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ORIGINAL RESEARCH

Differential Transthyretin Stabilization in Patients With Wild Type and Variant Transthyretin Amyloidosis

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ABSTRACT

BACKGROUND Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, often fatal disease caused by transthyretin (TTR) tetramer destabilization, leading to amyloid deposition from either age-related wild type TTR or pathogenic TTR variants. TTR variants are less stable than wild type TTR, leading to lower serum TTR (sTTR) and worse clinical outcomes. TTR stabilizers, tafamidis and acoramidis, are approved for treatment of patients with ATTR-CM.

OBJECTIVES The aim of this study was to evaluate the differences in stabilizing effect and magnitude of sTTR increases for acoramidis and tafamidis using data from the ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy) trial.

METHODS Stabilizing potency was analyzed using sTTR as an in vivo readout and by applying 2 orthogonal pharmacodynamic assays: Western blot and fluorescent probe exclusion. In vitro analyses used blood samples from patients with variant ATTR-CM at clinically relevant concentrations of acoramidis (10 μM) and tafamidis (16-26 μM).

RESULTS In ATTRibute-CM, treatment with acoramidis (n = 234) resulted in a greater rise in sTTR from baseline to month 30 vs placebo plus tafamidis (n = 34). Acoramidis achieved greater TTR stabilization than placebo plus tafamidis at month 30 by Western blot (90.2% [n = 83] vs 60.6% [n = 6]) and fluorescent probe exclusion (99.7% [n = 71] vs 68.0% [n = 4]), although this was limited by a small sample size. Subsequent in vitro analysis corroborated acoramidis was a more effective TTR stabilizer than tafamidis across all 51 individual participant samples tested, representing 17 unique variants.

CONCLUSIONS Acoramidis is a near-complete stabilizer of wild type and variant TTR. Although in vitro comparisons between acoramidis and tafamidis suggest greater stabilization by acoramidis, randomized prospective trial data comparing these TTR stabilizers are lacking, and further investigation is warranted. (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy [ATTRibute-CM]; NCT03860935) (JACC CardioOncol. 2026;8:299-313) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv-CM = variant transthyretin amyloid cardiomyopathy

ATTRwt-CM = wild type transthyretin amyloid cardiomyopathy

CVH = cardiovascular-related hospitalization

FDA = U.S. Food and Drug Administration

FPE = fluorescent probe exclusion

mITT = modified intention-to-treat

sTTR = serum transthyretin

TTR = transthyretin

TTRv = variant transthyretin

WB = Western blot

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, often fatal disease caused by destabilization of the transthyretin (TTR) tetramer, leading to monomer misfolding and amyloid deposition, arising from either age-related wild type TTR or pathogenic TTR variants.[1] Destabilization is associated with aging and is accelerated by >130 known pathogenic, destabilizing *TTR* gene variants.[1-3] Some variants are associated predominantly with ATTR-CM and others with TTR amyloid polyneuropathy, while many TTR variants show a mixed phenotype of cardiomyopathic and neuropathic manifestations.[1,4] The p.Val50Met variant (also referred to as Val30Met) is among the most prevalent pathogenic variants worldwide and manifests disease mainly as a sensorimotor and autonomic peripheral polyneuropathy, while the most common variant associated with ATTR-CM is p.Val142Ile (also referred to as Val122Ile).[1,5,6] Approximately 3.4% of the Black population in the United States are carriers of the p.Val142Ile allele, compared with <1% of the White population.[1,3,4,7] The TTR tetramer from individuals with pathogenic variants in the TTR gene is intrinsically less stable than the wild type TTR tetramer, and this relative instability results in lower serum TTR (sTTR); this is associated with a higher risk for ATTR-CM, with earlier disease onset and more rapid progression than wild type.[4,8]

Both acoramidis and tafamidis (TTR stabilizers) have demonstrated clinical benefits for cardiovascular outcomes[9,10] and are approved in several countries for the treatment of wild type ATTR-CM (ATTRwt-CM) or variant ATTR-CM (ATTRv-CM) in adults to reduce cardiovascular death and cardiovascular-related hospitalization (CVH).[11,12] Acoramidis is an oral, highly selective TTR stabilizer that mimics the binding mode of the disease-protective variant p.Thr139Met (also referred to as Thr119Met).[13,14] Both stabilizers have been shown to increase sTTR levels in patients with ATTR-CM and a directional trend whereby high stabilizer doses correlate with greater TTR stabilization and higher sTTR levels.[15,16] In the phase 3 ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy) trial, acoramidis demonstrated significant improvement in clinical outcomes over placebo in patients with ATTR-CM in a 4-component hierarchical analysis of death from any cause, cumulative frequency of CVH, change from baseline in N-terminal pro-B-type natriuretic peptide, and 6-minute walk distance ($P < 0.001$) and was generally well tolerated.[10] Approximately 10% of participants in ATTRibute-CM had ATTRv-CM, with 62% of these carrying the p.Val142Ile variant allele.[10] Participants in ATTRibute-CM with other common variants, such as p.Ile88Leu (also referred to as Ile68Leu) and p.Thr80Ala (also referred to as Thr60Ala), constituted 8% to 15% of the variant active and placebo groups.[10] Acoramidis has demonstrated efficacy in patients with ATTRv-CM[17] and has the potential to be an important treatment option for these patients who are at increased risk for morbidity and mortality from ATTR-CM.

In this study, we assessed whether acoramidis demonstrates potency against both wild type and variant forms of TTR by directly comparing in vivo changes from baseline in sTTR with TTR tetramer stabilization by acoramidis and tafamidis observed in the ATTRibute-CM trial as a post hoc analysis, and by evaluating whether these findings correlate with in vitro stabilization of variant TTR (TTRv) in samples from other clinical studies (which were collected before dosing with acoramidis and tested in vitro).

METHODS

SAMPLES COLLECTED FROM PARTICIPANTS ENROLLED IN ATTRibute-CM. ATTRibute-CM (NCT03860935) was a randomized, double-blind, placebo-controlled, phase 3 trial of acoramidis in patients with ATTR-CM. The design of ATTRibute-CM has previously been reported.[10] Briefly, adults 18 to 90 years of age with an established diagnosis of ATTR-CM (either ATTRwt-CM or ATTRv-CM) and clinical evidence of heart failure were randomized 2:1 to receive oral acoramidis hydrochloride 800 mg or matching placebo twice daily for 30 months. Treatment with tafamidis was not permitted during the initial 12 months of the trial; concomitant treatment with tafamidis was permitted thereafter at the discretion of the investigator using locally available doses and

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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formulations and was self-reported by the investigator. TTR genotyping was either confirmed through existing documentation at study entry or during screening. Blood samples for sTTR (entire study population) and stabilization assays (U.S. and U.K. participants) were collected at screening, predose on day 1, predose and 1 hour postdose on day 28, and predose every 3 months (sTTR), or 6 months (TTR stabilization), until month 30. ATTRibute-CM was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines and the Declaration of Helsinki. The trial was approved by an ethics committee at each participating site. All the participants provided written informed consent.

BLINDED ANALYSIS OF TTR STABILIZATION IN PARTICIPANTS FROM ATTRibute-CM. All ATTRibute-CM trial data were generated under blinded conditions by independent contracted laboratories. sTTR concentrations were determined in a central laboratory using an immunoturbidimetric procedure with the Abbott ARCHITECT system (Abbott Core Laboratory Systems). The reference range for serum concentrations of native (tetrameric) TTR (commonly referred to as a Clinical Laboratory Improvement Amendments-certified test for serum prealbumin) is 20 to 40 mg/dL.[15,18] The Western blot (WB) and fluorescent probe exclusion (FPE) assays were performed using established methods as described previously.[13,19] Additional details are included in the Supplemental Appendix, Supplemental Tables 1 and 2. Because of inherent variability of these biologic assays, when there is a small number of samples, or the absence of competing stabilizer in some samples, the point estimates may indicate values below or above 0% and 100%, respectively, which can be interpreted as artifacts. For WB samples with low sTTR, the band intensity of the sample at 72 hours may be stronger than the band intensity at 0 hours, thus resulting in a stabilization value >100%. For FPE samples, negative occupancy (eg, <0%) can occur in cases in which predose samples have very low fluorescence and samples from subsequent visits have higher fluorescence than predose samples. Occupancy >100% can occur if relative fluorescence becomes negative after background correction.

SAMPLES COLLECTED FOR UNBLINDED IN VITRO ANALYSIS OF TTRv. Blood samples for exploratory research were collected from patients with ATTRv-CM during the screening for ATTRibute-CM and other acoramidis clinical trials, including AG10-101, AG10-201, AG10-202, and patients who provided deidentified serum samples under Institutional Review Board protocol NA_00001192 at Johns Hopkins University. All samples were collected from patients who were not receiving any TTR stabilizer at the time of collection. Additional study and sample details are provided in the Supplemental Appendix.

UNBLINDED IN VITRO ANALYSIS OF TTRv STABILIZATION. TTR stabilization was also assessed via in vitro analysis of samples from patients with ATTRv-CM collected after providing informed consent. Assays directly comparing acoramidis and tafamidis were performed by the sponsor. Acoramidis (10 μM) was added to serum or plasma from these patients. The measured clinical steady-state trough concentration of acoramidis is 8 to 10 μM.[20] Tafamidis was also added to serum from patients with ATTRv-CM at its clinical peak (26 μM) and trough (16 μM) concentrations reported for its highest approved dose.[21] Samples were analyzed using WB and FPE as previously described. Pooled human serum and plasma (Innovative Research) were used as quality control samples for FPE and WB assays, respectively.

STATISTICAL ANALYSIS. Continuous data are presented with descriptive statistics using the number of participants or samples, mean, and SEM or SD. Change from baseline in sTTR at month 30 was analyzed using an analysis of covariance model in acoramidis-treated participants who never initiated tafamidis and in placebo-treated participants who were receiving U.S. Food and Drug Administration (FDA)-approved doses of tafamidis (ie, equivalent to the 61-mg free-acid formulation) at month 30. The model included treatment group as a factor and baseline sTTR, sex, genotype (ATTRwt-CM vs ATTRv-CM), baseline estimated glomerular filtration rate, and log-transformed baseline N-terminal pro-B-type natriuretic peptide as covariates (SAS version 9.4, SAS Institute). Differences in in vitro stabilization by acoramidis and tafamidis were calculated using Wilcoxon matched-pairs signed rank tests (Prism version 10; GraphPad Software). A 2-sided P value <0.05 was considered to indicate statistical significance. The relationship between sTTR change from baseline and TTR stabilization was evaluated across all treatment groups and by visit. Stabilization was assessed using WB and FPE assays. Associations were evaluated using scatterplots and quantified using Pearson correlation coefficients. Lines of best fit were generated using linear regression for visualization (Prism version 10). Participants on non-FDA-approved doses of tafamidis were excluded from the analysis.

RESULTS

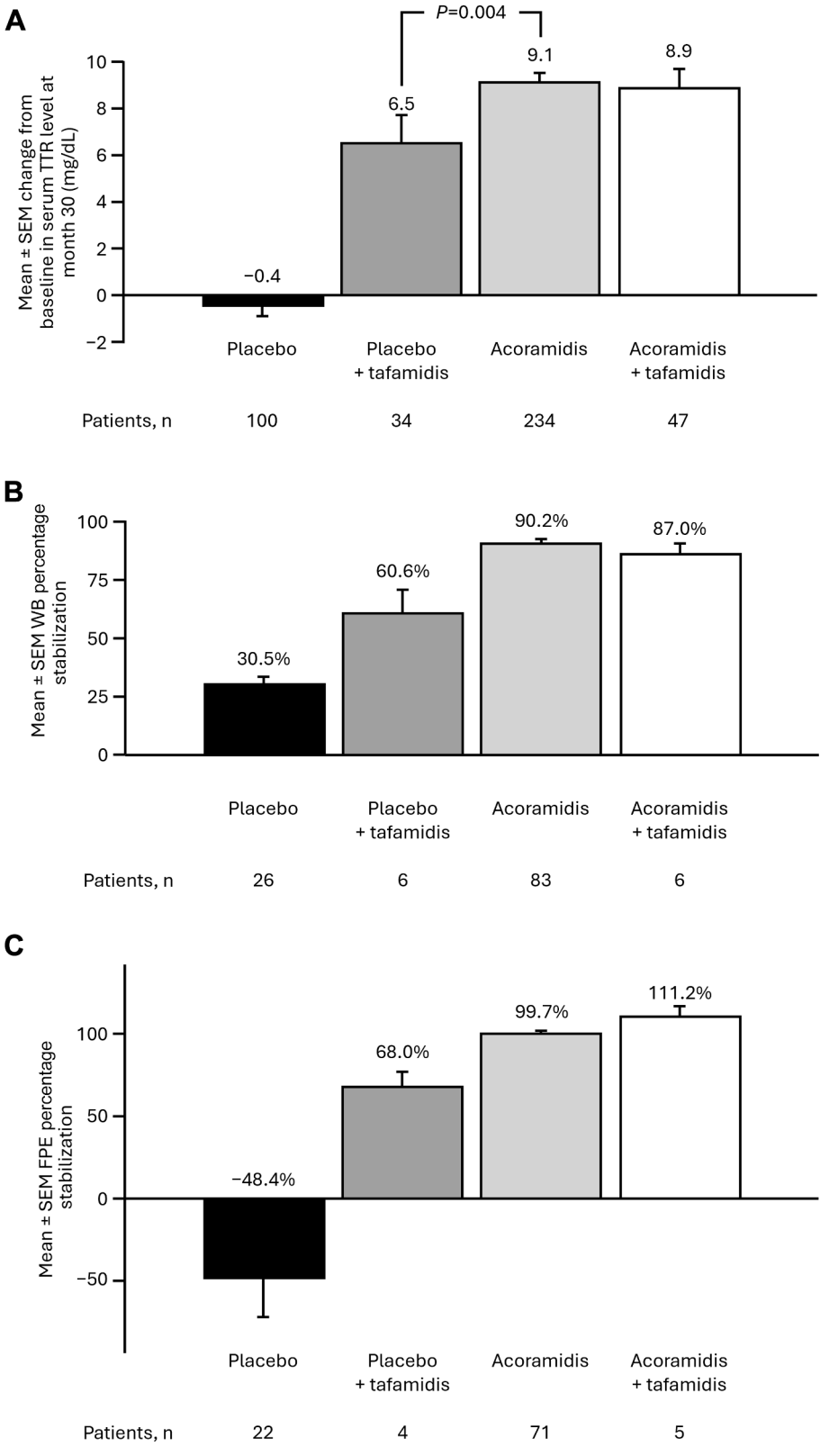
FINDINGS FROM ATTRibute-CM. Baseline demographics across the modified intention-to-treat (mITT) participant subgroups are shown in Supplemental Table 1. Clinically relevant disease characteristics are also shown, indicating relative balance between groups. Overall, 107 of 611 participants (17.5%) in the mITT population received tafamidis; this included 61 of 409 participants (14.9%) in the acoramidis group and 46 of 202 participants (22.8%) in the placebo group. At month 30, nearly all participants treated with tafamidis (n = 84) were receiving FDA-approved doses (equivalent to the 61-mg free-acid formulation once daily). Three participants were receiving non-FDA-approved doses of tafamidis (1 in the placebo arm and 2 in the acoramidis arm).

Acoramidis increased sTTR levels more than tafamidis in participants in ATTRibute-CM. In the mITT population at month 30, participants who received acoramidis only (n = 234) experienced a mean ± SEM change from baseline in circulating sTTR of 9.1 ± 0.4 mg/dL compared with 6.5 ± 1.3 mg/dL among participants who received placebo and subsequently also received concomitant tafamidis after ≥1 year from baseline (placebo plus tafamidis, n = 34; $P = 0.004$) (Figure 1A). The mean change from baseline in sTTR was −0.4 ± 0.5 mg/dL in participants who received placebo only (n = 100). Participants receiving blinded acoramidis who also received subsequent concomitant tafamidis displayed an increase of 8.9 ± 0.8 mg/dL in sTTR (n = 47), which was similar to the change from baseline observed with acoramidis alone.

At month 30, mean ± SEM stabilization of TTR by WB was 30.5% ± 2.9% for placebo (n = 26), 60.6% ± 9.5% for placebo plus tafamidis (n = 6), 90.2% ± 1.4% for acoramidis (n = 83), and 87.0% ± 4.6% for acoramidis plus tafamidis (n = 6) (Figure 1B). Samples for this post hoc exploratory analysis were included only if the participants were actively receiving concomitant tafamidis, including on the day of their month 30 blood draw. All results for placebo plus tafamidis included in this analysis were from participants who had initiated tafamidis ≥252 days before the month 30 blood draw. At month 30, mean ± SEM stabilization of TTR by FPE was −48.4% ± 24.0% for placebo (n = 22), 68.0% ± 8.7% for placebo plus tafamidis (n = 4), 99.7% ± 2.2% for acoramidis (n = 71), and 111.2% ± 6.2% for acoramidis plus tafamidis (n = 5) (Figure 1C).

In a composite analysis of all samples collected from months 1 to 30 from participants in ATTRibute-CM, in vivo mean ± SEM change from baseline in sTTR was greater for acoramidis than for placebo (Figure 2A). The mean ± SEM change from baseline in sTTR in participants with ATTRwt-CM was 8.1 ± 0.1 mg/dL for acoramidis (n = 2,712 samples from 321 participants) and −0.5 ± 0.1 mg/dL for placebo (n = 1,271 samples from 148 participants). The mean sTTR values at baseline in the ATTRv-CM participants were 18.1 and 16.3 mg/dL in the acoramidis and placebo groups, respectively, whereas in the ATTRwt-CM participants, values were 24.2 and 25.0 mg/dL, respectively. In participants with TTRv, acoramidis increased sTTR from baseline to a greater extent than in participants with wild type TTR (Figure 2A). The number of participants who received concomitant tafamidis in the placebo group (n = 46) was small compared with the acoramidis-only (n = 352) and placebo-only (n = 160) groups, and the delayed use of tafamidis limits the validity of direct comparisons. Composite analysis of percentage TTR stabilization by WB demonstrated greater TTR stabilization with acoramidis compared with placebo in participants from ATTRibute-CM (Figure 2B). In participants with ATTRwt-CM, mean ± SEM TTR percentage stabilization by WB was 91.9% ± 0.7% for acoramidis (n = 850 samples from 103 participants) and 38.7% ± 1.2% for placebo (n = 350 samples from 43 participants). For participants with ATTRv-CM, mean ± SEM TTR percentage stabilization by WB was 90.8% ± 1.5% for acoramidis (n = 158 samples from 18 participants) and 25.3% ± 2.1% for placebo (n = 56 samples from 9 participants). Composite WB results in the participants with ATTRv-CM treated with placebo reflect the intrinsic instability of TTR variants (represented predominantly by p.Val142Ile), which were substantially less stable compared with samples from participants with ATTRwt-CM. Composite analysis of percentage TTR stabilization by FPE also demonstrated greater TTR stabilization with acoramidis (97.3% ± 0.9%) compared with placebo (−24.1% ± 3.9%) in participants from ATTRibute-CM (Figure 2C). For participants with ATTRwt-CM, the mean ± SEM TTR percentage stabilization by FPE was 98.1% ± 0.9% for acoramidis (n = 777 samples from 91 participants) and −26.4% ± 4.4% for placebo (n = 323 samples from 38 participants). For participants with ATTRv-CM, the mean ± SEM TTR percentage stabilization by FPE was 92.8% ± 2.2% for acoramidis (n = 138 samples from 16 participants)

FIGURE 1 **TTR Stabilization at Month 30 by Acoramidis and Tafamidis in Participants From ATTRibute-CM**



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and −10.8% ± 7.6% for placebo (n = 55 samples from 9 participants). Correlations of WB and FPE vs sTTR change from baseline are presented in Supplemental Figure 1. ATTR-CM participants with p.Thr80Ala and p.Ile88Leu variants were represented in the ATTRibute-CM study population in both the acoramidis and placebo treatment groups without concomitant tafamidis (p.Thr80Ala: mean baseline TTR 20.5 mg/dL [n = 4]; p.Ile88Leu: mean baseline TTR 22.2 mg/dL [n = 5]). In the acoramidis treatment group (without concomitant tafamidis), participants with p.Thr80Ala and p.Ile88Leu variants were both observed to have consistent sustained increases in sTTR, with mean composite changes from baseline of 14.3 and 7.5 mg/dL, respectively. Assessment of TTR stabilization by WB in 12 samples from 1 participant with p.Thr80Ala in the acoramidis-only treatment group (without concomitant tafamidis) demonstrated a mean composite WB stabilization of 91.4% over the study period. Similar extent of stabilization for a participant with p.Thr80Ala is noted at month 45 in an open-label study of acoramidis.[22]

IN VITRO FINDINGS. Acoramidis was associated with near-complete stabilization of tetrameric TTR by in vitro WB analysis, with a greater degree of stabilization compared with tafamidis using concentrations achieved with oral dosing of each medication (Supplemental Figure 2). In vitro mean ± SD TTR percentage stabilization by WB was 103.3% ± 8.2% with acoramidis 10 μM compared with 26.6% ± 3.0% with dimethyl sulfoxide control. Tafamidis alone at peak (26 μM, 65.5% ± 4.5%) or trough (16 μM, 56.7% ± 6.9%) concentrations was insufficient to fully stabilize TTR in plasma samples in vitro. When acoramidis 10 μM was added in combination with tafamidis (16 or 26 μM) to plasma samples, near-complete TTR stabilization was observed (acoramidis 10 μM plus tafamidis 16 μM, 97.8% ± 14.6%; acoramidis 10 μM plus tafamidis 26 μM, 97.8% ± 12.4%).

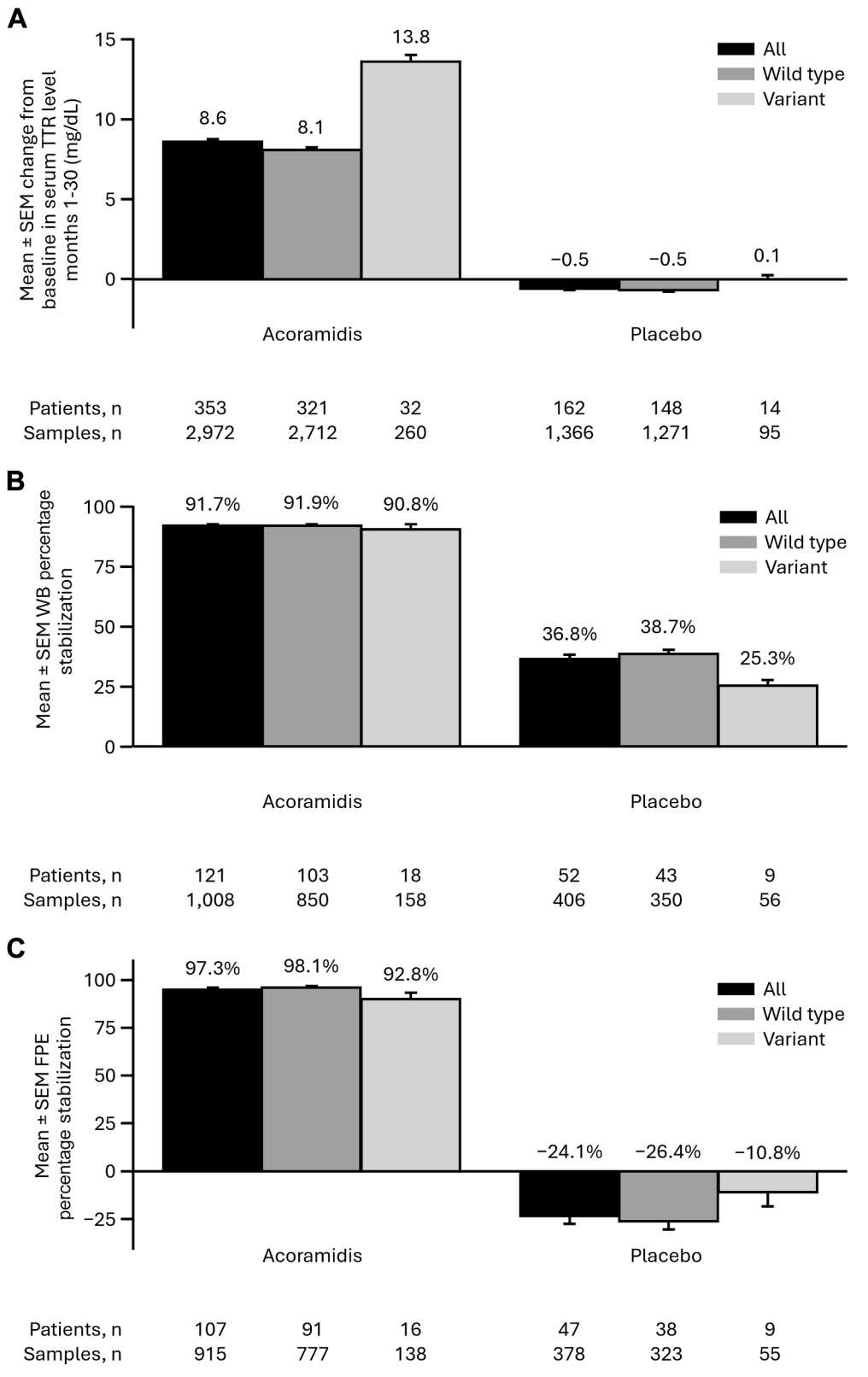
Acoramidis demonstrated consistent in vitro stabilization of TTR of 11 different TTR variants to a greater extent than tafamidis, as shown by WB and FPE (**Figure 3**). **Figure 3A** shows a representative WB of an individual p.Val142Ile participant sample after incubation for 0 or 72 hours with dimethyl sulfoxide control, acoramidis 10 μM, or tafamidis 26 or 16 μM. In all variants tested (n = 51), acoramidis 10 μM was associated with near-complete mean ± SD percentage TTR stabilization by WB (92.9% ± 14.2%), which was significantly greater than that demonstrated with either concentration of tafamidis (26 μM, 49.1% ± 14.2%; 16 μM, 36.2% ± 13.1%; $P < 0.001$ for acoramidis 10 μM vs tafamidis 26 μM) (**Figure 3B**, **Table 1**). Samples from participants with the p.Ile88Leu variant taken during the course of the ATTRibute-CM study were not available for WB or FPE stabilization assays; in vitro WB comparison of plasma samples collected during study screening demonstrated significantly higher WB stabilization of p.Ile88Leu TTR by acoramidis 10 μM compared with tafamidis 26 μM ($P = 0.016$) (**Figure 3B**, **Table 1**).

Acoramidis also demonstrated greater in vitro TTR stabilization vs tafamidis by FPE analysis (**Figure 3C**, **Table 2**). In all variants tested (n = 39), acoramidis 10 μM was associated with near-complete TTR percentage stabilization by FPE (mean ± SD 103.0% ± 12.8%), which was significantly greater than that demonstrated with either concentration of

FIGURE 1 Continued

(A) Mean change from baseline in serum transthyretin (TTR) in vivo at month 30. The difference between the acoramidis-only and placebo plus tafamidis treatment groups was calculated using the analysis of covariance model. The model included treatment group as a factor and baseline serum TTR, sex, genotype (wild type transthyretin amyloid cardiomyopathy vs variant transthyretin amyloid cardiomyopathy), baseline estimated glomerular filtration rate, and log-transformed baseline N-terminal pro-B-type natriuretic peptide as covariates. At month 30, nearly all participants treated with tafamidis (n = 84) were receiving the 61-mg free-acid formulation once daily. (B) Mean of Western blot (WB) percentage stabilization at month 30 by tafamidis use. (C) Mean of fluorescent probe exclusion (FPE) percentage stabilization at month 30 by tafamidis use. Analyses were performed in participants who were receiving U.S. Food and Drug Administration-approved doses of tafamidis (ie, equivalent to the 61-mg free-acid formulation) at month 30. Three participants (1 in the placebo arm and 2 in the acoramidis arm) were receiving tafamidis meglumine 20 to 40 mg/d and were not included in the analyses. In (A), results are shown for the modified intention-to-treat population. In (B) and (C), results are shown for the intention-to-treat population; "+ tafamidis" means that the visit date must be ≥1 day after the tafamidis start date and no more than 0 days since the tafamidis stop date; participants in the "+ tafamidis" groups that had visit dates outside this window were excluded. ATTRibute-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy.

FIGURE 2 **Change From Baseline in Serum TTR Levels in Participants With Wild-Type and Variant TTR Amyloid Cardiomyopathy From ATTRibute-CM**



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tafamidis (26 μM, 86.9% ± 13.7%; 16 μM, 71.7% ± 13.7%; $P < 0.001$ for acoramidis 10 μM vs tafamidis 26 μM) (**Table 2**).

Acoramidis demonstrated stabilization of rare TTR variants by WB and FPE analysis (**Figure 4**, Supplemental Table 2). However, as samples were limited in volume, stabilization by tafamidis was not analyzed for these rare TTR variants, most of which are associated with mixed ATTR phenotypes (ATTR-CM and TTR amyloid polyneuropathy signs or symptoms).

DISCUSSION

ATTR-CM is a disease driven by protein instability, characterized by the dissociation of tetrameric TTR into monomers, which subsequently misfold, aggregate into toxic amyloid precursors, and deposit as amyloid fibrils, a critical step in the disease's pathophysiology.[1] The mechanism of action of TTR stabilizers, such as acoramidis and tafamidis, is to stabilize the native (tetrameric) form of the protein, a mechanism of action that translates into clinical benefit.[9,10] In this report, we evaluate the pharmacodynamic properties of acoramidis using 3 orthogonal measures of TTR stabilization: circulating sTTR concentration, which has been correlated with the degree of TTR stabilization; WB assays, which measure a small molecule stabilizer's ability to prevent dissociation of the TTR tetramer; and FPE assays, which represent a measure of the occupancy of the TTR binding site by a stabilizer.

We have previously reported that acoramidis rapidly increased mean sTTR levels by day 28 in participants with ATTR-CM (wild type and variant), which was sustained through month 30 of the ATTRibute-CM trial, whereas the change from baseline in sTTR levels remained unchanged or declined in the placebo group.[10] In ATTRibute-CM, treatment with acoramidis alone demonstrated a greater increase in mean change from baseline in sTTR levels at 30 months compared with participants in the placebo group who also received concomitant tafamidis treatment (**Central Illustration**). Consistent with the near-complete stabilization of TTR by acoramidis, the observed mean increase in sTTR levels in participants receiving acoramidis and concomitant tafamidis treatment was comparable with that observed in participants who received acoramidis treatment alone. Adding tafamidis to acoramidis has no incremental effect on sTTR levels compared with the change from baseline in mean sTTR levels in the acoramidis-only group. The rise in sTTR as a marker of TTR tetramer stabilization has been used previously for acoramidis, tafamidis, diflunisal, and tolcapone,[15,23-25] although proof that this effect is due solely to TTR tetramer stabilization remains incomplete. Diflunisal is indeed an anti-inflammatory drug, which could increase sTTR levels by reducing inflammation. To address this, we used other methods to test TTR tetramer stability. Acoramidis achieved near-complete (≥90%) TTR stabilization in participants with either ATTRwt-CM or ATTRv-CM at month 30 as measured by both WB and FPE. These stabilization findings are consistent with subgroup analyses from ATTRibute-CM, showing similar clinical efficacy across both ATTRv-CM and ATTRwt-CM populations.[10,26] All 3 orthogonal measures of TTR stabilization yielded concordant results with modest correlation, demonstrating increased sTTR concentrations and greater TTR stabilization with acoramidis.

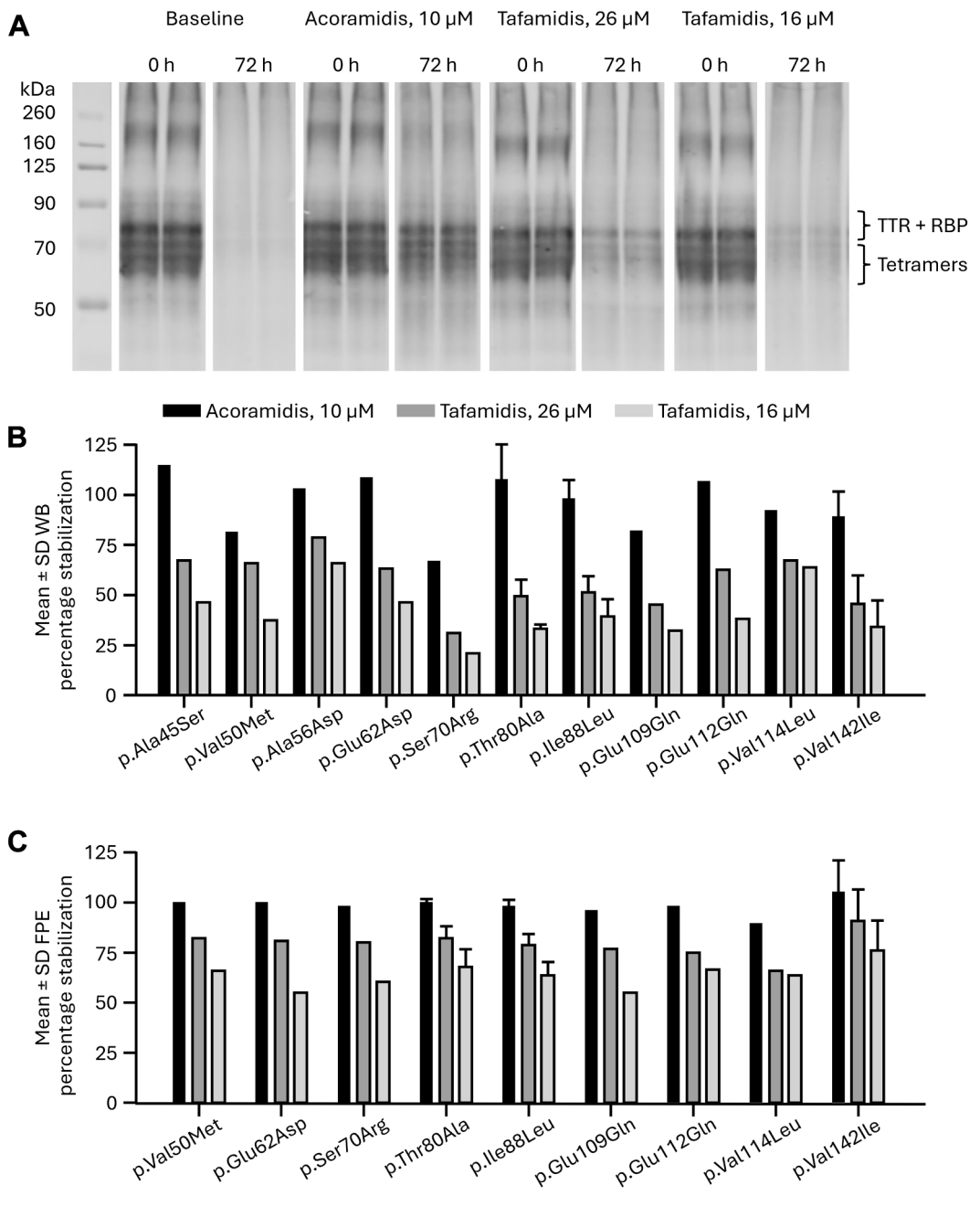
Acoramidis demonstrated activity in multiple variants, with 89.7% stabilization for the p.Val142Ile variant as measured by WB and 105.8% stabilization as measured by FPE. The mixed-phenotype variant p.Thr80Ala is one of the most prevalent TTR variants, particularly in Ireland, the United Kingdom, and North America.[27] Acoramidis increased circulating TTR levels in participants with the p.Thr80Ala variant, and this effect is further supported by the observed >90% stabilization by WB. While the majority of participants in ATTRibute-CM had wild type TTR, in vitro analyses across variants demonstrated significantly greater TTR stabilization with acoramidis than with tafamidis at its peak clinical concentration, on the basis of 2 complementary assays.

Potency and specificity of TTR stabilization have been compared by various methodologies in purified

FIGURE 2 Continued

(A) Change from baseline in serum TTR. (B) TTR percentage stabilization by WB. (C) TTR percentage stabilization by FPE. Results are shown for the intention-to-treat population. Variants are defined as participants with genetic status confirmed as mutation with the exception of participants with the nonpathogenic p.Gly26Ser variant, which were included in the wild type group. Abbreviations as in **Figure 1**.

FIGURE 3 **In Vitro Stabilization of Variant TTR by Acoramidis or Tafamidis in Participant Samples From ATTRibute-CM**



(A) WB of an individual p.Val142Ile (V122I) participant sample. All conditions were run in duplicate lanes. Brackets denoting the bands corresponding to tetrameric TTR with or without retinol-binding protein (RBP) are indicated. (B) TTR percentage stabilization by WB. (C) TTR percentage stabilization by FPE. SD is shown only for measurements with ≥2 samples. Abbreviations as in **Figure 1**.

protein experiments. Several studies have reported higher TTR binding specificity and TTR stabilization potency for acoramidis relative to tafamidis.[11-13,28,29] Relative activity between the 2 agents in vitro has also been reported in the presence of albumin and other plasma proteins, with acoramidis deemed a more potent stabilizer.[14] In vivo, TTR stabilization occurs in the plasma compartment and is therefore

TABLE 1 Summary of Western Blot Percentage Stabilization Results in Participant Samples From ATTRibute-CM

Variant	n	Acoramidis 10 μM	Tafamidis 26 μM	Tafamidis 16 μM	Baseline
p.Ala45Ser (Ala25Ser)	1	115.4	68.1	46.5	20.9
p.Val50Met (Val30Met)	1	81.7	66.5	37.5	32.0
p.Ala56Asp (Ala36Asp)	1	104.2	79.7	66.3	50.5
p.Glu62Asp (Glu42Asp)	1	109.6	63.6	46.1	24.1
p.Ser70Arg (Ser50Arg)	1	67.0	31.0	21.0	12.0
p.Thr80Ala (Thr60Ala)	3	108.5 ± 25.5	49.6 ± 8.3	33.4 ± 1.6	23.4 ± 6.6
p.Ile88Leu (Ile68Leu)	7	98.5 ± 9.4[a]	51.6 ± 8.0	39.3 ± 8.6	21.4 ± 7.6
p.Glu109Gln (Glu89Gln)	1	82.2	45.3	32.2	27.0
p.Glu112Gln (Glu92Gln)	1	107.2	62.8	38.5	25.9
p.Val114Leu (Val94Leu)	1	92.8	67.4	64.2	26.0
p.Val142Ile (Val122Ile)	33	89.7 ± 12.3	45.7 ± 14.1	33.9 ± 13.4	25.5 ± 13.0
Variant mean	51	92.9 ± 14.2[b]	49.1 ± 14.2	36.2 ± 13.1	25.1 ± 11.7

Mean ± SD is shown only for measurements with ≥2 samples. *P* values were calculated using Wilcoxon matched-pairs signed rank tests. Baseline represents the intrinsic stability of the sample, as it was only treated with vehicle dimethyl sulfoxide. [a]$P = 0.016$ for acoramidis 10 μM vs tafamidis 26 μM. [b]$P < 0.001$ for acoramidis 10 μM vs tafamidis 26 μM.

ATTRibute-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy.

determined by circulating drug concentrations. Differences in stabilization results across studies may reflect variation in assay conditions and concentrations tested. Notably, the results from this study are consistent with previous studies comparing TTR stabilization between acoramidis and tafamidis by subunit exchange. The subunit exchange assay uses in vitro addition of FLAG-tagged TTR homotetramers to endogenous TTR in plasma.[30] Nelson et al used this method and demonstrated that acoramidis was 4 times more potent as a TTR stabilizer compared with tafamidis at a 10-μM plasma concentration.[31-33] However, the subunit exchange method is impractical for use with blinded clinical samples. Compared with other stabilizers, acoramidis is known to form more extensive hydrogen bonds with the TTR tetramer.[13] Designed to mimic the protective p.Thr139Met variant, acoramidis stabilizes both wild type and TTRv through enthalpically driven hydrogen bonding, ionic interactions, and multisubunit engagement. These binding characteristics may contribute to the degree of TTR stabilization observed with acoramidis.[13,14]

TABLE 2 Summary of Fluorescent Probe Exclusion Percentage Stabilization Results in Participant Samples From ATTRibute-CM

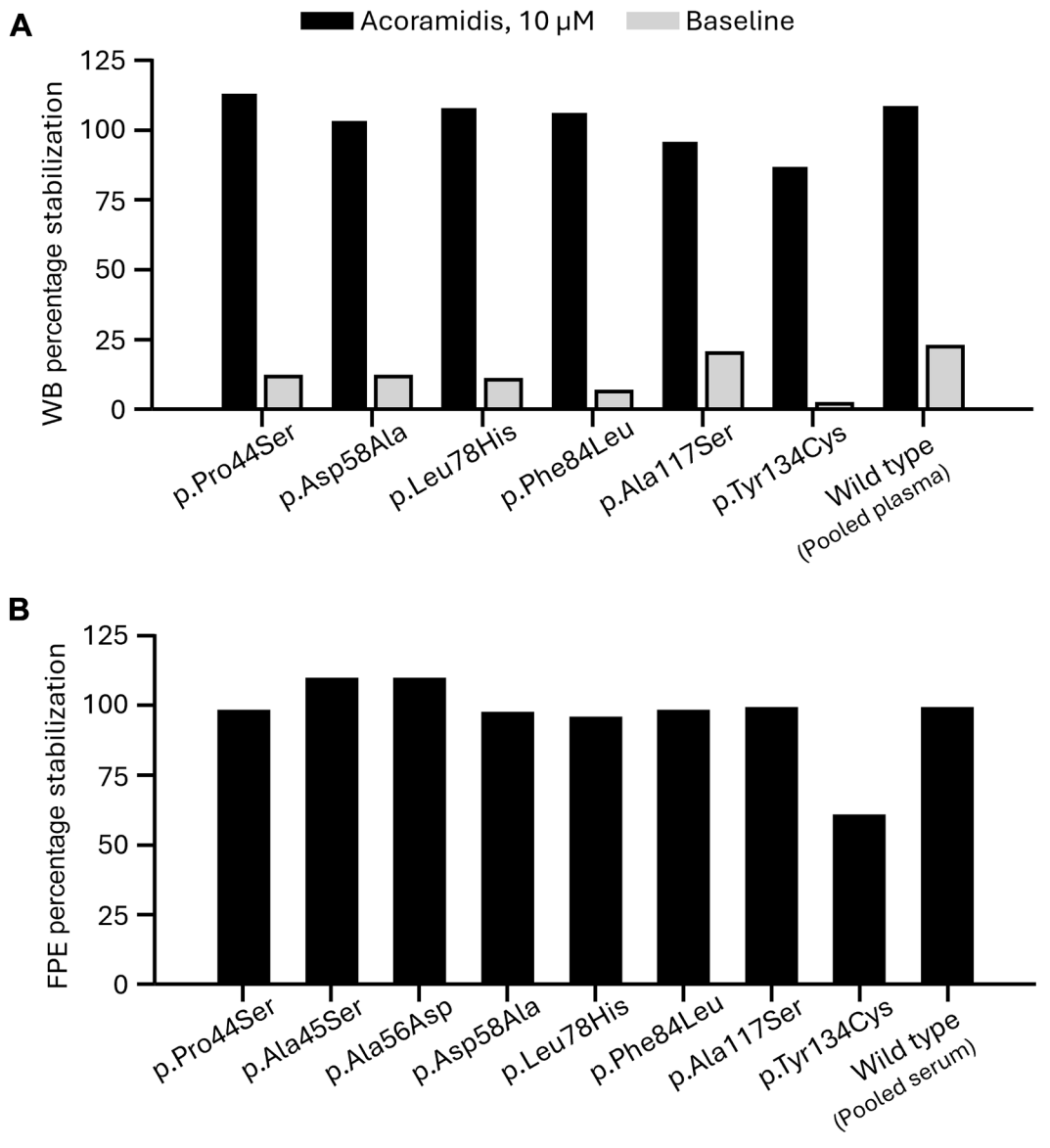
Variant	n	Acoramidis 10 μM	Tafamidis 26 μM	Tafamidis, 16 μM
p.Val50Met (Val30Met)	1	100.3	83.2	66.3
p.Glu62Asp (Glu42Asp)	1	100.1	81.0	55.3
p.Ser70Arg (Ser50Arg)	1	99.1	80.3	60.3
p.Thr80Ala (Thr60Ala)	4	100.1 ± 1.8	82.3 ± 6.1	68.1 ± 8.9
p.Ile88Leu (Ile68Leu)	5	98.6 ± 3.0	79.4 ± 5.3	64.0 ± 6.7
p.Glu109Gln (Glu89Gln)	1	96.4	76.7	55.5
p.Glu112Gln (Glu92Gln)	1	98.5	75.4	67.0
p.Val114Leu (Val94Leu)	1	90.1	66.5	64.2
p.Val142Ile (Val122Ile)	24	105.8 ± 15.7	91.6 ± 15.2	76.5 ± 14.8
Variant mean	39	103.0 ± 12.8[a]	86.9 ± 13.7	71.7 ± 13.7
Pooled serum (wild type)	6	99.4 ± 1.8	64.7 ± 5.5	48.6 ± 6.4

Mean ± SD is shown only for measurements with ≥2 samples. *P* value was calculated using a Wilcoxon matched-pairs signed rank test. [a]$P < 0.001$ for acoramidis 10 μM vs tafamidis 26 μM.

ATTRibute-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopath.

Although sTTR can be influenced by factors such as inflammation, nutrition, proteinuria, and liver disease, sTTR level is emerging as a useful biomarker for TTR stability (whether intrinsic or pharmacologically modified). Patients with ATTR-CM have lower circulating sTTR levels compared with healthy adults, and the lowest levels are correlated with earlier and more rapid declines of cardiac function, as well as an increased risk for mortality.[34] Increases in sTTR upon treatment with a TTR stabilizer have the potential to be affected by other mechanisms such as increased hepatic secretion, decreased lysosomal degradation, or reduced monomer misfolding.[33] Among these, the only known effect of both tafamidis and acoramidis is TTR stabilization, which has been positively correlated with sTTR levels. Recent studies have shown that higher circulating sTTR levels are associated with a lower risk for heart failure.[35] Additionally, relative increases in sTTR concentrations have been associated with reduced risk for all-cause and cardiovascular mortality in the general population.[36] Patients with ATTRv-CM typically have lower sTTR levels compared with those with ATTRwt-CM, likely because of greater TTR instability, which is correlated with earlier disease onset and more rapid clinical progression. Although

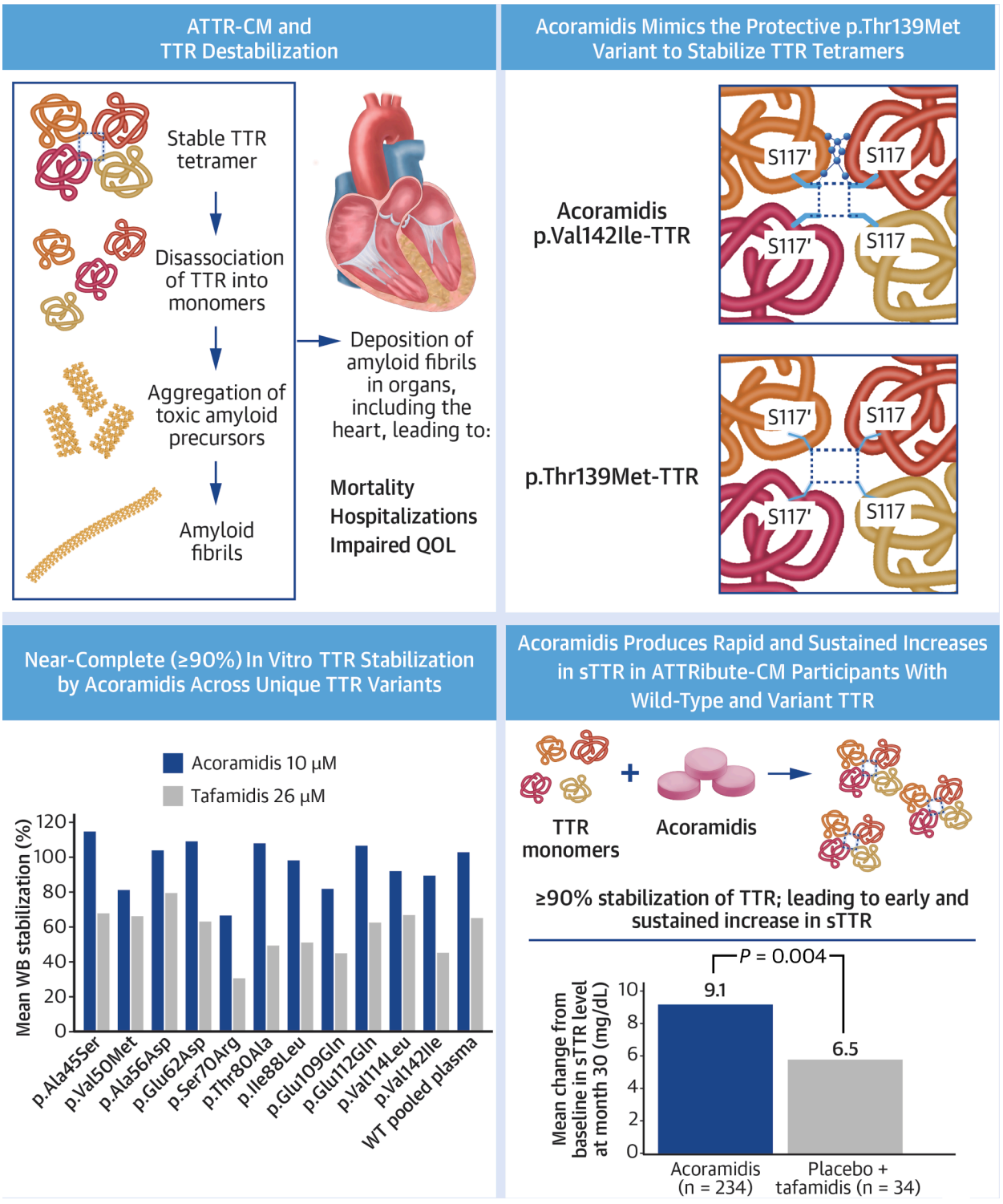
FIGURE 4 **In Vitro Stabilization of Rare TTR Variant Patient Samples**



TTR stabilization of individual variants as measured by (A) WB and (B) FPE (n = 1 for each variant), with wild type results as reference. Baseline represents WB stability of samples incubated only with vehicle. Abbreviations as in **Figure 1**.

earlier diagnosis and the development of targeted treatments for ATTR-CM have provided therapeutic benefits, 36% of patients still die within 2.5 years of initiating therapy, and fewer than one-half regain their quality of life.[37] The efficacy of acoramidis shown against TTR variants in this analysis has recently been confirmed in patients with ATTRv-CM.[26] In participants randomized to acoramidis and followed up in the open-label extension of ATTRibute-CM, reduction in all-cause mortality and CVH was similar in those with ATTRv-CM and ATTRwt-CM.[26] Rise in sTTR has been criticized as not

CENTRAL ILLUSTRATION **TTR Stabilization With Acoramidis in ATTRwt-CM and Across Unique TTR Variants**



Judge DP, et al. JACC CardioOncol. 2026;8(3):299–313.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the dissociation of transthyretin (TTR) into constituent monomers, which aggregate into toxic amyloid precursors and deposit as amyloid fibrils in the heart and other organs. Acoramidis stabilizes TTR by mimicking the protective p.Thr139Met variant. In this post hoc analysis, acoramidis was associated with a greater increase in serum TTR compared with tafamidis and demonstrated near-complete (≥90%) TTR stabilization across 17 unique variants, including greater stabilization of p.Val142Ile compared with tafamidis. ATTRibute-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; ATTRwt-CM = wild type transthyretin amyloid cardiomyopathy; QOL = quality of life; sTTR = serum transthyretin; WB = Western blot.

having clear correlation with outcomes in clinical trials.[33] To address this, recent analysis from the ATTRibute-CM trial analyzed outcomes on the basis of the degree of change in sTTR levels at day 28 of treatment.[38] In multivariate analysis, after adjusting for TTRv status, baseline New York Heart Association functional class, baseline National Amyloidosis Centre stage, and baseline sTTR level, an early increase in sTTR levels was independently associated with reduced all-cause mortality ($P < 0.001$). For every 5 mg/dL increase in sTTR levels, a logistic model predicted a 31.6% relative reduction in odds of all-cause mortality. Furthermore, these findings of a positive association between higher sTTR levels and improved survival outcomes have been confirmed independently in recent analyses.[39,40]

STUDY LIMITATIONS. The FPE and WB results with placebo plus tafamidis were limited by small sample size. The use of tafamidis was not randomized; importantly, this study does not reflect a direct comparison. Tafamidis treatment was initiated only after month 12, which may have resulted in the placebo plus tafamidis group having more advanced disease compared with baseline severity. Although this study uses 3 different methods to confirm the pharmacodynamic activity of acoramidis, its effect in pathogenic TTR variants herein is not based on clinical endpoints, and these results may need to be further confirmed in a clinical trial. This study examines the correlation between TTR stabilization and sTTR levels, which is directionally consistent but varies in magnitude. It does not establish any mechanistic or causal link between them. Although the fluorescent probe used in the FPE assay was added at a fixed concentration optimized for 1 M equivalent of tetrameric TTR, over a long enough time and with similarly reduced binding affinity from negative cooperativity, it can react with the second thyroxine binding pocket of TTR, which would reduce the stabilization readout for samples with stabilizers that cannot occupy the second binding pocket. TTR biology is complex and affected by multiple factors in addition to tetramer stability. The present data are on a population level and may not apply to patients on an individual basis. No formal adjustments were performed for multiple comparisons. Overall, the results of this study are exploratory and hypothesis generating.

CONCLUSIONS

Multiple assays confirm near-complete TTR tetramer stabilization by acoramidis in both ATTRwt-CM and ATTRv-CM. Although in vitro comparisons between acoramidis and tafamidis indicate greater stabilization by acoramidis, randomized prospective trial data comparing these 2 TTR stabilizers are currently lacking.

DATA AVAILABILITY Qualified academic investigators may submit requests for access to data via medinfo@bridgebio.com. Requests for access to study data will be evaluated by BridgeBio Pharma, Inc, and access will be provided contingent upon the approval of a research/ or study proposal and the execution of a data sharing agreement. BridgeBio Pharma, Inc will consider requests for access to participant-level data if participant privacy is ensured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law) and if such disclosures were included in the relevant study's informed consent form or study protocol.

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Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Caelum Biosciences, Cardior Pharmaceuticals, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Novo Nordisk, Pfizer, and Prothena Biosciences; owns stock or stock options in Myocardium and Lexeo Therapeutics; has received research grants from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc, and Pfizer; and has received salary from the British Heart Foundation Intermediate Fellowship. Dr Masri is a researcher for Attralus, Cytokinetics, Ionis Pharmaceuticals, and Pfizer; and is a consultant, an adviser, or a speaker for Akros Pharma, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BioMarin Pharmaceutical, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Bristol Myers Squibb, Cytokinetics, HAYA Therapeutics, Ionis Pharmaceuticals, Lexicon Pharmaceuticals, Pfizer, Prothena Biosciences, and Tenaya Therapeutics. Dr Gillmore is a consultant, an adviser, or a speaker for Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc, Ionis Pharmaceuticals, Intellia Therapeutics, Lycia Therapeutics, and Pfizer. Dr Garcia-Pavia is a speaker for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc, Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; is a consultant/ or an adviser for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio Pharma, Inc, Ionis Pharmaceuticals, Intellia Therapeutics, Pfizer, Neurimmune, and Novo Nordisk; and has received research and/or educational funding paid to his institution from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio Pharma, Inc, Intellia Therapeutics, Novo Nordisk, and Pfizer. Drs Cao, Fox, and Sinha are employees and stockholders of BridgeBio Pharma, Inc.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Across in vitro and in vivo analyses, this study suggests there may be increased TTR stabilization with acoramidis relative to tafamidis at clinically relevant concentrations. The difference in stabilization between acoramidis and tafamidis appeared to be more pronounced in patients with intrinsically unstable TTRv.

TRANSLATIONAL OUTLOOK: Change in sTTR after treatment with a stabilizer is inversely correlated with ATTR-CM disease progression and may potentially be predictive of disease prognosis.

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KEY WORDS **acoramidis, ATTR-CM, tafamidis, transthyretin, TTR stabilization, variant**

APPENDIX **For supplemental methods, supplemental figures, and supplemental tables, please see the online version of this paper.**