Early Increase in Serum Transthyretin Level Is an Independent Predictor of Improved Survival in ATTR Cardiomyopathy: Insights From Acoramidis Phase 3 Study ATTRibute-CM

Mathew S. Maurer[1], Nitasha Sarswat[2], Martha Grogan[3], Amrut Ambardekar[4], Anique Ducharme[5], Steen Hvitfeldt Poulsen[6], Satish Rao[7], Jean-François Tamby[7], Jonathan C. Fox[7], Brian Adam[8], Surendhar Reddy Chepyala[8], Bill Poland[8] and Uma Sinha[7]

[1]Department of Medicine–Division of Cardiology, Columbia University, New York, NY, US; [2]Biological Sciences Division, University of Chicago, Chicago, IL, US; [3]Cardiovascular Medicine, Mayo Clinic, Rochester, MN, US; [4]Cardiac Transplantation, Cardiac Amyloidosis Program, University of Colorado Anschutz Medical Campus, Aurora, CO, US; [5]Department of Medicine, Institut de Cardiologie de Montréal, Montréal, Quebec, Canada; [6]Department of Clinical Medicine–The Department of Cardiological Medicine B, Aarhus University, Arhaus, Denmark; [7]BridgeBio Pharma, Inc., San Francisco, CA, US; [8]Certara, Princeton, NJ, US

OBJECTIVE

- **To report the results of acoramidis-mediated change in serum TTR, an in vivo measure of TTR stabilization, and its relationship to all-cause mortality in ATTRibute-CM**

CONCLUSIONS

- **Results from the model suggest an exposure-response relationship between acoramidis treatment and serum TTR level**
- **These models suggest that increasing serum TTR levels through stabilization by acoramidis may be protective**
- **Acoramidis-mediated increase in serum TTR level on Day 28 may be an independent predictor of improved survival in patients with ATTR-CM**

INTRODUCTION

- Patients with ATTR-CM can have lower circulating TTR (also known as prealbumin) levels, which are associated with worsening of cardiac function and increased risk of mortality[1-3]
- Acoramidis is a novel, high-affinity TTR stabilizer which achieves >90% TTR stabilization in patients with ATTR-CM[4-6]
- In a pivotal phase 3 study (ATTRibute-CM; NCT03860935) acoramidis met its primary hierarchical efficacy endpoint with mortality, morbidity, and function components vs placebo (p<0.0001)[6]
  - Acoramidis treatment also resulted in a 25% RRR in ACM and 30% RRR in cardiovascular-related mortality[7,8]

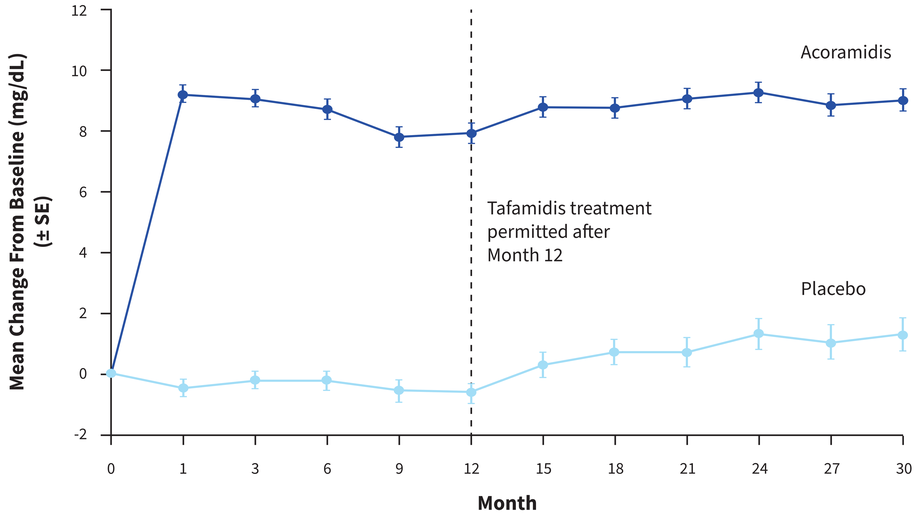
METHODS

- Details of the study design have been previously published[6]
- Modeling and simulation analyses were performed to describe the population pharmacokinetics of acoramidis and evaluate the safety and efficacy exposure-response relationships for acoramidis
- E-R relationships were modeled for ACM vs serum TTR
- ACM included CEC-reviewed and -adjudicated death, heart transplant, and implantation of CMAD, defined as a durable CMAD implanted in a participant with end-stage heart failure
- Change from baseline in serum TTR shows observed measurements without any imputation

RESULTS

- Baseline demographics and clinical characteristics were comparable between the treatment groups[6]
- Increased acoramidis concentrations were associated with increased serum TTR concentrations
- Acoramidis treatment increased serum TTR levels at Day 28, which remained stable through Month 30 (**Figure 1**)[8]

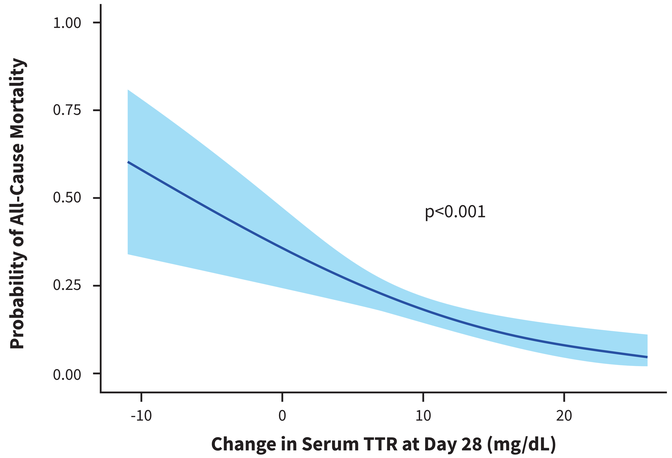
FIGURE 1. Change From Baseline in Serum TTR Levels—mITT Population



Observed measurements without any imputation. No adjustment was made for early discontinuation for any reason, including death.

- Serum TTR levels on Day 28 of dosing predicted survival in univariate analysis for the overall population (p<0.002) and the acoramidis-treated population (p<0.001) (**Figure 2**)

FIGURE 2. Probability of ACM as a Function of Change in Serum TTR Levels From Baseline to Day 28 in Acoramidis-Treated Patients



Logistic model of ACM probability based on change in serum TTR level at Day 28. Blue line is model prediction; shaded areas are 95% CI. P value describes the univariate association between ACM and change from baseline in serum TTR level at Day 28. Width of light blue band corresponds with goodness of fit at that specific serum TTR level.

- Through the mechanism of TTR stabilization, for every 5 mg/dL increase in serum TTR level, the risk of death was reduced by 30.9% by the logistic model and by 26.1% by the Cox proportional hazards model
- In a multivariate analysis, change in serum TTR remained an independent predictor of ACM (p<0.006), even after adjusting for baseline demographic variables, use of diuretics, New York Heart Association class, baseline serum TTR, TTR variant vs wild type, and National Amyloidosis Centre stage

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

ABBREVIATIONS: ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CEC, clinical events committee; CMAD, cardiac mechanical assist device; E-R, exposure-response; mITT, modified intent-to-treat; RRR, relative risk reduction; TTR, transthyretin.

ACKNOWLEDGMENTS: Under the direction of the authors, medical writing assistance was provided by Syneos Health Medical Communications, LLC, and supported by BridgeBio Pharma, Inc. Editorial support and critical review provided by Shweta Rane of BridgeBio Pharma, Inc.

REFERENCES: **1.** Rapezzi C, et al. *Nat Rev Cardiol*. 2010;7(7):398-408. **2.** Ruberg FL, et al. *JAMA*. 2024;331(9):778-791. **3.** Hanson JLS, et al. *Circulation Heart Fail*. 2018;11(2):1-9. **4.** Penchala SC, et al. *PNAS*. 2013;110(24):9992-9997. **5.** Miller M, et al. *Med Chem*. 2018;61(17):7862-7876. **6.** Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142. **7.** Judge DP, et al. Presented at: American Heart Association 2023 Scientific Sessions; November 10-13, 2023; Philadelphia, PA, US. **8.** Gillmore JD, et al. Presented at: European Society of Cardiology Congress; August 25-29, 2023; Amsterdam, Netherlands.

DISCLOSURES: **MSM:** Has contributed to research for NIH NIH R01HL139671 and R01AG081582-01, Alnylam, Pfizer, BridgeBio, Prothena, and Ionis; has been a consultant, advisor, and/or speaker for AstraZeneca, Akcea, Intellia, Novo Nordisk, Alnylam, Pfizer, BridgeBio, Prothena, and Ionis. **NS:** Has contributed to research for Pfizer; has been a consultant, advisor, and/or speaker for BridgeBio, Alnylam, and Pfizer. **MG:** Has contributed to research for Alnylam, BridgeBio, Janssen Pharmaceuticals, and Pfizer; has been a consultant, advisor, and/or speaker for Janssen Pharmaceuticals and Novo Nordisk. **AA:** No relevant financial relationships to disclose. **AD:** Has been a consultant, advisor, and/or speaker for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, and Novo Nordisk; has contributed to research for Abbott, AstraZeneca, Bayer, BridgeBio, Merck, and Novo Nordisk. **SHP:** No relevant financial relationships to disclose; **SR, JFT, JCF,** and **US:** Employees and shareholders of BridgeBio. **BA, SRC, BP:** Employees of Certara.

PRESENTED AT THE 2024 INTERNATIONAL SYMPOSIUM ON AMYLOIDOSIS, MAY 26-30; ROCHESTER, MN, US, AND VIRTUAL.