A Randomized, Multicenter, Multinational, Phase 3B, Open-Label, Parallel-Group Study of Fabrazyme (agalsidase beta) in Treatment-Naive Male Pediatric Patients with Fabry Disease Without Severe Symptoms

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The objectives of this open-label study are to evaluate the efficacy (GL-3 clearance), pharmacokinetics (PK), and safety parameters (including immunogenicity) for 2 alternative dose regimens of Fabrazyme (0.5 mg/kg every 2 weeks [q2w] and 1.0 mg/kg...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON35372

Source
ToetsingOnline

Brief title
FIELD (Fabrazyme: Intervening Early at a Lower Dose)

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Inborn errors of metabolism

Synonym
inherited enzyme deficiency, Metabolic disorder

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme
Source(s) of monetary or material Support: Fabrikant financiert het onderzoek.

Intervention

Keyword: Fabrazyme, Fabry Disease, Lower dosage, Pediatric Patients

Outcome measures

Primary outcome

The primary efficacy endpoint will be histological evaluation of GL-3 inclusions in the superficial skin vascular endothelium conducted using light microscopy (LM) histochemistry during Screening or Day 1, Week 52/Year 1, Week 156/Year 3, and Week 260/Year 5.

Secondary outcome

The secondary efficacy endpoints will be the effect of Fabrazyme treatment on GL-3 clearance in plasma and urine collection measured at Screening and every 3 months for the first year (through Week 52/Year 1) and every 6 months thereafter.

Study description

Background summary

This will be a randomized, multicenter, multinational, open-label, parallel-group study to evaluate 2 alternative dose regimens of Fabrazyme (0.5 mg/kg q2w and 1.0 mg/kg q4w) in treatment-naive male pediatric patients with Fabry disease without severe symptoms. Approximately 45 male patients *5 and *18 years of age will receive treatment with Fabrazyme. Patients will be stratified by age at enrollment (5 to 11 years [children] and 12 to 18 years

[adolescents]), to allow for a similar age representation in the 2 treatment arms, then randomized to receive intravenous (IV) infusions of Fabrazyme at a dose of 0.5 mg/kg q2w or 1.0 mg/kg q4w. Patients will be treated for 5 years (260 weeks). Patients who meet specific criteria may have the option of receiving infusions at home after Week 28/Month 6/Year 0.5 for the q2w infusion patients and Week 52/Year 1 for the q4w infusion patients. An independent Data Monitoring Committee (DMC) will oversee safety, dose adjustment, and disease progression. In cases of documented and significant progression of Fabry disease, the dose of Fabrazyme may be increased to the approved dosing regimen of 1.0 mg/kg q2w in the patients concerned, after consultation with and approval of the Genzyme Medical Monitor, the Study Investigator, and the DMC. A patient switched to 1.0 mg/kg q2w will continue to be evaluated in the study. After participating in the study for 5 years, patients are encouraged to enter the Fabry Registry.

Study objective

The objectives of this open-label study are to evaluate the efficacy (GL-3 clearance), pharmacokinetics (PK), and safety parameters (including immunogenicity) for 2 alternative dose regimens of Fabrazyme (0.5 mg/kg every 2 weeks [q2w] and 1.0 mg/kg every 4 weeks [q4w]) in treatment-naive male pediatric patients with Fabry disease without severe symptoms.

Study design

This will be a randomized, multicenter, multinational, open-label, parallel-group study to evaluate 2 alternative dose regimens of Fabrazyme (0.5 mg/kg q2w and 1.0 mg/kg q4w) in treatment-naive male pediatric patients with Fabry disease without severe symptoms. Approximately 45 male patients *5 and *18 years of age will receive treatment with Fabrazyme

Intervention

Patients will be treated with Fabrazyme 0.5 mg/kg q2w or 1.0 mg/kg q4w (131 or 66 infusions, respectively). The infusions will be administered at an initial rate of no more than 15 mg/hr. After 8 infusions and after patient tolerance has been established, the infusion rate can be increased by 5 mg/hr at each subsequent visit. For patients who are randomized to receive 0.5 mg/kg q2w, the total infusion time should not be less than 45 minutes and for patients who are randomized to receive 1.0 mg/kg q4w the total infusion time should not be less than 90 minutes. The infusions can either be infused at a constant rate or titrated. Patients are required to be observed in the study site or at home for at least 1 hour after each infusion. In cases of documented and significant progression of Fabry disease, the dose of Fabrazyme may be increased to the approved dosing regimen of 1.0 mg/kg q2w in the patients concerned, after consultation and agreement of the Medical Monitor, the Study

Investigator, and the DMC. These patients will continue to be evaluated in the study.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):
The burden for the patients is as followed.
1. A significant time investment is required. In year 1 study participation involves between 14 and 27 visits to the research center. Between year 2 and 5 these visits will take place twice a year, this excludes the infusions as it is expected that these will be done in the home setting.
2. Besides the above-mentioned time investment, the study participation also involves the burden of the insertion of an infusion line. This infusion line will also be used for blood draws to minimize the burden for the participant. Infusions may lead to infusion-associated reactions (esp. chills, fever) which can be managed by reducing the infusion rate together with the administration of NSAIDs, antihistamines and/or corticosteroids.
3. Some invasive assessments are scheduled:
a. Skin biopsy (4x): minor burden
b. GFR measurements using Iohexol (6x). This is a significant burden to the patients. The entire procedure takes over 5 hours and requires two infusion lines.
c. PK sampling at day 1 and year 1. This is a significant burden since the procedure can take up to 8 hours and requires an infusion line in the contra lateral arm
d. Kidney biopsy (optional 2x): significant burden. In general, children experience this procedure as scary. A mild sedative may be given to relax the child. After the procedure several hours of bed rest are required. There is a minor risk (<1%) for complications which might require intervention.
e. Retinal imaging (optional 3x) minor burden. For the procedure eydrops dilating the pupil will be used. The patient may have a blurred vision for a few hourse and it may cause mild pain when looking in very bright light.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients who meet the following inclusion criteria will be eligible for enrollment in this study: 1. The patient and/or patients parent(s)/legal guardian(s) must provide written informed consent prior to any protocol-related procedures being performed. 2. The patient must have a confirmed diagnosis of Fabry disease as documented by leukocyte a-Galactosidase A (AGAL) activity of <4 nmol/hr/mg leukocyte (preferred assay). If the leukocyte AGAL activity assay is difficult to obtain, the patient may be enrolled based on documented plasma AGAL <1.5 nmol/hr/mL, with the agreement of the Medical Monitor. (All results from a central laboratory). 3. The patient must have evidence of globotriaosylceramide (GL-3) accumulation as documented by plasma GL-3 (>7.0 microg/mL) and/or urinary GL-3 (>0.03 mg GL-3/mmol creatinine) levels (by central analysis laboratories). 4. The patient must be male *5 and *18 years of age.

Exclusion criteria

Patients who meet any of the following exclusion criteria will not be eligible for enrollment in this study: 1. Patient has albuminuria (first morning void urinary albumin/creatinine ratio >30 mg/g on at least 2 out of 3 consecutive samples, each at least 1 week apart). 2. Patient has a GFR iohexol >90 mL/min/1.73 m2. In
case of properly documented low protein intake, values as low
as 80 mL/min/1.73 m2 may be acceptable, after consultation
with the Genzyme Medical Monitor. 3. Patient has documented evidence of stroke or transient ischemic attack (TIA), or if a brain magnetic resonance imaging (MRI) has been performed,

bright lesions >2 mm on T2- or fluid attenuated inversion recovery- (FLAIR) weighted images within the white matter or the basal ganglia. 4. Patient has severe and recurrent acroparesthesia, judged by the physician as frequent (more than once a week) pain episodes for at least 3 months that influence daily activities, irrespective of medication. 5. Patient has an end-diastolic left ventricular posterior wall thickness (LVPWTd) and/or an end-diastolic interventricular septum thickness (IVSTd) *2 standard deviations (SD) compared to normal (based on body surface area [BSA] normal ranges from Kampmann, et al 2000) as read at the study site. 6. Patient has received prior treatment specific to Fabry Disease. 7. Patient has participated in a study employing an investigational drug within 30 days of the start of their participation in this study. 8. Patient has any medical condition or extenuating circumstance, which, in the opinion of the Study Investigator, could interfere with study compliance. 9. Patient has any medical condition or extenuating circumstance, for example diabetes mellitus, which, in the opinion of the Study Investigator, could interfere with the interpretation of study results. 10. Patient is on treatment with angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs). 11. Patient has any contra-indication mentioned in the labeling of Fabrazyme and/or iohexol (Omnipaque). 12. Patient or parent(s)/legal guardian(s) is unwilling to comply with the requirements of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2008
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Fabrazyme
Generic name:	Agalsidase beta
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
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	EUCTR2007-005668-28-NL
CCMO	NL22244.018.08