Continuous Acoramidis Treatment Significantly Reduced Risk of All-Cause Mortality and Cardiovascular-Related Hospitalization Through Month 42 in Participants with Wild-Type and Variant Transthyretin Amyloidosis Cardiomyopathy

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OBJECTIVES

- To assess the effects of continuous acoramidis treatment through Month 42 on ACM and CVH in participants with ATTRv-CM or ATTRwt-CM compared to 30 months of placebo followed by acoramidis through Month 42 in ATTRibute-CM and the ongoing OLE study

BACKGROUND

- ATTR-CM can develop due to the presence of a pathogenic *TTR* variant (ATTRv-CM) or through misfolding of the wild-type TTR protein (ATTRwt-CM)[1,2]
- ATTRv-CM is typically associated with younger age of onset and faster progression than ATTRwt-CM[3-5]
- Acoramidis is a highly selective, oral TTR stabilizer that achieves near-complete (⩾90%) TTR stabilization and is approved in the USA, Europe, Japan, and UK for treating ATTRv-CM or ATTRwt-CM in adults[6-9]
- In the 30-month phase 3 ATTRibute-CM study, acoramidis reduced ACM or first CVH risk by 36% and annual CVH frequency by 50%[10,11]
- In the OLE phase of ATTRibute-CM (NCT04988386), continuous acoramidis treatment led to risk reductions of 36% in ACM, 43% in ACM/first CVH, and 47% in first CVH through Month 42 versus the group switching from placebo to acoramidis after Month 30[12]

METHODS

- After completing 30 months of double-blind treatment in ATTRibute-CM, participants assigned to acoramidis 800 mg BID or placebo could enroll into the OLE[12]
- All participants in the OLE received acoramidis 800 mg BID regardless of treatment allocation in the double-blind period
  - Participants either continued acoramidis (continuous acoramidis) or switched from placebo to acoramidis (placebo to acoramidis)
  - Concomitant tafamidis was allowed after Month 12 of the double-blind period, but was prohibited during the OLE
- ACM and CVH events were adjudicated by an independent clinical events committee
  - ACM was defined as death due to any cause, receipt of a cardiac mechanical assist device placement, or receipt of a heart transplant
  - CVH included cardiovascular hospitalizations (⩾24 h) and urgent visits (<24 h) for decompensated heart failure requiring IV diuretics
- Risk of ACM and CVH through Month 42 (30 months ATTRibute-CM + 12 months OLE) was assessed for the mITT population from the start of ATTRibute-CM through Month 42 of the OLE
- Forest plots for HRs and associated 95% CIs by genotype used stratified Cox models with baseline 6MWD, treatment, genotype subgroup, and treatment by genotype interaction stratified by NT-proBNP and eGFR at randomization

RESULTS

Participants and Participant Characteristics

- 380 of 611 participants with ATTR-CM in the mITT population and 389 of 632 participants with ATTR-CM in the safety population entered the OLE
- The safety population included 263 continuous acoramidis recipients and 126 placebo to acoramidis recipients
  - 362 had ATTRwt-CM and 27 ATTRv-CM
- Baseline characteristics at randomization in the ATTRibute-CM double-blind study were mostly similar (**Table 1**)
- The 3 most common ATTRv-CM variants recorded in the clinical database: p.Val142Ile (n = 35, including 4 homozygotes), p.Ile88Leu (n = 7), and p.Thr80Ala (n = 5)
- Characteristics of the treatment groups at entry into the OLE remained mostly similar. However, the placebo to acoramidis group had a higher proportion of participants with NYHA Class III (35.7% vs 16.7%) and participants with higher levels of median NT-proBNP (2905.0 pg/mL vs 2094.0 pg/mL) compared with the continuous acoramidis group
  - There were 52 (13.4%) participants in the OLE who received concomitant tafamidis during the ATTRibute-CM double-blind study

Time-to-Event Analysis of ACM, ACM/First CVH, and First CVH Through Month 42

- Continuous acoramidis was associated with significantly less risk of death from any cause, first CVH, or a composite of both, compared with those who switched to acoramidis from the placebo group (**Figure 1**)
- This effect was consistent regardless of TTR genotype
  - In participants with ATTRv-CM, continuous acoramidis was associated with risk reductions of 59%, 65%, and 70% for ACM, ACM/first CVH, and first CVH, respectively, compared with placebo to acoramidis
  - In participants with ATTRwt-CM, continuous acoramidis was associated with risk reductions of 30%, 40%, and 42% for ACM, ACM/first CVH, and first CVH, respectively, compared with placebo to acoramidis

CONCLUSIONS

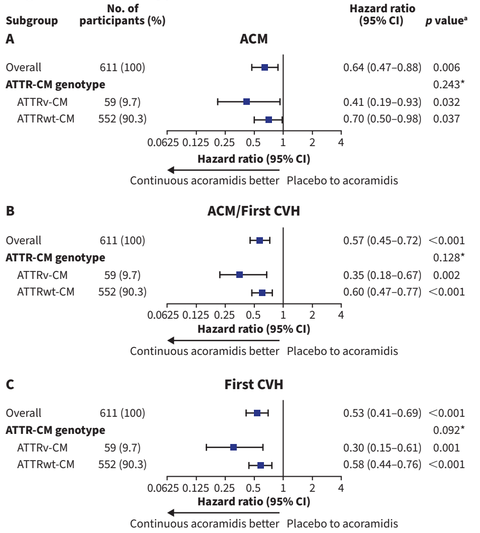
- In the ATTRibute-CM OLE through Month 42, continuous acoramidis treatment was associated with consistently lower risks of ACM, ACM/first CVH, and first CVH compared with participants who delayed initiation in participants with both ATTRv-CM and ATTRwt-CM genotypes
- No new clinically important safety issues were identified up to 42 months (data not shown)
- These findings highlight the long-term benefits of continuous acoramidis therapy regardless of variant or wild-type *TTR* genotypes, and underscore the importance of early treatment initiation

TABLE 1. Baseline Characteristics of Participants in ATTRibute-CM by Genotype (mITT, N = 611)

Participant Characteristics[a]	ATTRv-CM[b] (n = 59)		ATTRwt-CM[b] (n = 552)	
	Acoramidis (n = 39)[c]	Placebo (n = 20)[c]	Acoramidis (n = 370)[c]	Placebo (n = 182)[c]
Mean age, years (SD)	73.9 (7.60)	71.2 (7.84)	77.7 (6.25)	77.6 (6.32)
Male, n (%)	33 (84.6)	14 (70.0)	341 (92.2)	167 (91.8)
Duration of ATTR-CM, mean years (SD)	1.3 (1.06)	1.5 (1.07)	1.2 (1.22)	1.1 (1.21)
NYHA Class, n (%)				
I	2 (5.1)	1 (5.0)	49 (13.2)	16 (8.8)
II	35 (89.7)	16 (80.0)	253 (68.4)	140 (76.9)
III	2 (5.1)	3 (15.0)	68 (18.4)	26 (14.3)
sTTR level, mean mg/dL (SD)	17.8 (5.12)	17.2 (5.22)	23.5 (5.34)	24.3 (5.75)
NT-proBNP, median pg/mL (IQR)	2326.0 (1312.00–4567.00)	2340.5 (1521.50–3534.00)	2264.5 (1315.00–3729.00)	2273.5 (1105.00–3590.00)
6MWD, mean meters (SD)	364.6 (94.93)	354.7 (97.07)	362.6 (104.49)	351.2 (93.74)
Concomitant tafamidis,[d] n (%)	4 (10.3)	4 (20.0)	57 (15.4)	42 (23.1)

[a]Data are for the full analysis set. The full analysis set included the mITT population in ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy), which was defined as all participants who were randomized to acoramidis or placebo, received ⩾1 dose of acoramidis or placebo, had ⩾1 efficacy evaluation after baseline, and had a baseline eGFR of ⩾30 mL/1.73 m^2. [b]Genotype based on information at randomization. [c]n values vary slightly for various characteristics based on available data. [d]Concomitant tafamidis was allowed after Month 12 of the double-blind period of ATTRibute-CM, but was prohibited during the OLE.

FIGURE 1. Reduction in ACM (A), ACM/First CVH (B), and First CVH (C) with Continuous Acoramidis Was Consistent Regardless of Genotype



[a]*p* values with * are from testing the interaction of subgroup x treatment, and other *p* values are for testing the treatment difference at a given value of subgroup variable.

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ABBREVIATIONS: 6MWD: 6-minute walk distance; **ACM:** all-cause mortality; **ATTR-CM:** transthyretin amyloidosis cardiomyopathy; **ATTRv-CM:** transthyretin amyloidosis variant cardiomyopathy; **ATTRwt-CM:** transthyretin amyloidosis wild-type cardiomyopathy; **BID:** twice daily; **CI:** confidence interval; **CVH:** cardiovascular-related hospitalization; **eGFR:** estimated glomerular filtration rate; **HR:** hazard ratio; **IQR:** interquartile range; **IV:** intravenous; **mITT:** modified intent to treat; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **NYHA:** New York Heart Association; **OLE:** open-label extension; **SD:** standard deviation; **sTTR:** serum TTR; **TTR:** transthyretin.

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DISCLOSURES: L.K.S. has acted as a researcher for Intellia Therapeutics and Pfizer; advisor for BridgeBio Pharma (formerly Eidos Therapeutics) and Pfizer. **M.G.** has acted as a researcher for Alnylam Pharmaceuticals Inc, BridgeBio Pharma, Intellia Therapeutics, Janssen Pharmaceuticals, and Pfizer; consultant, advisor, speaker for Alnylam Pharmaceuticals, BridgeBio Pharma, Janssen Pharmaceuticals, Novo Nordisk, and Pfizer. **A.A.** has nothing to declare. **J.L.G.** has acted as a researcher for BridgeBio Pharma, NHLBI (grant R01HL160892) Pfizer, and Texas Health Resources Clinical Scholarship; and as a consultant, advisor, speaker for Alexion, AstraZeneca, BridgeBio Pharma, Intellia, Lumanity, Novo Nordisk, Pfizer, Tenax Therapeutics, and Ultromics. **P.S.** has acted as a researcher for Pfizer; consultant, advisor, speaker for Alnylam Pharmaceuticals, BridgeBio Pharma, and Pfizer. **M.F.** has acted as a consultant, advisor, speaker for Akcea Therapeutics, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Global Services, LLC, Novo Nordisk, and Pfizer; and has received research grants from BridgeBio Pharma and Pfizer. **P.G.P.** has acted as research/educational support for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Intellia Therapeutics, Novo Nordisk, and Pfizer; consultant, advisor, speaker for Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio Pharma, Intellia Therapeutics, Ionis Pharmaceuticals, Neuroimmune, Pfizer, and Novo Nordisk. **K.X.**, **S.S.**, **J. F. T.**, and **J.C.F.** are employees and stockholders of BridgeBio Pharma. **N.F.** has served on advisory panels for Alnylam Pharmaceuticals, AstraZeneca, Novo Nordisk, and Pfizer. **M.M.** has acted as a researcher for Alnylam Pharmaceuticals, BridgeBio Pharma, Eidos, Ionis Pharmaceuticals, NIH (grants NIH R01HL139671 and R01AG081582-01), Pfizer, and Prothena Biosciences; and as a consultant or advisor for Alnylam Pharmaceuticals, AstraZeneca, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Ionis Therapeutics, Novo-Nordisk, and Pfizer.

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