A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)

Published: 07-10-2019
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Key PrimaryPart A• To determine the efficacy of acoramidis (AG10) in the treatment of subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) by evaluating the difference between the acoramidis and placebo groups in the change from...

Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52840

Source
ToetsingOnline

Brief title
Efficacy and Safety of AG10 in Subjects with ATTRibute-CM; AG10-301

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Research involving

Human

Sponsors and support

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

Intervention

Keyword: AG10, Phase 3, Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Outcome measures

Primary outcome

Key Primary

Part A

• Change from baseline to Month 12 of treatment in distance walked during the

6MWT

Part B

• A hierarchical combination of All-Cause mortality, CV-related

hospitalization, and change from baseline in 6MWT over a 30-month period

Secondary outcome

Key Secondary

Part A

• Change from baseline to Month 12 of treatment in Kansas City Cardiomyopathy

Questionnaire Overall Score (KCCQ-OS)

Part B

• Change from baseline to Month 30 of treatment in distance walked during the

6MWT

• Change from baseline to Month 30 of treatment in KCCQ-OS

Secondary

Part A

• Safety parameters to be assessed: treatment- emergent serious adverse events (SAEs) and adverse events (AEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern

• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 12

• TTR stabilization as measured in established ex-vivo assays (fluorescent probe exclusion [FPE] and Western blot) at Month 12 in the PK-PD substudy

Part B:

• A hierarchical combination of All-Cause mortality and CV-related hospitalization over a 30-month period

• All-Cause Mortality by Month 30

• Cumulative frequency of CV-related hospitalization by Month 30

• CV mortality by Month 30

• Safety parameters: treatment-emergent SAEs and AEs, AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern

• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR

stabilization) at Month 30

• TTR stabilization measured in established ex-vivo assays (FPE and Western

blot) in the PK-PD substudy

Study description

Background summary

Background
Acoramidis is a potent and selective stabilizer of transthyretin (TTR) that is being developed by Eidos Therapeutics, Inc. for the treatment of TTR amyloidosis (ATTR), a progressive, fatal disease in which deposition of amyloid derived from either mutant or wild-type TTR causes severe organ damage and dysfunction.
Clinically, ATTR presents as either a cardiomyopathy (ATTR-CM), an infiltrative, restrictive cardiomyopathy characterized by progressive left and right heart failure, or as a peripheral polyneuropathy (ATTR-PN), a length-dependent neurodegenerative disease affecting sensorimotor and autonomic functions.
Familial ATTR-CM (ATTRm-CM), or FAC, and familial ATTR-PN or familial amyloid polyneuropathy (FAP), are driven by pathogenic point mutations in the TTR gene; over 140 such mutations have been described. In addition, older individuals may develop ATTR derived from wild-type TTR (ATTRwt, formerly called Senile Systemic Amyloidosis [SSA]). In ATTRwt, the major organ involved is the heart (ATTRwt-CM), although carpal tunnel syndrome and tendon involvement are also common.
Destabilization, misfolding, and aggregation of TTR lead to deposition of TTR amyloid and tissue damage. Several small molecules have been shown to bind to and stabilize TTR, potentially preventing the initiating event in amyloidogenesis. Eidos* therapeutic hypothesis is that a highly effective TTR stabilizer will halt or slow ATTR disease progression in ATTR-CM (both mutant ATTR [ATTRm] and ATTRwt) and ATTR-PN.
Acoramidis is a potent, highly selective, small molecule TTR stabilizer. It has demonstrated ability to stabilize TTR in vivo following oral dosing to nonhuman mammals, in healthy volunteers and in patients with ATTR-CM.

Study objective

Key Primary
Part A

• To determine the efficacy of acoramidis (AG10) in the treatment of subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) by evaluating the difference between the acoramidis and placebo groups in the change from baseline in the Six-Minute Walk test (6MWT)
Part B
• To determine the efficacy of acoramidis in the treatment of subjects with symptomatic ATTR-CM by evaluating the difference between the acoramidis and placebo groups in the combined endpoint of All-Cause Mortality and the cumulative frequency of cardiovascular (CV) related hospitalization, and change from baseline in 6MWT

Key Secondary
Part A
To evaluate the effects of acoramidis on quality of life (QoL) in subjects with symptomatic ATTR-CM
Part B
• To evaluate the effects of acoramidis on 6MWT
• To evaluate the effects of acoramidis on health-related QoL as measured by a heart failure (HF)-specific instrument (KCCQ) in subjects with symptomatic ATTR-CM

Secondary
Part A
• To assess safety and tolerability of acoramidis in subjects with symptomatic ATTR-CM
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by
o circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and
o established ex vivo assays of TTR stabilization
Part B:
• To determine the efficacy of acoramidis treatment as measured by the components of the primary endpoint
• To determine the efficacy of acoramidis in reducing CV mortality in subjects with symptomatic ATTR-CM
• To evaluate the safety and tolerability of acoramidis administered for 30 months in subjects with symptomatic ATTR-CM
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by
o circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and
o established ex vivo assays of TTR stabilization

Exploratory
Part A and B:
• To evaluate the effects of acoramidis on circulating biomarkers of myocardial wall stress and microvascular ischemia in subjects with symptomatic ATTR-CM
• To characterize PK of acoramidis and its predominant metabolite administered orally twice daily (BID) in subjects with symptomatic ATTR-CM

• To describe the population PK (PopPK) of acoramidis in subjects with ATTR-CM
• To describe the PD properties and the pharmacokinetic (PK)-PD relationship of acoramidis as assessed by circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and by established ex vivo assays of TTR stabilization, and correlated with acoramidis PK
• To evaluate the effects of acoramidis on health-related QoL as measured by EuroQol Health Outcomes Assessment tool (EQ-5D-5L) in subjects with symptomatic ATTR-CM
• To assess the ability of acoramidis to bind and stabilize a diverse array of pathogenic and likely pathogenic variant TTR tetrameric species, representing amino acid substitutions located throughout the sequence of TTR that are responsible for a spectrum of clinical presentations, from sera and/or plasma of subjects with ATTR-CM

Study design

Study Design and Investigational Plan
This prospective, Phase 3, randomized, multicenter, parallel-group study will evaluate the efficacy and safety of acoramidis in symptomatic subjects compared to placebo, administered on a background of stable heart failure therapy. Screening and randomization will be followed by a total of 30 months of blinded, placebo-controlled treatment. At the end of 12 months of treatment (Part A) efficacy of acoramidis will be assessed through analyses of the functional (6MWT) and health-related QoL (as measured by HF-specific instrument KCCQ) endpoints. At the end of 30 months of treatment (Part B), efficacy of acoramidis will be further assessed through analysis of All-cause mortality, CV-related hospitalizations, and change from baseline in 6MWT.

Subjects are not allowed to be treated with any ATTR-CM specific therapy during the first 12 months of the study. If a subject chooses treatment with ATTR-CM specific therapy, they will be asked to complete an early termination visit prior to discontinuation/withdrawal.

If, during participation in the study, tafamidis becomes available for the indication of ATTR-CM and subjects have access to it, subjects will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy. Currently, tafamidis is approved for the treatment of ATTR-CM in some regions. Subjects initiating therapy with tafamidis indicated for ATTR-CM must have completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, that subject should have an unscheduled visit with study assessments prior to initiation of the concomitant therapy. No other approved or investigational treatments, or therapies used off-label or as nonprescription supplements for the treatment of ATTR-CM will be permitted at any time during the study.

If a subject chooses to discontinue investigational medicinal product (IMP),

discontinue or withdraw from the trial at any time, they will be asked to complete an early termination visit and associated procedures. If a subject chooses to initiate treatment with another therapy, including tafamidis in the first 12 months of the study, they will be asked to complete an ET visit and associated procedures prior to discontinuation/withdrawal. Subjects will continue monthly telephone contact up to Month 30. All participating subjects will be asked to consent to determination of vital status (alive, death, heart transplant, receiving cardiac mechanical assist device [CMAD]) at Month 30, either via direct contact or through public records, regardless of discontinuation or withdrawal status. Unless precluded by governing law or regulation, consent for determination of vital status through public records may not be withdrawn.

All subjects who complete 30 months of blinded study therapy and the final assessments of the double-blind treatment period (Month 30 visit) may be eligible to participate in an Open Label Extension (OLE) study (Study AG10-304, a separate protocol) of long-term acoramidis treatment.

Eligible subjects will be randomized in a 2:1 ratio to acoramidis HCl 800 mg or matching placebo administered orally BID. Subjects will be stratified at randomization based on whether they have wild-type ATTR-CM (ATTRwt CM) or mutant ATTR-CM (ATTRm-CM) with a target of 20% of subjects with ATTRm-CM. Subjects will also be stratified according to NT-proBNP level (<= 3000 vs > 3000 pg/mL) and renal function defined by eGFR (>= 45 vs < 45 mL/min/1.73 m2) at Screening. Samples for plasma PK and serum/plasma PD will be collected in the PK-PD substudy.
Information on AEs and concomitant medications will be collected throughout the study. The safety and conduct of the study will be monitored by an independent Data Monitoring Committee (DMC).

Intervention

Test Product, Dosage, and Mode of Administration:
Day 1 through end of Double-blind Treatment: 800 mg acoramidis hydrochloride (HCl) or matching placebo, BID, by mouth

Study burden and risks

See ICF section 7.0

Contacts

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Scientific
Eidos Therapeutics, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible to participate in the study, subjects must meet all the following criteria:
1. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
2. Male or female >= 18 to <= 90 years of age at time of randomization.
3. Have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype (confirmed by genotyping) based on either:
1. endomyocardial biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry; or
2. positive technetium-99m (99mTc)-pyrophosphate (PYP) or bisphosphonate (DPD or HMDP/HDP) scan, combined with accepted laboratory criteria excluding a diagnosis of AL amyloidosis (based on both immunofixation electrophoresis (IFE) of serum and urine, and serum free light chain (sFLC) analysis).
Subjects with concurrent monoclonal gammopathy of undetermined significance (MGUS) may require confirmation of the diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry.
4. Have

a. a history of heart failure evidenced by at least one prior hospitalization for heart failure or
b. clinical evidence of heart failure without prior heart failure hospitalization manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral edema) or
c. heart failure symptoms that required or require ongoing treatment with a diuretic.
5. Have NYHA Class I-III symptoms due to ATTR-CM.
6. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception beginning with randomization and continuing for 30 days after the last dose of IMP. A male subject who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control.
7. Subjects taking cardiovascular medical therapy, with the exception of diuretic dosing, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.
8. Have completed >= 150 m on the 6MWT on at least 2 tests > 24 hours to <= 3 weeks apart and prior to randomization. The distance walked must be within 15% on two tests.
If one of the first two tests is not >= 150 m or the first two tests are not within 15% of distance walked, a third test must be conducted <= 3 weeks of the first test. If the third test is still not >= 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation.
9. Must have NT-proBNP levels >= 300 pg/mL at Screening.
10. Must have LV wall (interventricular septum or LV posterior wall) thickness >= 12 mm as measured by transthoracic echocardiogram (ECHO) or cardiac magnetic resonance (CMR) documented in medical history within 10 years of Screening or at Screening ECHO or CMR.

Exclusion criteria

Subjects who meet any of the following criteria at the Screening visit will not be eligible to participate in the study:
1. Acute myocardial infarction, acute coronary syndrome or coronary revascularization within 90 days prior to Screening.
2. Stroke or transient ischemic attack (TIA) within 90 days prior to Screening.
3. Has hemodynamic instability at Screening or Randomization that, in the judgment of the Investigator, would pose too great a risk for participation in the study.
4. Is likely to undergo heart transplantation within a year of Screening.
5. Has confirmed diagnosis of light-chain (AL) amyloidosis.

6. Has abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) or total bilirubin > 3 × ULN.
7. Has NT-proBNP levels >= 8500 pg/mL at Screening.
8. Has estimated glomerular filtration rate (eGFR) by modification of diet for renal disease (MDRD) formula < 15 mL/min/1.73 m2 at Screening.
9. Known hypersensitivity to IMP (acoramidis or placebo), its metabolites, or formulation excipients.
10. Treatment for ATTR-CM with tafamidis, with marketed drug products lacking a labeled indication for ATTR-CM (e.g., diflunisal, doxycycline), or with natural products or derivatives used as unproven therapies for ATTR-CM (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) within 14 days prior to dosing; treatment with patisiran, inotersen, or other gene silencing agent: within 90 days for patisiran, 180 days for inotersen, and 5 half-lives for any other gene silencing agent, prior to dosing.
If, during participation in the study, subjects gain access to tafamidis, they will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy.
11. Requires treatment with calcium channel blockers with conduction system effects (e.g., verapamil, diltiazem). The use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.
12. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before IMP is administered. A negative urine pregnancy test at Screening and at Randomization are required for female subjects of childbearing potential.
13. In the judgment of the Investigator or Medical Monitor, has any clinically important ongoing medical condition or laboratory abnormality or condition that might jeopardize the subject*s safety, increase their risk from participation, or interfere with the study.
14. Participation in another investigational clinical trial within 30 days prior to dosing with potential residual effects that might confound the results of this study. Participation in observational and/or registry studies should be discussed with the Medical Monitor.
15. Has any condition that, in the opinion of the Investigator or Medical Monitor, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition.

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):	10-02-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AG10
Generic name:	3-(3-(3,5-DIMETHYL-1H-PYRAZOL-4-YL)PROPOXY)-4-FLUOROBENZOIC ACID

Ethics review

Approved WMO Date:	07-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2020
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	07-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2018-004280-32-NL
ClinicalTrials.gov	NCT03860935
CCMO	NL70635.056.19

Study results

Date completed:	04-05-2023
Results posted:	06-05-2024

First publication
22-04-2024

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents

File