A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz 112638 in Patients with Gaucher Disease Type 1 who have been Stabilized with Cerezyme

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The primary objective of this study is to assess the efficacy and safety of Genz-112638 compared with Cerezyme after 52 weeks of treatment in patients with Gaucher disease type 1 who have been stabilized with Cerezyme. The secondary objective of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON33436

Source
ToetsingOnline

Brief title
ENCORE

Condition

- Haematological disorders NEC
- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
lysosomal storage disease, metabolic disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Gaucher disease, Genz-112638, Glucocerebrosidase, Glucosylceramide

Outcome measures

Primary outcome

The primary efficacy endpoint will be the percentage (%) of patients who remain stable for 52 weeks (the primary analysis period) assessed for both treatment groups separately along with a difference between the two treatment groups. For a patient to be considered to have demonstrated a clinically meaningful response to treatment with Genz 112638 or Cerezyme, patients must remain stable in hematological parameters (hemoglobin levels and platelet counts), and organ volumes (spleen, when applicable, and liver volumes in multiples of normal [MN]). A blinded Independent Adjudication Board (IAB) will review and confirm that failure to meet the primary endpoint is attributed to a decline in Gaucher disease.

Secondary outcome

The secondary efficacy endpoints will include the following: Total T- and Z-scores for bone mineral density (dual-energy X-ray absorptiometry [DXA]) of femur and lumbar spine, hemoglobin level, platelet count, and spleen and liver volumes (in MN) (assessed by magnetic resonance imaging [MRI]).

The tertiary efficacy endpoints include the following: Biomarkers (chemokine CC motif ligand 18 [CCL18] and chitotriosidase); bone disease assessments (X-ray, MRI and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); Quality of Life (QOL) (Brief Pain Inventory [BPI], Fatigue Severity Score [FSS], Short Form-36 Health Survey (SF-36®), and treatment preference (oral vs intravenous therapy).

Exploratory endpoints include Gaucher disease Severity Score System (DS3) and the percent changes from Baseline in investigational biomarkers including glucosylceramide (GL-1) assayed from dried blood spots [DBS] on filter paper and from plasma, as well as ceramide, high-sensitivity C-reactive protein (hsCRP), apolipoprotein-B-100, sphingomyelin, and macrophage inflammatory protein-1 beta (MIP1-*) (assayed from plasma).

Study description

Background summary

This is a Phase 3, randomized, multi-center, multi-national, open-label, active comparator study to evaluate the
efficacy and safety of Genz-112638 in male and female patients with Gaucher disease type 1 who have been
treated with Cerezyme for at least 3 years.

After patients provide informed consent, each patient will undergo Screening assessments to determine study eligibility. The randomization will be a stratified randomization. Patients will be stratified into 1 of 2 groups based on the patient*s Cerezyme dose in the past year (Cerezyme < 35 U/kg/every 2 weeks [q2w] or Cerezyme * 35 U/kg/q2w) prior to a treatment interruption, dose reduction, or regimen change. The stratified patients will then be randomized in a 2:1 ratio to receive Genz 112638 or remain on Cerezyme, respectively for 52 weeks (the primary analysis treatment period).

The study will include a screening period (Days 28 to 1), a primary analysis treatment period (Day 1 to Week 52), a long-term treatment period (post-Week 52 [Week 52 +1 Day which refers to the first dosing day after all Week 52 study assessments have been completed] through study completion), and a safety follow up period (30 to 37 days after the patient*s last dose of treatment).

Patients randomized to Genz-112638 will have study visits at Day 1, Weeks 2, 4, 6, 8, 13, 26, 39, 52, 65, 78, 91, and 104, and every 3 months thereafter until study completion. Patients randomized to Cerezyme will have study visits at Day 1, Weeks 13, 26, 39, 52, Week 52 +1 Day, 54, 56, 58, 60, 65, 78, 91, and 104, and every 3 months thereafter until study completion.

Study objective

The primary objective of this study is to assess the efficacy and safety of Genz-112638 compared with Cerezyme after 52 weeks of treatment in patients with Gaucher disease type 1 who have been stabilized with Cerezyme. The secondary objective of this study is to demonstrate that, in patients with Gaucher disease type 1 who have been stabilized with Cerezyme, the majority of patients who receive Genz-112638 remain stable after 52 weeks of treatment. The tertiary objective of this study is to evaluate the long-term efficacy, safety, and pharmacokinetics (PK) of Genz 112638 in patients with Gaucher disease type 1 who have been stabilized with Cerezyme.

Study design

see 'background of the study'

Intervention

see 'background of the study'

Study burden and risks

The burden for the patients is as follows:
- A significant time investment is required. 16 visits are planned in the first 104 weeks. After which the patients will be required to visit the site every 3 months. On average, each visit wil take 1 to 8 hours.
- Some invasive assessments are scheduled:
1. PK assessments at most visits until Week 104 and annually thereafter. See protocol table 9-4 in section 9.5 (Pharmacokinetic Assessments).
2. In this study, an X-ray will be done of the chest and spine. The energy of the light used for the photographs may cause cell damage. This damage is mostly repaired by the body. The radiation committee qualifies the risk of the effective dose as intermediate.
3. Nerve Conduction Velocity will be assessed twice in the first year and once

at the end of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The patient is willing and able to provide signed informed consent prior to any study-related procedures to be performed.
2. The patient is 18 to 65 years of age at the time of randomization.
3. The patient*s Tanner Stage should be * 4 prior to randomization.
4. The patient has a diagnosis of Gaucher disease type 1 confirmed by a documented deficiency of acid *-glucosidase activity by enzyme assay.
5. The patient consents to provide a blood sample for genotyping for Gaucher disease (unless the patient*s Gaucher genotype is already available), chitotriosidase, and for genotyping of cytochrome P450 2D6 (CYP2D6) to categorize the patient*s predicted rate of metabolism.

6. The patient has received treatment with Cerezyme for at least 3 years at a prescribed dose of * 20 U/kg to * 60 U/kg (± 5 U/kg) q2w during the last year of treatment and has not had a dose reduction, regimen change, or treatment interruption for greater than 6 consecutive months prior to randomization.
7. The patient has clinically stable Gaucher disease prior to randomization. Stable Gaucher disease is defined as a patient with all of the following:
A. No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within the last year, and no documentation of acute pathological bone involvement by imaging (e.g., osteonecrosis, pathological fractures, etc.) as determined in review with a central bone reviewer.
B. Mean hemoglobin level of * 11 g/dL if female and * 12 g/dL if male at the time of screening.
C. Mean platelet count * 100,000/mm3 at the time of screening.
8. Spleen volume < 10 times Normal or total splenectomy (provided the splenectomy occurred > 3 years prior to randomization).
9. Liver volume < 1.5 times Normal.
10. Female patients of childbearing potential must have a documented negative pregnancy test prior to randomization. In addition, all female patients of childbearing potential must use a medically accepted form of contraception throughout the study (either a barrier method or hormonal contraceptive with ethinyl estradiol and norethindrone or similar active components).
11. The patient is willing to abstain from consumption of grapefruit or grapefruit juice for 72 hours prior to administration of the first dose of Genz 112638 and throughout the duration of the study.

Exclusion criteria

1. The patient received pharmacological chaperone or substrate reduction therapies within 6 months prior to randomization.
2. The patient has had a partial or total splenectomy within 3 years prior to randomization.
3. The patient has any evidence of neurologic (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension) as related to Gaucher disease.
4. The patient is transfusion-dependent.
5. The patient has a documented deficiency of iron, vitamin B-12, or folate that requires treatment not yet initiated or not yet stable under treatment for at least 3 months prior to randomization.
6. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine transaminase [ALT]/aspartate aminotransferase [AST]) or Total Bilirubin > 2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.
7. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (e.g. hypokalemia, hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that, in the opinion of the Investigator, may preclude

participation in the study.
8. The patient is known to have any of the following: Clinically significant coronary artery disease including history of myocardial infarction [MI] or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree atrioventricular (AV) block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia (VT).
9. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.
10. The patient has received an investigational product within 30 days prior to randomization.
11. The patient is scheduled for in-patient hospitalization, including elective surgery, during the study.
12. The patient has a history of cancer within 5 years of randomization, with the exception of basal cell carcinoma.
13. The patient is pregnant or lactating.
14. The patient has received any medication that may cause QTc interval prolongation or any medication that is a mechanistic inhibitor of PGP within 30 days prior to randomization.
15. The patient has received any medication that may induce or inhibit CYP2D6, apart from premedications for Cerezyme infusion, within 30 days prior to randomization. Premedications for Cerezyme infusion are allowed up to 7 days prior to the first dose of Genz-112638.
16. The patient has received for the first time (i.e., the patient is not already chronically using), medications known to induce or inhibit CYP3A4, or medications known to be competitive inhibitors or inducers of PGP, 30 days prior to randomization.
17. The patient is a CYP2D6 poor metabolizer who is chronically receiving inhibitors of CYP3A4 and for whom no reasonable alternative medication exists.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-09-2009
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cerezyme
Generic name:	imiglucerase
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet beschikbaar
Generic name:	nog niet beschikbaar

Ethics review

Approved WMO Date:	20-07-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2008-005223-28-NL
CCMO	NL28513.018.09