A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACODYNAMICS OF AT1001 IN PATIENTS WITH FABRY DISEASE AND AT1001-RESPONSIVE GLA MUTATIONS

Published: 15-12-2009
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The purpose of this study is to compare the effect of AT1001 (migalastat hydrochloride) versus placebo on GL-3 in the kidney.

Ethical review	Approved WMO
Status	Pending
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON34756

Source
ToetsingOnline

Brief title
Oral AT1001 in patients with Fabry disease

Condition

- Inborn errors of metabolism

Synonym
Fabry disease, metabolic disease

Research involving
Human

Sponsors and support

Primary sponsor: Amicus Therapeutics
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: AT1001, Fabry, GLA mutation, metabolic disease

Outcome measures

Primary outcome

Kidney GL-3 (interstitial capillary histology):

The average number of GL-3 inclusions per kidney interstitial capillary is

assessed by a quantitative histological method used to count GL-3 inclusions in

a sample of interstitial capillaries at baseline and at Month 6

Secondary outcome

* Urine GL-3 levels

* Renal Function (assessed by Iohexol GFR, estimated GFR, and 24-hour urine

protein)

* Safety and tolerability

* Cardiac Function

* Patient Reported Outcomes

* WBC *-Gal A activity

* Exploratory Kidney Histology Assessments

* Pharmacokinetics

Study description

Background summary

Patients with Fabry disease have inherited a change of the genetic material (DNA), which results in lower than normal levels of an enzyme called alpha-galactosidase A (alpha-Gal A). The alpha-Gal A enzyme is important in helping the body break down and get rid of certain types of fatty substances. These fatty substances are called glycolipids and are present in most cells of healthy human beings. In Fabry disease, because the enzyme is absent or present in small amounts, there is a buildup of fatty substances in several tissues such as the kidneys, heart, skin, and blood vessels. The increased level of these fatty substances, especially the glycolipid globotriaosylceramide (GL-3), is believed to cause the clinical symptoms common to Fabry disease.
When enzymes such as alpha-Gal A are produced by the cells, they need to be folded into a form capable of getting rid of the excess GL-3. Some changes in the gene that cause Fabry disease affect the correct folding of the alpha-Gal A enzyme in such a way that the protein is destroyed by the cell. AT1001 is believed to help the enzyme to fold correctly, and may increase the enzyme levels in the cells of the human body. As a result, AT1001 may interrupt the buildup of fatty substances such as GL-3 in the body, which might help improve disease symptoms.
This study will measure the effect of AT1001 treatment on GL-3 levels in the kidney. GL-3 in the kidney will be measured in two different ways: by taking samples (biopsies) of tissue from the kidney to look at GL-3 buildup (inclusions) in certain cells, and by measuring the levels of GL-3 in the urine. In addition, the effects of AT1001 treatment on kidney function, heart function, and health status will be studied.

Study objective

The purpose of this study is to compare the effect of AT1001 (migalastat hydrochloride) versus placebo on GL-3 in the kidney.

Study design

This double-blind, randomized, placebo-controlled study will be conducted in 60 patients at approximately 30 sites worldwide. The study will consist of two stages:

Stage 1 includes a screening period of up to 2 months followed by a 6-month treatment period which will involve 4 visits to the clinic. Patients will be randomized in equal proportions to receive either AT1001 or placebo.

After completing the 6-month double-blind phase, all patients will enter Stage 2 of the study and receive AT1001 in an open-label manner. Stage 2 treatment will last for 6 months and will involve 4 visits to the clinic.

Intervention

Subjects will be randomized in equal proportions to receive either 150 mg of AT1001 once every other day or placebo once every other day during Stage 1. During the open-label treatment period (Stage 2) subjects will only receive AT1001

Study burden and risks

Participation in the study will involve a total of nine visits, which will take place over 15 months. Study assessments will include clinical laboratory tests (at every visit), 12-lead ECG (at every visit), kidney biopsy (at 3 visits), kidney function testing (at 3 visits), echocardiography (at 3 visits), and patient reported outcomes (at 3 visits).

AT1001 has undergone extensive nonclinical and clinical testing, and no significant safety concerns have emerged to date. The major potential risks to subjects participating in this study are expected to be the risks associated with undergoing multiple kidney biopsies, and possible progression of disease. Use of intravenous iohexol has a low incidence of side effects. Subjects will be informed of other treatment options that are available for Fabry disease and alternatives to study participation.

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. Male or female between the ages of 16 and 74 inclusive, diagnosed with Fabry disease. 2. Confirmed GLA mutation that has been shown to be responsive to AT1001 in vitro
3. Subject has never been treated with ERT or has not received ERT for at least 6 months before the screening visit.
4. Urine GL-3 greater than four times the upper limit of normal at Screening
5. Subjects taking angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) must be on a stable dose for a minimum of 4 weeks before the baseline visit
6. Women who can become pregnant and all men agree to be sexually abstinent or use medically accepted methods of birth control during study and for 30 days after study completion
7. Subject is willing and able to provide written informed consent, and assent if applicable

Exclusion criteria

1. Subject has undergone or is scheduled to undergo kidney transplantation, or is currently on dialysis
2. eGFR < 30 mL/min/1.73m2 (Chronic Kidney Disease Stage 4 or 5) based on Modification of Diet in Renal Disease equation at Screening
3. QTc * 450 msec for males or * 470 msec for females at screening
4. Pregnant or breast-feeding
5. History of allergy or sensitivity to study medication (including excipients) or other iminosugars (e.g., miglustat, miglitol)
6. Subject is treated or has been treated with any investigational drug within 30 days of the screening visit
7. Subject is currently treated or has ever been treated with AT1001
8. Any intercurrent condition or concomitant medication use considered to be an absolute contraindication to kidney biopsy or that may preclude accurate interpretation of study data
9. Otherwise unsuitable for the study, in the opinion of the Investigator.

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):	01-03-2010
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Migalastat Hydrochloride

Ethics review

Approved WMO Date:	15-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2010
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2011
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	EUCTR2009-013459-31-NL
CCMO	NL29907.018.09