A Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in 10 -18 Year Old Patients with Duchenne Muscular Dystrophy

Published: 11-01-2010
Last updated: 04-05-2024

To assess the efficacy of idebenone, compared to placebo, in improving or delaying the loss of respiratory function in patients with DMD

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

Summary

ID

NL-OMON32760

Source
ToetsingOnline

Brief title
DuchEnne MD Long-term IdebenOne Study (DELOS)

Condition

- Other condition

Synonym
Progressive Muscular Dystrophy of Childhood; Rapid progression of muscle degeneration

Health condition

muscular dystrophy, a group of genetic, degenerative diseases primarily affecting skeletal muscles

Research involving
Human

Sponsors and support

Primary sponsor: Santhera Pharmaceuticals
Source(s) of monetary or material Support: Santhera Pharmaceuticals (Switzerland) Ltd

Intervention

Keyword: Duchenne Muscular Dystrophy, Idebenone

Outcome measures

Primary outcome

The change from Baseline to Week 52 in percent predicted Peak Expiratory Flow

Secondary outcome

* Pulmonary function: other than the PEF

* Muscle strength / motor function

* Quality of life

* Measures of safety and tolerability of idebenone:

Study description

Background summary

Duchenne Muscular Dystrophy (DMD) is the most common and devastating type of muscular dystrophy (incidence 1 in 3500 live birth males worldwide). DMD is characterised by a complete loss of dystrophin, a subsarcolemmal protein critical in membrane stabilization and prevention of contraction-induced cell membrane damage. The primary defect in this disease is usually caused by one of the many possible mutations, in the dystrophin gene on the X chromosome. Muscle wasting occurs initially in proximal and later in distal muscle groups leading to the loss of ambulation in early teenage patients. Despite the exponential increase in our understanding of the disorder since the discovery and characterization of the causative mutations in the dystrophin gene in 1987, no effective treatment is currently available.

A Phase II double blind, randomised, placebo-controlled study has provided promising evidence of the efficacy of idebenone on the functional respiratory and cardiac parameters that are sensitive markers for respiratory insufficiency and cardiac disease. Patients on idebenone showed significant improvement in cardiac functions. Direct measures of respiratory weakness assessed as secondary endpoints improved in patients on idebenone, suggesting that idebenone treatment can improve the early signs of respiratory insufficiency.

The aim of the present Phase III study is to assess the effect of idebenone on respiratory function, muscle strength and quality of life in patients with DMD. Furthermore, the safety and tolerability of idebenone will be monitored.

Study objective

To assess the efficacy of idebenone, compared to placebo, in improving or delaying the loss of respiratory function in patients with DMD

Study design

Double-blind, randomised, placebo-controlled, parallel-group, multicentre study

Intervention

As required by study procedures:
-8 study visits
where some of the following will be performed (depending on visits):
-questionnaires
-physical examination
-safety blood/urine samples
-respiratory function and muscle strength/motor function assessment
-12-lead electrocardiogram (ECG) and transthoracic echocardiography

(See also page 36 of the protocol SNT-III-003, Version 2.0 for the Schedule of Assessments.)

Study burden and risks

Burden associated with participation as required by study procedures:
- 8 study visits
where some of the following will be performed (depending on visits):
-questionnaires
-physical examination
-safety blood/urine samples
-respiratory function and muscle strength/motor function assessment
-12-lead electrocardiogram (ECG) and transthoracic echocardiography

The risks of treatment are considered to be acceptable. For an investigational drug there has already been considerably market use in other indications, initially in cerebrovascular and in Alzheimer*s disease at low doses and more latterly in FRDA, amounting to over 400*000 patient-years. The dose of idebenone in the planned trial DELOS, 900 mg/day, is covered by safety data accrued in recent years. The visit schedule planned in DELOS will ensure careful safety monitoring of blood and urine laboratory findings as well as by physical examination and monitoring of vital signs and cardiac function.

The proposed clinical trial is therefore considered to be justified in view of the positive balance of potential benefit versus risks and in view of the planned careful monitoring of patients in the trial.

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)
Elderly (65 years and older)

Inclusion criteria

1.Patients 10 * 18 years of age at Baseline.
2.Signed and dated informed consent.
3.Documented diagnosis of DMD or severe dystrophinopathy and clinical features consistent of typical DMD at diagnosis (i.e. documented delayed motor skills and muscle weakness by age 5 years). DMD should be confirmed by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (i.e. absent or <5% of normal) on Western blot or immunostain.
4.Ability to provide reliable and reproducible repeat PEF within 15% of the first assessment (i.e. Baseline vs. Screening).
5.Patients assessed by the investigator as willing and able to comply with the requirements of the study, possess the required cognitive abilities and are able to swallow study medication.

Exclusion criteria

1.Patients dependent on assisted ventilation at Screening and/or Baseline (defined as non-invasive nocturnal ventilation, daytime non-invasive ventilation or continuous invasive ventilation).
2.Patients with documented DMD-related hypoventilation for which assisted ventilation is needed according to current standard of care guidelines (e.g. FVC< 30%) or is required in the opinion of the Investigator.
3.Patients with a percent predicted PEF > 80% at Baseline.
4.Patients unable to form a mouth seal to allow precise respiratory flow measurements and mouth pressures.
5.Symptomatic heart failure (high probability of death within one year of Baseline) and/or symptomatic ventricular arrhythmias.
6.Participation in the previous Phase II or Phase II Extension study (SNT-II-001 or SNT-II-001-E) for idebenone.
7.Participation in any other therapeutic trial and/or intake of any investigational drug within 90 days prior to Baseline.
8.Use of carnitine, creatine, glutamine, oxatomide, or any herbal medicines within 30 days prior to Baseline.
9.Use of coenzyme Q10 or vitamin E (if taken at a dose of 5 times above the daily physiological requirement) within 30 days prior to Baseline.
10.Any previous use of idebenone.
11.Any concomitant medication with a depressive or stimulating effect on respiration or the respiratory tract.
12.Planned or expected spinal fixation surgery during the study period (as judged by the investigator).
13.Asthma, bronchitis/COPD, bronchiectasis, emphysema, pneumonia or the presence of any

other non-DMD respiratory illness that affects PEF.
14.Use of bronchodilating medication (i.e. inhaled steroids, sympatomimetics, anti-cholinergics).
15.Moderate or severe hepatic impairment or severe renal impairment.
16.Prior or ongoing medical condition or laboratory abnormality that in the Investigator*s opinion could adversely affect the safety of the subject
17.Relevant history of or current drug or alcohol abuse or use of any tobacco/marijuana products/smoking
18.Known individual hypersensitivity to idebenone or to any of the ingredients/excipients of the study medication
19. For *glucocorticoid non-users* only
a)Chronic use of systemic glucocorticoid therapy for DMD related conditions within 12 months of Baseline (the *12 month non-use period*)
b)More than 2 rounds of acute systemic glucocorticoid burst therapy (of *2 week duration) for non-DMD related conditions within the 12 month non-use period
c)Use of any round of systemic glucocorticoid burst therapy of longer than 2 weeks duration within the 12 month non-use period
d)Use of systemic glucocorticoid burst therapy less than 8 weeks prior to baseline
20. For *glucocorticoid users* only
a) Prior to Interim Analysis 1: All *glucocorticoid users*
b) After the Interim Analysis 1: Initiation, cessation or any relevant change (i.e. dose change of >15% above any dose adaptation for body weight increase/decrease) in systemic glucocorticoid therapy within 6 months prior to Baseline

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):	07-07-2010

Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	idebenone

Ethics review

Approved WMO Date:	11-01-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-06-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	03-08-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-12-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-012037-30-NL
ClinicalTrials.gov	NCT01027884
CCMO	NL31070.058.09