In Patients Treated With Acoramidis, Addition of Concomitant Tafamidis Does Not Further Increase Serum TTR Levels

Mathew S. Maurer,[1] Francesco Cappelli,[2] Marianna Fontana,[3] Pablo Garcia-Pavia,[4,5] Martha Grogan,[6] Mazen Hanna,[7] Daniel P. Judge,[8] Ahmad Masri,[9] Nitasha Sarswat,[10] Jing Du,[11] Suresh Siddhanti,[11] Jean-François Tamby,[11] Alan X. Ji,[11] Uma Sinha,[11] Jonathan C. Fox,[11] and Julian D. Gillmore[3]

[1]Columbia College of Physicians and Surgeons, New York, NY, USA; [2]Tuscan Amyloid Referral Centre, Careggi University Hospital, Florence, Italy; [3]University College London, Royal Free Hospital, London, UK; [4]Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [5]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [6]Mayo Clinic, Rochester, MN, USA; [7]Cleveland Clinic, Cleveland, OH, USA; [8]Medical University of South Carolina, Charleston, SC, USA; [9]Oregon Health and Science University, Portland, OR, USA; [10]University of Chicago Medicine, Chicago, IL, USA; [11]BridgeBio Pharma, Inc., San Francisco, CA, USA

Poster number: 16579

Scan QR code to access a PDF copy of the poster

OBJECTIVE

- **To assess the effect of tafamidis taken concomitantly with acoramidis on serum transthyretin (sTTR) levels in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) in the phase 3 ATTRibute-CM study (NCT03860935)**

BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, significantly impaired quality of life, hospitalization, and death[1–3]
- Acoramidis, a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved by the FDA for the treatment of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization. Acoramidis is also approved in Europe for the treatment of wild-type or variant ATTR-CM in adults[4–6]
- In the phase 3 ATTRibute-CM study in participants with ATTR-CM, acoramidis treatment increased sTTR levels from baseline to Day 28 significantly more than placebo[7]
  - The increase in sTTR with acoramidis was sustained through Month 30 and was associated with lower all-cause mortality and cardiovascular-related hospitalizations[7]

METHODS

- The study design of ATTRibute-CM has been described previously[7]
  - Briefly, participants with ATTR-CM aged 18–90 years were randomized 2:1 to receive acoramidis HCl (800 mg) or matching placebo twice daily for 30 months[7]
  - Efficacy analyses were conducted in the modified intention-to-treat (mITT) population, which consisted of all randomized participants who had received at least one dose of acoramidis or placebo, had at least one efficacy evaluation after baseline, and had a baseline estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2
- Participants were permitted to initiate concomitant open-label tafamidis treatment at any time from Month 12 onwards, at the discretion of the investigator
  - In the mITT population, 14.9% of participants in the acoramidis group and 22.8% of participants in the placebo group received concomitant tafamidis at any time during the trial[7]
  - The median time to initiation of open-label tafamidis was 17.2 months, and the median duration of exposure to tafamidis was 11.4 months.[7] The median times to initiation in the acoramidis and placebo groups were 17.8 and 16.1 months, respectively; the median durations of exposure were 11.6 and 10.5 months for the acoramidis and placebo groups, respectively[7]
- sTTR concentrations were determined at baseline, on Day 28, and then every 3 months through to Month 30
- In this *post hoc* analysis, the change from baseline in sTTR levels was determined for four participant subgroups: acoramidis alone, acoramidis + tafamidis, placebo alone, and placebo + tafamidis

RESULTS

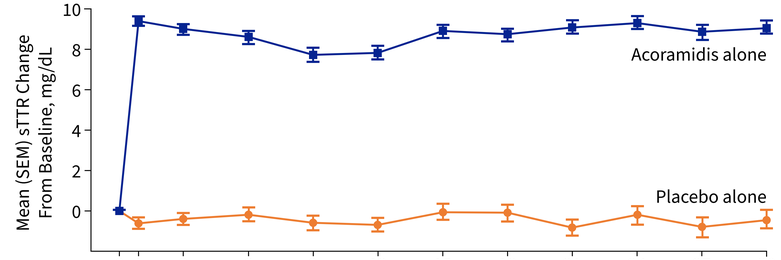
- Baseline demographics and clinical characteristics were generally well balanced between the treatment subgroups (**Table**)

TABLE: Baseline Demographics and Characteristics; mITT Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)

Demographic/ Characteristic	Acoramidis Alone (n = 348)	Acoramidis + Tafamidis (n = 61)	Placebo Alone (n = 156)	Placebo + Tafamidis (n = 46)
Age, years, mean (SD)	77.3 (6.60)	77.5 (5.79)	77.2 (6.68)	76.2 (6.95)
Sex, male, n (%)	319 (91.7)	55 (90.2)	141 (90.4)	40 (87.0)
Duration of ATTR-CM, years, mean (SD)	1.2 (1.15)	1.4 (1.48)	1.2 (1.23)	1.0 (1.09)
NT-proBNP, pg/mL, median (IQR)	2325.5 (1327.0–3764.5)	2119.0 (1240.0–4057.0)	2251.0 (1013.5–3800.5)	2321.5 (1396.0–3351.0)
eGFR, mL/min/1.73 m^2, mean (SD)	61.4 (17.18)	65.3 (18.10)	62.1 (18.08)	64.2 (15.58)
sTTR, mg/dL, mean (SD)	23.0 (5.75)	22.8 (4.50)	23.8 (6.11)	22.8 (6.00)

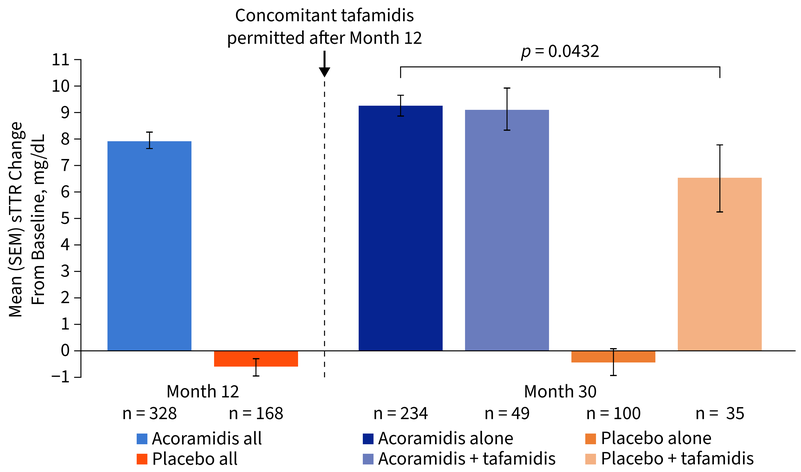
- The increases in sTTR levels from baseline to Day 28 were greater in participants who received acoramidis alone compared with those who received placebo alone; this early increase in sTTR levels with acoramidis alone was sustained until Month 30 compared with placebo alone (mean [standard error of the mean (SEM)] change from baseline at Month 30: 9.1 [0.38] mg/dL versus −0.4 [0.49] mg/dL; **Figures 1 and 2**)
- At Month 12, the mean (SEM) change from baseline in sTTR levels was 7.9 (0.31) mg/dL for the acoramidis all group and −0.6 (0.32) mg/dL for the placebo all group (**Figure 2**)
- At Month 30, the change from baseline in sTTR levels was 42% greater in the acoramidis alone subgroup than in the placebo + tafamidis subgroup: the mean (SEM) change from baseline in sTTR levels was 9.1 (0.38) mg/dL and 6.4 (1.24) mg/dL with acoramidis alone and placebo + tafamidis, respectively (p = 0.0432; **Figure 2**)
- At Month 30, the mean (SEM) changes from baseline in sTTR levels in the acoramidis alone versus the acoramidis + tafamidis subgroup were similar (9.1 [0.38] mg/dL versus 8.9 [0.79] mg/dL; **Figure 2**)

FIGURE 1: Mean Change From Baseline in sTTR Levels in Participants Receiving Acoramidis Alone or Placebo Alone; mITT Population (Acoramidis Alone and Placebo Alone Subgroups, n = 504)



Number of participants											
Acoramidis alone	346	311	301	275	270	276	256	248	244	245	228	234
Placebo alone	153	138	142	124	121	126	118	118	113	107	95	100

FIGURE 2: Mean Change From Baseline in sTTR Levels by Concomitant Tafamidis Treatment at Month 12 and Month 30; mITT Population (N = 611)



The p value (0.0432) was calculated from a two-sample t-test comparing acoramidis alone and placebo + tafamidis for the change from baseline in sTTR levels using the Satterthwaite method with unequal variance.

CONCLUSIONS

- **In participants with ATTR-CM in ATTRibute-CM, treatment with acoramidis alone led to a 42% greater increase from baseline to Month 30 in sTTR levels, compared with placebo + tafamidis**
- **The addition of tafamidis to acoramidis did not lead to any further increase in sTTR levels, suggesting that acoramidis alone achieves the highest level of TTR stabilization among available TTR stabilizers**

CORRESPONDING AND PRESENTING AUTHOR: Mathew S. Maurer, msm10@cumc.columbia.edu

REFERENCES: 1. Rapezzi C, et al. *Nat Rev Cardiol.* 2010;7(7):398-408. **2.** Ruberg FL, Berk JL. *Circulation*. 2012;126(10):1286-1300. **3.** Lane T, et al. *Circulation*. 2019;140(1):16-26. **4.** Judge DP, et al. *J Am Coll Cardiol.* 2019;74(3):285-295. **5.** BridgeBio Pharma, Inc. Prescribing Information, Attruby (acoramidis). 2024. Accessed February 12, 2025. www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf. **6.** BridgeBio Europe B.V. SmPC, Beyonttra. EMA, 2025. Accessed February 19, 2025. https://ec.europa.eu/health/documents/community-register/2025/20250210165087/anx_165087_en.pdf. **7.** Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142.

FUNDING: This study was sponsored by BridgeBio Pharma, Inc., San Francisco, CA, USA.

ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SEM, standard error of the mean; sTTR, serum transthyretin; TTR, transthyretin.

ACKNOWLEDGMENTS: Under the guidance of the authors, medical writing assistance was provided by Anson Shek, PhD, of Oxford PharmaGenesis, Inc., and was funded by BridgeBio Pharma, Inc. Editorial support and critical review were provided by Souhiela Fawaz, PhD, and Shweta Rane, PhD, CMPP, BCMAS, of BridgeBio Pharma, Inc.

DISCLOSURES: M.S.M. has acted as a researcher for NIH (R01HL139671 and R01AG081582-01), Alnylam Pharmaceuticals, Attralus, BridgeBio Pharma, Inc. (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, and Pfizer; and as a consultant or advisor for Akcea Therapeutics, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc. (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer. **J.D.G.** has acted as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc. (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, Lycia Therapeutics, and Pfizer.

PRESENTED AT: THE AMERICAN COLLEGE OF CARDIOLOGY 74TH ANNUAL SCIENTIFIC SESSION & EXPO, MARCH 29–31, 2025; CHICAGO, IL, USA