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Brief Report

# Efficacy of Acoramidis in Transthyretin Amyloid Cardiomyopathy With and Without Atrial Fibrillation: Results From ATTRibute-CM

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**Key Words:** Acoramidis, ATTR-CM, ATTRibute-CM, arrhythmia.

## Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease caused by transthyretin tetramer destabilization and characterized by arrhythmias and heart failure.[1] Atrial fibrillation and/or atrial flutter (hereafter AF) are common tachyarrhythmias in ATTR-CM and often precede symptoms of heart failure.[1,2] With a reported prevalence of up to 70%,[2] AF in ATTR-CM is associated with a high burden of symptomatic heart failure, reduced quality of life, and adverse outcomes.[2,3] Acoramidis is an oral transthyretin stabilizer for ATTR-CM that achieves near-complete (≥90%) stabilization.[4] In the phase 3 ATTRibute-CM trial (NCT03860935), acoramidis reduced the hierarchical composite primary endpoint (all-cause mortality [ACM], cardiovascular-related hospitalization [CVH], N-terminal pro-B-type natriuretic peptide [NT-

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proBNP] concentration, and 6-minute walk distance [6MWD]) vs placebo.[4]

In this post hoc analysis from ATTRibute-CM, we describe the baseline prevalence and characteristics of participants with and without a diagnosis of AF at baseline (AF+ and AF−, respectively), evaluate clinically relevant endpoints by baseline AF status, and characterize the prevalence of new or worsening AF by treatment.

## Methods

### Study Design and Population

Participants in ATTRibute-CM were randomized 2:1 to receive acoramidis hydrochloride (800 mg) or placebo for 30 months.[4] Concomitant tafamidis was allowed after ≥12 months of study treatment. Eligible participants who completed treatment through month 30 could enroll in the open-label extension.[5] Efficacy was assessed in the ATTRibute-CM modified intention-to-treat population ($n = 611$). The occurrence of new or worsening AF was evaluated in the safety population ($n = 632$).

ATTRibute-CM and the open-label extension were conducted in accordance with the Declaration of Helsinki, and the protocol was independently approved by the ethics committees at each participating site. All participants provided written informed consent.

Baseline AF was defined as the presence of any of the following: (1) a documented medical history of AF at baseline, including previous AF-related procedures (eg, ablation or cardioversion) or the previous use of anticoagulation medication specifically noted for the indication of AF; or (2) evidence of AF on baseline electrocardiograms. New or worsening AF was defined by investigator-reported AF-related treatment-emergent adverse events ("atrial fibrillation," "atrial flutter," or "cardiac flutter") recorded in the clinical database and coded using the Medical Dictionary for Regulatory Activities. CVH included nonelective admissions to an acute care setting for cardiovascular-related morbidity (≥24 hours) or urgent heart failure visits (<24 hours). All CVH were adjudicated by an independent and blinded Clinical Events Committee.

### Statistical Analysis

The risks of ACM or first CVH and ACM were evaluated using Cox proportional hazards models, and cumulative CVH frequency was analyzed using negative binomial regression. Changes from baseline in 6MWD, Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, and NT-proBNP concentration were analyzed using a mixed-effects model for repeated measures, including randomization stratification factors, treatment group, visit, AF diagnosis at baseline, and interactions between treatment, visit, and AF diagnosis at baseline as factors, with baseline value as a covariate. Changes from baseline in serum transthyretin (sTTR) concentrations were compared between treatment groups using a 2-sample $t$ test. Recurrent event analysis of AF-related CVH and new or worsening AF was performed using a Prentice–Williams–Peterson model.

## Results

### Baseline Demographics and Characteristics

Among 611 participants in the efficacy analysis, 68.7% ($n = 420$) had baseline AF (Table 1). The AF+ subgroup was less likely to have variant ATTR-CM and had more advanced disease (ie, greater New York Heart Association functional class and National Amyloidosis Centre stage and lower 6MWD and KCCQ-OS scores) than the AF− subgroup. Mean baseline sTTR concentrations were similar across subgroups and treatment arms.

### Efficacy in Participants With and Without Baseline AF

Treatment with acoramidis reduced the risk of ACM or first CVH, and the annualized frequency of CVH vs placebo, irrespective of baseline AF status through month 30 (Figure 1A, B). Treatment with acoramidis also lowered the risk of ACM in the AF− subgroup through month 42 and had a trend toward a benefit in the AF+ subgroup (Figure 1C). No interaction was observed between baseline AF diagnosis and treatment effect.

Compared with placebo, acoramidis reduced the decline in 6MWD (least-squares mean difference [standard error {SE}]: AF+, 35.0 [11.4] m, $P = .002$; AF−, 50.6 [16.9] m, $P = .003$), KCCQ-OS score (least-squares mean difference [SE]: AF+, 10.0 [2.4], $P < .001$; AF−, 10.0 [3.6], $P = .006$), and blunted increases in NT-proBNP (ratio of adjusted geometric mean fold change [95% confidence interval]: AF+, 0.56 [0.48–0.66]; AF−, 0.46 [0.36–0.59], both $P < .001$) irrespective of baseline AF through month 30. In both AF subgroups, acoramidis demonstrated early and sustained increases from baseline in sTTR concentrations through month 30 (mean [SE] change from baseline at month 30: AF+, 8.8 [0.4] mg/dL; AF−, 9.4 [0.6] mg/dL, both $P < .001$), whereas sTTR concentrations remained relatively unchanged in both AF subgroups with placebo.

### Frequency of New or Worsening AF and AF-Related CVH

The use of acoramidis was associated with a 26% risk reduction in recurrent new or worsening AF events over 30 months vs placebo, regardless of baseline AF status (Figure 2A). A numerically lower frequency of adjudicated AF-related CVH over 30 months was observed in participants treated with acoramidis vs placebo (Figure 2B).

## Discussion

In ATTRibute-CM, AF was common at baseline and was accompanied by increased heart failure symptom severity, disease stage and biomarker values (NT-proBNP),

**Table 1** Baseline demographics and characteristics in AF subgroups (modified intention-to-treat population)

| | With AF Diagnosis at Baseline (AF+)* | | | Without AF Diagnosis at Baseline (AF−)* | | |
|---|---|---|---|---|---|---|
| | Acoramidis (*n* = 282) | Placebo (*n* = 138) | Overall (*N* = 420) | Acoramidis (*n* = 127) | Placebo (*n* = 64) | Overall (*N* = 191) |
| Age, y | 77.6 (6.4) | 77.1 (6.9) | 77.4 (6.6) | 76.8 (6.6) | 76.6 (6.4) | 76.7 (6.5) |
| Male, *n* (%) | 263 (93.3) | 126 (91.3) | 389 (92.6) | 111 (87.4) | 55 (85.9) | 166 (86.9) |
| Race, *n* (%) | | | | | | |
| White | 250 (88.7) | 130 (94.2) | 380 (90.5) | 108 (85.0) | 49 (76.6) | 157 (82.2) |
| Black | 9 (3.2) | 2 (1.4) | 11 (2.6) | 10 (7.9) | 8 (12.5) | 18 (9.4) |
| Asian | 7 (2.5) | 0 | 7 (1.7) | 3 (2.4) | 3 (4.7) | 6 (3.1) |
| Other† | 16 (5.7) | 6 (4.3) | 22 (5.2) | 6 (4.7) | 4 (6.3) | 10 (5.2) |
| Transthyretin genotype,‡ *n* (%) | | | | | | |
| Wild-type ATTR-CM | 255 (90.4) | 129 (93.5) | 384 (91.4) | 115 (90.6) | 53 (82.8) | 168 (88.0) |
| Variant ATTR-CM | 27 (9.6) | 9 (6.5) | 36 (8.6) | 12 (9.4) | 11 (17.2) | 23 (12.0) |
| New York Heart Association functional class, *n* (%) | | | | | | |
| I | 35 (12.4) | 9 (6.5) | 44 (10.5) | 16 (12.6) | 8 (12.5) | 24 (12.6) |
| II | 197 (69.9) | 105 (76.1) | 302 (71.9) | 91 (71.7) | 51 (79.7) | 142 (74.3) |
| III | 50 (17.7) | 24 (17.4) | 74 (17.6) | 20 (15.7) | 5 (7.8) | 25 (13.1) |
| National Amyloidosis Centre stage, *n* (%) | | | | | | |
| 1 | 156 (55.3) | 76 (55.1) | 232 (55.2) | 85 (66.9) | 44 (68.8) | 129 (67.5) |
| 2 | 96 (34.0) | 50 (36.2) | 146 (34.8) | 34 (26.8) | 16 (25.0) | 50 (26.2) |
| 3 | 30 (10.6) | 12 (8.7) | 42 (10.0) | 8 (6.3) | 4 (6.3) | 12 (6.3) |
| 6MWD, m | 354.8 (102.0) | 346.8 (95.7) | 352.2 (99.9) | 380.5 (105.1) | 361.6 (89.7) | 374.2 (100.3) |
| KCCQ-OS score | 70.3 (20.0) | 68.9 (21.2) | 69.8 (20.4) | 74.9 (17.6) | 73.8 (19.1) | 74.6 (18.0) |
| NT-proBNP, pg/mL, median (Q1−Q3) | 2545.5 (1708.0−4283.0) | 2430.0 (1308.0−4115.0) | 2496.5 (1493.5−4279.5) | 1430.0 (864.0−2540.0) | 1879.5 (774.0−2881.0) | 1542.0 (844.0−2638.0) |
| Serum transthyretin, mg/dL | 22.2 (5.3) | 23.8 (6.3) | 22.8 (5.7) | 24.7 (5.8) | 23.0 (5.5) | 24.2 (5.8) |
| eGFR, mL/min/1.73 $m^2$ | 60.5 (16.6) | 60.6 (17.4) | 60.5 (16.8) | 65.2 (18.6) | 66.8 (17.2) | 65.7 (18.1) |
| Source of AF diagnosis at baseline, *n* (%) | | | | | | |
| Medical history | 282 (100.0) | 133 (96.4) | 415 (98.8) | 0 | 0 | 0 |
| Electrocardiogram | 165 (58.5) | 78 (56.5) | 243 (57.9) | 0 | 0 | 0 |
| Both medical history and electrocardiogram | 165 (58.5) | 73 (52.9) | 238 (56.7) | 0 | 0 | 0 |
| Concomitant tafamidis,§ *n* (%) | 39 (13.8) | 32 (23.2) | 71 (16.9) | 22 (17.3) | 14 (21.9) | 36 (18.8) |

Values are mean (standard deviation) unless specified otherwise. Percentages are calculated using the number of participants assigned to each treatment arm as the denominator.

6MWD, 6-minute walk distance; AF, atrial fibrillation and/or atrial flutter; ATTR-CM, transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Baseline AF was defined as the presence of any of the following: (1) a documented medical history of AF at baseline, which also included a previous AF-related procedure (eg, ablation or cardioversion) or the previous use of anticoagulation specifically noted to be for the indication of AF; or (2) evidence of AF on baseline electrocardiograms.

†Other races include American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, and not reported.

‡Transthyretin genotype was reported in the interactive voice/web response system at randomization.

§Concomitant tafamidis was allowed after ≥12 months of study treatment.





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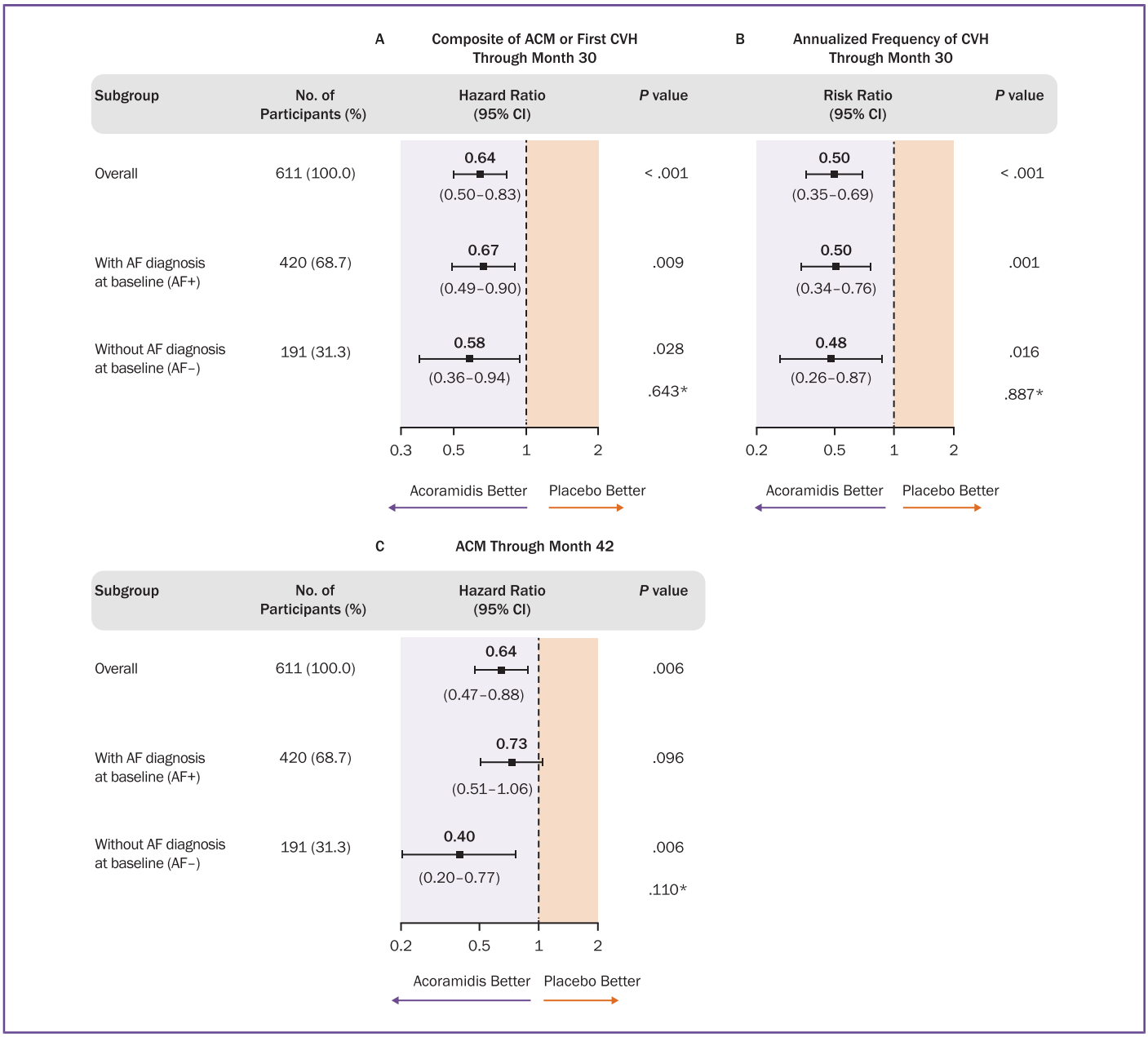


**Fig. 1.** ACM and CVH in AF subgroups. Cox proportional hazards models were used to evaluate the risks of ACM or first CVH and ACM, and negative binomial regression was used to evaluate the annualized frequency of CVH in the modified intention-to-treat population. Treatment with acoramidis significantly reduced the risk of ACM or first CVH (A) and the annualized frequency of CVH (B) through month 30, regardless of baseline AF diagnosis, compared with placebo. Acoramidis significantly lowered the risk of ACM through month 42 (C) in the AF− subgroup compared with placebo; the effect trended toward significance in the AF+ subgroup, with a nonsignificant interaction by baseline AF. Cox proportional hazards models included treatment as an explanatory factor; baseline 6MWD, AF diagnosis at baseline, and the interaction of AF diagnosis at baseline with treatment as covariates; and randomization stratification factors of genotype, NT-proBNP concentration, and eGFR. Negative binomial regression model covariates included treatment group, AF diagnosis at baseline, interaction of AF diagnosis at baseline with treatment, genotype, NT-proBNP concentration, eGFR, and the offset term included in the model. **P* value of the interaction between AF diagnosis at baseline and treatment effect. 6MWD, 6-minute walk distance; ACM, all-cause mortality; AF, atrial fibrillation and/or atrial flutter; CI, confidence interval; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

impaired functional capacity (6MWD) and health status (KCCQ-OS score), and reduced kidney function (estimated glomerular filtration rate). The use of acoramidis demonstrated consistent efficacy across clinical outcomes, biomarkers, and functional and quality-of-life parameters, regardless of baseline AF status, vs placebo.

The current study used a comprehensive and rigorous AF definition to capture the full burden of AF in this population. The only other analysis of treatment efficacy in an ATTR-CM clinical trial population (ATTR-ACT), showed that baseline or historical AF was prognostic for ACM in limited models, but not after more extensive adjustment;

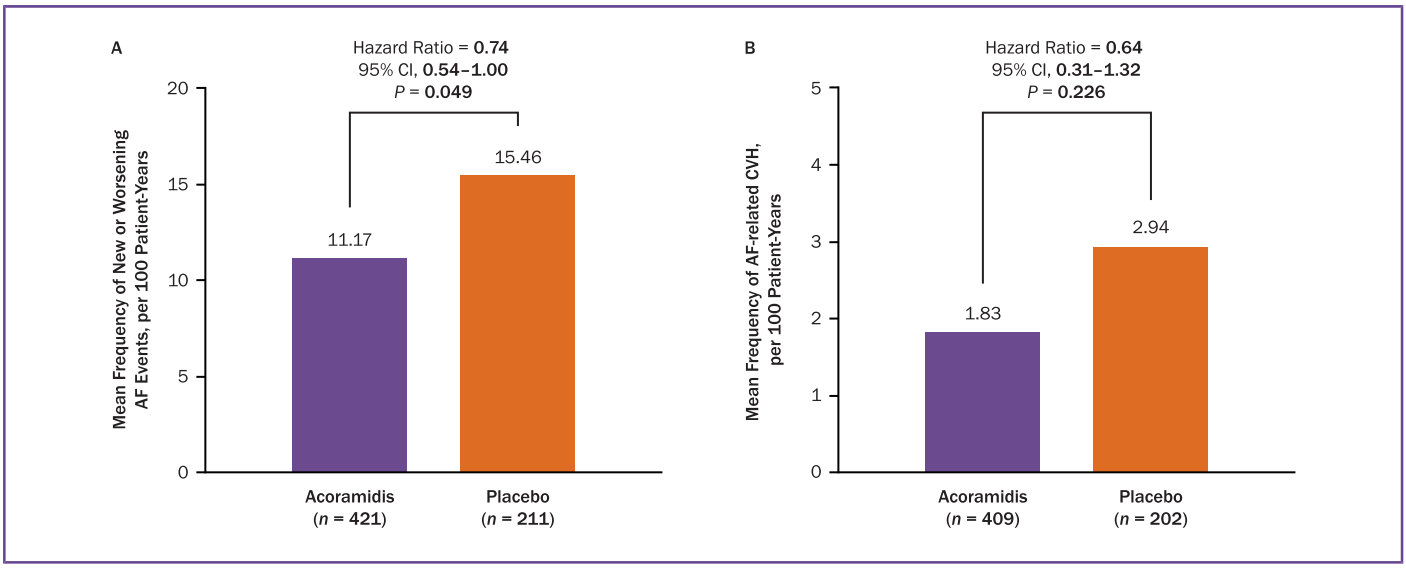


**Fig. 2.** Frequency of new or worsening AF and AF-related CVH. Treatment with acoramidis was associated with a lower frequency of recurrent new or worsening AF events (A) and numerically fewer adjudicated AF-related CVHs (B) compared with placebo. The frequency of CVH attributable to an AF event was assessed in the modified intention-to-treat population, and the frequency of new or worsening AF events was assessed in the safety population, using a Prentice–Williams–Peterson model stratified by baseline randomization stratification factors and adjusted for baseline 6MWD. 6MWD, 6-minute walk distance; AF, atrial fibrillation and/or atrial flutter; CI, confidence interval; CVH, cardiovascular-related hospitalization; HR, hazard ratio.

there was no interaction between tafamidis treatment and baseline AF on the endpoint of ACM.[3]

The greater symptom burden, lower functional capacity, and lower quality of life associated with baseline AF are likely multifactorial. The restrictive physiology of ATTR-CM, progressive left atrial dilatation, and impaired atrial compliance result in new or worsening AF. The frequently impaired cardiac output can be further exacerbated by several factors, including the loss of atrial systole and atrioventricular synchrony.[6]

The use of acoramidis was associated with a lower burden of new or worsening AF events and numerically fewer AF-related CVHs vs placebo. Several underlying mechanisms may be hypothesized related to the ability of acoramidis to slow myocardial amyloid deposition (as suggested by imaging studies),[7] amyloid stabilization, reduced congestion, and reduced fibrosis development and adverse atrial remodeling.

Limitations include the exploratory, post hoc design, warranting confirmation in future prospective studies. Participant randomization was not stratified by baseline AF, AF prevalence was not captured as a time-dependent variable, and the study was not powered to analyze outcomes in these smaller subgroups. ATTRibute-CM participants were predominantly White men with wild-type ATTR-CM, reflective of the disease population enrolled in ATTR-CM clinical trials to date, which may limit the generalizability of our findings.

## Conclusions

In ATTRibute-CM, acoramidis showed consistent benefit across efficacy endpoints, including clinical outcomes, irrespective of baseline AF diagnosis and was associated with a reduced frequency of new or worsening AF. Numerically lower frequencies of AF-related CVH were observed with acoramidis vs placebo.

## Disclosures

BWS has acted as a speaker for Alnylam Pharmaceuticals, AstraZeneca, and Pfizer and as a consultant for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, and Pfizer. AM has acted as a researcher for Attralus, Cytokinetics, Ionis Pharmaceuticals, and Pfizer and as a consultant, advisor, or speaker for Akros Pharma, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BioMarin Pharmaceutical, BridgeBio Pharma, Bristol Myers Squibb, Cytokinetics, Haya Therapeutics, Ionis Pharmaceuticals, Lexicon Pharmaceuticals, Pfizer, Prothena Biosciences, and Tenaya Therapeutics. KMA has acted as a consultant, advisor, or speaker for Arbor Biotechnologies, Attralus, Intellia Therapeutics, and Prothena Biosciences. YB has received an educational grant from Pfizer and has served on advisory boards for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, and Pfizer. FC has acted as a consultant, advisor, or speaker for

Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio Pharma, Novo Nordisk, and Pfizer. RKC has no relevant financial relationships to disclose. MG has acted as a researcher for Alnylam Pharmaceuticals, BridgeBio Pharma, Intellia Therapeutics, Janssen Pharmaceuticals, Novo Nordisk, and Pfizer and as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, BridgeBio Pharma, Janssen Pharmaceuticals, Novo Nordisk, and Pfizer. WJ has acted as a consultant for Boston Scientific and Pfizer. JLJ has received research grants or held a contract with Abbott Diagnostics, Applied Therapeutics, AstraZeneca, Bristol Myers Squibb, HeartFlow, and Novartis; has acted as a consultant, advisor, or speaker for Abbott, AbbVie, AstraZeneca, Bayer, Beckman Coulter, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, Intellia Therapeutics, Jana Care, Merck, Novartis, Pfizer, Roche Diagnostics, Siemens, and Takeda; and has stock interest in Fibrosys, Imbria Pharmaceuticals, Jana Care, and Prevencio. MK has received speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Mochida Pharmaceutical, Nova Biomedical, and Novartis. MSM has acted as a researcher for Alnylam Pharmaceuticals, Attralus, BridgeBio Pharma, Inc, Intellia Therapeutics, Ionis Pharmaceuticals, and the National Institutes of Health (R01HL139671 and R01AG081582-01), and Pfizer; and as a consultant or advisor for Akcea Therapeutics, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer. SSM has acted as a consultant for EmblemHealth and as an advisory board and/or speaker bureau consultant for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, BridgeBio Pharma, Cytokinetics, Novo Nordisk, and Pfizer. DM has acted as a consultant, advisor, or speaker for BridgeBio Pharma and Pfizer. LO has acted as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Ionis Pharmaceuticals, Novo Nordisk, Pfizer, and Sobi – Swedish Orphan Biovitrum. CC, TB, GM, J-FT, AC, and JCF are employees and stakeholders of BridgeBio Pharma. PS has received grants from Pfizer and has acted as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, BridgeBio Pharma, Pfizer, and Spectrum Dynamics. DPJ has received consultancy fees from Alexion Pharmaceuticals, Alleviant Medical, Alnylam Pharmaceuticals, Attralus, BridgeBio Pharma, Cytokinetics, Lexeo Therapeutics, Novo Nordisk, Pfizer, Renovacor, Rocket Pharmaceuticals, and Tenaya Therapeutics and his institution received clinical trial funding from Array Biopharma, BridgeBio Pharma, Lexeo Therapeutics, MyoKardia (now part of Bristol Myers Squibb), and Pfizer. MH has served on advisory boards for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, Attralus, BridgeBio Pharma, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer. RW has received consulting fees from Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Medison, Novo Nordisk, and Pfizer.

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## Data-Sharing Statement

Qualified academic investigators may submit requests for access to data at MedInfo@BridgeBio.com. Requests for access to study data will be evaluated by BridgeBio Pharma, and access will be provided contingent on the approval of a research or study proposal and the execution of a data sharing agreement. BridgeBio Pharma will consider requests for access to participant-level data if participant privacy is ensured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law) and if such disclosures were included in the informed consent form or study protocol of the relevant study.

## CRediT authorship contribution statement

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## Patient consent

ATTRibute-CM and the open-label extension were conducted in accordance with the Declaration of Helsinki, and the protocol was independently approved by the ethics committees at each participating site. All participants provided written informed consent.

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