcome measure: • Change of Performance of Upper Limb 2.0 (PUL) total score at 18 months of treatment of givinostat compared to placebo group [time frame: baseline and 18 months]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**EPIDYS**, NCT02851797; Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients with Duchenne Muscular Dystrophy. **Phase III**: Completed **Locations**: 6 EU countries, UK, USA, Canada, and other countries **Actual study completion date**: February 2022
Trial Design	Randomised, parallel assignment, quadruple-masked
Population	N=179 (actual); ambulant males aged 6 to 17 years with DMD
Intervention(s)	Givinostat oral suspension (10 mg/mL) twice daily
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: • Mean change from Baseline in time to climb 4 standard stairs (4SC) after 18 months of treatment [time frame: baseline and 18 months]. See trial record for full list of other outcomes.
Results (efficacy)	The study met its primary endpoint and givinostat demonstrated a statistically significant difference in change from baseline at 18 months in 4SC (GLSmean ratio [SD] = 0.86 [0.071]; p=0.0345).[22]

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Results (safety)	In 95% of the participants the Adverse Events (AE) were mild to moderate in severity, 2.5% (3 boys) withdrew from the clinical trial due to an AE. AE seen in at least one in ten participants were abdominal pain, diarrhoea, platelet decrease and triglyceride increase. The AEs were managed with dose alterations and appropriate monitoring.[23]

Clinical Trial Information

Trial	NCT03373968, **EudraCT** 2017-000397-10; Open Label, long-term safety, tolerability, and efficacy study of GIVINOSTAT in all DMD patients who have been previously treated in one of the GIVINOSTAT studies. **Phase II/III:** Enrolling by invitation **Locations**: 6 EU countries, UK, USA, Canada, and other countries **Primary completion date**: December 2025
Trial Design	Single group assignment, open-label
Population	N=206 (estimated); Participants aged 7 years and older who have been previously treated in one of the Givinostat studies.
Intervention(s)	Givinostat oral suspension (10 mg/mL) twice daily in a fed state
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of treatment-emergent adverse events [safety and tolerability] [time frame: through study completion, an average of 1 year]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of givinostat is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Delandistrogene moxeparvovec for treating Duchenne muscular dystrophy in children 4 to 7 years (GID-TA11437). Expected date: To be confirmed.
- NICE technology appraisal in development. Fordadistrogene movaparvovec for treating Duchenne muscular dystrophy (GID-TA11044). Expected date: To be confirmed.
- NICE technology appraisal in development. Givinostat for treating Duchenne muscular dystrophy in people 6 years and over (GID-TA11373). Expected date: To be confirmed.
- NICE technology appraisal in development. Vamorolone for treating Duchenne muscular dystrophy (GID-TA11135). Expected date: To be confirmed.
- NICE highly specialised technologies guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST22). February 2023.

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NHS England (Policy/Commissioning) Guidance
• NHS England. Diagnostic service for rare neuromuscular disorders (all ages). D04/S(HSS)/a
Other Guidance
• Childs *et al.* Development of respiratory care guidelines for Duchenne muscular dystrophy in the UK: key recommendations for clinical practice. December 2023.[24]

Additional Information

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