ORIGINAL ARTICLE

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND

Transthyretin amyloid cardiomyopathy is characterized by the deposition of misfolded monomeric transthyretin (TTR) in the heart. Acoramidis is a high-affinity TTR stabilizer that acts to inhibit dissociation of tetrameric TTR and leads to more than 90% stabilization across the dosing interval as measured ex vivo.

METHODS

In this phase 3, double-blind trial, we randomly assigned patients with transthyretin amyloid cardiomyopathy in a 2:1 ratio to receive acoramidis hydrochloride at a dose of 800 mg twice daily or matching placebo for 30 months. Efficacy was assessed in the patients who had an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area. The four-step primary hierarchical analysis included death from any cause, cardiovascular-related hospitalization, the change from baseline in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in the 6-minute walk distance. We used the Finkelstein–Schoenfeld method to compare all potential pairs of patients within strata to generate a P value. Key secondary outcomes were death from any cause, the 6-minute walk distance, the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary, and the serum TTR level.

RESULTS

A total of 632 patients underwent randomization. The primary analysis favored acoramidis over placebo (P<0.001); the corresponding win ratio was 1.8 (95% confidence interval [CI], 1.4 to 2.2), with 63.7% of pairwise comparisons favoring acoramidis and 35.9% favoring placebo. Together, death from any cause and cardiovascular-related hospitalization contributed more than half the wins and losses to the win ratio (58% of all pairwise comparisons); NT-proBNP pairwise comparisons yielded the highest ratio of wins to losses (23.3% vs. 7.0%). The overall incidence of adverse events was similar in the acoramidis group and the placebo group (98.1% and 97.6%, respectively); serious adverse events were reported in 54.6% and 64.9% of the patients.

CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, the receipt of acoramidis resulted in a significantly better four-step primary hierarchical outcome containing components of mortality, morbidity, and function than placebo. Adverse events were similar in the two groups. (Funded by BridgeBio Pharma; ATTRibute-CM ClinicalTrials.gov number, NCT03860935.)

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*A list of the ATTRibute-CM investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Transthyretin amyloid cardiomyopathy is characterized by destabilization of transthyretin (TTR) tetramers, dissociation into unstable monomers, and their subsequent deposition as amyloid fibrils in the myocardium.[1,2] This condition is a restrictive cardiomyopathy that causes heart failure, usually with preserved ejection fraction.[2] Delays in diagnosis and impaired quality of life are common.[3,4]

Pathogenic TTR variants that show greater destabilization are associated with increased penetrance, earlier disease onset, and increased clinical severity.[5] Thus, TTR stabilization represents a logical therapeutic strategy that has been shown to be effective for the treatment of transthyretin amyloid cardiomyopathy. In a phase 3 trial, tafamidis was associated with lower risks of death from any cause and cardiovascular-related hospitalization and a lower rate of decline than placebo at 30 months in both the 6-minute walk distance and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS).[6] Dose-related reductions in mortality associated with a dose-related increase in TTR stabilization were reported in a long-term extension study with a median follow-up of 58 months.[7] These data support the concept that greater stabilization of TTR may be associated with better clinical outcomes.

A rare mutation (T119M) in the gene encoding TTR results in a variant with better stabilization of the tetramer than wild-type TTR because of unique hydrogen bonding, protection of V30M compound heterozygotes from amyloidosis,[5] and increased TTR levels; the T119M variant may also reduce cardiovascular events and prolong survival in the general population.[5,8,9] Acoramidis (also called AG10) is a novel TTR stabilizer that is designed to mimic the action of the T119M variant.[10] Consistent with its rational design, acoramidis achieves near-complete stabilization (>90% across the entire dosing interval)[9,11] in both wild-type TTR and across all variants that have been tested.[12-14] As compared with other well-characterized TTR stabilizers (tafamidis, diflunisal, and tolcapone), acoramidis has shown improved potency, binding affinity, binding-site occupancy, binding thermodynamics, and TTR stabilization when assayed by a number of quantitative techniques. Structural analysis by x-ray crystallography of cocrystals of TTR with acoramidis bound to the T4 binding sites corroborated those measurements. The more efficient stabilization by acoramidis was attributed to its primarily enthalpic binding mode (which involves hydrogen bonding mimicking the T119M variant) as compared with the predominantly entropic (hydrophobic) binding mode of tafamidis and diflunisal.[10] In findings that were consistent with these data, in a phase 2 study, we observed near-complete stabilization (>90% across the dosing interval) of both wild-type and variant TTR with acoramidis.[11] We subsequently performed a phase 3 trial — Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM) — to evaluate acoramidis in patients with this condition.



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METHODS

OVERSIGHT

The trial was conducted in accordance with the International Council for Harmonisation, Good Clinical Practice guidelines, and the Declaration of Helsinki. The trial was approved by an ethics committee at each participating site. All the patients provided written informed consent.

An independent data and safety monitoring committee monitored unblinded data throughout the trial. An independent clinical events committee adjudicated all outcome events. An independent data reporting center contributed to the statistical analysis plan, independently analyzed the data, and confirmed the results. Data were entered electronically and remained blinded until analyzed in parallel by representatives of the sponsor, BridgeBio Pharma, and the data reporting center. All the authors had full access to the trial data.

The trial was designed by representatives of BridgeBio Pharma. Clinical and laboratory data were collected centrally by a clinical research organization (ICON); a different clinical research organization (UBC) collected safety data. The first draft of the manuscript was written by the last author; the decision to submit the manuscript for publication was made by all the authors. The protocol (available with the full text of this article at NEJM.org) and related documents were filed with regulatory authorities and ethics committees. The authors and the independent data reporting center vouch for the data and their analyses; representatives of BridgeBio Pharma vouch for the fidelity of the trial to the protocol.

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PATIENTS

Eligible patients were between the ages of 18 and 90 years and had met the following two criteria: an established diagnosis of transthyretin amyloid cardiomyopathy on the basis of either an endomyocardial biopsy with confirmatory typing or positive results (Perugini grade, ≥2) on technetium-99m scintigraphy combined with biochemical exclusion of a monoclonal gammopathy characteristic of light chain (AL) amyloidosis; and clinical heart failure with at least one previous hospitalization for heart failure, signs and symptoms of volume overload, or heart failure that resulted in diuretic treatment. Randomization required a 6-minute walk distance of 150 m or more on at least two tests performed 24 hours to 3 weeks apart, a level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) of 300 pg per milliliter or more, and a left ventricular wall thickness of 12 mm or more on a previous imaging study.

Exclusion criteria included acute coronary syndrome, coronary revascularization, stroke, or transient ischemic attack within 90 days before screening; likely heart transplantation within a year after screening; a diagnosis of AL amyloidosis; a level of alanine aminotransferase or aspartate aminotransferase of more than two times the upper limit of the normal range or a total bilirubin level of three times the upper limit of the normal range; an NT-proBNP level of 8500 pg per milliliter or more; or an estimated glomerular filtration rate (eGFR) of less than 15 ml per minute per 1.73 m^2 of body-surface area. Treatment with tafamidis was not permitted during the initial 12 months of the trial, although such treatment was permitted thereafter.

RANDOMIZATION AND TREATMENT

The patients were randomly assigned in a 2:1 ratio to receive acoramidis hydrochloride at a dose of 800 mg or matching placebo twice daily for 30 months. Randomization was stratified according to the TTR genotype (wild-type or variant), NT-proBNP level (≤3000 or >3000 pg per milliliter), and eGFR (<45 or ≥45 ml per minute per 1.73 m^2), values that corresponded to the staging criteria of the National Amyloidosis Centre.[15] Patients with an eGFR of less than 30 ml per minute per 1.73 m^2 (stage 4 chronic kidney disease) were excluded from the primary efficacy analysis but were included in an exploratory safety analysis. Details regarding the rationale for the exploratory safety analysis are provided in the Supplementary Appendix, available at NEJM.org. Patients who completed the 30-month assessments were offered enrollment in an open-label extension trial.

OUTCOMES

The four-step primary hierarchical analysis included death from any cause (which was defined in the trial as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device), cumulative frequency of cardiovascular-related hospitalization, the change from baseline in the NT-proBNP level, and the change from baseline in the 6-minute walk distance. Within each stratum, we compared all the patient pairs using the same four-step hierarchical sequence. For each comparison, we evaluated pairs using the latest common data available over the 30-month trial duration (Fig. S1 in the Supplementary Appendix).

Key secondary outcomes were the change from baseline until month 30 in the following three measures: 6-minute walk distance, KCCQ-OS score, and serum TTR level; the final key secondary outcome in the alpha-controlled sequence was death from any cause. Vital status at 30 months was determined in the patients who had undergone randomization regardless of early discontinuation.

Safety was assessed by analyzing all reported adverse events and serious adverse events as coded according to the definitions of the *Medical Dictionary for Regulatory Activities*, laboratory findings, vital signs, and 12-lead electrocardiography. The incidence of each adverse event during treatment was summarized according to system organ class, preferred term, and treatment assignment. Multiple adverse events that mapped to the same preferred term were counted once per patient.

12-MONTH ANALYSIS

The trial design included an embedded readout at 12 months, with a primary analysis of the 6-minute walk distance, which did not achieve statistical significance, incurring an alpha penalty of 0.01. In the 12-month readout, the two groups had a similar decrease from baseline in the 6-minute walk distance. The least-squares mean change from baseline in the distance walked

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was –26.51 m (95% confidence interval [CI], –37.07 to –15.96) in the acoramidis group and –24.54 m (95% CI, –37.26 to –11.83) in the placebo group. The 12-month KCCQ-OS score (which ranges from 0 to 100, with higher values indicating fewer symptoms and a higher quality of life) — a key secondary outcome — showed a least-squares mean change from baseline of –7.00 (95% CI, –9.65 to –4.34) in the acoramidis group and –10.21 (95% CI, –13.45 to –6.96) in the placebo group. By design, the blinding of the trial continued until the 30-month readout.

STATISTICAL ANALYSIS

Sample-size calculations were based on simulations with a two-sided alpha level of 0.04, given an alpha penalty of 0.01 for the 12-month analysis. In making this calculation, we assumed a risk of death from any cause of 40% in the placebo group, with a hazard ratio of 0.70 and a mean number of cardiovascular-related hospitalizations of 0.75 in the acoramidis group and 1.15 in the placebo group by 30 months, with a trial power of more than 90%.

The modified intention-to-treat population included all the patients who had undergone randomization, received at least one dose of acoramidis or placebo, and had at least one efficacy evaluation after baseline; patients with stage 4 chronic kidney disease (eGFR, <30 ml per minute per 1.73 m^2) were excluded from this population. The safety population included all the patients who had undergone randomization and received at least one dose of acoramidis or placebo.

For the primary analysis, we used the stratified Finkelstein–Schoenfeld method,[16] a modified Wilcoxon score test. During the trial, the prespecified primary analysis was changed from an initial two-component Finkelstein–Schoenfeld analysis of death from any cause and cardiovascular-related hospitalization to a three-component analysis (death from any cause, cardiovascular-related hospitalization, and 6-minute walk distance) and then to a four-component analysis (death from any cause, cardiovascular-related hospitalization, NT-proBNP level, and 6-minute walk distance). The timing, rationale, and details associated with these changes are provided in the Supplementary Appendix.

Because the Finkelstein–Schoenfeld procedure does not generate a useful treatment estimate, we also calculated a win ratio. The stratified win ratio can be expressed as the proportion of pairwise comparisons for which active treatment wins over placebo divided by the proportion of pairwise comparisons for which placebo wins, taking into account both the hierarchical ordering of the comparisons and the strata in which the comparisons are performed.[17]

We formally tested the 30-month key secondary outcomes sequentially at an alpha level of 0.04 in the order of 6-minute walk distance, KCCQ-OS score, serum TTR level, and death from any cause. The 6-minute walk distance, KCCQ-OS score, and serum TTR level were analyzed with the use of a mixed model for repeated measures, with an unstructured covariance matrix, including additional terms for randomization stratification factors, trial visit, and treatment-by-visit interaction. All the patients in the modified intention-to-treat population contributed to each of the analyses of the mixed model for repeated measures as well as to the primary analysis. The handling of missing data for individual observations because of intercurrent events of treatment discontinuation or death is summarized in the Supplementary Methods and in Table S1. Graphical displays of the results of the mixed model for repeated measures used least-squares means to show modeled (not observed) effects. The time until death from any cause was analyzed with the use of a stratified Cox proportional-hazards model that included treatment as an explanatory factor along with the baseline 6-minute walk distance. All statistical analyses were performed with the use of SAS software, version 9.2 or higher (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From April 2019 through October 2020, a total of 632 patients underwent randomization (421 to the acoramidis group and 211 to the placebo group) and were included in the intention-to-treat population. Of these patients, 21 who had stage 4 kidney disease (12 in the acoramidis group and 9 in the placebo group) were excluded from the primary analysis in the modified intention-to-treat population, which included 611 patients (409 in the acoramidis group and 202 in the placebo group).

The mean (±SD) age of the patients was 77±6.6 years; 90.2% were men, and 90.3% had

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Acoramidis (N=421)	Placebo (N=211)	All Patients (N=632)
Age — yr	77.4±6.5	77.1±6.8	77.3±6.6
Sex — no. (%)			
Male	384 (91.2)	186 (88.2)	570 (90.2)
Female	37 (8.8)	25 (11.8)	62 (9.8)
Race or ethnic group — no. (%)†			
White	368 (87.4)	187 (88.6)	555 (87.8)
Black	20 (4.8)	10 (4.7)	30 (4.7)
Asian	10 (2.4)	3 (1.4)	13 (2.1)
Other racial or ethnic group	23 (5.5)	11 (5.2)	34 (5.4)
Transthyretin genotype — no. (%)			
Transthyretin amyloidosis wild-type cardiomyopathy	380 (90.3)	191 (90.5)	571 (90.3)
Transthyretin amyloidosis variant cardiomyopathy	41 (9.7)	20 (9.5)	61 (9.7)
Transthyretin variant — no./total no. (%)			
V30M	1/39 (2.6)	0	1/58 (1.7)
V122I	24/39 (61.5)	12/19 (63.2)	36/58 (62.1)
T60A	3/39 (7.7)	2/19 (10.5)	5/58 (8.6)
E89Q	0	1/19 (5.3)	1/58 (1.7)
Other	11/39 (28.2)	4/19 (21.1)	15/58 (25.9)
NT-proBNP — ng/liter			
Mean	2946±2226	2725±1971	2872±2145
Median (IQR)	2326 (1332–4019)	2306 (1128–3754)	2326 (1278–3910)
Mean eGFR — ml/min/1.73 m^2	61±18	61±19	61±18
NAC stage — no. (%)‡			
I	241 (57.2)	120 (56.9)	361 (57.1)
II	134 (31.8)	69 (32.7)	203 (32.1)
III	46 (10.9)	22 (10.4)	68 (10.8)
NYHA functional class — no. (%)			
I	51 (12.1)	17 (8.1)	68 (10.8)
II	293 (69.6)	162 (76.8)	455 (72.0)
III	77 (18.3)	32 (15.2)	109 (17.2)
Mean serum transthyretin — mg/dl	23±6	24±6	23±6

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, IQR interquartile range, NAC National Amyloidosis Centre, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

† Race or ethnic group was reported by the patients. Other ethnic groups include American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and not reported.

‡ The staging criteria of the National Amyloidosis Centre (NAC) are as follows: stage I, NT-proBNP value of 3000 ng per milliliter or less and eGFR of 45 ml per minute per 1.73 m^2 of body-surface area or more; stage III, NT-proBNP value of more than 3000 ng per milliliter and eGFR of less than 45 ml per minute per 1.73 m^2; the remainder of results are categorized as stage II.

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