A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1

Published: 29-06-2009
Last updated: 06-05-2024

The primary objective of this study is to confirm the efficacy and safety of Genz 112638 after 39 weeks of treatment in patients with Gaucher disease type 1.The secondary objective of this study is to determine the long term efficacy, safety, and...

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

Summary

ID

NL-OMON35650

Source
ToetsingOnline

Brief title
ENGAGE

Condition

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

Synonym
lysosomal storage disorder, metabolic disorder

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: Eliglustat tartrate, Gaucher Disease, Genz-112638

Outcome measures

Primary outcome

The primary efficacy endpoint is the percentage change in spleen volume (in MN)

from Baseline to 39 weeks of treatment with Genz 112638 as compared to placebo.

Secondary outcome

Secondary efficacy endpoints include the following: Absolute changes from

Baseline in hemoglobin level (in g/dL), percentage changes from Baseline in

liver volume (in MN), and percentage changes from Baseline in platelet count.

Study description

Background summary

This Phase 3 study, ENGAGE, will consist of 2 periods: The Double Blind Primary Analysis Period (Day 1 to Week 39) and the Open Label Period (post Week 39 [Day 1 of the Open Label Period] through study completion).

The Double Blind Primary Analysis Period will include a screening period (Days 45 to 1), a dose adjustment period (Day 1 to Week 4), and a treatment period (post Week 4 to Week 39). After the patient (and/or their parent/legal guardian) provides informed consent, the patient will undergo Screening assessments and, if all eligibility criteria are met, the patient will be randomized to receive Genz 112638 or placebo for 39 weeks.
After Week 39 assessments are completed, each patient will enter the Open Label Period where all patients will receive Genz 112638 from post Week 39 (Day 1 of

the Open Label Period) through study completion. The Open Label Period will include a dose adjustment period (post Week 39 to Week 47), a long-term treatment period (Week 48 through study completion which includes a safety follow up period [30 to 37 days after the patient*s last dose of treatment]).

In order to achieve balance between the treatment groups, all patients will be stratified based on their spleen volume (in multiples of normal [MN]) into 1 of 2 groups. The patients within a given group will then be randomized in a 1:1 ratio to receive either Genz 112638 or placebo.

The 2 groups are as follows:
* Group 1: Low severity spleen volume (8 to 20MN)
* Group 2: High severity spleen volume (> 20 to 30MN)

DOUBLE BLIND PRIMARY ANALYSIS PERIOD:
At Screening, during the Double Blind Primary Analysis Period, patients will be randomized (once a patient meets all of eligibility criteria) in a 1:1 ratio to receive either Genz 112638 or placebo.

On Day 1 of the Double Blind Primary Analysis Period, patients randomized to receive Genz 112638 will receive 50 mg of Genz 112638 (provided as one 50 mg Genz 112638 capsule and one 100 mg placebo capsule) at the study site. Patients randomized to receive placebo will receive matching placebo capsules (one 50 mg placebo capsule and one 100 mg placebo capsule) at the study site. Patients will only receive the morning dose of Genz 112638 or placebo on Day 1. The Investigator and the Genzyme Investigational Team will remain blinded to these PK data.

BID dosing will begin on Day 2. Patients randomized to receive placebo will receive matching placebo capsules BID (provided as one 50 mg placebo capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 39. Patients randomized to receive Genz 112638 will receive 50 mg of Genz 112638 BID (provided as one 50 mg Genz 112638 capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 4. For patients randomized to receive Genz 112638, dose-adjustments will occur based on plasma trough concentrations of Genz 99067 collected during the Week 2 PK. For patients who have a Genz 99067 plasma trough concentration of < 5 ng/mL, the treatment dose will be increased at Week 4 to 100 mg of Genz 112638 BID (provided as one 100 mg Genz 112638 capsule and one 50 mg placebo capsule per dose) for the remainder of the Double Blind Primary Analysis Period. Patients who have a Genz 99067 plasma trough concentration of * 5 ng/mL will continue to receive 50 mg of Genz 112638 BID (provided as one 50 mg Genz 112638 capsule and one 100 mg placebo capsule per dose) for the remainder of the Double Blind Primary Analysis Period.

During the Double Blind Primary Analysis Period, the patient, Investigator, and

the Genzyme Investigational Team will be blinded to the identity of the placebo or Genz 112638 capsules; the Investigator and the Genzyme Investigational Team will also be blinded to the PK data. Genzyme Clinical Pharmacy Research Services will remain unblinded throughout the study in order to provide the appropriate investigational product to patients. The appropriate drug kits will be assigned to each patient by Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) according to treatment randomization and dose adjustment PK results provided by the Central Laboratory. Note: The Primary Analysis Period will not be unblinded until all patients have completed the Double Blind Primary Analysis Period.

OPEN LABEL PERIOD:
After all Week 39 study assessments have been completed, patients will enter the Open Label Period. On Day 1 of the Open Label Period, all patients will begin BID dosing and will receive their morning dose of 50 mg of Genz 112638 (provided as one 50 mg Genz 112638 capsule) at the study site to allow for blood sample collection at the scheduled post-dose time points for 4-hour PK analysis. All patients will receive 50 mg of Genz 112638 BID (provided as one 50 mg Genz 112638 capsule per dose) until Week 43.

Dose-adjustments during the Open-Label Period will occur based on plasma trough concentrations of Genz 99067 collected during the Week 41and Week 45 PK. For patients who have a Genz 99067 plasma trough concentration of < 5 ng/mL at Week 41, the treatment dose will be increased at Week 43 to 100 mg of Genz 112638 BID (provided as one 100 mg Genz 112638 capsule per dose). Patients who have a Genz 99067 plasma trough concentration of * 5 ng/mL at Week 41 will continue to receive 50 mg of Genz 112638 BID (provided as one 50 mg Genz 112638 capsule per dose) until Week 47. Plasma trough concentrations of Genz 99067 will be collected for all patients during Week 45. For patients who have a Genz 99067 plasma trough concentration of <5 ng/mL at Week 45, the Genz 112638 dose will be increased at Week 47 either from 50 mg to 100 mg of Genz 112638 BID or from 100 mg to 150 mg of Genz 112638 BID for the remainder of the Open-Label Period. Patients receiving 50 mg or 100 mg of Genz 112638 who have a Genz 99067 plasma trough concentration of *5 ng/mL at Week 45 will continue to receive 50 mg or 100 mg of Genz 112638 BID for the remainder of the Open-Label Period. During the Open Label Period, patients will return to the study site at Weeks 41, 43, 45, 47, and 52, and every 3 months thereafter until study completion.

Study objective

The primary objective of this study is to confirm the efficacy and safety of Genz 112638 after 39 weeks of treatment in patients with Gaucher disease type 1.

The secondary objective of this study is to determine the long term efficacy, safety, and pharmacokinetics (PK) of Genz 112638 in patients with Gaucher

disease type 1.

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. 18 visits are planned in the first 130 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 130 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.

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 (and/or their parent/legal guardian) is willing and able to provide signed informed consent prior to any study related procedures to be performed.
2. The patient is at least 16 years old 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 has the following symptoms of Gaucher disease during the Screening period:
A. At least one of the following laboratory abnormalities:
1. Hemoglobin level of 8.0 to 11.0 g/dL if female or 8.0 to 12.0 g/dL if male (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
2. Platelet count of 50,000 to 100,000/mm3 (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
B. Splenomegaly (spleen volume of 8 to 30MN).
C. If hepatomegaly is present, the liver volume must be < 2.5MN.
6. The patient consents to provide a blood sample to Genzyme for genotyping for Gaucher disease, chitotriosidase, and cytochrome P450 2D6 (CYP2D6, to categorize the patient*s predicted rate of metabolism), unless the patient*s genotypes for Gaucher disease, chitotriosidase, and CYP2D6 are already available.
7. 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).
8. The patient is willing to abstain from consumption of grapefruit or grapefruit juice for 72 hours prior to administration of the first dose of study medication and throughout the duration of the Double-Blind Primary Analysis Period.

Exclusion criteria

1. The patient has had a partial or total splenectomy.

2. The patient has received pharmacological chaperone or substrate reduction therapies for Gaucher disease within 6 months prior to randomization.
3. The patient has received enzyme replacement therapy for Gaucher disease within 9 months prior to randomization.
4. 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.
5. The patient has documentation of acute pathological bone involvement (e.g. osteonecrosis and/or pathological fractures, as assessed by X ray and/or magnetic resonance imaging [MRI]) as determined in review with a central bone reviewer or has a bone crisis in the 12 months prior to randomization.
6. The patient is transfusion dependent.
7. The patient has the following laboratory abnormalities during the Screening period:
A. Hemoglobin level < 8 g/dL (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
B. Platelet count of < 50,000/mm3 (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
8. The patient has documented anemia due to causes other than Gaucher disease that requires treatment not yet initiated or not yet stable under treatment for at least 3 months (e.g., iron, vitamin B-12, and/or folate deficiency) prior to randomization.
9. The patient has documented thalassemia minor or sickle cell trait with a platelet count of < 50,000 or >100,000/mm3.
10. The patient has ever had any radiation treatment in the abdominal region.
11. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine aminotransferase [ALT]/ aspartate aminotransferase [AST]) or total bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.
12. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal (GI), 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.
13. 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).
14. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.
15. The patient has received an investigational product within 30 days prior to randomization.
16. The patient is scheduled for in patient hospitalization, including elective surgery, during the study.
17. The patient has a history of cancer within 5 years of randomization, with the exception of basal cell carcinoma.
18. The patient is pregnant or lactating.
19. The patient has received any medication that may cause QTc interval prolongation within 30 days prior to randomization

20. The patient has received (acute or chronic) treatment with a CYP3A4 or CYP2D6 inducer within 30 days prior to randomization.
21. The patient is not a CYP2D6 poor metabolizer, and has received any medication that is a strong inhibitor of CYP3A4 or CYP2D6 within 30 days prior to randomization, except where a patient has been receiving chronic treatment with either a strong inhibitor of CYP3A4 or a strong inhibitor of CYP2D6 (but not both medications) for at least 30 days prior to randomization and plans to continue on the same dosing regimen during the Double-Blind Primary Analysis Period.
22. The patient is a CYP2D6 poor metabolizer and has received (acute or chronic) treatment with a strong inhibitor of CYP3A4 within 30 days prior to randomization.

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:	Pending
Start date (anticipated):	01-08-2009
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet beschikbaar
Generic name:	Eliglustat tartrate

Ethics review

Approved WMO Date:	29-06-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2011
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	EUCTR2008-005222-37-NL
ClinicalTrials.gov	NCT00891202
CCMO	NL28189.018.09