An Open-Label Extension and Safety Monitoring Study of Acoramidis (AG10) in Participants with Symptomatic Transthyretin Amyloid Cardiomyopathy Who Completed the Phase 3 ATTRibute-CM Trial (AG10-301)

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This study has been transitioned to CTIS with ID 2024-515092-36-00 check the CTIS register for the current data. Primary• To assess safety and tolerability of acoramidis in participants with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM)…

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

Summary

ID

NL-OMON53804

Source
ToetsingOnline

Brief title
Extension study and safety monitoring of AG10 in ATTR-CM

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Transthyretin Amyloid Cardiomyopathy (ATTRibute-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 (ATTRibute-CM)

Outcome measures

Primary outcome

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

Secondary outcome

• All-cause mortality and CV mortality

• Change from Baseline in distance walked during the 6MWT (6MWD)

• Change from Baseline in KCCQ Overall Summary Score (KCCQ-OS)

• CV-related hospitalization

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

• TTR stabilization measured in established ex vivo assays (FPE and Western blot) in the PK-PD substudy

Study description

Background summary

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 variant 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.
Variant ATTR-CM (ATTRv-CM) and ATTR-PN (formerly referred to as 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). In ATTRwt, the major organ involved is the heart (ATTRwt-CM), although carpal tunnel syndrome and tendon involvement are common, and may also involve the peripheral nervous system.
Destabilization, misfolding, and aggregation of TTR lead to the 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 variant ATTR [ATTRv] and ATTRwt) and ATTR-PN.
Acoramidis is a potent, highly selective, small-molecule TTR stabilizer. It has demonstrated the ability to stabilize TTR in vivo following oral dosing to nonhuman mammals, in healthy volunteers and participants with ATTR-CM.

Study objective

This study has been transitioned to CTIS with ID 2024-515092-36-00 check the CTIS register for the current data.

Primary
• To assess safety and tolerability of acoramidis in participants with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM)

Secondary
• To evaluate the effect of acoramidis on all-cause mortality (ACM) and cardiovascular (CV) mortality
• To evaluate the effect of acoramidis on the 6- minute walk test (6MWT)
• To evaluate the effect of acoramidis on health- related quality of life (QoL) Kansas City Cardiomyopathy Questionnaire (KCCQ)

• To evaluate the effect of acoramidis on the frequency of CV-related hospitalization (CVH)
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by
o circulating TTR concentration as an in vivo biomarker of stabilization and
o established ex vivo assays of TTR stabilization

Study design

The primary objective of this prospective, multi-center, open-label study is to evaluate the long-term safety and tolerability of acoramidis in patients with an established diagnosis of ATTR-CM and heart failure who are concomitantly treated with currently recommended heart failure therapies. Secondary efficacy and PD objectives will be assessed. Exploratory objectives may also be assessed.
All participants who complete 30 months of blinded study treatment and the Month 30 assessments of the double-blind treatment period of the Phase 3 ATTRibute-CM trial (AG10-301) may be eligible to participate in this Open Label Extension (OLE) study of acoramidis. The Day 1 visit in Study AG10-304 may be the same as the Month 30 visit in Study AG10-301. Under these circumstances, the last dose of Investigational Medicinal Product (IMP) in Study AG10-301 (either blinded acoramidis or matching placebo) will be the night before the day of the Month 30 visit. The first dose of open-label acoramidis in Study AG10-304 will be during the Study AG10-304 Day 1 visit after baseline assessments have been completed.
Currently, tafamidis is approved for the treatment of ATTR-CM in some regions. Participants are not allowed to be treated with tafamidis or any other ATTR-CM-specific approved or investigational treatment, or therapies used off-label or as non-prescription supplements for ATTR-CM at any time during the study. If participants choose treatment with an alternative treatment as described above, they will be asked to discontinue acoramidis and complete an End of Treatment (EoT) form, and they may be asked to discontinue/withdraw from the study. If a participant discontinues/withdraws from the study, the participant will be asked to complete an early termination visit and a safety follow-up visit.
Participants are not permitted to participate in another interventional clinical trial (except Study AG10-301) within 30 days prior to dosing and throughout Study AG10-304. Participants who choose to participate in another interventional clinical trial will be asked to withdraw from acoramidis and complete an EoT form, and they may be asked to discontinue/withdraw from the study. If a participant discontinues/withdraws from the study, the participant will be asked to complete an early termination visit and a safety follow-up visit. Participation in observational and/or registry studies should be discussed with the Medical Monitor.
If a participant chooses to withdraw from acoramidis, the participant will be asked to complete an EoT form, and they may be asked to discontinue/withdraw from the study. If a participant discontinues/withdraws from the study, the participant will be asked to complete an early termination visit and a safety

follow-up visit (in a clinic or AE collection by phone, if the participant refuses a visit to the clinic) 30 days after the last dose of acoramidis.
Vital status (alive, death, heart transplant, receiving cardiac mechanical assist device [CMAD]) will be collected yearly until Month 60, either via direct contact or through public records. Unless precluded by governing law or regulation, consent for determination of vital status through public records may not be withdrawn.
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: 712 mg acoramidis (equivalent to 800 mg acoramidis HCl), BID, by mouth

Study burden and risks

See ICF section 7.0

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

To be eligible to participate in this OLE study, participants must meet all the following criteria:
1. Completed 30 months of the blinded study treatment in Study AG10-301 and the Study AG10-301 Month 30 visit including assessments and procedures.
2. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
3. Female participants of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception beginning with enrollment and continuing for 30 days after the last dose of acoramidis. Female participants using oral contraceptives must agree to use an additional birth control method. While not considered highly effective, a double-barrier method is acceptable. A male participant 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.

Exclusion criteria

Participants who meet any of the following criteria at the Day 1 visit will not be eligible to participate in the study:
1. Has hemodynamic instability, that in the judgment of the Investigator, would pose too great a risk for participation in the study.
2. Has had a heart and/or liver transplant within the year prior to Day 1.
3. Has had implantation of a cardiac mechanical assist device (CMAD).
4. Has confirmed diagnosis of light-chain (AL) amyloidosis at any time during Study AG10-301.
5. Is on dialysis or has a degree of renal impairment that in the opinion of the Investigator might jeopardize the participant*s safety, increase their risk from participation, or interfere with the study.
6. Known hypersensitivity to acoramidis, its metabolites, or formulation excipients.
7. At the end of Study AG10-301 or at Day 1 of Study AG10-304 (or any time during the study), participant is on prohibited medication.
8. Females who are pregnant or breastfeeding. A negative urine pregnancy test at the Day 1 visit and at each study visit are required for female participants of childbearing potential.

9. 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 participant*s safety, increase their risk from participation, or interfere with the study.
10. Participation in another interventional clinical trial (with the exception of Study AG10-301) within 30 days prior to dosing. Participation in observational and/or registry studies should be discussed with the Medical Monitor.
11. 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
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-12-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Registration:	No
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:	23-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2024
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
EU-CTR	CTIS2024-515092-36-00
EudraCT	EUCTR2020-005643-22-NL
CCMO	NL81127.056.22