An open-label phase 2A study to investigate drug-drug interactions between AT1001 (migalastat hydrochloride) and agalsidase in subjects with Fabry disease.

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The primary objectives of this study are: * To characterize the effects of 150 mg and 450 mg of AT1001 administered 2 hours before administration of agalsidase on the safety and plasma pharmacokinetics of agalsidase in subjects with Fabry Disease*...

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

Summary

ID

NL-OMON36355

Source
ToetsingOnline

Brief title
AT1001-013 COMBO trial

Condition

- Inborn errors of metabolism

Synonym
Fabry Disease, metabolic disease

Research involving
Human

Sponsors and support

Primary sponsor: Amicus Therapeutics, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: agalsidase, AT1001 (migalastat hydrochloride), drug-drug interaction, Fabry disease

Outcome measures

Primary outcome

Primary Endpoints:

* AT1001 plasma pharmacokinetic parameter values after administration of a

single oral dose of AT1001 alone and in combination with agalsidase

* Agalsidase plasma pharmacokinetic parameter values by measurement of *-Gal A

enzyme levels and protein levels after agalsidase infusion alone and in

combination with AT1001

* Safety variables: adverse events, clinical laboratory tests, 12-Lead ECGs,

physical examinations, vital signs and infusion reactions

Secondary outcome

Secondary Endpoint:

* Distribution of agalsidase to skin after dosing with agalsidase alone and

agalsidase in combination with AT1001 at 24 hours and 7 days after dosing by

measuring *-Gal A levels and protein levels

Exploratory Endpoints:

* Urinary GL-3 excretion before and 14 days after each agalsidase dose

* GL-3 in skin after dosing with agalsidase alone and agalsidase in combination

with AT1001 at 24 hours and 7 days after dosing

* WBC *-Gal A enzyme levels, determined before initiation of the agalsidase

infusion and at 2, 4 and 24 hours and 7 and 14 days after dosing

* Antibody titer (IgG) before initiation of an infusion of agalsidase

* Plasma globotriaosylsphingosine (lyso-GB3) concentrations and urinary

excretion of lyso-GB3 before each dose of agalsidase and 14 days after each

dose of agalsidase

Study description

Background summary

This study will provide drug-drug interaction information after co-administration of AT1001 and agalsidase to support dosing instructions for AT1001. In addition, information on the effect of 150 mg and 450 mg doses of AT1001 on agalsidase will be obtained for proof of concept that AT1001 has the potential to improve the pharmacokinetic properties of agalsidase. Patients receiving either agalsidase alfa (Replagal*) or agalsidase beta (Fabrazyme®) will be eligible to participate in this study. A favorable change in the disposition of agalsidase may support further development of AT1001 in combination with Enzyme Replacement Therapy.

Study objective

The primary objectives of this study are:
* To characterize the effects of 150 mg and 450 mg of AT1001 administered 2 hours before administration of agalsidase on the safety and plasma pharmacokinetics of agalsidase in subjects with Fabry Disease
* To characterize the effect of agalsidase on the safety and plasma pharmacokinetics of 150 mg of AT1001 administered 2 hours before administration of agalsidase in subjects with Fabry Disease
The secondary objective of this study is:
* To characterize the effect of 150 mg and 450 mg AT1001 on the distribution of *-Gal A to skin after administration of agalsidase

Study design

This open-label study will consist of two stages. Stage 1 will consist of

screening and a three period study to evaluate the effect of 150 mg AT1001 on the pharmacokinetics and safety of agalsidase and the effect of agalsidase on the pharmacokinetics and safety of 150 mg AT1001. Stage 2 will consist of screening and a two-period study to evaluate the effect of 450 mg AT1001 on the pharmacokinetics and safety of agalsidase. In Stage 2, the effect of agalsidase on the pharmacokinetics and safety of a 450 mg dose of AT1001 will not be evaluated; the plasma exposure of AT1001 will be characterized when AT1001 is administered with agalsidase solely to confirm the attainment of adequate AT1001 plasma concentrations.

Intervention

Stage 1
Each subject will receive each of the following treatments in the order described below:
Period 1: Agalsidase alone as an intravenous infusion
Period 2: A 150 mg oral dose of AT1001 two hours before initiation of an intravenous infusion of agalsidase
Period 3: A 150 mg oral dose of AT1001
Note: the dose of agalsidase administered in Periods 1 and 2 will be identical. Agalsidase alfa will be administered as a 40-minute intravenous infusion; agalsidase beta will be administered as a 2 hour intravenous infusion.

Stage 2
Each subject will receive each of the following treatments in the order described below:
Period 1: Agalsidase alone as an infusion
Period 2: A 450 mg oral dose of AT1001 two hours before initiation of an intravenous infusion of agalsidase
Note: the dose of agalsidase administered in Periods 1 and 2 will be identical. Agalsidase alfa will be administered as a 40-minute intravenous infusion; agalsidase beta will be administered as a 2 hour intravenous infusion.

Study burden and risks

Non-clinical studies have shown that AT1001 has the potential to improve the efficacy of enzyme replacement therapy in patients with Fabry disease. It is not known if the improvement in enzyme efficacy observed in vitro and in mice and rats will also be demonstrated in humans. The objective of this study is to provide data to support potential clinical studies evaluating the efficacy of AT1001 in combination with enzyme replacement therapy with Fabrazyme and Replagal in patients with Fabry.

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, diagnosed with Fabry disease and between 18 and 65 years of age, inclusive
2. Body Mass Index (BMI) between 18-35
3. Subject initiated treatment with agalsidase at least 1 month, having received at least two infusions, before Screening Visit
4. Subject*s dose level, dosing regimen and form (i.e., alfa or beta) of agalsidase have been stable (stable dose defined as not varying by more than ± 20%) for at least 1 month before Screening Visit
5. Subject has a estimated creatinine clearance * 60 mL/min at Screening; creatinine clearance to be estimated using the 4-parameter MDRD equation:
eGFR (mL/min/1.73 m2) <= 186 x (Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African-American)
6. Subject agrees to use medically accepted methods of contraception during the study and

for 30 days after study completion
7. Subject is willing and able to provide written informed consent

Exclusion criteria

1. Subject has had a documented transient ischemic attack, ischemic stroke, unstable angina, or myocardial infarction within the 3 months before Screening
2. Subject has clinically significant unstable cardiac disease (e.g., cardiac disease requiring active management, such as symptomatic arrhythmia, unstable angina, or NYHA class III or IV congestive heart failure)
3. Subject has a history of allergy or sensitivity to study drug (including excipients) or other iminosugars (e.g., miglustat, miglitol)
4. Subject requires a concomitant medication prohibited by the protocol: Glyset® (miglitol), or Zavesca® (miglustat)
5. Any investigational/experimental drug or device within 30 days of Screening
6. Subject is currently being treated with or has previously received AT1001
7. Subject has any intercurrent illness or condition that may preclude the subject from fulfilling the protocol requirements or suggests to the investigator that the potential subject may have an unacceptable risk by participating in this study

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-03-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Migalastat hydrochloride
Product type:	Medicine
Brand name:	Fabrazyme
Generic name:	Agalsidase beta
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Replagal
Generic name:	Agalsidase alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2012
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	EUCTR2010-022709-16-NL
ClinicalTrials.gov	NCT01196871
CCMO	NL34807.018.10