Background
- Transthyretin (TTR) amyloidosis (ATTR) is a progressive, fatal disease in which deposition of amyloid derived from either mutant or wild-type TTR causes severe organ damage and dysfunction.
- ATTR typically presents predominantly as either TTR amyloid cardiomyopathy (ATTR-CM) or as a peripheral neuropathy (ATTR-PN).
- ATTR results in progressive morbidity and high mortality due to the lack of disease-modifying therapies and limited responsiveness to standard heart failure treatments.1
- The initiating step of disease pathogenesis is the destabilization of the TTR tetrameric protein into its constituent monomers and subsequent misfolding into amyloid fibrils.
- AG10 is a highly selective and potent stabilizer of TTR that mimics the T119M rescue mutation and has the potential to become a disease-modifying treatment for patients with either mutant or wild-type ATTR cardiomyopathy.2

Primary Objective
- Evaluate the safety and tolerability of single and multiple doses of AG10 orally administered to healthy adult subjects.

Secondary Objectives
- Characterize the pharmacokinetics (PK) of AG10 in healthy adult subjects.
- Describe the pharmacodynamic (PD) properties of AG10, as well as the PK-PD relationship of AG10 in healthy adult subjects.
- Evaluate the effect of food on the PK of AG10.

Study Design
- Part A: A single ascending dose (SAD) design, where 4 cohorts of 6 healthy men and women were randomized to AG10 or matching placebo in a 3:1 overall ratio.
- Part B: A multiple ascending dose (MAD) design, where 3 cohorts of 6 healthy men and women were randomized to AG10 or its placebo in a 3:1 overall ratio.

Study Design (continued)

Key Inclusion Criteria
- Adult healthy volunteers ages 18 to 55 years, inclusive.

Key Exclusion Criteria
- Recent use of prescription drugs or over-the-counter medications.
- Clinically relevant history or presence of prespecified medical conditions.
- Clinically significant electrocardiogram (ECG) abnormalities at screening.

Pharmacokinetics of AG10
- Part A: Single ascending dose (SAD) design, where 4 cohorts of 6 healthy men and women were randomized to AG10 or matching placebo in a 3:1 overall ratio.
- Part B: Multiple ascending dose (MAD) design, where 3 cohorts of 6 healthy men and women were randomized to AG10 or its placebo in a 3:1 overall ratio.

Pharmacodynamics of AG10
- AG10 was well tolerated, with no serious adverse events at single doses up to 800 mg, and at steady state during daily administration of up to 800 mg every 12 hours.
- Target steady state concentration achieved in MAD with near-complete, sustained TTR stabilization of >95% across the dosing interval.
- Increased TTR stabilization achieved with higher circulating concentrations of AG10 in MAD.
- Demonstrated evidence of in vivo TTR stabilization by AG10 given 59% increase in circulating TTR concentrations in treated subjects in MAD cohorts.
- AG10’s unique mode of binding mimics the disease-suppressing T119M TTR variant and differentiates AG10 from other small molecule TTR stabilizers.
- AG10 is currently being evaluated in a Phase 2 study in patients with symptomatic ATTR cardiomyopathy (NCT03458130).

Conclusions & Clinical Implications

References