Italfarmaco - Givinostat in Younger DMD patients

A Phase 2 Open label (Core Phase Plus Extension Phase) With 2 Cohorts Study to Assess the Pharmacokinetics and Safety of Givinostat in DMD Patients Ages from at Least 2 Years to Less Than 6 Years Old

Hub Summary

The purpose of the study is to find out about the safety and tolerability of givinostat for the treatment of Duchenne muscular dystrophy (DMD) in patients aged from at least 2 years old to less than 6 years old. The study will also evaluate how the body absorbs, distributes, breaks down and eliminates givinostat.

DMD is a genetic disorder which causes muscle degeneration and weakness due to the changes of a protein called dystrophin. Dystrophin helps keep muscle cells intact. Lack of dystrophin causes repetitive muscle damage and can lead to inflammation and the breakdown of muscle fibers which then get replaced by fat and connective tissue (tissue that supports, protects, and gives structure to other tissues and organs in the body). The regular treatment for DMD usually includes a corticosteroid. Givinostat has been developed to treat DMD by helping to protect the muscle fibers and promote muscle regeneration.

Approximately 18 males aged from at least 2 years old to less than 6 years old will take part in this study at several different locations internationally.

Study Number: DSC/14/2357/52

Description by Italfarmaco

This is an openlabel, multicentre, multi country, 2 cohorts study to evaluate the PK profile and safety of givinostat in patients with DMD aged 4 to <6 years for Cohort 1 and aged 2 to <4 years for Cohort 2.

The starting dose for Cohort 2 will be confirmed/adjusted with results of the interim analysis of Cohort 1.

The study will consist of 2 phases, a Core Phase of 48 weeks and an Extension Phase of 2 years.

After a **screening period** (2 weeks ±14 days) during which enrolment eligibility will be confirmed, a **baseline visit** will occur at Day 1 on Week 1, during which ongoing eligibility will be confirmed and baseline assessments performed. The subjects will receive givinostat for 48 weeks (**Core Phase).** At the end of this period, the subject/parent/legal guardian will have an option to continue the study drug by reconsenting to participate in the **Extension Phase** for 2 years. Otherwise, he will be asked to return for the **followup visit** to be performed within 4 weeks of the last dose of the study drug. If the subject is discontinued/withdrawn from the Core Phase, the subject will be asked to return for the **early termination visit** to be performed within 2 weeks of the last dose of study.

During the **Extension Phase,** the subject/parent/legal guardian will be asked to attend the study visit at site every 6 months, until the end of the Extension Phase when the **EOS visit** will occur at Week 144 (±7 days). A final **followup visit** will be performed within 4 weeks (±7 days) after the last dose administered for safety reasons

If the subject discontinues/is withdrawn from the extension period, an ET visit will be conducted within 2 weeks from the last dose of study drug.

Primary Outcome Measures

Core Phase:
The PK analysis at steady state for the primary endpoint includes:
- Area under the concentration-time curve from dosing (time 0) to time t at steady state (AUC0-T,ss) after at least 7 days of dosing (at Week 1 and at 6 months)
- Maximum plasma concentration at steady state (Cmax,ss) after at least 7 days of dosing (at Week 1 and at 6 months)
- Elimination half life (t1/2) assessed after at least 7 days of dosing (at Week 1 and at 6 months)

Extension Phase:
The primary endpoints include:
- Type, incidence, and severity of TEAEs and SAEs from baseline up to Week 144
- Proportion of subjects experiencing TEAEs from baseline to Week 144

Secondary Outcome Measures

Core Phase:
The secondary endpoints for safety include:

Trial Status
Recruiting

UK Locations
London - GOSH, Not yet recruiting, Leeds, Recruiting, Newcastle, Recruiting, Oxford, Recruiting

Trial Sponsor
Italfarmaco

Phase
Phase 2

Length Of Participation
approximately 18 subjects, 9 each cohort

Recruitment Target
Cohort 1: First patient in expected in January 2025 Last patient Last visit expected in March 2028 (including extension phase) Cohort 2: First patient in March 2026 Last patient Last visit expected in July 2029 (including extension phase)

Ambulatory
Ambulant

Therapeutic Category
Interventional

Age
2-6 years

Mutation Specific
Non-mutation specific therapies

Muscle Biopsy
No Muscle Biopsy Required

MRI
No

- Type, incidence, and severity of treatment-emergent AEs (TEAEs) and SAEs from baseline to Week 48
- Proportion of subjects experiencing TEAEs from baseline to Week 48
- Change from baseline vital signs and clinical laboratory tests to each postbaseline visit up to Week 48
- Change from baseline ECG to each postbaseline visit up to Week 48

The secondary endpoints for muscular functional parameters include:
- Change in physical function as per the Bayley III Gross Motor scale from baseline to Week 48 for subjects aged 2 to <3.5 years of age
- Change in physical function as per the North Star Ambulatory Assessment (NSAA) total score from baseline to Week 48 for subjects aged 3.5 years of age

The secondary endpoint for HRQOL includes:
- Change in Paediatric Outcomes Data Collection Instrument (PODCI) from baseline to Week 48 for subjects aged 4 years of age in Cohort 1 only

Exploratory Endpoints
Full details regarding the PK/PD endpoints will be outlined in a separate modelling and simulation analysis plan.

Extension Phase:
The secondary endpoints for safety include:
- Change from baseline vital signs and clinical laboratory tests to each postbaseline up to Week 144
- Change from baseline ECG to each postbaseline visit up to Week 144

The exploratory efficacy endpoint for muscular functional parameters includes:
- Change in physical function as per the NSAA total score from baseline up to Week 144 for subjects aged 3.5 years of age

The exploratory endpoint for HRQOL includes:
Change in PODCI from baseline up to Week 144 for subjects aged 4 years of age

Other Outcome Measures

Can I take part?

Inclusion Criteria

Core Phase:

Subjects must satisfy all the following criteria at the screening visit unless otherwise stated:
1. Male children aged 2 to <6 years at screening (subjects 6 years of age at screening will not be enrolled into the study)
2. Written consent provided by parent/legal guardian and subject written assent, if applicable (according to local regulation)
3. A genetic diagnosis of DMD
4. Corticosteroid treatment considerations:

a. For subject receiving a stable dose or oral systemic corticosteroids:
No significant change in dose or dosing regimen (except for adjustments due to body weight change) for a minimum of 3 months immediately prior to the start of the study drug
or
b. For subjects without current corticosteroid treatment:
Must not start corticosteroids in the Core Phase of the study (ie, first 48 weeks).

Extension Phase:
Subjects who complete the Core Phase should continue to satisfy the criteria detected at screening visit unless otherwise stated:
1. Must have participated in the Core Phase study (48 weeks) and have attended the End of Treatment Visit (EOT /V12)
2. Give informed consent and /or assent in writing signed by the parent/legal guardian and/or subject (according to local regulation)
3. In stable oral systemic corticosteroids treatment with no significant change in dose or dosing regimen (except for adjustments due to body weight change). For subjects without corticosteroids during the Core Phase, the treatment can be started based on the Investigator's clinical medical judgement.

Exclusion Criteria

Core Phase:
Subjects will be excluded from the study if they meet any of the following criteria at the screening visit unless otherwise stated:
1. Exposure to another investigational drug within 3 months prior to the start of the study drug
2. Exposure to any dystrophin restoration product (eg, Ataluren, Exon skipping) within 6 months prior to the start of study drug
3. Received any gene therapy (eg, AAV Micro-dystrophin delivery) within 12 months prior to start of study drug
4. Use of any pharmacologic treatment, other than corticosteroids, that might have had an effect on muscle strength or function within 3 months prior to the start of the study drug (eg, growth hormone). Note: Vitamin D, calcium, and any other supplements will be allowed.
5. Have had surgery that might have an effect on muscle strength or function within 3 months prior to start of the study drug or planned surgery at any time during the study
6. The presence of other clinically significant disease, which, in the Investigator's opinion, could adversely affect subject's safety, making it unlikely to complete the study or to be compliant with study-specific requirements that could impair the assessment of study results
7. Diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD, based on Investigator clinical medical judgement
8. Platelet count, white blood cells, and/or haemoglobin counts < lower limit of normal (LLN) at screening (Note: for abnormal screening laboratory test results [<LLN], the platelet count, white blood cell, and haemoglobin will be repeated once; if the repeat test result is still <LLN, the subject will be

excluded)
9. Current or history of liver disease or impairment, including but not limited to a baseline elevated total bilirubin (ie, >1.5 × upper limit of normal [ULN]), unless secondary to Gilbert disease or pattern consistent with Gilbert disease
10. Inadequate renal function, as defined by serum Cystatin C result >2 × ULN (Note: if the value is >2 × ULN, the serum Cystatin C will be repeated once; if the repeated test result is still >2 × ULN, the subject will be excluded)
11. Fasting triglycerides >300 mg/dL (3.42 mmol/L) at screening (Note: if the value is >300 mg/dL, the triglycerides will be repeated once; if the repeated test result is still >300 mg/dL in fasting, the subject should be excluded)
12. Positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus at screening
13. Baseline corrected QT interval using Fridericia's formula (QTcF) >450 msec (as the mean of 3 consecutive readings taken 5 minutes apart) or history of additional risk factors for torsades de pointes (ie, heart failure, hypokalaemia, or family history of long QT syndrome)
14. Psychiatric illness or social situations rendering the potential subject unable to understand and comply with the muscle function tests and/or with the study protocol procedures, based on the Investigator's clinical medical judgement
15. Hypersensitivity to any component of study drug
16. Sorbitol intolerance or malabsorption or have the hereditary form of fructose intolerance.
17. Body weight <10 kg at screening.

At the discretion of the Investigator, subjects who do not meet the eligibility criteria may be rescreened twice with an interval of at least 3 months between assessments.

Extension Phase:

Subjects who meet the criteria for permanent discontinuation in the Core Phase will not be enrolled in the Extension Phase. Subjects will be excluded from the Extension Phase if they meet any of the following criteria at the EOT/V12 visit unless otherwise stated:
1. Platelet count, white blood cells, and/or haemoglobin <LLN at EOT/V12 (Note: for abnormal laboratory test results [<LLN], the platelet count, white blood cell, and haemoglobin will be repeated once; if the repeat test result is still <LLN, the subject will be excluded)
2. Current liver disease or impairment, including but not limited to an elevated total bilirubin (ie, >1.5 × ULN), unless secondary to Gilbert disease or pattern consistent with Gilbert disease
3. Inadequate renal function, as defined by serum Cystatin C result >2 × ULN (Note: if the value is >2 × ULN, the serum Cystatin C will be repeated once; if the repeated test result is still >2 × ULN, the subject will be excluded)
4. Fasting triglycerides >300 mg/dL (3.42 mmol/L; Note: if the value is >300 mg/dL, the triglycerides will be repeated once; if the repeated test result is still >300 mg/dL in fasting condition, the subject should be excluded)
5. Have presence of other clinically significant disease, which, in the Investigator's opinion, could adversely affect the safety of the subject, making it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results
6. Evidence of psychiatric illness or social situations rendering the potential subject unable to understand and comply with the muscle function tests and/or with the study protocol procedures, based on the Investigator's clinical medical judgement.

For contact details and to find out more, please refer to dmdhub.org.

Duchenne UK