Background

- Transthyretin (TTR) amyloidosis (ATTR) is an under-diagnosed cause of heart failure driven by TTR destabilization due to pathogenic mutations and/or aging.
- 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.
- 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.
- 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.
- 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.

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 amyloidosis or amyloid cardiomyopathy, with New York Heart Association Class II-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.

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 gammapathy 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 requiring institution of medication requiring medical management.
4. Have NYHA Class II-III symptoms due to ATTR-CM.
5. Patients taking cardiovascular medical therapy, with the exception of diuretics. 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.

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
   - Expressed 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.
4. Is likely to undergo heart transplantation within a year of screening.
5. Current treatment for ATTR-CM with tafamidis, diflunisal, green tea, or any other gene silencing agent.
6. Prior to randomization:
   - Have completed ≥150 meters on the 6MWT on 2 tests
   - Have NT-proBNP levels ≤200 pg/mL
   - Have left ventricular wall thickness ≥12 mm.

Key Secondary Endpoints

1. 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.
2. Change from baseline to Month 30 of treatment in distance walked during the 6MWT will be compared between treatment and placebo groups.
3. Change in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS), as defined by either positive endomyocardial biopsy or positive technetium bone scan.
4. Change in Kansas City Cardiomyopathy Questionnaire-Physical Health Subscale.
5. Change in Kansas City Cardiomyopathy Questionnaire-Symptoms Subscale.
6. Change in Kansas City Cardiomyopathy Questionnaire-Cardiac Health Index Subscale.
7. Clinical event rates of cardiovascular (CV)-related hospitalizations (CV hosp.) will be compared between treatment and placebo groups.
8. Change from baseline in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).
9. Change from baseline in the Kansas City Cardiomyopathy Questionnaire-Physical Health Subscale.
10. Change from baseline in the Kansas City Cardiomyopathy Questionnaire-Symptoms Subscale.
11. Change from baseline in the Kansas City Cardiomyopathy Questionnaire-Cardiac Health Index Subscale.

References