Randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy EPIDYS (Epigenetic Rescue of Dystrophin Dysfunction)

Published: 14-12-2016
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Primary objective:* To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD subjects.Secondary objectives:* To assess the safety and tolerability of givinostat versus...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON50281

Source
ToetsingOnline

Brief title
DSC/14/2357/48 study in patients with Duchenne Muscular Dystrophy.

Condition

- Muscle disorders

Synonym
Duchenne / Duchenne muscular dystrophy

Research involving

Human

Sponsors and support

Primary sponsor: ITALFARMACO S.p.A.
Source(s) of monetary or material Support: ITALFARMACO S.p.A.

Intervention

Keyword: DSC/14/2357/48, Duchenne Muscular Dystrophy, Givinostat, Phase 3

Outcome measures

Primary outcome

Primary endpoints:

* Mean change in 4SC before and after 18 months of treatment of givinostat

versus placebo.

Secondary outcome

Secondary endpoints:

Key endpoints (all subjects):

* Mean change in time to rise from floor

* Mean change in 6MWT

* Mean change in NSAA

* Cumulative loss of function on the NSAA

* Mean change in muscle strength evaluated by knee extension, elbow flexion as

measured by HHM

Imaging (MR cohort):

* Mean change in vastus lateralis muscles fat fraction; comparing the MRS

before and after 12 months of treatment of givinostat versus placebo;

* Mean change in 4SC before and after 12 months of treatment of givinostat versus placebo;
* Mean change in time to rise from floor before and after 12 months of treatment of givinostat versus placebo;
* Mean change in 6MWT before and after 12 months of treatment of givinostat versus placebo;
* Mean change in NSAA before and after 12 months of treatment of givinostat versus placebo;
* Mean change in muscle strength evaluated by knee extension before and after 12 months of treatment of givinostat versus placebo;
* Mean change in fat fraction of vastus lateralis muscles comparing the MRS before and after 18 months of treatment of givinostat versus placebo.

Safety endpoints:

* Number of subjects experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) (Baseline through end of study [EOS]);
* Type, incidence, and severity of TEAEs and SAEs (Baseline through EOS);
* Changes from baseline to end of study of:
o Vital signs and clinical laboratory tests (blood chemistry and hematology);
o Respiratory function evaluated by forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), FVC/FEV1, Peak Expiratory Flow (PEF);
o Cardiac function evaluated by ECG and ECHO;
o Cognitive function evaluated by the Raven coloured progressive matrices;
o Weight, height, and body mass index (BMI).

Pharmacokinetic Endpoints:

* Description of the PK of givinostat and its major metabolites: ITF2374 and ITF2375 in the subject population;

* Identification of the relevant demographic and pathophysiological covariates influencing the PK of givinostat.

Exploratory endpoints:

* Mean changes in:

o time to walk/run 10 meters;

o PODCI scores;

o %-predicted 6MWT;

o Only in the MR cohort: MRI parameters (e.g., fat fraction of thigh muscles, CSA of vastus lateralis and other thigh muscles).

* Time to 10% persistent worsening in 6MWT (Baseline through end of study);

* Proportion of subjects with *10% worsening in 6MWT at end of study;

* Time to loss of standing (Baseline through end of study);

* Proportion of subjects who loose ambulation during the study;

* Evaluation of any correlation between the effect of Givinostat on disease progression and the type of DMD mutation, LTBP4 and Osteopontin genotype;

* Evaluation of any possible DMD serum biomarker;

* PK-PD analyses: relationships between metrics of exposure and efficacy/safety endpoints of givinostat.

Study description

Background summary

There are still no curative treatments for Duchenne muscular dystrophy and the current management of the disease is based on prevention and management of complications. Therefore, there is an unmet therapeutic need exists for the treatment of this disabling and fatal condition. The risk/benefit ratio of this study is postulated to be favorable for the clinical safety for the efficacy based in the preclinical and the human Phase 2 study. This randomised, double blind, placebo controlled, multicentre study is aimed to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy (DMD). The main objective is to establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD subjects. Ambulant male paediatric subjects aged *6 years at baseline affected by DMD will be included.

Study objective

Primary objective:
* To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD subjects.

Secondary objectives:
* To assess the safety and tolerability of givinostat versus placebo administered chronically in DMD subjects.
* To evaluate the pharmacokinetic (PK) profile of givinostat administered chronically in the target population;
* To evaluate the impact on quality of life and activities of daily living of givinostat versus placebo administered chronically.

Secondary exploratory objectives:
* To evaluate the correlation between PK profile of givinostat and pharmacodynamics (PD) data;
* To explore whether the effects of givinostat versus placebo administered chronically may be related to the type of DMD mutation or to the biomarkers.

Study design

This is a Phase 3, randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant subjects with DMD. This study will include ambulant male paediatric subjects aged *6 years at baseline affected by DMD. Approximately 213 subjects will be randomised in order to have 192 fully evaluable subjects (10% of drop out). Subjects who assent to participate in this study (if capable of doing so) and

whose parent/legal guardian sign the Informed Consent Form (ICF) to participate will undergo pre-study screening assessments up to 4 weeks before the first scheduled dose of study drug.

At the randomisation visit, in addition to the continued standard of care corticosteroids regimen, DMD subjects will be randomised (2:1 ratio) to receive givinostat oral suspension 10 mg/mL or placebo oral suspension bid (in a fed state).
At randomisation, subjects will be stratified for their concomitant use of steroids in 2 strata:
1. Daily regimen
2. Intermittent regimen

The study duration is planned for 19 months and comprises 2 phases:
1. Screening period: starting 4 weeks (± 2 weeks) before randomisation
2. Treatment period: 18 months of treatment

There will be a total of 15 visits, including the Screening and the Randomisation Visits and excluding the Follow up Visit. Subjects may be evaluated more often if necessary for safety reasons. Subjects who discontinue the study drug early will be asked to come in for an EOS
Visit within 2 weeks after the last dose of study drug. Subjects who have ongoing AEs at discontinuation will be followed until resolution or stabilization. In order to guarantee the continuation of treatment with givinostat, the Sponsor has planned a long-term safety study which will start when the first subject enrolled in this study has attended his last visit. As a consequence, at the end of the treatment, parent/ legal guardian will be asked to consent and subject will be asked to assent/consent to his participation to the long-term safety study. In case the subject will not assent/consent and/or the parent/ legal guardian will not consent it, a final follow up visit will be performed 4 weeks after last dose administration.

Intervention

A total of 213 male ambulant subjects will be randomised to provide 192 fully evaluable subjects (10% of drop-out subjects is foreseen).
Subjects will be stratified for their concomitant use of steroids in 4 strata:
1. Deflazacort Daily regimen
2. Deflazacort Intermittent regimen
3. Other steroids Daily regimen
4. Other steroids Intermittent regimen

Randomisation ratio:
2:1 (about 142 subjects in givinostat arm and 71 in placebo arm to give 128 and 64 evaluable subjects respectively)

Study burden and risks

Concerning the clinical experience in DMD, the aforementioned histological results observed in the mdx mouse model were replicated in a Phase 2 study of givinostat (Study DSC/11/2357/43, EudraCT n. 2012-002566-12) in 20 ambulant DMD subjects (from 7 to 10 years of age at study start, on stable steroid treatment) where, after one year of treatment, the muscle biopsy analysis showed a significant increase in muscle fibers area fraction (MFAF) and a significant reduction of muscle necrosis, fatty replacement and fibrosis. Analysis of the effect on CSA of the muscle fibers showed that givinostat significantly increases CSA of all type of fibers (small, medium, large) in a similar manner and that such effect on CSA predicts the increase in MFAF and the reduction of fibrosis. In addition, an increase in the number of regenerating fibers and satellite cells was observed. Moreover, descriptive analysis conducted on the secondary efficacy endpoints on muscle function (i.e., six-minute walking test [6MWT], North Star Ambulatory Assessment [NSAA], time function tests and pulmonary function tests) showed an overall stability after 1 year of treatment in this population.
The most common AEs observed were thrombocytopenia, as well as gastrointestinal toxicities. Adverse events were generally mild to moderate and reversible upon discontinuation of study drug. Moreover, dose-dependent asymptomatic and reversible platelets count reductions were observed both in healthy volunteers and subjects treated with givinostat. These decreases typically occurred within the first week after treatment initiation. The majority of thrombocytopenic events were mild in severity with fewer than 10% of subjects developing platelets count below 75 x 109/L. All occurrences resolved completely within 2 to 3 weeks of discontinuation of treatment, suggesting a rapidly reversible effect. No hemorrhagic episodes were observed. In addition, during the study particular attention will be paid in monitoring possible effects on QTc (see Table 4 for details), since some episodes (20 episodes in 14 subjects) of Corrected QT interval (QTc) prolongation have been recorded during the clinical studies performed so far. It is worth noting that 90% of the recorded events were reported in oncological studies in subjects treated at highest doses (e.g., *100 mg/daily) and no events were recorded during the previous study in DMD subjects.
The risk/benefit ratio of the proposed study is postulated to be favorable for both the results of the clinical safety and pre-clinical toxicology studies and for the efficacy results in the previous Phase 2 DMD study.

(for more information see section 4.2.2 and 4.2.3 of the protocol; Clinical Experience with Givinostat Including Risks and Benefits, pages 33-38)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Subjects must meet all the following inclusion criteria:
1. Are ambulant males aged *6 years at randomisation with DMD characteristic clinical symptoms or signs (e.g., proximal muscle weakness, Gowers* maneuver, elevated serum creatinine kinase level) already present at screening;
2. Have DMD diagnosis confirmed by genetic testing;
3. Are able to give informed assent and/or consent in writing signed by the subject and/or parent/legal guardian (according to local regulations);
4. Are able to complete 2 Four Stairs Climb test (4SC) screening assessments; the results of these tests must be within ±1 second of each other;
5. Have the mean of 2 screening 4SC assessments *8 seconds;
6. Have time to rise from floor between *3 and <10 seconds at screening;
7. Have manual muscle testing (MMT) of quadriceps at screening * Grade - 3;
8. Have used systemic corticosteroids for a minimum of 6 months immediately prior to the start of study treatment, with no significant change in

corticosteroids type or dosage or dosing regimen (excluding changes related to body weight change) for a minimum of 6 months immediately prior to start of study treatment and a reasonable expectation that dosage and dosing regimen will not change significantly for the duration of the study.
9. Subjects must be willing to use adequate contraception.
Contraceptive methods must be used from Randomization Visit 3 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-based contraceptive, or a diaphragm or a barrier method of contraception in conjunction with spermicidal jelly such as for example cervical cap with spermicide jelly.

Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the study:
1. Have exposure to another investigational drug within 3 months prior to the start of study treatment (only exception allowed is use of Deflazacort in US as part of the Expanded Access Program and in Canada as part of the Special Access Program;
2. Have exposure to idebenone within 3 months prior to the start of study treatment;
3. Have exposure to any dystrophin restoration product (e.g., Ataluren, Exon-skipping) within 6 months prior to the start of study treatment;
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 study treatment (e.g., growth hormone); Vitamin D, calcium, and any other supplements will be allowed as long as their intake has been stable for 3 months prior to the start of study treatment. Testosterone will also be allowed if it is used as a replacement therapy for the treatment of delayed puberty, and testosterone dose and regimen have been stable for at least 6 months and circulating testosterone levels are within the normal ranges for the subject's age;
5. Have 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;
6. Loss of *30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (i.e. fixed loss of more than 10 degrees of plantar flexion from plantigrade, assuming normal range of dorsiflexion of 20 degrees);
7. Change in contracture treatment such as serial casting, contracture control

devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study;
8. 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;
9. Have a diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD;
10. Have platelets count, White Blood Cell and Hemoglobin at screening Limit of Normal (LLN) (for abnormal screening laboratory test results (the platelets count, White Blood Cell and Hemoglobin will be repeated once; if
the repeat test result is still 11. Have symptomatic cardiomyopathy or heart failure (New York Heart
Association Class III or IV) or left ventricular ejection fraction <50% at screening;
12. Have a current or history of 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;
13. Have inadequate renal function, as defined by serum Cystatin C >2 x the upper limit of normal (ULN). 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);
14. Have Triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition at screening visit;
15. Have a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus at screening;
16. Have a baseline corrected QT interval, Fridericia*s correction (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);
17. Have a psychiatric illness/social situations rendering the potential subject unable to understand and comply with the muscle function tests and/or with the study protocol procedures;
18. Have any hypersensitivity to the components of study medication;
19. Have a sorbitol intolerance or sorbitol malabsorption, or have the hereditary form of fructose intolerance.
20. Have contraindications to MRI or MRS (e.g., claustrophobia, metal implants, or seizure disorder)., At the discretion of the Investigator, subjects not meeting inclusion/exclusion criteria may be re-screened twice with an interval of at least 3 months between assessments.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Givinostat
Generic name:	Givinostat

Ethics review

Approved WMO

Date:	14-12-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	28-06-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	21-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	15-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 24-06-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 27-06-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 18-10-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 10-01-2020

Application type: Amendment

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Approved WMO
Date: 23-06-2020

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 10-08-2020

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000401-36-NL
ClinicalTrials.gov	NCT03373968
CCMO	NL58595.058.16