# AG10, A Novel, Potent, and Selective Transthyretin Stabilizer, Is Well-Tolerated at Doses Resulting in Target Therapeutic Blood Levels, and Demonstrates Clinical Proof-of-Concept in Healthy Volunteers

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## 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 polyneuropathy (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.
- Evaluated 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)

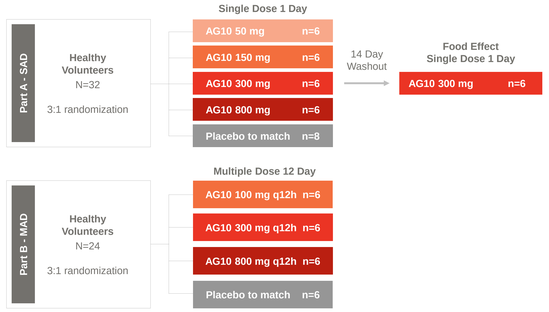



*Figure 1: AG10-001 Study Schema*

## Key Inclusion Criteria

1. Adult healthy volunteers ages 18 to 55 years, inclusive.

## Key Exclusion Criteria

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

## Pharmacokinetics of AG10

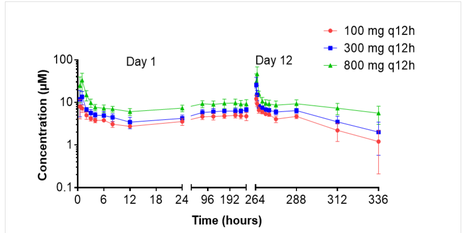



*Figure 2: Multiple Ascending Dose Cohorts 1-3 PK Profiles*

## Safety of AG10

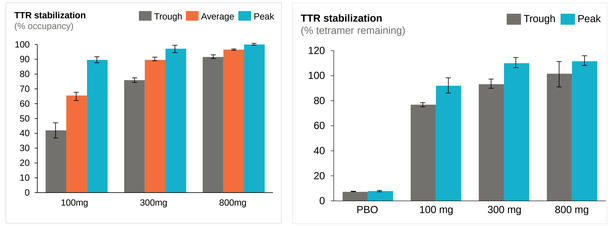
**Single Ascending Dose**

| | Placebo (n = 8) | 50 mg (n = 6) | 150 mg (n = 6) | 300 mg, fasted (n = 6) | 300 mg, fed (n = 6) | 800 mg (n = 6) |
|---|---|---|---|---|---|---|
| Patients with SAEs | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Patients with AEs | 2 (25%) | 3 (50%) | 2 (33%) | 0 (0%) | 1 (17%) | 1 (17%) |

**Multiple Ascending Dose (q12h)**

| | Placebo (n = 6) | 100 mg (n = 6) | 300 mg (n = 6) | 800 mg (n = 6) |
|---|---|---|---|---|
| Patients with SAEs | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Patients with AEs | 3 (50%) | 2 (33%) | 5 (83%) | 1 (17%) |

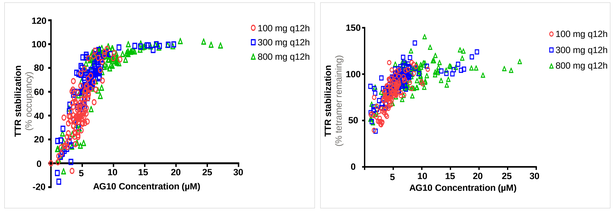
## Pharmacodynamics of AG10




A B

*Figure 3: Multiple Ascending Dose Cohorts 1-3 PD as Measured by A) Fluorescent Probe Exclusion (FPE) Assay and B) Western Blot Assay*

## PK-PD Relationship of AG10




A B

*Figure 4: Multiple Ascending Dose Cohorts 1-3 PK-PD as Measured by A) Fluorescent Probe Exclusion (FPE) Assay and B) Western Blot Assay. Placebo subjects and samples with <1 μM and >30 μM AG10 not shown.*

## In Vivo Stabilization of TTR

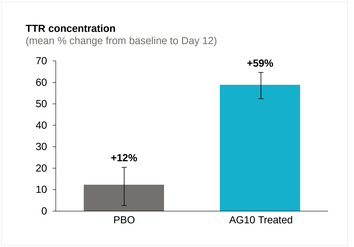



*Figure 5: Circulating TTR concentration from Multiple Ascending Dose Cohorts 1-3*

## Conclusions & Clinical Implications

- 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).

## References

1. Ruberg FL, et al. Transthyretin (TTR) Cardiac Amyloidosis Circulation. 2012;126:1286-1300.
2. Penchala S. et al. AG10 inhibits amyloidogenesis and cellular toxicity of the familial amyloid cardiomyopathy-associated V122I transthyretin. Proc Natl Acad Sci USA 2013, 110:9992-7.