AG10 potently and selectively stabilizes transthyretin in vitro and upon oral dosing in dogs: Potential for treating transthyretin amyloidosis

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High unmet medical need

**ATTR cardiomyopathy (ATTR-CM)**
- Deposition of mutant (e.g., V122I) or wild-type TTR amyloid in the heart
  - Leads to predominantly diastolic heart failure
  - Afib/stroke and heart block frequently seen
- Affects 200K+ worldwide, likely underdiagnosed
- Late onset (50-60+), death within 4-6 years
- No FDA-approved treatments

**ATTR polyneuropathy (ATTR-PN)**
- Affects ~10K worldwide, primarily in EU and JP
- Exclusively caused by mutant TTR (e.g., V30M)
- No FDA-approved treatments

Disease mechanism and therapeutic approach

Native TTR tetramer

Dissociation into monomers initiates pathogenesis

Monomers aggregate, deposited as amyloid

Disease mechanism

Therapeutic hypothesis

Stable tetramer
Reduced amyloid formation and deposition
AG10 stabilizes TTR by mimicking the disease suppressing T119M variant
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AG10 Dose Responsively stabilizes TTR in Human Serum

- AG10 binds to TTR at native ligand binding sites
- Fluorescence probe binding assay correlates to other measures of stabilization
Pharmacokinetics of Orally Dosed AG10

- Low systemic clearance and volume of distribution in all species tested
- Absolute oral bioavailability = 31% – 60%
Orally administered AG10 effectively stabilizes TTR in Dogs

Dashed line = Background RFU
Line = Median, ♦ = Mean
AG10 effectively stabilizes TTR in Monkeys

![Graph showing fluorescence (RFU) vs. AG10 concentration (μg/mL). The dashed line represents background RFU, the line represents the median, and ♦ = mean.](image-url)
AG10, a small molecule transthyretin stabilizer, targets disease at its source
  - TTR mutants with decreased stability predisposes patients to disease, whereas T119M TTR is stabilizing and protective
  - AG10 binding to TTR mimics structure of T119M variant
  - Animal PK shows consistent exposure across species
  - Dog and monkey PD measurements show dose-dependent TTR stabilization

Phase 1 trial in healthy volunteers is in progress
  - Establish tolerability and PK profile
  - Measure TTR stabilization
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