A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tadalafil for Duchenne Muscular Dystrophy

Published: 16-07-2013
Last updated: 22-04-2024

The primary objective is to test the hypothesis that once daily tadalafil administered orally for 48 weeks lessens the decline in ambulatory ability as measured by the 6MWD compared to placebo in boys with Duchenne muscular dystrophy (DMD). Two...

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

Summary

ID

NL-OMON40274

Source
ToetsingOnline

Brief title
H6D-MC-LVJJ (219-732)

Condition

- Muscle disorders

Synonym
Duchenne muscular dystrophy, Duchennes disease

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Child, Duchenne Muscular dystrophy, PDE5 inhibition, tadalafil

Outcome measures

Primary outcome

The primary efficacy measure is:

- 6-minute walk distance (6MWD)

Secondary outcome

Secondary efficacy measures are:

- North Star Ambulation Assessment (NSAA)

- Timed function tests (rise from floor from supine, 10 meter walk/run, 4-stair

climb/descend)

Study description

Background summary

Duchenne muscular dystrophy (DMD) is a fatal, muscle-wasting disease typically diagnosed in young boys, for which there are no approved disease-specific treatments. Gene therapy and stem cell transplants have yielded limited clinical progress. While approaches to restore dystrophin expression in muscle by overcoming specific mutations (for example, exon-skipping or stop codon read-through strategies) have been more encouraging, these approaches are limited in their applicability to a relatively small percentage of boys with DMD with these specific mutations. A pharmacological approach to treat the broader population of boys with DMD irrespective of genetic mutation by targeting a pathophysiological mechanism downstream from dystrophin deficiency would address a substantial unmet medical need.

Non-clinical and early clinical studies have provided proof-of-concept that PDE5 inhibition with tadalafil may have favorable effects to preserve muscle

function in DMD by improving exercise-induced blood flow to muscle, ameliorating a key dysfunction in this disease. Study H6D-MC-LVJJ (LVJJ), is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel, 3-arm study to determine the efficacy and safety of tadalafil administered orally once daily in ambulatory boys with DMD who are already receiving treatment with corticosteroids.

Study objective

The primary objective is to test the hypothesis that once daily tadalafil administered orally for 48 weeks lessens the decline in ambulatory ability as measured by the 6MWD compared to placebo in boys with Duchenne muscular dystrophy (DMD). Two doses of tadalafil (0.3 mg/kg and 0.6 mg/kg) will be compared to placebo.

The secondary objectives of the study are to:

• test the hypothesis that once daily tadalafil administered orally for 48 weeks compared with placebo in boys with DMD:

- lessens the decline in North Star Ambulatory Assessment (NSAA) global score,
- lessens the decline in performance on timed function tests: rise from floor from supine, 10 meter walk/run, stair climb and stair descend,
- delays the time to persistent 10% worsening in the 6MWD,
- delays the time to persistent 10% worsening in timed function tests: rise from floor from supine, 10 meter walk/run test, stair climb, and stair descend,
- lessens the decline in Quality of Life (QoL), as measured by the Pediatric Outcomes Data Collection Instrument (PODCI) global functioning scale and the following core scales: Upper Extremity/Physical Functioning, Transfer/Basic Mobility and Sports/Physical Functioning (Daltroy et al. 1998).

• characterize the PK of tadalafil in pediatric DMD patients, and assess relationships between tadalafil exposure and efficacy and safety outcomes.

The exploratory objectives related to ambulatory endpoints of the study are to assess the effect that once daily tadalafil administered orally for 48 weeks compared with placebo in boys with DMD:

• lessens the decline in ambulatory ability as measured by:

- Percent change from baseline in the 6MWD, and
- Change from baseline in the percent of predicted 6MWD based on patient age and height

• lessens the decline in ambulatory ability as measured by individual components of the NSAA

The other exploratory objectives of the study are to assess the effect that once daily tadalafil administered orally for 48 weeks compared with placebo in boys with DMD:

- lessens the decline in upper limb performance as measured by the Performance of the Upper Limb (PUL) Scale
- lessens the decline in pulmonary function as measured by spirometry
- reduces resting heart rate as measured by ECG.

Study design

Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil in patients with DMD. The study will consist of a 48-week double-blind treatment phase, followed by a 48-week open label extension phase. The two daily tadalafil target doses to be tested are 0.3 mg/kg and 0.6 mg/kg.

Intervention

During the double-blind period, tadalafil or matching placebo will be administered orally once daily at one of 2 target doses (0.3 mg/kg or 0.6 mg/kg). A dosing algorithm will be used to achieve each of the 2 daily target doses in different weight categories using a combination of existing tadalafil (Cialis) tablet strengths (2.5-, 5-, 10-, and 20-mg) or matching placebo tablets.

During the open-label extension period all patients will initially receive tadalafil, but still blinded to the target dose, either 0.3 mg/kg or 0.6 mg/kg. Patients assigned to tadalafil during the double-blind treatment period will begin the extension period on the same target dose of tadalafil. Patients assigned to placebo during the double-blind treatment phase will be randomized to receive either tadalafil 0.3 mg/kg or 0.6 mg/kg during the OLE. The final target dose studied in the extension period will be dependent on the final unblinded results from the primary 48-week efficacy analysis at the completion of the double-blind treatment period.

Study burden and risks

There are risks involved with the use of the investigator product tadalafil and the study procedures. An overview is provided in appendix 3 of the informed consent document for parents / legal guardians. There may also be other unknown risks involved with the medication and study procedures and their combination.

Although the study drug is being tested as a possible treatment for DMD, the subject may not receive any medical benefit. The results of the tests may provide the patient information on his health and information obtained from

this study may benefit patients in the future.

Contacts

Public
Eli Lilly

Lilly Corporate Center NA
Indianapolis IN 46285
US
Scientific
Eli Lilly

Lilly Corporate Center NA
Indianapolis IN 46285
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Males with proven DMD ;• Ages 7-14 years inclusive;• Ambulant, defined as baseline 6MWD between 200 and 400 meters inclusive ;• Baseline 6MWD measurements within 20% of the screening 6MWD;• Left ventricular ejection fraction (LVEF) >=50% ;• Receiving systemic corticosteroids for a minimum of 6 months immediately prior to screening, with no significant change in total daily dosage or dosing regimen (except those adjusting for weight changes) for a minimum of 3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen will not change significantly (except for adjustments for weight) for the duration of the study.

Exclusion criteria

• Symptomatic cardiomyopathy or heart failure (New York Heart Association Class III or IV) ;• Change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or reinitiating) in prophylactic treatment for heart failure within 3 months prior to start of study treatment;• Cardiac rhythm disorder defined as sinus rhythm with ectopic contractions or conductance disturbances, or any rhythm other than sinus, observed on screening ECG ;• Use of continuous mechanical ventilator assistance. [Evening use of bi-level positive airway pressure (BPAP) or continuous positive airway pressure (CPAP) therapy is allowed];• Previous treatment with investigational drugs or interventions (including shock training system) within 3 months of the first administration of study medication, or planned use during the study ;• History of participation in gene or cell-based therapy ;• History of antisense oligonucleotide (AON) or stop codon read-through therapy ;• Unable to take orally administered tablets (without chewing, crushing or breaking), as assessed by the investigator ;• Use of L-arginine supplements within 4 weeks (+/- 1 day) of the first administration of study medication ;• Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength within 3 months prior to the start of study treatment (e.g., growth hormone, anabolic steroids including testosterone). Vitamin D, calcium, and combinations thereof will be allowed.;• New or changed treatment with herbal or dietary supplements being taken with an expectation of an effect on muscle strength or function during 1 month prior to first dose of study drug. Patients taking herbal or dietary supplements as defined above with no change in type or dose for 1 month prior to first dose of study drug with no expectation of adding or changing supplements for the 48 week double-blind period may be enrolled. ;• 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;• Evidence of a lower limb injury that may in the judgment of the investigator affect performance on the 6MWD;• Severe behavioral problems, including severe autism or attention deficit disorders, that may in the judgment of the investigator interfere with completion of the 6MWD ;• Any contraindication to tadalafil (use of any form of organic nitrate, either regularly and/or intermittently, or known serious hypersensitivity to tadalafil);• History of significant renal insufficiency, defined as receiving renal dialysis or having a screening serum cystatin C level >= 2.35 mg/L ;• Clinical evidence of cirrhosis ;• Diagnosed with a retinal disorder (for example, hereditary retinal disorders, retinopathy of prematurity);• Have severe hypotension or uncontrolled hypertension as determined by the investigator;• Current treatment with potent CYP3A4 inhibitors, such as antiretroviral therapy (protease inhibitor), systemic ketoconazole, or systemic itraconazole, or chronic use of potent CYP3A4 inducers, such as rifampicin;• Currently receiving treatment with doxazosin, nitrates, or cancer therapy;• Have known allergy to any of the excipients in tadalafil tablets, notably lactose;• Current PDE5 inhibitor therapy or treatment within the past 6 months ;• Other medical condition deemed to place the patient at potential increased risk or reduced adherence to the study protocol ;• History of loss of vision in 1 eye because of nonarteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous phosphodiesterase type 5 (PDE5) inhibitor exposure.

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):	06-05-2014
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cialis
Generic name:	tadalafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-07-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-12-2013
Application type:	First submission

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-07-2015
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	EUCTR2013-001194-25-NL
ClinicalTrials.gov	NCT01865084
CCMO	NL45034.058.13