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 (TTVs) and age-related factors.
- Development of TTR amyloid cardiomyopathy (ATTR-CM) and amyloid polyneuropathy (ATTR-PN) are driven by pathogenic point mutations in the ATTR gene, over 150 such variants have been described, and the number of variant-containing TTVs is associated with more severe clinical phenotypes.
- The rate of TTR tetramer into its constituent monomers is the rate-limiting step in amyloidogenesis. TTR stabilizers have demonstrated clinical benefit for neuropsychiatric and cardiovascular correlates correlated with the extent of TTR stabilization.
- Acoramidis (AG10) is novel TTR stabilizer in development for the treatment of ATTR-CM. Acoramidis binds the tetrameric form of TTR and prevents its dissociation into dimers and monomers.

OBJECTIVES

- Determine if acoramidis at its target steady-state trough concentration can demonstrate pan-variant potency.
- Stably complex in vitro tetramer stabilization by acoramidis against clinically relevant variants.
- Determine if in vitro TTR stabilization assay findings are consistent with changes in plasma TTR observed in the recently completed Phase 3 ATTRcleare-CM study of acoramidis.

HYPOTHESIS

- Acoramidis is a highly effective and potent stabilizer of TTR.
- Acoramidis achieves near-complete in vitro tetramer stabilization, exceeding levels achieved with clinically relevant concentrations of tafamidis, when added to blood samples from ATTR patients across a spectrum of destabilizing TTR variants.

METHODS

- Two established pharmacodynamic assays measure the stabilization of TTR tetramers in vitro: Fluorescence Blur (FB) and Tetramerization Efficiency (TE). The FB assay assesses relative TTR tetramer after acid-mediated accelerated denaturation.
- The TE assay uses a highly specific and selective fluorescent probe to measure TTR ligand binding site occupancy.
- Blood samples were collected from subjects with TTR variants currently being treated in the Phase 3 ATTRcleare-CM clinical trial and other acoramidis clinical studies.
- Over 80 individual patient samples representing 18 unique TTRs across a spectrum of clinical instability and clinical phenotypes were assessed.
- Acoramidis was added to patient samples at 10 µM concentration. TTR tetramer stability was assessed by FB and TE assays.
- Acoramidis was added to patient samples at its clinical peak (20 µM) and trough (10 µM) concentrations for its maximal approved dose.

ACORAMIDIS DEMONSTRATES PAN-VARIANT ACTIVITY TO A GREATER EXTENT THAN TAFAmidIS

- Acoramidis demonstrates near-complete stabilization of TTR tetramers in vitro.
- Acoramidis achieves greater stabilization than tafamidis.

EX VIVO TTR STABILIZATION CORRELATES WITH IN VIVO MEASUREMENT OF SERUM TTR

- Acoramidis more effectively stabilizes ATTR TTR than Tafamidis.
- In vitro TTR stabilization correlates with in vivo measurement of serum TTR.

CONCLUSIONS

- Acoramidis achieved near-complete stabilization in vitro and in ATTR patients across a unique 18-variant TTR variants.

REFERENCES