



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)

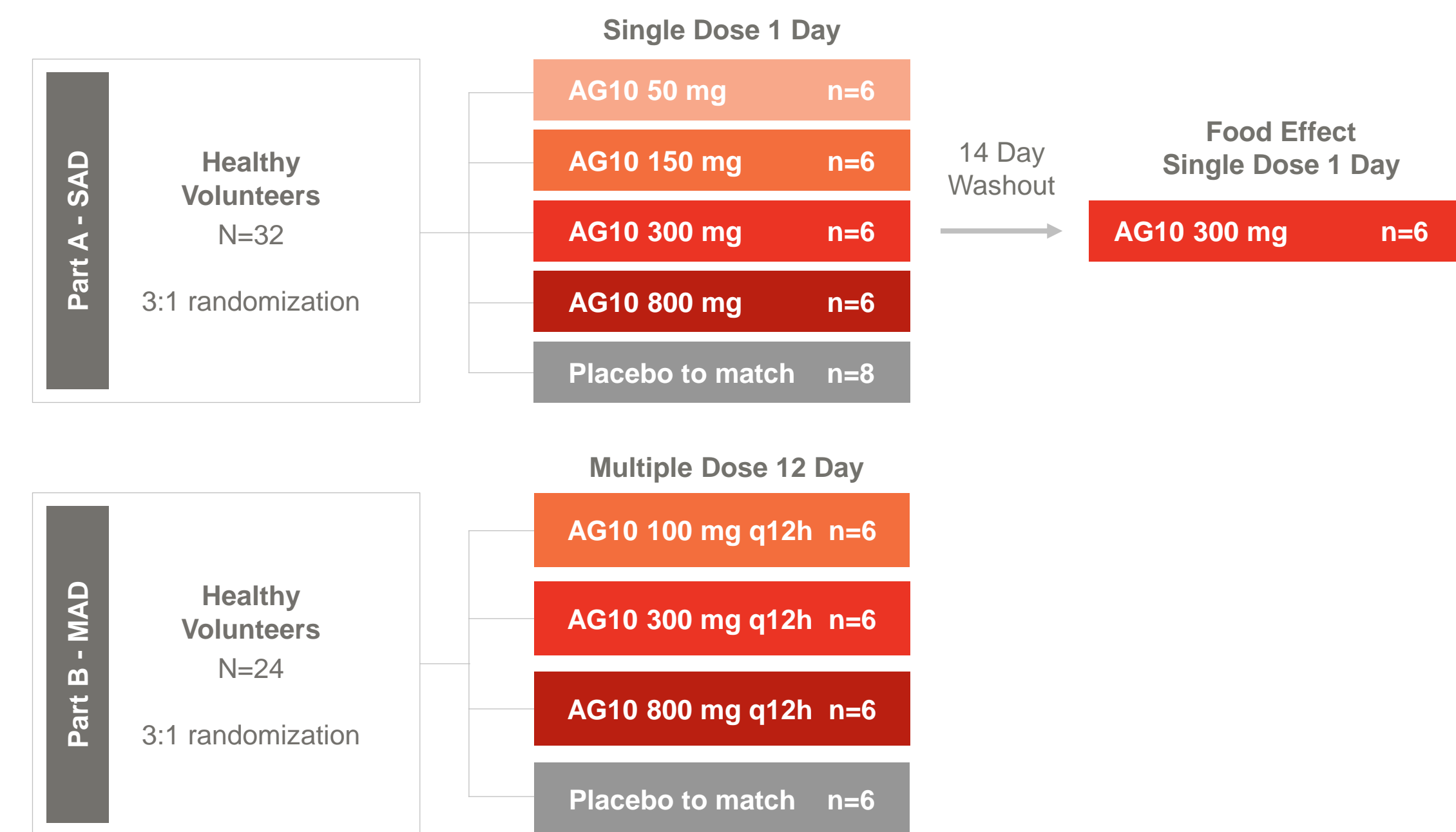


Figure 1: AG10-001 Study Schema

Key Inclusion Criteria

- 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

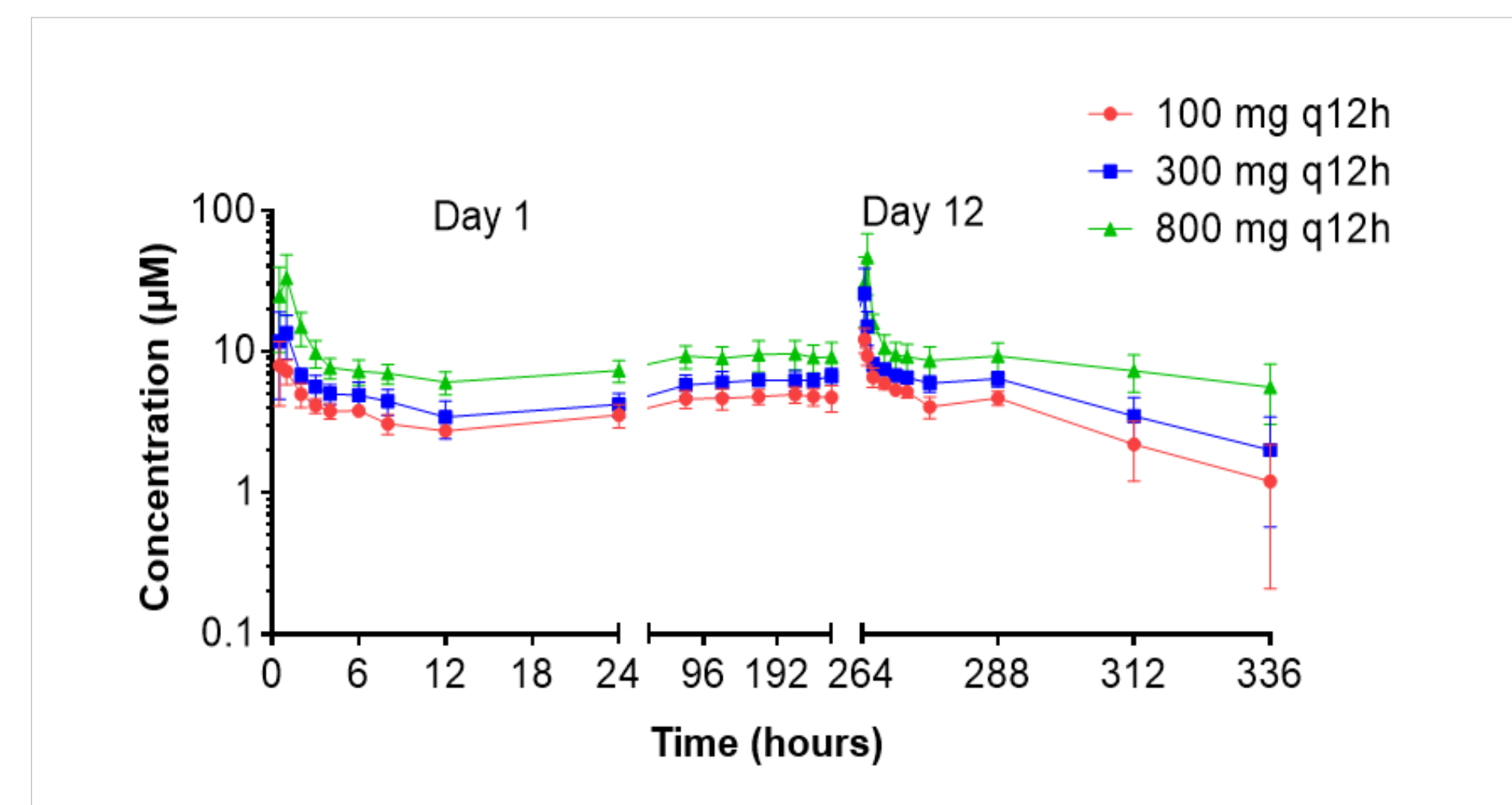


Figure 2: Multiple Ascending Dose Cohorts 1-3 PK Profiles

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

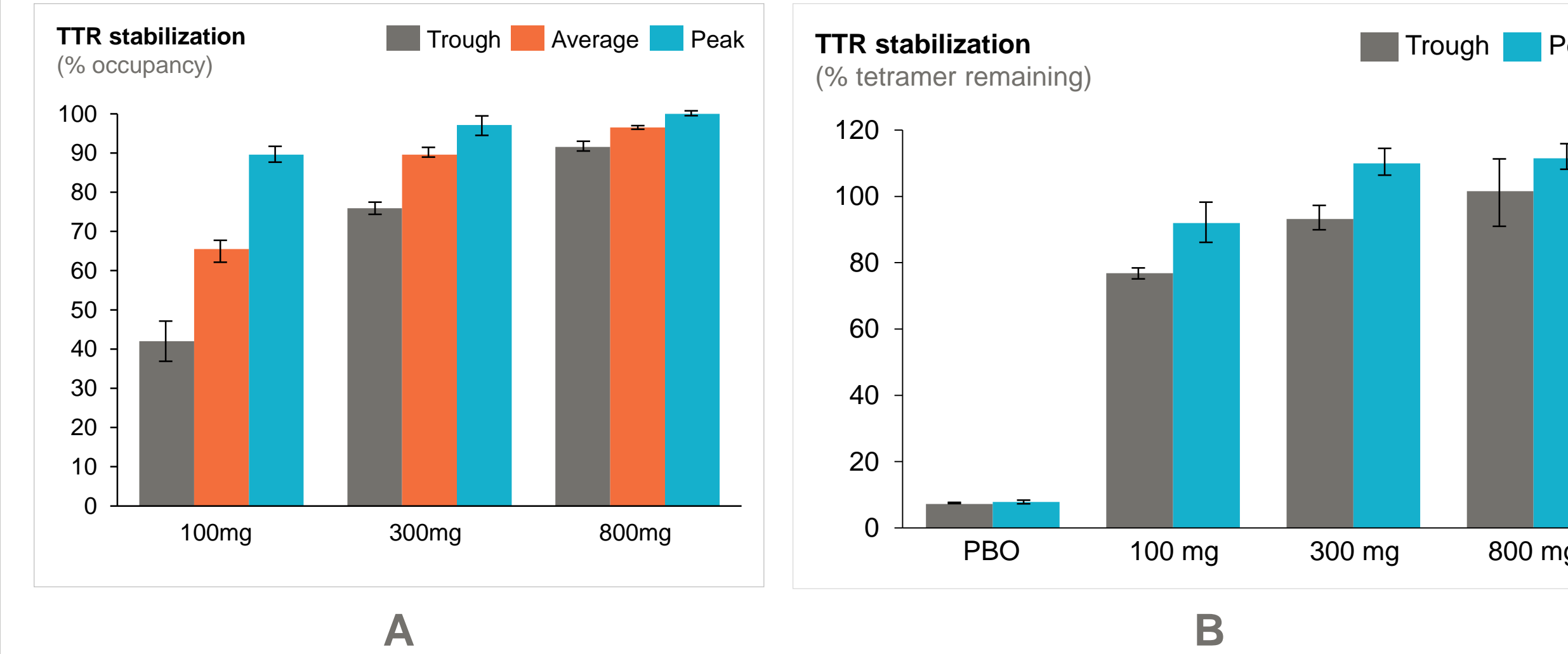


Figure 3: Multiple Ascending Dose Cohorts 1-3 PD as Measured by A) Fluorescent Probe Exclusion (FPE) Assay and B) Western Blot Assay

PK-PD Relationship of AG10

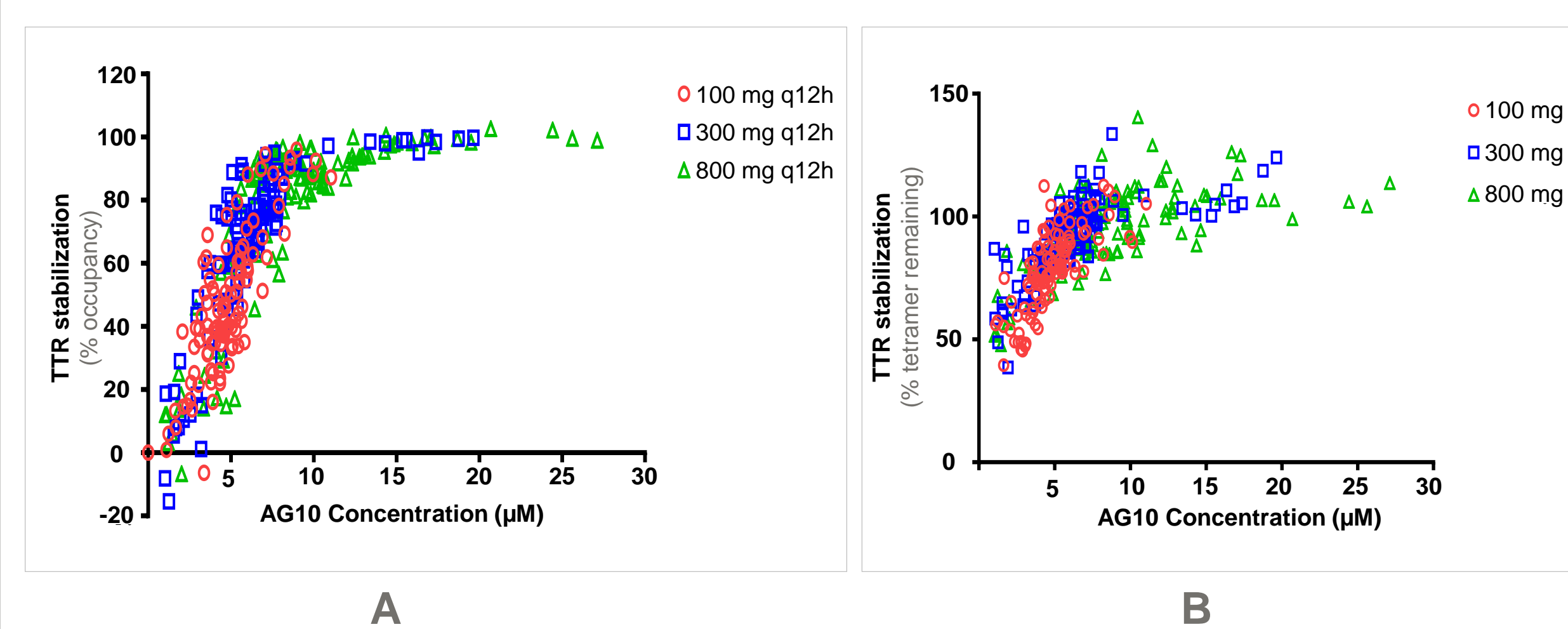


Figure 4: Multiple Ascending Dose Cohorts 1-3 PK-PD as Measured by A) Fluorescent Probe Exclusion (FPE) Assay and B) Western Blot Assay. Placebo subjects and samples with <1 µM and >30 µM AG10 not shown.

In Vivo Stabilization of TTR

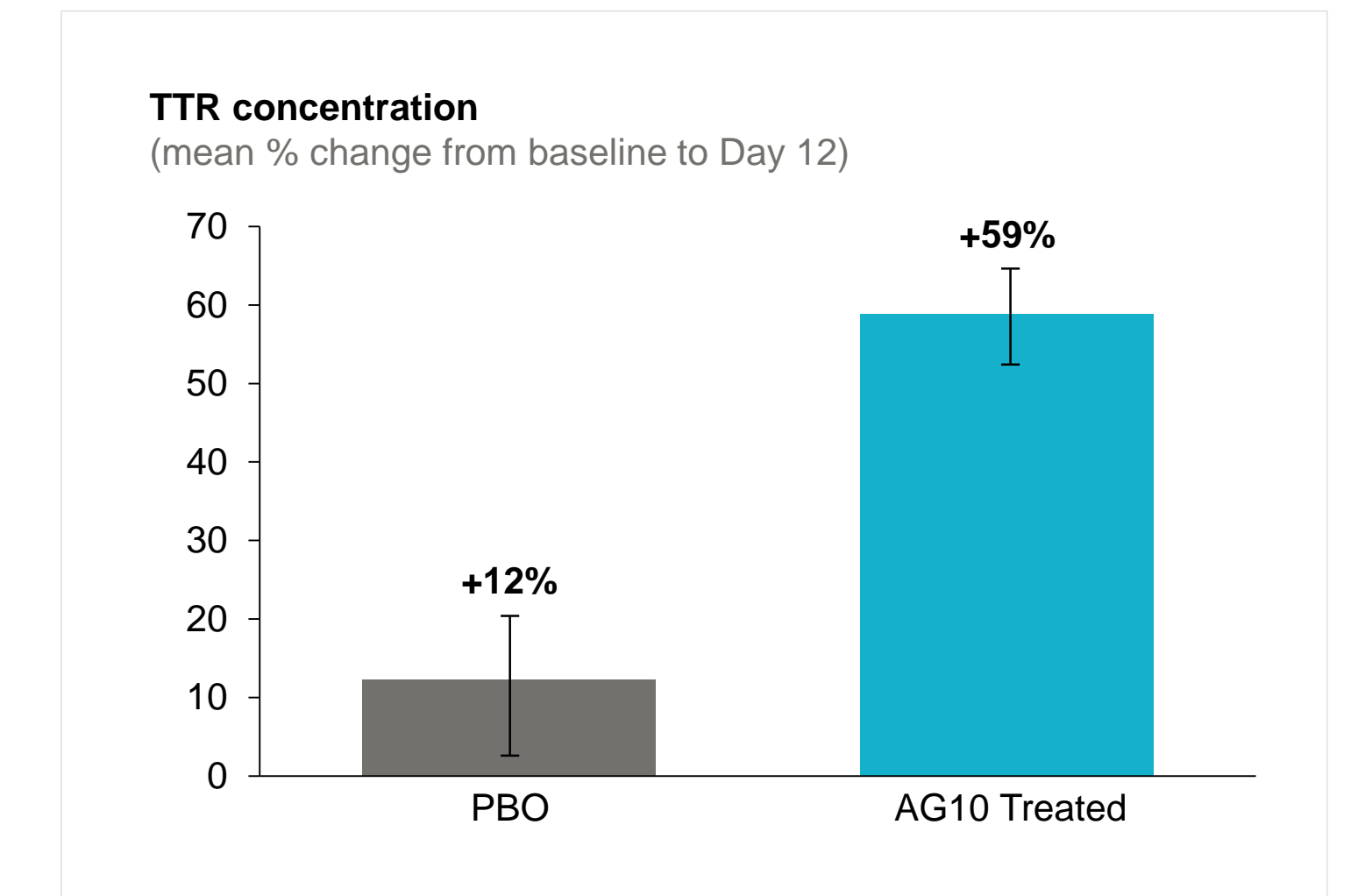


Figure 5: Circulating TTR concentration from Multiple Ascending Dose Cohorts 1-3

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

- Ruberg FL, et al. Transthyretin (TTR) Cardiac Amyloidosis Circulation. 2012;126:1286-1300.
- 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.