ACORAMIDIS IMPROVES SERUM TTR LEVELS IN PATIENTS WITH WILD-TYPE OR VARIANT TRANSTHYRETIN AMYLOID CARDIOMYOPATHY – RESULTS FROM ATTRibute-CM

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INTRODUCTION

- ATTR-CM is a progressive and debilitating cardiomyopathy caused by TTR tetramer destabilization.[1,2] Greater TTR destabilization generally results in lower sTTR levels and an elevated risk of worse clinical disease[2–4]
- TTR amyloid aggregation can occur due to age-related factors (ATTRwt-CM) or *TTR* mutations (ATTRv-CM)[1,5]
  - ATTRv-CM is typically associated with lower sTTR levels, earlier disease onset, and more rapid progression than ATTRwt-CM[2,6]
- Acoramidis is a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, and is approved in Europe, the USA, and Japan for the treatment of adults with ATTR-CM[7–10]
- In the pivotal phase 3 ATTRibute-CM study (NCT03860935), acoramidis led to better clinical outcomes compared with placebo ($p < 0.0001$) and was well tolerated[11,12]

OBJECTIVE:

To determine the effects of acoramidis on sTTR levels in the subgroups of participants in ATTRibute-CM with ATTRv-CM or ATTRwt-CM[a]

[a]As categorized at randomization.

ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; sTTR, serum transthyretin; TTR, transthyretin.

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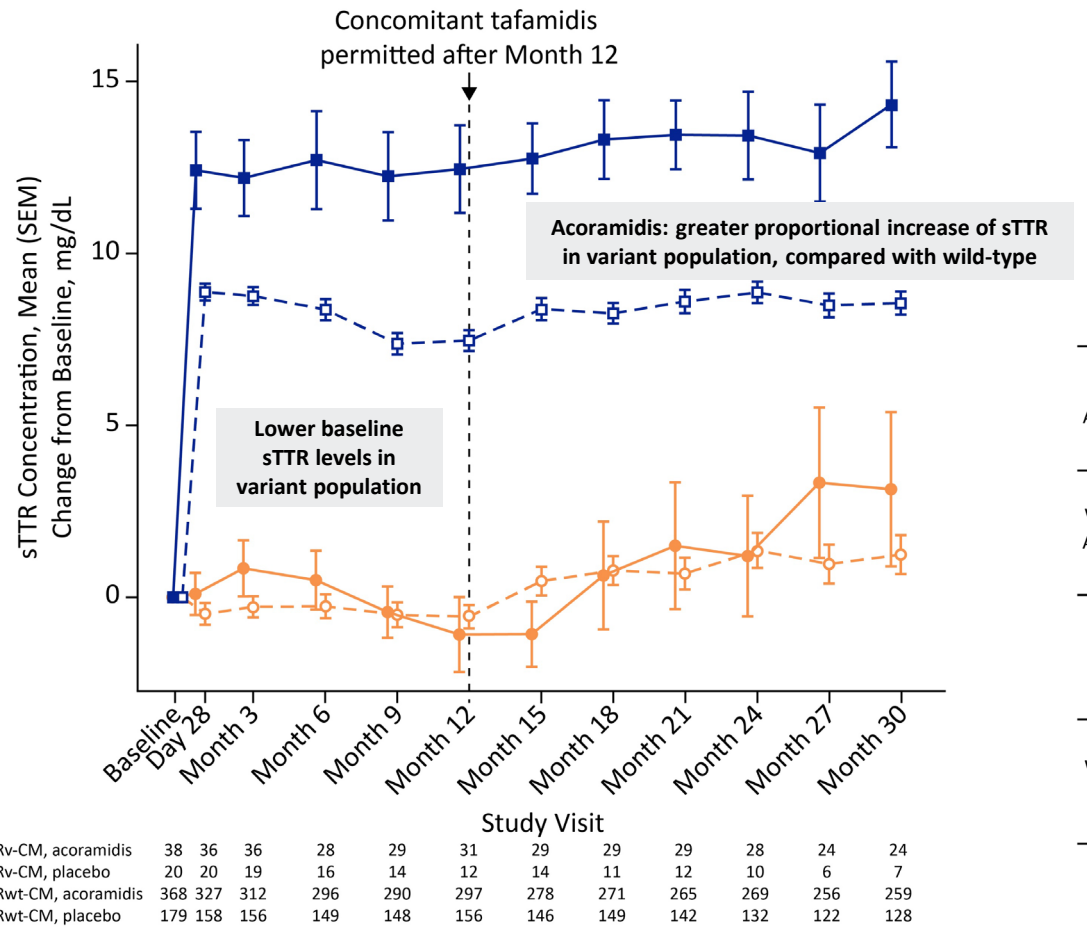
BASELINE sTTR LEVELS WERE LOWER IN ATTRv-CM THAN IN ATTRwt-CM

Baseline Demographic/Characteristic	Acoramidis (mITT, n = 409)		Placebo (mITT, n = 202)	
	ATTRv-CM (n = 39)	ATTRwt- CM (n = 370)	ATTRv-CM (n = 20)	ATTRwt-CM (n = 182)
Age, years, mean (SD)	73.9 (7.60)	77.7 (6.25)	71.2 (7.84)	77.6 (6.32)
Sex, n (%)				
Male	33 (84.6)	341 (92.2)	14 (70.0)	167 (91.8)
Female	6 (15.4)	29 (7.8)	6 (30.0)	15 (8.2)
Most common *TTR* variants, n/N (%)[a]				
p.V142I	23/37 (62.2)	NA	12/19 (63.2)	NA
p.I88L	4/37 (10.8)	NA	3/19 (15.8)	NA
p.T80A	3/37 (8.1)	NA	2/19 (10.5)	NA
NT-proBNP, pg/mL, median (Q1, Q3)	2326.0 (1312.0, 4567.0)	2264.5 (1315.0, 3729.0)	2340.5 (1521.5, 3534.0)	2273.5 (1105.0, 3590.0)
NYHA functional class, n (%)				
I	2 (5.1)	49 (13.2)	1 (5.0)	16 (8.8)
II	35 (89.7)	253 (68.4)	16 (80.0)	140 (76.9)
III	2 (5.1)	68 (18.4)	3 (15.0)	26 (14.3)
sTTR, mg/dL, median (Q1, Q3)[b]	19.0 (13.0, 21.0)	23.0 (20.0, 27.0)	18.0 (12.5, 20.0)	24.0 (21.0, 28.0)

[a]In total, 59/611 participants were categorized as having ATTRv-CM at randomization; subsequently, mutations were identified in the clinical database in 56/611 participants.
[b]sTTR concentrations were determined using a standardized clinical assay for serum prealbumin (sTTR) performed in a central laboratory.
ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; mITT, modified intention-to treat; NA, not applicable; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; Q1, first quartile; Q3, third quartile; SD, standard deviation; sTTR, serum transthyretin; TTR, transthyretin.

ACORAMIDIS TREATMENT LED TO RAPID AND SUSTAINED INCREASES IN sTTR LEVELS IN BOTH ATTRv-CM AND ATTRwt-CM

Change from Baseline in sTTR Level Through Month 30, mITT Population[a,b]

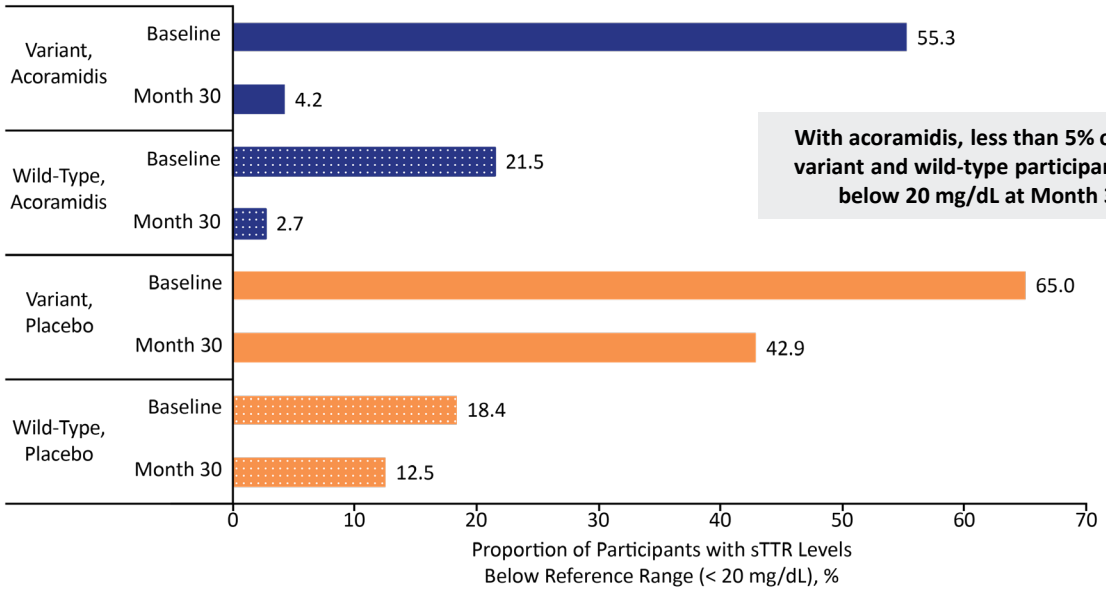


Acoramidis-Mediated Changes in sTTR Levels (mg/dL) at Day 28 and Month 30[a]

		ATTRv-CM	ATTRwt- CM
Day 28	n/N	37/39	328/370
	sTTR, mg/dL, mean (SD)	**30.0 (6.5)**	**32.5 (6.5)**
Month 30	n/N	24/39	260/370
	sTTR, mg/dL, mean (SD)	**33.3 (6.3)**	**32.7 (6.2)**

Similar sTTR levels in both variant and wild-type at Day 28 and Month 30

Proportions of Participants with sTTR Levels Below the Reference Range at Baseline and Month 30, mITT population[a]

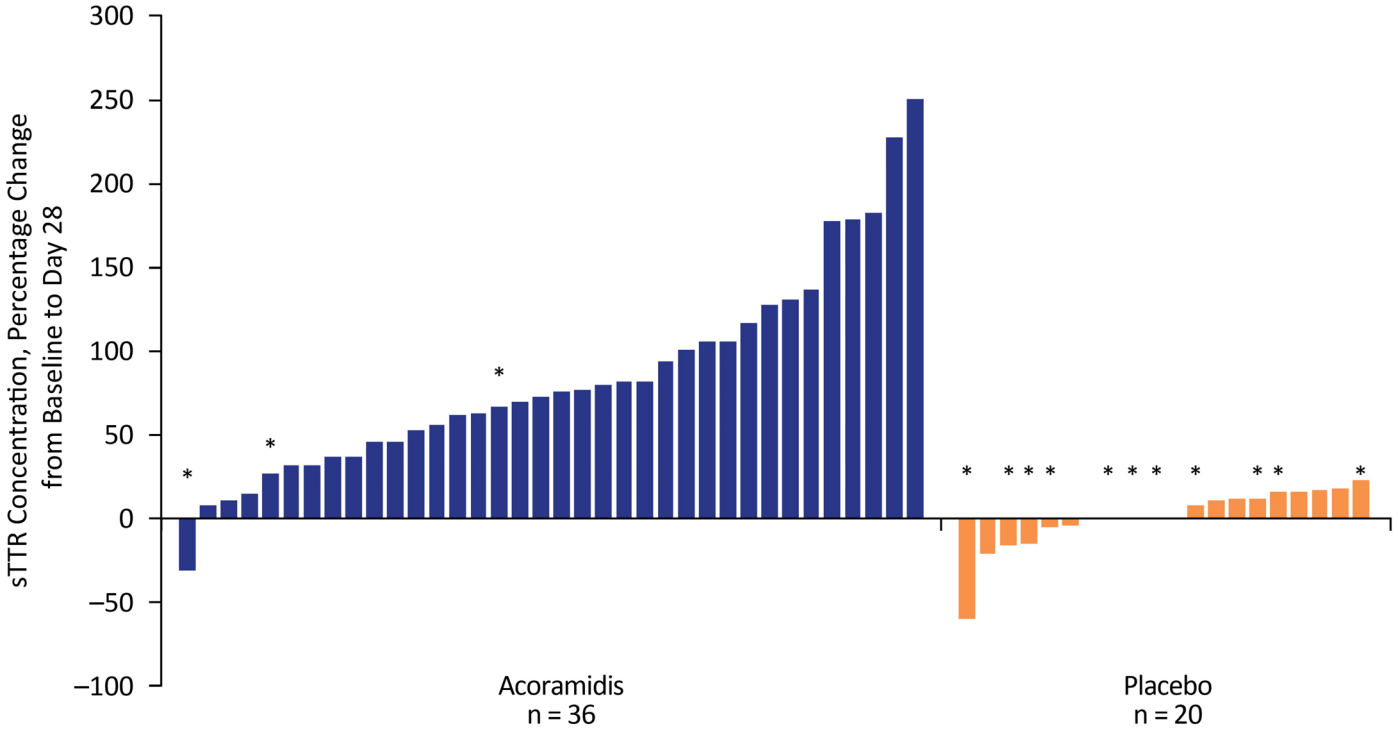


With acoramidis, less than 5% of both variant and wild-type participants are below 20 mg/dL at Month 30

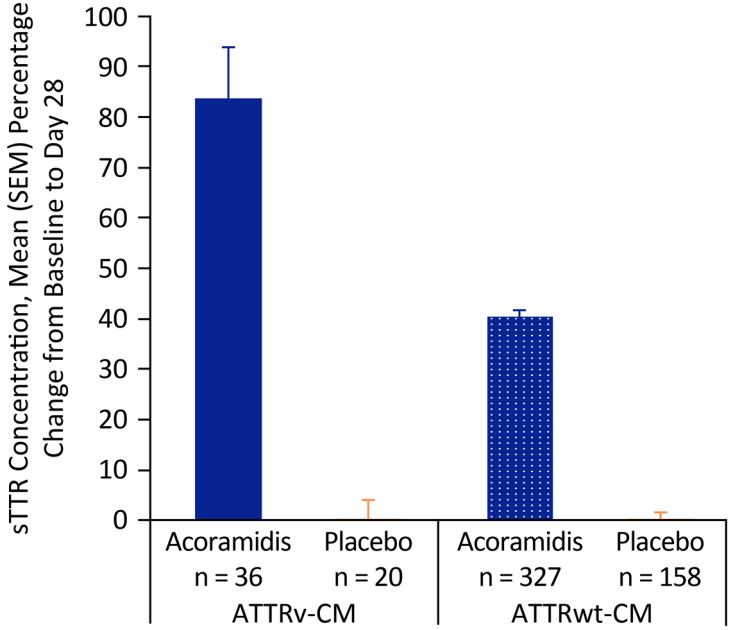
[a]From mITT population; in total, 59/611 participants were categorized as having ATTRv-CM at randomization; subsequently, mutations were identified in the clinical database in 56/611 participants. sTTR concentrations were determined using a standardized clinical assay for serum prealbumin (sTTR) performed in a central laboratory. [b]Data are shown for participants who had non-missing change from baseline values. ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; mITT, modified intention-to treat; SEM, standard error of the mean; sTTR, serum transthyretin.

ACORAMIDIS TREATMENT LED TO INCREASES IN sTTR LEVELS FROM BASELINE TO DAY 28 IN 97% OF ATTRv-CM PARTICIPANTS

Percentage Change from Baseline to Day 28 in sTTR Levels for Each ATTRv-CM Participant[a,b]



Mean Percentage Change from Baseline to Day 28 in sTTR Levels for ATTRv-CM and ATTRwt-CM Participants[a]



[a]In total, 59/611 participants were categorized as having ATTRv-CM at randomization; subsequently, mutations were identified in the clinical database in 56/611 participants. sTTR concentrations were determined using a standardized clinical assay for serum prealbumin (sTTR) performed in a central laboratory. Data are shown for participants who had sTTR concentrations recorded at baseline and Day 28.
[b]Asterisks indicate participants with serum TTR levels below the lower limit of the reference range (< 20 mg/dL) at Day 28.
ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; SEM, standard error of the mean; sTTR, serum transthyretin.

CONCLUSIONS

- In ATTRibute-CM, acoramidis treatment provided near-complete (≥ 90%) TTR stabilization that was consistent, rapid, and sustained over 30 months in participants with ATTRv-CM or ATTRwt-CM
  - At baseline, sTTR levels were lower in participants with ATTRv-CM than in those with ATTRwt-CM
  - Acoramidis treatment induced a greater proportional increase in sTTR levels in participants with ATTRv-CM than in those with ATTRwt-CM, resulting in similar absolute sTTR levels at Day 28 and Month 30
- These results demonstrate the ability of acoramidis to:
  - increase sTTR levels (a measure of TTR stabilization), irrespective of *TTR* genotype, and
  - overcome the lower baseline sTTR levels observed in the variant patient population

ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; sTTR, serum transthyretin; TTR, transthyretin.