A phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeatdose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency

Published: 20-07-2015
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The primary objective of this study is to evaluate the efficacy of olipudase alfa in adult patients with acid sphingomyelinase deficiency.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54584

Source
ToetsingOnline

Brief title
ASCEND

Condition

- Metabolic and nutritional disorders congenital

Synonym
Nieman-Pick syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi B.V.
Source(s) of monetary or material Support: Genzyme Europe B.V.

Intervention

Keyword: acid spyngomyelinase deficiency, double-blinded, olipudase alfa, phase 2/3

Outcome measures

Primary outcome

Spleen volume

Pulmonary function

Secondary outcome

-To confirm the safety of olipudase alfa administered intravenously once every

2 weeks for 52 weeks.

-To characterize the effect of olipudase alfa on the splenomegaly related

symptom score from an eDiary after 52 weeks of study drug administration.

-To characterize the effect of olipudase alfa after 52 weeks of study drug

administration on a symptom based composite score obtained from an eDiary

comprising 4 symptom domains (pain, fatigue, dyspnea, and splenomegaly related

symptoms).

-To characterize the effect of olipudase alfa on liver volume after 52 weeks of

study drug administration.

-To characterize the effect of olipudase alfa on platelet count after 52 weeks

of study drug

administration.

Study description

Background summary

Niemann-Pick disease in a rare inhereditary lysosomal stacking disease, for which currently no treatment available is and patients die as a result of this disease . See page 49 of the protocol.
In the phase 1 studies with olipudase alfa an improvement of symptoms was seen, and in this trial with a bigger patient population this will be investigated further.

Study objective

The primary objective of this study is to evaluate the efficacy of olipudase alfa in adult patients with acid sphingomyelinase deficiency.

Study design

A randomized, double blinded, placebo-controlled study.
Patients receiving placebo will also receive olipudase alpha after the first year.

Intervention

Patients will receive 3 mg/kg olipudase alpha or placebo.

Study burden and risks

Its an intensive study, and a lot is asked from the patients (see E2 and E4).
Besides the risks of the study procedures the following side effects are seen:
• Four out of five patients receiving olipudase alfa, experienced and acute phase reaction (fever, pain, fatigue, nausea and vomiting). These symptoms were usually mild and dissapeared within 72 hours.
• Liver abnormalities (high billirubine values, inflammation) were seen in two patients which disappeared after stopping therapy.
• Infusion associated reactions. the Majority of these reactions were not severe and all patients recovered.
• CRS syndrome: research in mice suggest that cytokine-release-syndrome could be a potential side effect of the use of olipudase alfa.

Contacts

Public
Sanofi B.V.

Paasheuvelweg 25
Amsterdam 1105 BP
NL
Scientific
Sanofi B.V.

Paasheuvelweg 25
Amsterdam 1105 BP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

The patient is willing and able to provide signed written informed consent., The patient is male or female aged 18 years or older., The patient has documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes; and a clinical diagnosis consistent with Niemann-Pick disease type B (NPD B)., The patient has diffuse capacity of the lung for carbon monoxide <=70% of the predicted normal value., The patient has a spleen volume >=6 multiples of normal (MN) measured by MRI; patients who have had partial splenectomy will be allowed if the procedure was performed >=1 year before screening/baseline and the residual spleen volume is >=6 MN., Female patients of childbearing potential must have a negative serum pregnancy test for beta-human chorionic gonadotropin (β-HCG)., Female patients of childbearing potential and male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle, or use 2

acceptable effective methods of contraception.

Exclusion criteria

The patient has received an investigational drug within 30 days before study enrollment., The patient has a medical condition, including significant intercurrent illness; significant cardiac disease (eg, clinically significant arrhythmia, moderate or severe pulmonary hypertension or valvular dysfunction, or below 40% left ventricular ejection fraction by echocardiogram); active hepatitis B or hepatitis C, or infection with human immunodeficiency virus (HIV); cirrhosis (as determined by clinical evaluation or liver biopsy); malignancy diagnosed within the past 5 years (other than basal cell carcinoma), or any other extenuating circumstance that may significantly interfere with study compliance, including all prescribed evaluations and follow-up activities., The patient has a platelet count below 60,000/µL (based on the average of 2 samples obtained at least 12 hours but no longer than 24 hours apart)., The patient has an international normalized ratio (INR) larger than 1.5., The patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 250 IU/L or total bilirubin above1.5 mg/dL (except for patients with Gilbert's syndrome)., The patient has had a major organ transplant (eg, bone marrow or liver)., The patient is scheduled during the study for in-patient hospitalization including elective surgery and excluding the liver biopsies required per protocol., The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study., The patient is unwilling or unable to abstain from the use of alcohol for 1 day before and 3 days after each study drug infusion. Testing for blood alcohol levels will not be required., The patient is unwilling or unable to avoid 10 days before and 3 days after the protocol scheduled liver biopsies that are required at screening/baseline and at week 52, the use of medications or herbal supplements that are potentially hepatotoxic (e.g., 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, anti-depressants, kava, echinacea) and/or may cause or prolong bleeding (e.g., anti-coagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng)., The patient requires medications that may decrease olipudase alfa activity (e.g., fluoxetine, chlorpromazine, tricyclic antidepressants [e.g., imipramine, or desipramine])., The patient requires use of invasive ventilatory support., The patient requires use of noninvasive ventilator support while awake for longer than 12 hours daily., The patient is breast-feeding.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-10-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	na
Generic name:	olipudase alfa

Ethics review

Approved WMO Date:	20-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2019
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Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	01-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.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	2015-000371-26
EudraCT	EUCTR2015-000371-26-NL
CCMO	NL53369.018.15