Italfarmaco - Givinostat Extension

Givinostat in Duchenne's Muscular Dystrophy Long-term Safety and Tolerability Study

Hub Summary

This study is an open label extension, looking at the long-term safety and tolerability of GIVINOSTAT in patients who have already taken part in and completed any of the previous studies.

GIVINOSTAT is a drug that may help to promote muscle regeneration and reduce inflammation and fibrosis in DMD patients.

This extension is expected to last until the drug receives the necessary approvals and is available on the market or the study needs to be stopped due to safety and/or efficacy reasons.

Study Number: NCT03373968

Description by Italfarmaco

This is an open label, long-term safety, tolerability, and efficacy study of GIVINOSTAT in all DMD (Duchenne's muscular dystrophy) patients who have been previously treated in one of the GIVINOSTAT studies.

GIVINOSTAT oral suspension (10 mg/mL) has to be administered orally as 2 oral doses daily while the subject is in a fed state. The starting dose of GIVINOSTAT in the present long term study will be the same that the subject was receiving at the end of the previous DMD GIVINOSTAT study.

As weight affects GIVINOSTAT exposures, the dosage will be modified based on subject weight according the rules detailed in the study protocol section 11.2.2.1.

In addition, in case a subject will have a consistent (e.g., at least 2 consecutive evaluations) platelets count ≤150 x 10^9/L and not meet the stopping criteria for platelets, the Investigator will have to reduce the dose of 1/3 or 20% less of the current dose as described in the study protocol section 10.5.1.3. During the first month of treatment, platelets count assessment will be performed weekly, while during the second month it will be performed every 2 weeks, in order to strictly monitor this parameter for safety reasons, with the exclusion of subjects coming from study DSC/11/2357/43 for which the first visit will be 4 months after the Visit 1/baseline visit.

Study drug should be permanently interrupted if any of the following occurs:

- severe drug-related diarrhoea (i.e., increase of ≥7 stools per day);
- any drug-related SAE;
- QTcF >500 msec;
- platelets count ≤50 x 10^9/L;
- white blood cells ≤2.0 x 10^9/L;
- hemoglobin ≤8.0 g/dL; To avoid laboratory errors and anomalous values, test must be confirmed with a repeated test performed on the next working day. The treatment should be stopped until the retest result becomes available. If the repeated test is still under the stopping limit value, study drug must be permanently discontinued. If the repeated test is acceptable, the subject can resume treatment.

The Investigator will follow up the patient until resolution or acceptable stabilization of the event occurs and document all the relevant information, as applicable. After the resolution/stabilization of the event, the subject will be withdrawn from the study and the EOS Visit (see Section 12.1.10) will be performed.

Any decision relevant to the dose adjustment and/or modification of schedule of assessments can be discussed with the Medical Monitor, but the final decision remains with the Investigator only or its authorized designee.

Primary Outcome Measures

- Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability]

Trial Status
Enrolling by invitation

UK Locations
Alder Hey, Enrolling by invitation, Newcastle, Enrolling by invitation

Trial Sponsor
Italfarmaco

Age
7+

Mutation Specific
All treatment types

Muscle Biopsy
No Muscle Biopsy Required

MRI
No

Phase
2-3

Length Of Participation
Ongoing

Recruitment Target
100

Ambulatory
Ambulant and non-ambulant

Therapeutic Category
Inflammation and fibrosis

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[Time Frame: Through study completion, an average of 1 year]

- Type, incidence, and severity of treatment related/not related adverse events(AEs) and serious adverse event (SAEs)

Can I take part?

Inclusion Criteria

- Must have participated in one of the previous studies with GIVINOSTAT in DMD and have attended the End of Study Visit or must have been screened in study DSC/14/2357/48 and met:
  - all the inclusion criteria and none of the exclusion criteria,
  - had a baseline vastus lateralis muscle fat fraction (VL MFF) assessed by MRS in the range ≤5% or >30%, i.e. included in"off-target" group,
  - never been randomized because, the enrollment in the off target group was completed.
- Aged ≥6 years old;
- Are able to give informed assent and/or consent in writing signed by the subject and/or parent/legal guardian (according to local regulations
- Subjects must be willing to use adequate contraception:
  Contraceptive methods must since the previous GIVINOSTAT study through 3 months after the last dose of study drug, and include the following:
  - True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject.
  - Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
  - Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral,
  - transdermal, injectable or implanted steroid-basedcontraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such asfor example cervical cap with spermicide jelly.

Exclusion Criteria

- Use of any pharmacologic treatment, other than corticosteroids, that might have had an effect on muscle strength or function within 3 months prior to be enrolled in this study (e.g., growth hormone); Vitamin D, calcium, and any other supplements will be allowed;
- Use of any current investigational drug other than Givinostat;
- 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;
- Have a diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD;
- Have platelets count, White Blood Cell and Hemoglobin at screening < Lower Limit of Normal (LLN)* (for abnormal screening laboratory test results (<LLN), the platelets count, White Blood Cell and Hemoglobin will be repeated once; if the repeat test result is still <LLN, then exclusionary);
- Have Triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition at screening visit* (for abnormal screening laboratory test results (>300 mg/dL), the triglycerides will be repeated once; if the repeat test result is still >300 mg/dL, then exclusionary);
- Have inadequate renal function, as defined by serum Cystatin C >2 x the upper limit of normal (ULN) at screening visit*. If the value is >2 x ULN, the serum Cystatin C will be repeated once; if the repeated test result is still >2 x ULN, the subject should be excluded);
- Have heart failure (New York Heart Association Class III or IV)
- Have a current liver disease or impairment, including but not limited to an elevated total bilirubin* (i.e. > 1.5 x ULN), unless secondary to Gilbert disease or pattern consistent with Gilbert's;
- Have a baseline QTcF >450 msec, (as the mean of 3 consecutive readings 5 minutes apart) or history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalemia, or family history of long QT syndrome);

- Have a psychiatric illness/social situation rendering the potential subject unable to understand and comply with the muscle function tests and/or with the study protocol procedures.
- Have any hypersensitivity to the components of study medication;
- Have a sorbitol intolerance or sorbitol malabsorption or have the hereditary form of fructose intolerance.
    - the Investigators to evaluate these exclusion criteria can use the laboratory results obtained within 5 months from V1, to allow the continuity of the treatment. It is worth noting, as soon as the site will receive the laboratory results done in screening/baseline (Visit 1) visit they will check the GIVINOSTAT dose and modify it as per protocol safety rules and/or dosage modifications rules.

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