ATTRibute-CM: A randomized, double-blind, placebo-controlled, multi-center, global Phase 3 study of AG10 in patients with transthyretin amyloid cardiomyopathy (ATTR-CM)

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Background

- Transthyretin (TTR) amyloidosis (ATTR) is an under-diagnosed cause of heart failure driven by TTR destabilization due to pathogenic mutations and/or aging[1]
- ATTR-CM occurs when transthyretin amyloid fibrils aggregate and deposit in the myocardium, resulting in an infiltrative, restrictive cardiomyopathy characterized by both right and left heart failure, initially with preserved ejection fraction[2]
- Unstable TTR tetramers dissociate into monomers and misfold leading to reduced serum TTR concentration in patients with ATTR-CM, which has been associated with a higher mortality risk[3]
- AG10 is a highly selective and potent oral stabilizer of TTR under development for the treatment of patients with either mutant or wild-type ATTR cardiomyopathy[4,5]
- In a randomized, double-blind Phase 2 study in patients with symptomatic ATTR cardiomyopathy (ATTR-CM), AG10 was well tolerated, demonstrated near-complete stabilization of TTR, and increased serum TTR levels to normal in all treated subjects[5]

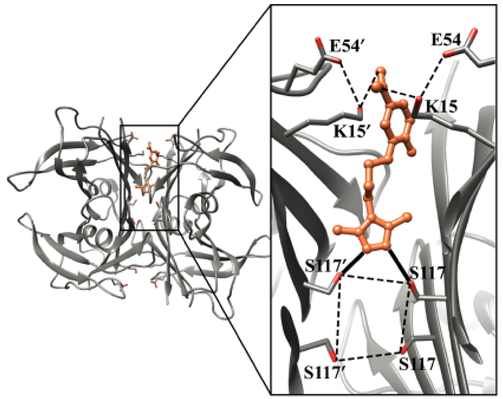
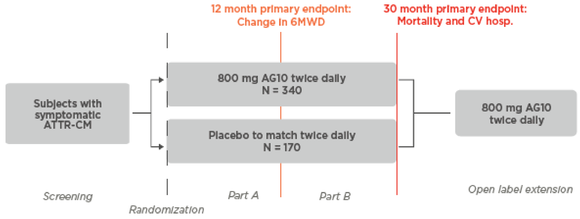


Figure 1: AG10-TTR binding induces strong inter-monomer hydrogen bonds[4]

Study Design

- Prospective, randomized, double-blind, placebo-controlled, multicenter, global Phase 3 study designed to evaluate AG10's ability to slow or halt progression of ATTR-CM
- Approximately 510 patients with symptomatic ATTR-CM, including those with either wild-type or mutant TTR, with New York Heart Association Class I-III symptoms will be enrolled
- Eligible subjects will be randomized in a 2:1 ratio to AG10 800 mg twice daily or matching placebo and followed for 30 months
- Following completion of double-blind treatment phase, subjects may continue in a separate open-label extension study



Secondary endpoints include: Kansas City Cardiomyopathy Questionnaire, serum TTR, TTR stabilization

Figure 2: ATTRibute-CM Study Schema

Primary Endpoints

- **Part A (at 12 Months)**: Change from baseline to Month 12 of treatment in distance walked during the Six-Minute Walk test (6MWT) will be compared between treatment and placebo groups.
- **Part B (at 30 Months)**: A hierarchical combination of all-cause mortality and cardiovascular (CV)-related hospitalizations (CV hosp.) will be compared between treatment and placebo groups.

Key Secondary Endpoints

- **Part A (at 12 Months)**: Change from baseline to Month 12 of treatment in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).
- **Part B (at 30 Months)**: Change from baseline to Month 30 of treatment in distance walked during the 6MWT and in KCCQ-OS.

Key Inclusion Criteria

1. Be a male or female ≥18 to ≤90 years of age.
2. Have an established diagnosis of ATTR-CM, with either wild-type transthyretin or a variant transthyretin genotype (assessed by genotyping, patients with concurrent monoclonal gammopathy of undetermined significance requiring a confirmatory test using mass spectrometry) as defined by either positive endomyocardial biopsy or positive technetium bone scan.
3. Have a history of heart failure evidenced by at least one prior hospitalization for heart failure **OR** clinical evidence of heart failure (without hospitalization) requiring medical management.
4. Have NYHA Class I-III symptoms due to ATTR-CM.
5. For patients taking cardiovascular medical therapy, with the exception of diuretic dosing, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to screening.
6. Prior to randomization:
   - Have completed ≥150 meters on the 6MWT on 2 tests
   - Have NT-proBNP levels ≥300 pg/mL
   - Have left ventricular wall thickness ≥12 mm.

Key Exclusion Criteria

1. Has confirmed diagnosis of light-chain amyloidosis.
2. Within 90 days prior to screening:
   - Acute myocardial infarction, acute coronary syndrome or coronary revascularization
   - Experienced stroke or transient ischemic attack.
3. Has hemodynamic instability or abnormalities in clinical laboratory tests or clinically significant ongoing medical condition at screening or randomization that, in the judgment of the PI, would pose too great a risk for participation in the study.
4. Is likely to undergo heart transplantation within a year of screening.
5. Current treatment for ATTR-CM with tafamidis, diflunisal, green tea, doxycycline, TUDCA/ursodiol within 14 days prior to dosing. If during participation in the study, subjects gain access to tafamidis in their geography, they may be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy.
6. Prior to dosing, treatment with patisiran, inotersen, or other gene silencing agent: within 90 days for patisiran, 180 days for inotersen, and 5 half-lives for any other gene silencing agent

Participating Centers in United States

As of October 2019, 35 clinical sites are active in the US, Europe, Australia, and Israel [ClinicalTrials.gov Identifier: NCT03860935]

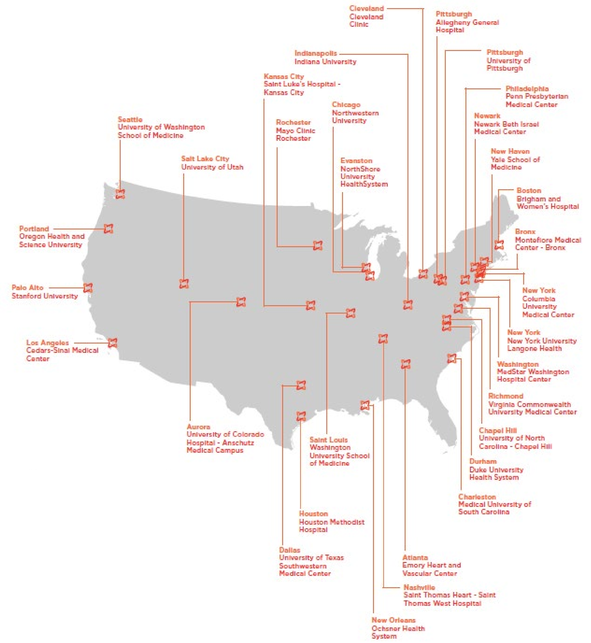


Figure 3: ATTRibute-CM Active Clinical Sites in United States (as of October 2019)

References

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2. Donnelly JP, Hanna M. Cleve Clin J Med. 2017;84(12)(suppl 3):12-26.
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