A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo.

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The objective of the study is to asses the efficacy and safety of intravenous ATB200 co-administration with oral AT2221 by evaluating the changes in key clinical outcome measures (eg, motor, respiratory, fatigue) in adult subjects with late-onset...

Ethical review	Approved WMO
Status	Completed
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON48527

Source
ToetsingOnline

Brief title
Amicus ATB203 Studie

Condition

- Musculoskeletal and connective tissue disorders congenital
- Musculoskeletal and connective tissue disorders congenital

Synonym
Glycogen storage disease type II, Pompe disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Double-blind, Enzyme Replacement Therapy, Late-onset Pompe disease, Randomized

Outcome measures

Primary outcome

The primary efficacy endpoint is the change from baseline to Week 52 in 6MWD.

Secondary outcome

Key secondary efficacy endpoints are as follows:

• change from baseline to Week 52 in the manual muscle test score for the lower extremities

• change from baseline to Week 52 in the total score for the PROMIS - physical function

• change from baseline to Week 52 in the total score for the PROMIS - fatigue

• change from baseline to Week 52 in GSGC total score

• change from baseline to Week 52 in sitting FVC (% predicted)

• change from baseline to Week 26 in 6MWD

Other secondary efficacy endpoints are as follows:

• change from baseline to Week 52 in the following variables related to motor function:

* time to complete the 10-meter walk (ie, assessment of gait) of the GSGC test

* time to complete the 4-stair climb of the GSGC test

* time to complete the Gower*s maneuver of the GSGC test

* time to arise from a chair as part of the GSGC test

* time to complete the TUG test

• change from baseline to Week 52 in the following variables related to muscle strength:

* manual muscle test score for the upper extremities

* manual muscle test total score

* quantitative muscle test value (kg) for the upper extremities

* quantitative muscle test value (kg) for the lower extremities

* quantitative muscle test total value (kg)

• change from baseline to Week 52 in the following variables from patient-reported outcome measures:

* total score for the PROMIS - dyspnea

* total score for the PROMIS - upper extremity

* R-PAct Scale total score

* EQ-5D-5L health status

• actual value of the subject*s functional status (improving, stable, or declining) pertaining to the effects of study drug in the following areas of life at Week 52, as measured by the Subject*s Global Impression of Change

* overall physical wellbeing

* effort of breathing

* muscle strength

* muscle function

* ability to move around

* activities of daily living

* energy level

* level of muscular pain

• actual value of the subject*s functional status (improving, stable, or declining) at Week 52, as measured by the Physician*s Global Impression of Change

• change from baseline to Week 52 in the following measures of pulmonary function, as follows:

* sitting SVC (% predicted)

* MIP (cmH2O)

* MIP (% predicted)

* MEP (cmH2O)

* MEP (% predicted)

* SNIP (cmH2O)

Pharmacodynamic endpoints are as follows:

• change from baseline to Week 52 in serum CK level

• change from baseline to Week 52 in urinary Hex4 level

Pharmacokinetic endpoints from a population PK analysis of total GAA protein

level and AT2221 concentration will be provided in a separate modeling and simulation plan. The safety profile of ATB200/AT2221 will be characterized using incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of study drug, frequency and severity of immediate and late IARs, and any abnormalities noted in other safety assessments. Immunogenicity to ATB200 and alglucosidase alfa will also be described.

Study description

Background summary

Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II, is an autosomal recessive genetic disorder caused by mutations in the GAA gene that encodes acid α-glucosidase (GAA), an enzyme that catalyzes the breakdown of lysosomal glycogen.The objective of the study is to assess the efficacy and safety of intravenous ATB200 co-administration with oral AT2221 in adult subjects with late-onset pompe disease compared with alglucosidase alfa/placebo.

Study objective

The objective of the study is to asses the efficacy and safety of intravenous ATB200 co-administration with oral AT2221 by evaluating the changes in key clinical outcome measures (eg, motor, respiratory, fatigue) in adult subjects with late-onset Pompe disease (LOPD) in comparison with the standard-of-care enzyme replacement therapy, alglucosidase alfa, with placebo.

Study design

This is a double-blind, randomized, multicenter, international study of ATB200/AT2221 in adult subjects with late-onset Pompe disease (LOPD) who have received enzyme replacement therapy with alglucosidase alfa (ie, ERT-experienced) or who have never received ERT (ie, ERT-naïve) compared with alglucosidase alfa/placebo.

Intervention

Investigational Product, dosage and mode of administration:
ATB200/AT2221 will be administered as a combination treatment regimen, consisting of AT2221 260 mg (4 × 65 mg oral capsules), followed approximately 1 hour later by ATB200 20 mg/kg (reconstituted lyophilized drug product for intravenous [IV] infusion, 105 mg/vial). The ATB200/AT2221 combination regimen will be administered every 2 weeks.

Reference Therapy, dosage and mode of administration:
Alglucosidase alfa/placebo will be administered as a combination treatment regimen, consisting of placebo (4 × placebo oral capsules) followed approximately 1 hour later by alglucosidase alfa 20 mg/kg (reconstituted lyophilized drug product for IV infusion, 50 mg/vial). The alglucosidase alfa/placebo combination regimen will be administered every 2 weeks.

Study burden and risks

Participation in this study will include 13 months. During this study the following study procedures will be performed:
Questions about health and medication, physical exam (including blood pressure, heart rate, temperature, breathing, height and weight), ECG, questionnaires ((Rasch-built Pompe-specific Activity [R-PAct] Scale, EuroQol 5 Dimensions-5 Levels Instrument [EQ-5D-5L], Patient-Reported Outcomes Measurement Information System [PROMIS®] instruments for physical function, fatigue, dyspnea, and upper extremity, and
Subject*s and Physician's Global Impression of Change), pulmonary function tests (forced vital capacity [FVC], slow vital capacity [SVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and sniff nasal inspiratory pressure [SNIP]), muscle strength testing (manual muscle testing and quantitative muscle testing), motor function testing including six-minute walk test (additional tests; (Gait, Stair, Gower, and Chair maneuver [GSGC] test and Timed Up and Go [TUG] test), blood tests (venapuncture), urine collection, genetics test and pregnancy test.

Risks: When taking the bloodsamples redness, swelling and/or pin can occur at the site of injection. When removing the ECG some irritation of the skin can occur. The genetic test for Pompe disease can be uncomfortable for the subjects.

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. Subject must provide signed informed consent prior to any study-related procedures being performed.
2. Male and female subjects are >= 18 years old and weigh >= 50 kg at screening.
3. Female subjects of childbearing potential and male subjects must agree to use medically accepted methods of contraception during the study and for 90 days after the last dose of study drug.
4. Subject must have a diagnosis of LOPD based on documentation of one of the following:
a. deficiency of GAA enzyme
b. GAA genotyping
c. muscle biopsy
5. Subject is classified as one of the following with respect to ERT status:
a. ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen (ie, 20 mg/kg dose every 2 weeks) for >= 24 months
b. ERT naïve, defined as never having received investigational or commercially available ERT
6. Subject has a sitting FVC >= 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening.
7. Subject performs two 6MWTs at screening that are valid, as determined by the clinical evaluator, and that meet all of the following criteria:
a. both screening values of 6MWD are >= 75 meters

b. both screening values of 6MWD are <= 90% of the predicted value for healthy adults
c. the lower value of 6MWD is within 20% of the higher value of 6MWD

Exclusion criteria

1. Subject has received any investigational therapy or pharmacological treatment for Pompe disease, other than alglucosidase alfa, within 30 days or 5 half lives of the therapy or treatment, whichever is longer, before Day 1 or is anticipated to do so during the study.
2. Subject has received gene therapy for Pompe disease.
3. Subject is taking any of the following prohibited medications within 30 days before Day 1:
• miglitol (eg, Glyset*)
• miglustat (eg, Zavesca*)
• acarbose (eg, Precose* or Glucobay*)
• voglibose (eg, Volix*, Vocarb*, or Volibo*)
Note: None of these medications have a half-life that, when multiplied by 5, is longer than 30 days.
4. Subject requires the use of invasive or noninvasive ventilation support for > 6 hours per day while awake.
5. Subject has a medical condition or any other extenuating circumstance that may, in the opinion of the investigator or medical monitor, pose an undue safety risk to the subject or may compromise his/her ability to comply with or adversely impact protocol requirements. This includes clinical depression (as diagnosed by a psychiatrist or other mental health professional) with uncontrolled or poorly controlled symptoms.
6. Subject, if female, is pregnant or breastfeeding at screening.
7. Subject, whether male or female, is planning to conceive a child during the study.

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:	Completed
Start date (anticipated):	04-11-2019
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AT2221
Generic name:	N-butyl-deoxynojirimycin
Product type:	Medicine
Brand name:	ATB200
Generic name:	recombinant human acid &alfa;-glucosidase (rhGAA)
Product type:	Medicine
Brand name:	Myozyme®
Generic name:	alglucosidase alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-000755-40-NL
ClinicalTrials.gov	NCT03729362
CCMO	NL68006.078.18

Study results

Date completed: 17-11-2020

Results posted: 26-07-2021

First publication
17-05-2021