Poster: 1419-241

Association Between Early Increase in Serum Transthyretin (sTTR) With Acoramidis and Long-Term Effects on Heart Failure-Related Health Status in Transthyretin Amyloid Cardiomyopathy (ATTR-CM): Results From ATTRibute-CM

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OBJECTIVE

- **To evaluate the association between the acoramidis-mediated early increase in the change from baseline in serum transthyretin concentrations (ΔsTTR) at Day 28 and the change in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) scores at Month 30 in participants with transthyretin amyloid cardiomyopathy (ATTR-CM)**

BACKGROUND

- Low serum transthyretin (sTTR) concentrations and worsening KCCQ-OS scores are independent predictors of mortality in ATTR-CM; however, there is limited evidence linking low sTTR concentrations and reduced KCCQ-OS scores[1,2]
- Acoramidis, an oral transthyretin (TTR) stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, the European Union, Japan, Switzerland, and the UK for the treatment of ATTR-CM in adults[3–8]
- In the ATTRibute-CM study (NCT03860935), acoramidis significantly increased sTTR concentrations early by Day 28, and this increase was sustained through Month 30[1,9]
  - The acoramidis-mediated early ΔsTTR was independently associated with improved survival[1]
- Acoramidis treatment also reduced the decline in heart failure-related health status (as assessed by KCCQ-OS score) versus placebo at Month 30[9]

METHODS

- The ATTRibute-CM study design has been described previously[9]
- Eligible adult participants (≤ 90 years old) were randomized 2:1 to receive acoramidis HCl 800 mg or placebo twice daily for 30 months
  - Efficacy analyses were conducted in the ATTRibute-CM 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) of ≥ 30 mL/min/1.73 m^2
  - Participants were permitted to initiate concomitant open-label tafamidis after Month 12, at the discretion of the investigator
- sTTR concentrations were determined in a central laboratory using an immunoturbidimetric procedure with the Abbott ARCHITECT system (Abbott Laboratories, Lake Forest, IL, USA)
  - The reference range for serum concentrations of native (tetrameric) TTR is 20–40 mg/dL[1]
- This analysis assessed:
  - the least-squares mean change from baseline in KCCQ-OS score according to early ΔsTTR at Day 28 of 5 mg/dL or 10 mg/dL, using a mixed model for repeated measures (MMRM)
  - the least-squares mean change from baseline in KCCQ-OS score through Month 30 according to sTTR concentrations at Day 28 of < 20 mg/dL (lower limit of normal reference range for the sTTR assay) or ≥ 20 mg/dL, using an MMRM
- A difference of ≥ 5 points in KCCQ-OS score is considered clinically meaningful[10]

RESULTS

- Baseline demographics and characteristics were generally well balanced between the treatment groups (**Table 1**)

TABLE 1: Baseline Demographics and Characteristics; mITT Population

	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.5)	77.0 (6.7)
Sex, male, n (%)	374 (91.4)	181 (89.6)
Wild-type ATTR-CM,[a] n (%)	370 (90.5)	182 (90.1)
NYHA functional class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
6MWD,[b] m, mean (SD)	362.8 (103.5)	351.5 (93.8)
NT-proBNP, pg/mL, median (Q1–Q3)	2273 (1315–3872)	2274 (1128–3590)
sTTR,[c] mg/dL, mean (SD)	23.0 (5.6)	23.6 (6.1)
KCCQ-OS score,[d] mean (SD)	71.7 (19.4)	70.5 (20.7)

[a]TTR genotype was reported at randomization. [b]Acoramidis, n = 407. [c]Acoramidis, n = 406; placebo, n = 199. [d]Acoramidis, n = 408.

- Acoramidis treatment increased sTTR concentrations by Day 28 versus placebo (mean [standard error (SE)]) change from baseline: 9.2 (0.3) mg/dL and −0.4 (0.3) mg/dL, respectively; **Figure 1**)
- Compared with no change in sTTR concentration at Day 28, a 5 mg/dL early ΔsTTR was associated with an improvement in KCCQ-OS score of +3.2 points with acoramidis (p = 0.0147) and +1.4 points with placebo (p = 0.5376) at Month 30 (**Table 2**)

FIGURE 1: (A) Mean sTTR Concentrations at Baseline and Day 28 and (B) Mean ΔsTTR at Day 28; mITT Population (Observed Values)

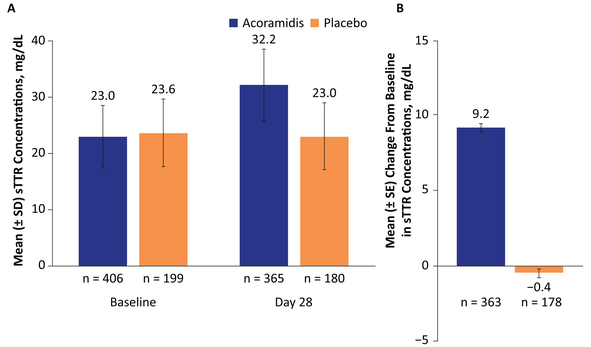


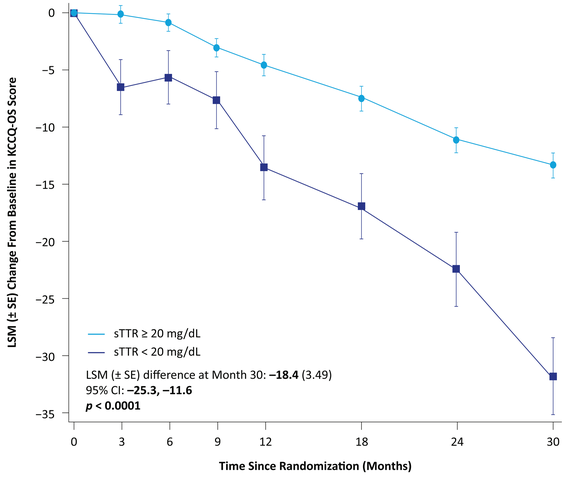
TABLE 2: Change From Baseline in KCCQ-OS Score at Month 30 by Treatment Group and by Early ΔsTTR at Day 28 of 5 mg/dL or 10 mg/dL; mITT Population

	Acoramidis (n = 409)	Placebo (n = 202)
	Month 30 KCCQ-OS score, LSM change from baseline (95% CI)	
ΔsTTR at Day 28		
No change	−17.6 (−23.0, −12.2)	−21.7 (−25.2, −18.3)
5 mg/dL	−14.4 (−17.8, −11.1)	−20.3 (−26.3, −14.4)
10 mg/dL	−11.3 (−13.7, −8.8)	−18.9 (−28.9, −8.9)
	Month 30 KCCQ-OS score, LSM change from baseline difference (95% CI); p value	
ΔsTTR at Day 28		
5 mg/dL vs no change	3.2 (0.6, 5.7); p = 0.0147	1.4 (−3.1, 6.0); p = 0.5376
10 mg/dL vs no change	6.3 (1.3, 11.4); p = 0.0147	2.9 (−6.2, 11.9); p = 0.5376

The MMRM included TTR genotype (wild-type vs variant), NT-proBNP concentration (≤ 3000 vs > 3000 pg/mL), eGFR (< 45 vs ≥ 45 mL/min/1.73 m^2), treatment group, visit, Day 28 ΔsTTR, and all interactions among treatment group, visit, and Day 28 ΔsTTR as fixed effects, and included baseline KCCQ-OS score as a covariate. Only participants with non-missing Day 28 ΔsTTR values were included in the analysis. Missing measurements due to early discontinuation of treatment were imputed using the jump to reference method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values.

- Regardless of treatment group, sTTR concentrations at Day 28 < 20 mg/dL (lower limit of the sTTR reference range) were associated with lower KCCQ-OS scores at Month 30 compared with sTTR concentrations at Day 28 of ≥ 20 mg/dL, with a least-squares mean difference of −18.4 points (p < 0.0001; **Figure 2**)

FIGURE 2: Change From Baseline in KCCQ-OS Score by sTTR Concentration at Day 28 < 20 mg/dL (Lower Limit of the sTTR Reference Range) Versus ≥ 20 mg/dL for Pooled Treatment Groups; mITT Population



No. of Participants

sTTR ≥ 20 mg/dL	490	317	466	469	478	483	488	487
sTTR < 20 mg/dL	54	35	51	53	51	54	54	54

The sTTR concentration subgroup MMRM included TTR genotype (wild-type vs variant), NT-proBNP concentration (≤ 3000 vs > 3000 pg/mL), eGFR (< 45 vs ≥ 45 mL/min/1.73 m^2), treatment group, visit, Day 28 sTTR concentration group (< 20 mg/dL vs ≥ 20 mg/dL), and the interaction between Day 28 sTTR concentration group and visit as factors, and included baseline KCCQ-OS score as a covariate. Only participants with non-missing Day 28 ΔsTTR values were included in the analysis. Missing measurements due to early discontinuation of treatment were imputed using the jump to reference method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values.

CONCLUSIONS

- In ATTR-CM, early increases in sTTR at Day 28 with acoramidis were associated with a clinically meaningful slower decline in KCCQ-OS score at Month 30 versus placebo
- Regardless of treatment, sTTR concentrations below the normal range were associated with lower KCCQ-OS scores at Month 30
- The findings suggest that therapies, such as acoramidis, that lead to an early increase in sTTR concentrations could help to slow the decline in KCCQ-OS scores

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

ABBREVIATIONS: 6MWD, 6-minute walk distance; ΔsTTR, change from baseline in sTTR concentrations; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LSM, least-squares mean; mITT, modified intention-to-treat; MMRM, mixed model for repeated measures; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; SD, standard deviation; SE, standard error; sTTR, serum transthyretin; TTR, transthyretin.

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

DISCLOSURES: J.M.G. has acted as a consultant for AstraZeneca, BridgeBio Pharma, and Pfizer; and has received research grants from BridgeBio Pharma and Pfizer.

PRESENTED AT: THE AMERICAN COLLEGE OF CARDIOLOGY (ACC) 75TH ANNUAL SCIENTIFIC SESSION & EXPO, MARCH 28–30, 2026; NEW ORLEANS, LA, USA