Acoramidis produces near-complete TTR stabilization in blood samples from patients with variant transthyretin amyloidosis that is greater than that achieved with tafamidis

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Introduction: Transthyretin (TTR) amyloidosis (ATTR) is a progressive, fatal disease caused by destabilizing TTR variants (TTRv) and age-related factors. Dissociation of tetrameric TTR initiates protein misfolding, aggregation, and tissue deposition which constitutes the mechanism of disease. More destabilizing variants drive more severe clinical phenotypes. TTR stabilizers have demonstrated clinical benefits for neuropathic and cardiovascular outcomes correlated with the extent of TTR stabilization. Acoramidis (AG10) is a novel TTR stabilizer in development for the treatment of TTR amyloid cardiomyopathy.

Hypothesis: Acoramidis achieves near-complete in vitro TTR stabilization, exceeding levels achieved with clinically relevant concentrations of tafamidis (a TTR stabilizer in clinical use), when added to blood samples from ATTRv patients across a spectrum of destabilizing TTR variants.

Methods: Two established assays assessed TTR stabilization: fluorescent probe exclusion (FPE; measures binding site occupancy), and Western blot (WB; quantifies tetrameric TTR persistence under conditions of accelerated dissociation). Over 60 individual patient samples representing 18 unique TTRv across a spectrum of intrinsic instability and clinical phenotypes were assayed. Acoramidis was added at its target clinical trough concentration (10 µM) and compared to tafamidis added at its clinical peak (26 µM) and trough (16 µM) concentrations reported for its maximal approved dose.

Results: Acoramidis bound serum TTR to a greater extent (103 ± 13%) than either peak (87 ± 14%) or trough (71 ± 14%) concentrations of tafamidis. WB assays showed that addition of acoramidis resulted in significantly greater and more durable TTR stabilization (93 ± 14%) than adding tafamidis (peak: 49 ± 14%, trough: 36 ± 13%) in all paired individual patient plasma samples tested (Figure 1, p < 0.0001). Rare variants (A97S, D38A, F64L, L58H, P24S, Y114C) also demonstrated near complete stabilization upon in vitro addition of acoramidis.

Conclusions: At its target therapeutic trough concentration, acoramidis achieved near-complete TTR stabilization across 18 unique genotypes; in the subset of paired samples, the stabilization was significantly greater for acoramidis than for tafamidis even at its peak clinical concentration. This observation held across a range of destabilizing mutations, including ~2-fold greater stabilization than tafamidis for the prevalent cardiomyopathic V122I variant. Based on the mechanism of disease and the association between TTR destabilization and severity of clinical outcomes, these data suggest that acoramidis has the potential to be a clinically differentiated and efficacious treatment option for patients with ATTRv, independent of variant genotype.

Figure 1. TTR WB %Stabilization by variant.
SD is only shown for conditions with two or more samples.