CLINICAL STUDY RESULTS

Title of clinical study	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)
Protocol no.	Eidos AG10-301
EudraCT study no.	2018-004280-32
Date	22 April 2024
Study Sponsor	Eidos Therapeutics, Inc.
Name and contact details of medical liaison	Principal Investigator, Professor Julian D. Gillmore, MBBS, MD, PhD; Professor of Medicine and Honorary Consultant Nephrologist, Division of Medicine, University College, London

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GENERAL INFORMATION ABOUT THE STUDY

Why was this study done?

Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM) is a rare heart disease that occurs when the protein, transthyretin (TTR), becomes unstable, clumps together in the blood and deposits in the heart, which causes the disease, called cardiac amyloidosis. The build-up of this amyloid protein in the heart muscle can cause serious damage leading to heart failure. Heart failure occurs when the heart is not able to pump enough blood to the body and the body's organs can then become damaged. Heart failure can lead to hospital visits and can result in death.

The Sponsor for this study, Eidos Therapeutics, Inc., a BridgeBio company, is trying to find out if a potential medicine called acoramidis, (AG10), can help people who have ATTR-CM, and to see if this investigational medicine slows down the deposition of amyloid protein in the heart. To do this, researchers looked at whether acoramidis could be effective and whether acoramidis had any side effects when given to people with ATTR-CM.

The researchers gave acoramidis pills to participants with ATTR-CM or placebo pills (that looked the same as acoramidis pill but did not contain acoramidis) for a period of up to 30 months. The researchers wanted to find out if giving acoramidis was better than giving placebo for treating ATTR-CM.

To answer the question, researchers looked at whether participants receiving acoramidis when compared to those taking placebo were less likely to die, were less likely to visit and stay in the hospital for heart problems, had lower blood levels of laboratory measure of N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP) associated with worsening of ATTR-CM, and were able to walk further in 6 minutes. In addition, the researchers looked at how the participants answered questions about their health and overall quality of life and looked at the levels of TTR protein in the blood.

Researchers also looked at whether giving acoramidis caused any side effects and if participants were able to take it without problems throughout the 30 months of the study period. To answer this question the researchers looked at the possible side effects, and other measurements including laboratory tests.

Where did this study take place?

The study took place in 95 centres (clinics specialised in the care of ATTR-CM participants) in the following 18 countries:

- Australia: 71 participants
- Belgium: 27 participants
- Brazil: 7 participants
- Canada: 32 participants
- Czech Republic: 28 participants
- Denmark: 43 participants
- Greece: 8 participants
- Ireland: 6 participants

- Israel: 20 participants
- Italy: 68 participants
- Netherlands: 16 participants
- New Zealand: 28 participants
- Poland: 2 participants
- Portugal: 2 participants
- South Korea: 4 participants
- Spain: 58 participants
- United Kingdom: 86 participants
- United States: 126 participants

When was this study done?

This study was conducted from April 2019 to May 2023.

Who took part in the study?

Six hundred and thirty-two male and female participants aged between 18 and 90 who had been diagnosed with ATTR-CM took part in the study. To participate in the study, they had to meet criteria such as:

- Providing informed consent
- Diagnosis of ATTR-CM
- Genetic testing to see if they had a hereditary variant TTR gene (gene abnormality that might cause the disease) or if they had ATTR-CM without an identified gene abnormality
- History of heart failure symptoms
- Able to walk 150 metres or more on at least two 6-minute walk tests
- Have an elevated level of NT-proBNP in their blood
- The thickness of the muscle walls in the heart was at least 12 millimetres

Participants could not participate in the study for reasons such as:

- A confirmed diagnosis of a different type of amyloidosis also known as light chain amyloidosis
- Any of the following recent medical problems happening shortly before the start of the study:
    - Heart attack (acute myocardial infarction)
    - Decreased blood flow to the heart (acute coronary syndrome)
    - Procedures to restore the blood flow to areas of the heart that are not getting enough blood
    - Stroke or mini stroke
- Laboratory measurements showing severe kidney disease

What happened during the study?

The study, known as ATTRibute-CM (AG10-301), was a large Phase 3 study. A Phase 3 study tests the safety and how well a new treatment works. This study looked at how effective and safe acoramidis was in participants diagnosed with ATTR-CM.

The study included 632 participants. Participants were assigned to either the acoramidis treatment and received two pills each containing 400 milligrams of acoramidis hydrochloride (total 800 milligrams), or the matching placebo (sugar pill) treatment. For every two participants who received acoramidis, one participant received placebo. There were 421 participants receiving acoramidis and 211 receiving placebo treatment. Neither the study participants nor the doctors knew which treatment they would receive (this is called a "double blind" study). This was done to make sure the study results were not influenced in any way.

The total length of the study for a participant was up to 32 months. This included 30 months of taking acoramidis or placebo. Vital status (collection of health status including determination of whether a participant is alive or has died) was collected at the end of the study (Month 30) for all participants even if they had stopped the treatment earlier.

During the study, participants were required to visit their study doctor approximately every 3 months for up to 30 months.

During these visits, the study doctor assessed their health status including checking their symptoms, performing a physical examination, laboratory tests on blood and urine, and a heart test (EKG).

On the months that participants were not required to visit their study doctor, the study doctor contacted them by telephone.

At the end of the study, researchers wanted to look at the study data to see how effective acoramidis had been. Researchers evaluated the results by observing:

- How many participants had died during the study from any cause
- How many participants had gone into hospital with heart problems
- If there were changes in the blood NT-proBNP levels compared to when participants started the study
- Whether there had been any changes in the distance walked in the 6-minute walk test compared to when the test was taken at the start of the study

At the end of this study, participants were offered the possibility to continue acoramidis treatment in a separate study (extension study) to help researchers collect more data on the safety of continuing use of acoramidis.

OVERALL STUDY RESULTS

The average age of participants taking part in the study was 77 years. Nearly all were 65 years or older (96.6%). Most were male (90.8%), white (87.9%), and recently diagnosed with ATTR-CM. About 10% of the study participants carried the variant TTR gene.
The results of the study showed that there was a beneficial effect in participants taking acoramidis compared with those participants who took placebo. This was based on the measurements the researchers had taken throughout the study that looked at deaths, hospital stays for heart problems, measures of levels of NT-proBNP, and distance walked in 6

minutes. Based on these measures, the results showed that those who had taken acoramidis had a higher chance (77.2%) of obtaining a benefit compared with those who took the placebo.

The results at the end of the study included:

- Looking at the data of those participants that had died during the study of any cause, acoramidis treatment was associated with a reduction (25%) in risk of death by any cause.
- Looking at the data of those participants that visited hospital due to heart related problems during the study, a reduction (50%) in the annual number of visits to the hospital for those participants who took acoramidis was found.
- When the deaths and hospital visits for heart-related problems were analyzed together, the researchers found that the treatment benefit in the group receiving acoramidis was observed as early as 3 months after starting treatment and continued until Month 30.
- The participants treated with acoramidis were able to walk on average approximately 40 metres more than those who took placebo, a clinically meaningful difference.
- Participants treated with acoramidis had a better effect than placebo on quality of life.
- Participants treated with acoramidis had a better effect than placebo on blood levels of NT-proBNP.

Researchers look at the results of many studies to decide which drugs work well and are safe for participants. It takes participants in many studies all around the world to advance medical science. The results from this study may be different than other studies that researchers review.

Were there any side effects?

This study evaluated the safety of acoramidis, and the results showed that it was generally well tolerated (participants were able to take it without problems) with no identified side effects of potential safety concern.

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could have been caused by a study treatment, or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across the different groups, doctors try to understand what the side effects of an experimental drug might be.

Overall, medical problems were reported in the same proportion in participants receiving acoramidis and in participants receiving placebo.

Six-hundred nineteen out of 632 participants (97.9%) in this study had at least 1 medical problem. In this study, the percentage of participants with medical problems was similar in each group:

- Acoramidis: 98.1% (413 out of 421 participants)
- Placebo: 97.6% (206 out of 211 participants)

Some of the medical problems were considered by the study doctor as related to the study drug. In this study, more participants in the acoramidis group had medical problems that were

considered by the study doctor as related to the study drug, compared to participants in the placebo group.

- Acoramidis: 11.9% (50 out of 421 participants)
- Placebo: 5.2% (11 out of 211 participants)

The most common medical problems are listed here.

Most Common Medical Problems (Reported by More Than 15% of Participants)		
Medical Problem	**Acoramidis (421 Participants treated)**	**Placebo (211 Participants treated)**
Cardiac failure	101 (24.0%)	83 (39.3%)
COVID-19	89 (21.1%)	30 (14.2%)
Atrial fibrillation (irregular heartbeat)	70 (16.6%)	46 (21.8%)
Fall	67 (15.9%)	39 (18.5%)
Dyspnoea (shortness of breath)	52 (12.4%)	40 (19.0%)
Constipation	52 (12.4%)	32 (15.2%)

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems. Out of 632 participants, 367 (58.1%) had serious medical problems. A total of 2 participants (0.3%) had serious medical problems that study doctor thought were related to acoramidis.

In most cases, the medical problems reported in the study could be explained by the existing medical conditions present in these study participants. Acoramidis was generally well tolerated with no identified side effects of potential safety concern.

Ninety-six out of 632 participants (15.2%) died during the study. None of these deaths were determined to be related to study treatment but were due to participant’s medical conditions.

COMMENTS ON THE OUTCOME OF THE TRIAL

What do these results mean for the general population?

The purpose of this summary is to share the results of the AG10-301 study with the general public. Researchers look at the results of many studies to decide which drugs work best and are safest for participants. It takes participants in many studies all around the world to advance medical science. The results from this study may be different to other studies that researchers review.

The results from this study have shown that there was in general a beneficial effect to the participants with ATTR-CM (participants with either the naturally occurring TTR gene or the variant gene) that took acoramidis treatment during the study. This was demonstrated in the measurements that the researchers took during the study which included looking at how many participants died during the study (of all causes) and the number of times participants had to stay in a hospital because of heart problems.

In this study, researchers showed that giving acoramidis was better than giving placebo for treating participants with ATTR-CM and was generally well tolerated with no identified side effects that may cause concern.

The results of the study are summarized for the groups of participants that were treated with either acoramidis or placebo. Not every participant in the study had the same result.

What other studies are being done on this disease/condition?

Several other studies are being conducted in participants with ATTR-CM. More information can be obtained from your doctor. Researchers are also looking at different ways of treating ATTR-CM.

ADDITIONAL INFORMATION

Some additional information on different aspects of the ATTR-CM disease can be found at:

- **Amyloidosis Research Consortium** (www.arci.org) – An organisation dedicated to driving advances in the awareness, science, and treatment of amyloid diseases.
- **Amyloidosis Alliance** (www.amyloidosisalliance.org) – A global organisation that fosters communication and mutual support between patient associations, to bring together voices from around the world to hopefully fight amyloidosis.
- **Amyloidosis Support Groups** (www.amyloidosissupport.org) – An organisation that provides resources and support to those living with amyloidosis in the US.