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 peripheral polyneuropathy (ATTR-PN).
- 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 amyloid cardiomyopathy.

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.

Safety of AG10

- AG10 was well-tolerated without any 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