Increase in Serum TTR Levels Observed With Acoramidis Treatment in Patients With Transthyretin Amyloid Cardiomyopathy (ATTR-CM): Insights From ATTRibute-CM and Its Open-Label Extension

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PURPOSE

- To evaluate serum transthyretin (TTR) levels at Month 30 in participants who received acoramidis compared with those who received tafamidis in the placebo group in ATTRibute-CM (NCT03860935)
- To evaluate serum TTR levels in participants who transitioned from placebo + tafamidis to acoramidis in the open-label long-term extension (OLE) study of ATTRibute-CM (NCT04988386)

BACKGROUND

- Patients with wild-type transthyretin amyloid cardiomyopathy (ATTR-CM) can have lower circulating serum TTR levels, which are associated with worsening prognosis and increased risk of cardiovascular mortality (CVM)[1]
- Acoramidis is an investigational, next-generation treatment for ATTR-CM with near-complete TTR stabilization (≥90%)[2-5]
  - Acoramidis is a high-affinity TTR stabilizer compared with tafamidis (in vitro)[2]
- In a phase 3, randomised, double-blind study (ATTRibute-CM; NCT03860935), acoramidis demonstrated improved clinical outcomes in participants with ATTR-CM and was generally well-tolerated[5]
- An early (Day 28) and greater increase in serum TTR with acoramidis treatment was associated with significantly lower risk of all-cause mortality (ACM), CVM, and cardiovascular hospitalization (CVH) in patients with ATTR-CM[5-8]

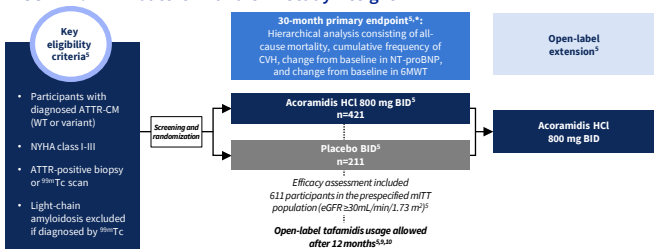
CONCLUSIONS

- **Change from baseline in serum TTR levels was significantly greater in participants in the acoramidis-only treatment group compared to those in the placebo + tafamidis treatment group at Month 30 in ATTRibute-CM**
- **In the OLE study, participants who switched from treatment with placebo + tafamidis to acoramidis had a further significant increase in serum TTR levels**

METHODS

- Details of the ATTRibute-CM study design have been previously published[5]
- Briefly, eligible participants with ATTR-CM were randomized in a 2:1 ratio to receive either acoramidis HCl (800 mg twice daily) or placebo for 30 months. Participants in both arms had the option of initiating open-label, commercially available tafamidis after 12 months in the study **(Figure 1)**
- Upon completion of Month 30 of ATTRibute-CM, participants were invited to roll over into the OLE study
- In the OLE study, all participants received acoramidis only; participants who had previously received acoramidis in ATTRibute-CM continued to receive it, and participants who received placebo were switched to acoramidis only treatment. Participants who received tafamidis at some point in the study were required to discontinue it, prior to switching to acoramidis only treatment

FIGURE 1. ATTRibute-CM[5] and OLE Study Designs



*Primary analysis assessed using the Finkelstein-Schoenfeld method.
6MWT, 6-minute walk test; 99mTc, technetium-99m; ATTR-CM, transthyretin amyloid cardiomyopathy; BID, twice daily; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WT, wild-type.

- The modified intent-to-treat (mITT) population (N=611) was the primary analysis population for efficacy endpoints in ATTRibute-CM and included randomized participants who received at least 1 dose of study drug and had a baseline estimated glomerular filtration rate ≥30 mL/min/1.73 m^2
- Serum TTR levels were assessed by a central laboratory
- Change from baseline in serum TTR levels at Month 30 of ATTRibute-CM and Months 1 and 6 of the OLE study at data cutoff (October 9, 2023) were analysed and summarised using descriptive statistics

RESULTS

- In the phase 3 ATTRibute-CM study (mITT population), 61/409 (14.9%) participants in the acoramidis arm and 46/202 (22.8%) participants in the placebo arm received tafamidis (placebo + tafamidis)
- The median times to tafamidis initiation in the acoramidis and placebo arms were 17.8 and 16.1 months, respectively; median durations of exposure to tafamidis were 11.6 and 10.5 months for the acoramidis and placebo groups, respectively[5]
- Serum TTR levels in the placebo-only group remained unchanged throughout the study: mean [SD] change from baseline at Months 12, 24, and 30 was –0.7 [4.03], –0.2 [4.75], and –0.4 [4.92] mg/dL, respectively
- Mean [SD] change from baseline in serum TTR levels in the acoramidis-only group at Months 12, 24, and 30 was 7.8 [5.74], 9.3 [5.40], and 9.1 [5.78] mg/dL, respectively
- Characteristics of participants analysed are described in the **Table**

TABLE. Baseline Characteristics for Participants in Acoramidis-Only and Placebo + Tafamidis Groups in ATTRibute-CM

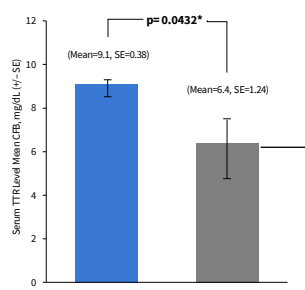
	Acoramidis Only n=348	Placebo + Tafamidis n=46
Age at randomization (years), mean (SD)	77.3 (6.59)	76.2 (6.95)
Sex, n (%) Male Female	319 (91.7) 29 (8.3)	40 (87.0) 6 (13.0)
BMI (kg/m^2) Mean (SD) Min, Max	27.1 (3.85)[a] 18.1, 42.7[a]	26.3 (3.43) 20.5, 34.4
Duration of ATTR-CM (years) Mean (SD) Min, Max	1.2 (1.15)[a] 0.0, 8.3[a]	1.0 (1.09) 0.0, 4.8
Serum TTR levels, (mg/dL) Mean (SD) Min, Max	23.0 (5.75)[b] 8.0, 48.0[b]	22.8 (5.99) 6.0, 32.0
NT-proBNP (ng/L) Median (Q1, Q3) Min, Max	2325.5 (1327.0, 3764.5) 280.0, 15711.0	2321.5 (1396.0, 3351.0) 474.0, 6419.0
eGFR (mL/min/1.73 m^2) Mean (SD) Min, Max	61.4 (17.18) 30.0, 125.0	64.2 (15.58) 33.0, 96.0

[a]Based on the data for n=347 participants; missing value for n=1 participant.
[b]Based on the data for n=346 participants; missing value for n=2 participants.
ATTR-CM, transthyretin amyloid cardiomyopathy; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

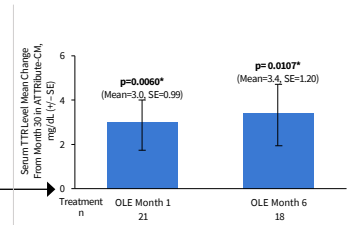
- A total of 380 participants from the mITT population in the double-blind study entered the OLE study (229 participants continued acoramidis only, and 23 switched from placebo + tafamidis to acoramidis)
  - At the time of data cutoff for the OLE study, 214 participants who had received acoramidis only completed Month 6 of the OLE study vs 18 who switched from placebo + tafamidis to acoramidis
- At Month 30 in ATTRibute-CM, participants who received acoramidis only demonstrated a 42% greater increase in the mean change from baseline in serum TTR levels compared with those in the placebo + tafamidis treatment group **(Figure 2A)**
  - Participants in the placebo + tafamidis group did not experience a meaningful decrease in serum TTR (mean [SD] change from baseline at Month 12: –0.3 [4.74] mg/dL) and thus did not impact the difference in change from baseline in serum TTR in the acoramidis-only and placebo + tafamidis groups at Month 30
- Serum TTR levels increased further in participants who switched from placebo + tafamidis to acoramidis in the OLE study (3.0 and 3.4 mg/dL at Month 1 and 6, respectively) **(Figure 2B)**
  - TTR levels remained stable after Month 1 in the OLE. The OLE results are limited by the small sample size
- The OLE study is ongoing

FIGURE 2. Incremental Serum TTR Change in Participants Receiving Placebo + Tafamidis in ATTRibute-CM who Switched to Acoramidis in the OLE

A. ATTRibute-CM— Change From Baseline in Serum TTR at Month 30



*p value was from 2-sided, 2 sample t test (unequal variance) for change from baseline in serum TTR at Month 30 comparing the acoramidis-only group and placebo + tafamidis group.
CFB, change from baseline; SE, standard error of the mean; TTR, transthyretin.



B. Serum TTR Change From Month 30 of ATTRibute-CM to Month 1 and Month 6 of OLE Study in Participants who Switched to Acoramidis From Placebo + Tafamidis

*p values were based on 2-sided paired t test. P values represent comparison between serum TTR in OLE study (Month 1, Month 6) and serum TTR from ATTRibute-CM at Month 30.
OLE, open-label long-term extension; SE, standard error of the mean; TTR, transthyretin.

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