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.

Published: 17-01-2019
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This study has been transitioned to CTIS with ID 2023-504520-26-00 check the CTIS register for the current data. Primary objective:To assess the long term safety and tolerability of GIVINOSTAT in patients with DMD following core protocols program...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54775

Source
ToetsingOnline

Brief title
LONG TERM STUDY in givinostat

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Congenital, hereditary muscular dystrophy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Duchenne Muscular Dystrophy, Givinostat, Long-term safety, Previously treated in study

Outcome measures

Primary outcome

Type, incidence, and severity of treatment related/not related AEs and SAEs

(Baseline through week 48 and then yearly till the end of the study)

Secondary outcome

For ambulant patients:

• Change from baseline in physical function as measured by 6MWT, NSAA, Time

function tests (e.g. time to rise from floor, time to climb 4-stairs, time to

10m walk)(week 48 and then yearly till the end of the study)

• Change from baseline in muscle strength (e.g. knee extension and elbow

flexion) as measured by HHM (week 48 and then yearly till the end of the study)

For non-ambulant patients:

• Change in physical function from baseline in the Egen Klassifikation (EK)

score (week 48 and then yearly till the end of the study)

• Change in patient and/or parent/caregiver reports of activities of daily

living as measured by Barthel Index (week 48 and then yearly till the end of

the study

• Change in upper limbs muscle strength (week 48 and then yearly till the end

of the study) evaluated by handheld myometry (HHM)

For all patients:

• Change from baseline in physical function as measured by the Performance of Upper Limb (PUL) and MFM (week 48 and then yearly till the end of the study)

• Change from baseline in respiratory function (week 48 and then yearly till the end of the study) (e.g. FVC, FEV1, PEF)

• Change in patient and/or parent/caregiver reports of quality of life as measured by PedsQL for paediatric patients and by SF-36 for adults patients (week 48 and then yearly till the end of the study),

• Age at major disease milestones (e.g. age at loss of ambulation, age at respiratory support needed during the day, age at scoliosis surgery, age at death).

In addition to the declared time points, the statistical analysis will be performed every year of treatment till the MA will be granted.

Exploratory Endpoints:

• Comparison between the results of the *delayed GIVINOSTAT group* (i.e. all patients in placebo group during the Study DSC/14/2357/48 or Study DSC/14/2357/50 which will be switched to GIVINOSTAT in this study) and the results of the *GIVINOSTAT group* (i.e., the patients already treated with GIVINOSTAT in Study DSC/14/2357/48 or Study DSC/14/2357/50) of the following endpoints:

• Mean change from baseline and week 48 and then yearly till the end of the

study, in physical function as measured by the Performance of Upper Limb (PUL)
;
• Mean change of MFM from baseline and week 48 and then yearly till the end of the study;
• Mean change from baseline and week 48 and then yearly till the end of the study, in respiratory function (e.g. FVC, FEV1, PEF);
• Age at major disease milestones (e.g. age at loss of ambulation, age at respiratory support needed during the day, age at scoliosis surgery, age at death) (Baseline through end of study).

For ambulant patients:
• Mean change from baseline and week 48 and then yearly till the end of the study, in physical function as measured by 6MWT, NSAA, Time function tests (e.g. time to rise from floor, time to climb 4-stairs, time to 10m walk);
• Mean change in muscle strength (e.g. knee extension and elbow flexion) as measured by HHM from baseline and week 48 and then yearly till the end of the study;

For non-ambulant patients:
• Mean change from baseline and week 48 and then yearly till the end of the study in the Egen Klassifikation (EK) score,
• Mean change from baseline and week 48 and then yearly till the end of the study in patient and/or parent/caregiver reports of activities of daily living as measured by Barthel Index,
• Mean change from baseline and week 48 and then yearly till the end of the

study in muscle strength (e.g. elbow flexion) as measured by HHM.

Study description

Background summary

Although different interventions have now become standard of practice and have prolonged life expectation and time to wheelchair, DMD prognosis still provides little hope and even with the best supportive care basic life achievements are thrown into question. Currently only one product, Ataluren, is approved for this serious debilitating and life threatening disease. However the approval is for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older, which only accounts for 13% of the population. In addition, FDA has granted an accelerated approval to Eteplirsen, which targets DMD gene mutations skippable with exon 51 skipping, which are relevant for only 13% of DMD population, or approximately 2,000 patients in the United States (US) and 2,500 patients in the European Union (EU). Thus a significant unmet therapeutic need exists for DMD patients. Since GIVINOSTAT treatment in DMD is expected to be a chronic treatment, the aim of this long-term study is to formally evaluate long term safety and tolerability and to continue monitoring signs of efficacy of GIVINOSTAT in this patients* population until the Marketing Authorization will be granted and the product will become available. Moreover, non clinical data indicate that GIVINOSTAT has shown to produce functional and morphological beneficial effects in the mdx mice. Histological data from DMD children treated with GIVINOSTAT for 1 year showed the same morphological effect as was seen in the mdx mouse model. This evidence supports the potential therapeutic role of GIVINOSTAT in slowing down DMD progression, it is considered ethical to continue the treatment with GIVINOSTAT in this rare disease with an unmet medical need.

Moreover, the treatment with GIVINOSTAT showed a statistically significant (p=0.035) reduction in the decline in 4SC compared to placebo in the patient treated in the phase III, randomized, double-blind, placebo controlled, DSC/14/2357/48 trial. The study meets the primary endpoint and the results demonstrate the clinical benefit of GIVINOSTAT to slow disease progression in ambulant DMD patients after 18 months of treatment.

Study objective

This study has been transitioned to CTIS with ID 2023-504520-26-00 check the CTIS register for the current data.

Primary objective:
To assess the long term safety and tolerability of GIVINOSTAT in patients with

DMD following core protocols program and with naïve GIVINOSTAT DMD subjects , i.e. subjects screened in study DSC/14/2357/48 who met:
- all the inclusion criteria and none of the exclusion criteria, and
- never been randomized because, the enrollment in the off-target group was completed.

Secondary objective:
To evaluate the effects of long-term administration of GIVINOSTAT on muscular function and strength;
To evaluate the effects of long-term administration of GIVINOSTAT on respiratory function;
To evaluate the impact on daily activities and quality of life following long-term administration of GIVINOSTAT.

Exploratory Objective(s):
Sparse PK sampling will be also collected to continue the evaluation of GIVINOSTAT PK.
To compare the functional effects of long-term administration of GIVINOSTAT between the *delayed GIVINOSTAT* and *GIVINOSTAT* treatment groups. The former group comprises those patients randomised to placebo in their previous GIVINOSTAT study; the latter group comprises those patients randomised to GIVINOSTAT in their previous GIVINOSTAT study.

Study design

This is an 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

Intervention

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 ((DSC / 14/2357/48).

Study burden and risks

The research will last approximately several years, until Givinostat receives marketing authorization and is available on the market or until the Sponsor and/or the competent authorities provide different instructions due to safety and/or efficacy issues. Throughout the treatment period, the patient has to attend a series of visits, the frequency of which will differ according to whether the patient is already participating in a study that also involves the administration of a placebo (DSC/14/2357/48 or DSC/14/2357/50) or a study that only involves the administration of Givinostat. The initial study visit will

coincide with the final visit of the previous study, whilst subsequent visits are scheduled every four months throughout the study. If the patient is currently undergoing treatment in a study that also involves a placebo, given that we do not know which treatment the patient is receiving, the patient will need to attend weekly visits for the first month, every two weeks visits for the second month and then visits at the end of the third and fourth months. This is because the study doctor needs to check how the patients body responds to the Givinostat treatment, in the event that the patients is receiving it for the first time. From month four, visits will be every four months until the end of the study. Most study visits will last between two and four hours. However, some visits may take longer. The patients will undergo the following examinations: - Physical examination and monitoring of vital functions (blood pressure, heart rate, body temperature, body height (baseline and then annual) and weight, electrocardiogram (every visit) & echocardiogram (baseline and then annually)) - A lung function examination (every year as patients can walk and every 4 years if they can not walk) - Detailed examination about the medical history - Question about previous used and current medication and possible side effects. - Blood samples and urine samples will be taken. Blood sample for haematology, blood coagulation and biochemistry (18 ml each during each visit) and for pharmacokinetics (2.5 ml each time during the visit every 8 months). Urine samples also during each visit. - Completing questionnaires (quality of life, with respect to mobility, physical activity and pain) - Taking study medication twice a day depending on body weight during the course of the study. - If the patients can walk, their muscular strength is tested, some tests are done on time (ie climbing stairs of 4 steps, standing up from the floor, running / running 10 meters and walking distance for 6 minutes). - If patients can not walk, physical capabilities and muscle strength are measured by determining daily activities. -General determination of the motor capacitance, especially the arm function. Blood collection: some known risks are, although rare, that the blood collection procedure may involve, pain, (after) bleeding, burning, discomfort, or bruise or infection at the site where the needle is inserted. Blood pressure measurement: the cuff that is inflated can possibly feel unpleasant to the arm. ECG: the cures and removal of the ECG patch (small sticky pads) can cause a transient skin reaction, such as a red house or itching. Local skin discomfort and / or hair loss can also occur by applying the electrodes. Echocardiogram: patients may suffer from the sounds that are part of the Doppler signal. The position the patients must adopt / the body must turn may cause inconvenience. The patient may feel the cooling of the gel on the transducer and a slight pressure of the transducer on the chest. There are no special risks associated with the administration of GIVINOSTAT. Very common side effects of GIVINOSTAT (equal to or greater than 10% of the subjects) are: - Thrombocytopenia, accompanied by a nose bleed or bleeding gums, blood in the urine or faces, purple or red bruises and small red or purple spots on the skin - Diarrhea Common side effects (more than 2% to 10% of the subjects): - Nausea, anemia, vomiting, headache, neutropenia, asthenia, abdominal pain, anorexia, ECG abnormality (ie QTc prolongation), fatigue and fever. The above mentioned side effects are generally mild to moderate and are

reversible after stopping the study medication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Subjects must meet all of the following criteria in order to be included in the study: 1. Must have participate in one of the previous study 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: o all the inclusion criteria and none of the exclusion criteria, o 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, o never been randomized because, the enrolment in the off-target group

was completed. 2. Aged >=6 years old 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. Subjects must be willing to use adequate contraception: Contraceptive methods must be used 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-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. GIVINO

Exclusion criteria

Patients who meet any of the following criteria will NOT be eligible for enrolment into the trial: 1. 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; 2. Use of any current investigational drug other than Givinostat; 3. 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; 4. Have a diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD; 5. Have platelets count, White Blood Cell and Hemoglobin at screening < Lower Limit of Normal (LLN)* (for abnormal screening laboratory test results (300 mg/dL (3.42 mmol/L) in fasting condition at screening visit* (for abnormal screening laboratory test results (>ULN), the triglycerides will be repeated once; if the repeat test result is still >ULN, then exclusionary), 7. 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) 8. Have heart failure (New York Heart Association Class III or IV); 9. 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; 10. 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); 11. 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. 12. Have any hypersensitivity

to the components of study medication; 13. Have a sorbitol intolerance or sorbitol malabsorption, or have the hereditary form of fructose intolerance.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-01-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GIVINOSTAT
Generic name:	Hydrochloride monohydrate

Ethics review

Approved WMO

Date:	17-01-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	01-10-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-08-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	29-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	09-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	13-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	03-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
Other	clinicaltrials.gov:NCT03373968 en https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000397-10/IT#summary
EU-CTR	CTIS2023-504520-26-00
EudraCT	EUCTR2017-000397-10-NL
CCMO	NL68387.058.18