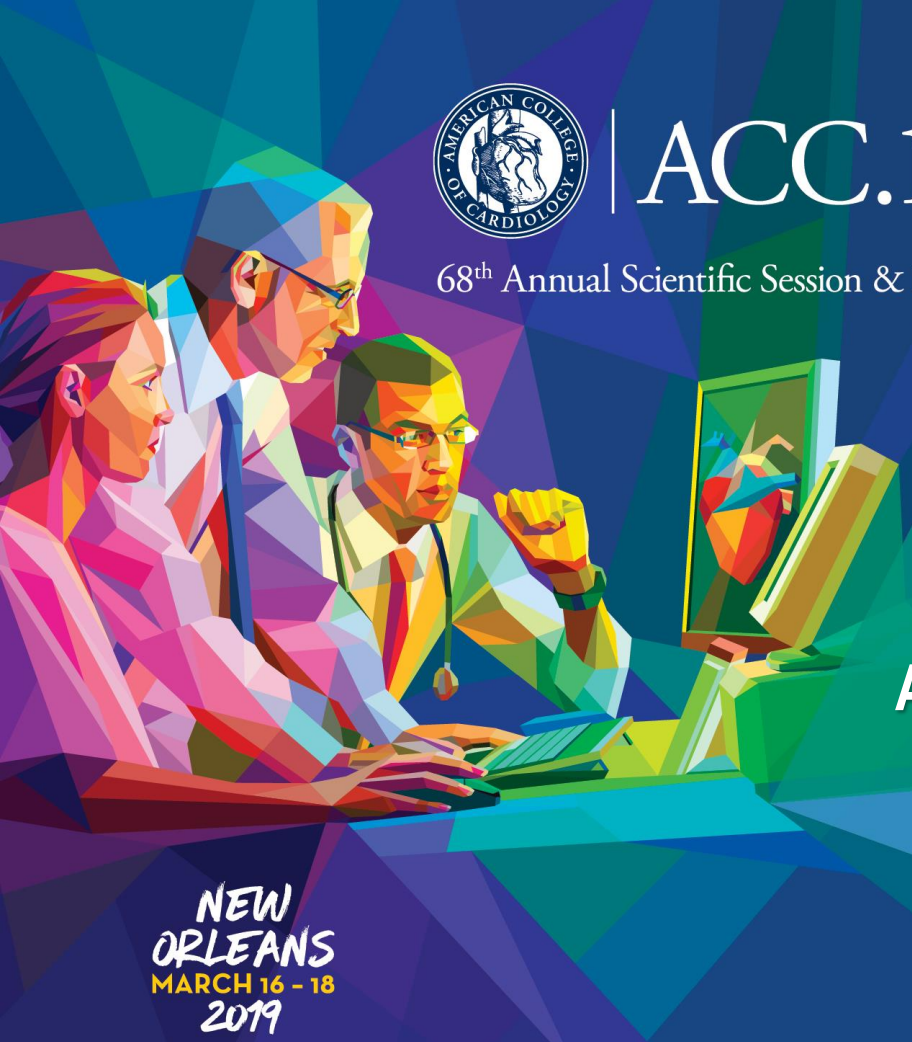

ACC.19

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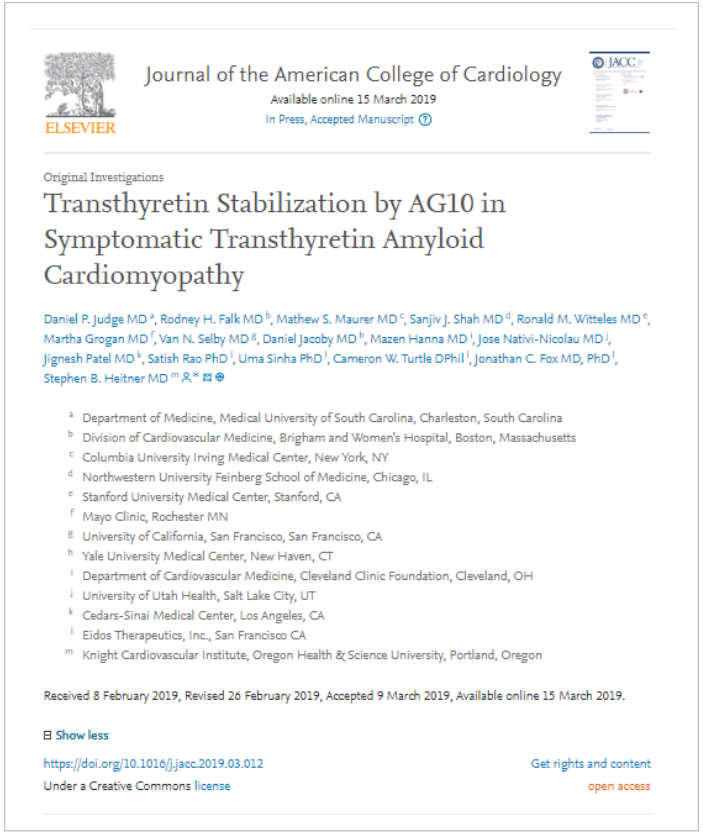
AG10 Consistently Stabilizes Transthyretin to a High Level in Both Wild Type and Mutant Amyloid Cardiomyopathy: Responder Analyses from a Phase 2 Clinical Trial

Heitner, Stephen B; Falk, Rodney H; Grogan, Martha; Jacoby, Daniel; Judge, Daniel P; Maurer, Mathew S; Selby, Van N; Shah, Sanjiv J; Witteles, Ronald M; Rao, Satish; Sinha, Uma; and Fox, Jonathan C

Stephen Heitner presenting on behalf of the AG10 Phase 2 study investigators



Journal of the American College of Cardiology
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Original Investigations

Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy

Daniel P. Judge MD [a], Rodney H. Falk MD [b], Mathew S. Maurer MD [c], Sanjiv J. Shah MD [d], Ronald M. Witteles MD [e], Martha Grogan MD [f], Van N. Selby MD [g], Daniel Jacoby MD [h], Mazen Hanna MD [i], Jose Nativi-Nicolau MD [j], Jignesh Patel MD [k], Satish Rao PhD [l], Uma Sinha PhD [l], Cameron W. Turtle DPhil [l], Jonathan C. Fox MD, PhD [l], Stephen B. Heitner MD [m]

[a] Department of Medicine, Medical University of South Carolina, Charleston, South Carolina
[b] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts
[c] Columbia University Irving Medical Center, New York, NY
[d] Northwestern University Feinberg School of Medicine, Chicago, IL
[e] Stanford University Medical Center, Stanford, CA
[f] Mayo Clinic, Rochester MN
[g] University of California, San Francisco, San Francisco, CA
[h] Yale University Medical Center, New Haven, CT
[i] Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH
[j] University of Utah Health, Salt Lake City, UT
[k] Cedars-Sinai Medical Center, Los Angeles, CA
[l] Eidos Therapeutics, Inc., San Francisco CA
[m] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon

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Judge, D.P. et al. JACC, 2019, DOI: 10.1016/j.jacc.2019.03.012

ATTR Cardiomyopathy Clinical Presentation

Clinical presentation

- ATTR-CM is an infiltrative, restrictive cardiomyopathy resulting from deposition of wild-type or mutant TTR amyloid in the heart
- Cardiac amyloid deposition can lead to edema, interventricular wall thickening, and diastolic heart failure

Growing patient population

Non-invasive diagnosis by Tc-PYP scans increasingly finding ATTR-CM patients "hiding in plain sight":

- 13-19% of HFpEF patients[1-3]
- 16% of patients undergoing TAVR[4]
- 5% of patients with presumed hypertrophic cardiomyopathy[5]
- 8% of patients undergoing bilateral carpal tunnel release surgery[6]

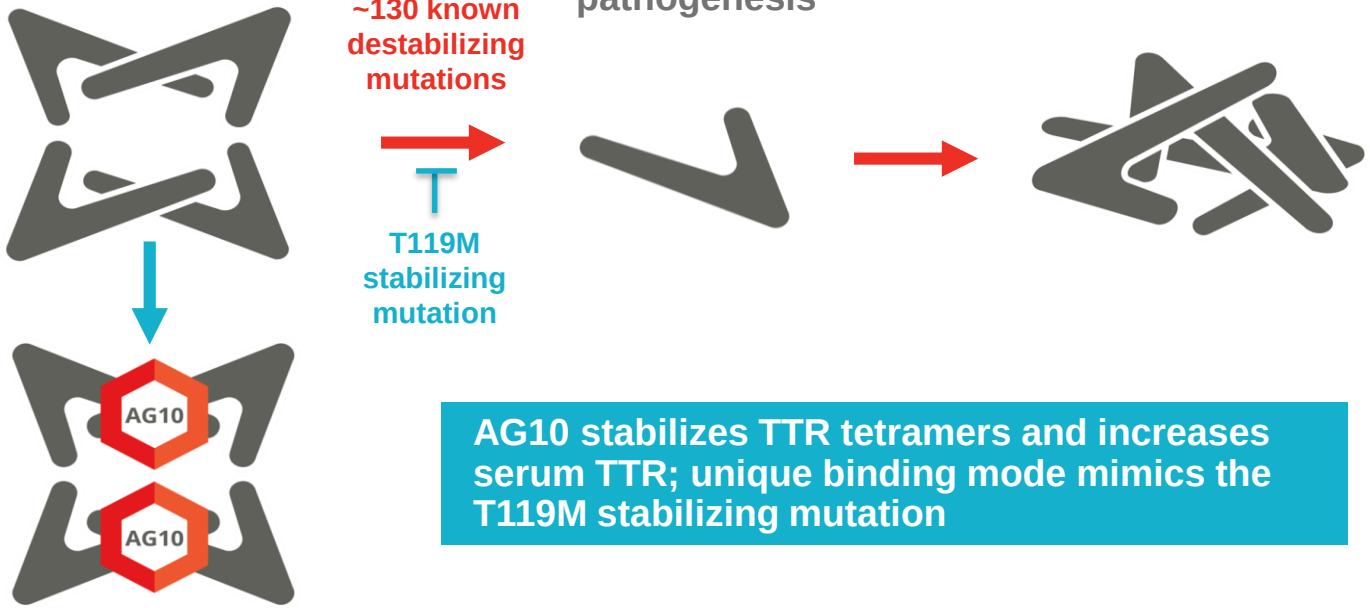
ATTR-CM = Transthyretin Amyloid Cardiomyopathy; TTR = Transthyretin; Tc-PYP = Technetium pyrophosphate; HFpEF = Heart Failure with Preserved Ejection Fraction; TAVR = Transcatheter Aortic Valve Replacement

1) Gonzalez-Lopez, E. et al. Eur Heart J., 2015, 36(38):2585-94; 2) Mohammed, S.F. et al. JACC: Heart Failure, 2014, 2(2):113-22; 3) Horvath, S.A. et al. Circulation, 2018, 138:A16205; 4) Castano, A. et al. Eur Heart J., 2017, 38(38):2879–87; 5) Damy, T. et al. Eur Heart J., 2015, 37:1826-34; 6) Sperry, B.W. et al. JACC, 2018, 72(17):2040-50

Disease Mechanism and Therapeutic Hypothesis

Disease mechanism

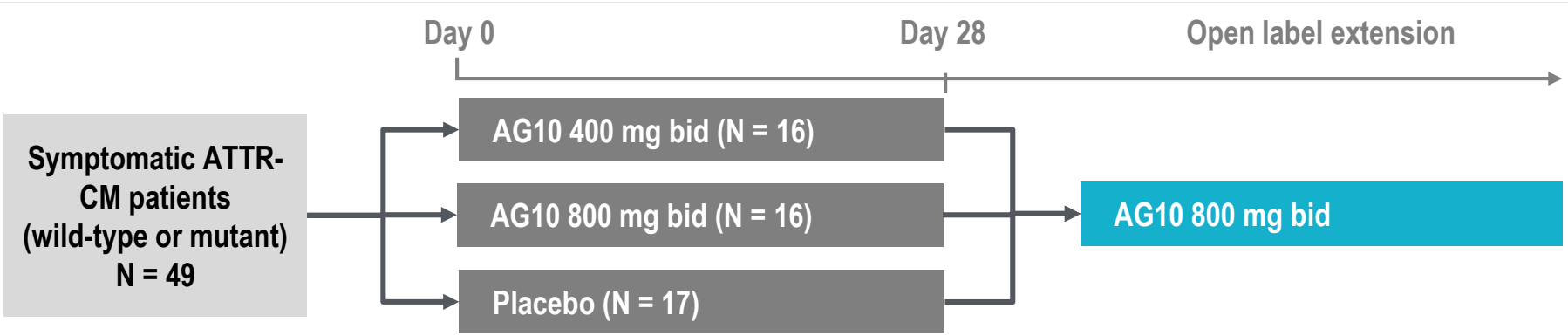
Therapeutic hypothesis



AG10 stabilizes TTR tetramers and increases serum TTR; unique binding mode mimics the T119M stabilizing mutation

Phase 2 Study Design

Randomized, double-blind, placebo controlled, multi-center study of AG10 in ATTR-CM patients



- **Key inclusion criteria:** ≥1 prior hospitalization for heart failure or clinical evidence of heart failure, confirmed ATTR by scan or biopsy, NYHA Class II/III
- **Primary endpoint:** safety and tolerability
- **Secondary endpoints:** Pharmacokinetics, TTR stabilization as measured by FPE and Western blot, serum TTR concentration
- **Open label extension (ongoing):** safety and tolerability, cardiac biomarkers, echocardiographic measurements

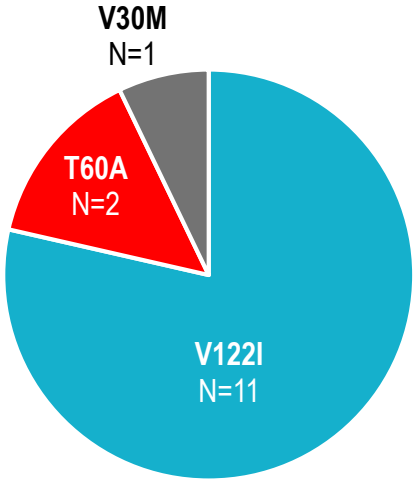
NYHA = New York Heart Association; FPE = Fluorescent Probe Exclusion

Subject Demographics

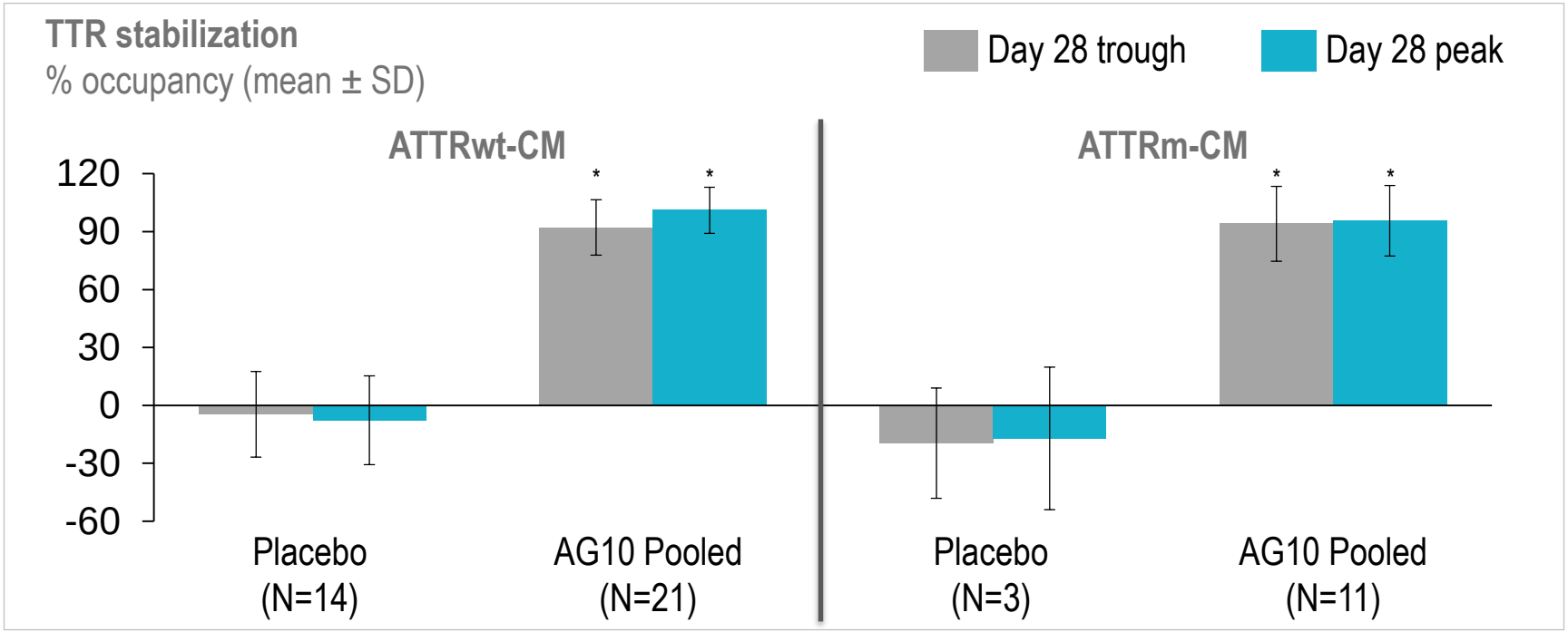
Characteristic	ATTRwt-CM N = 35	ATTRm-CM N = 14	Total N = 49
Age, mean (range)	74 (60 - 85)	73 (60 - 86)	74 (60 - 86)
Male, n (%)	33 (94%)	12 (86%)	45 (92%)
NYHA Class III, n (%)	10 (29%)	4 (29%)	14 (29%)
Race, n (%)			
White	31 (89%)	4 (29%)	35 (71%)
Black	2 (6%)	8 (57%)	10 (20%)
Asian	1 (3%)	0 (0%)	1 (2%)
Other	1 (3%)	2 (14%)	3 (6%)
TTR (mg/dL)[1]	23.7 ± 4.7	17.5 ± 4.6*	22.0 ± 5.4
NT-proBNP (pg/mL)[2]	2612 ± 2108	5258 ± 3423	3368 ± 2789
Troponin I (ng/mL)[3]	0.09 ± 0.05	0.34 ± 0.38†	0.16 ± 0.22
Interventricular Wall Thickness (cm)	1.74 ± 0.30	1.75 ± 0.33	1.74 ± 0.30

1 TTR normal range = 20 – 40 mg/dL; * TTR concentration not available at baseline for one ATTRm-CM subject
2 NT-proBNP normal range = 0 – 449 pg/mL
3 Troponin I normal range = 0 – 0.02 ng/mL; † Troponin I not available at baseline for one ATTRm-CM subject

ATTRm-CM Genotype
N=14

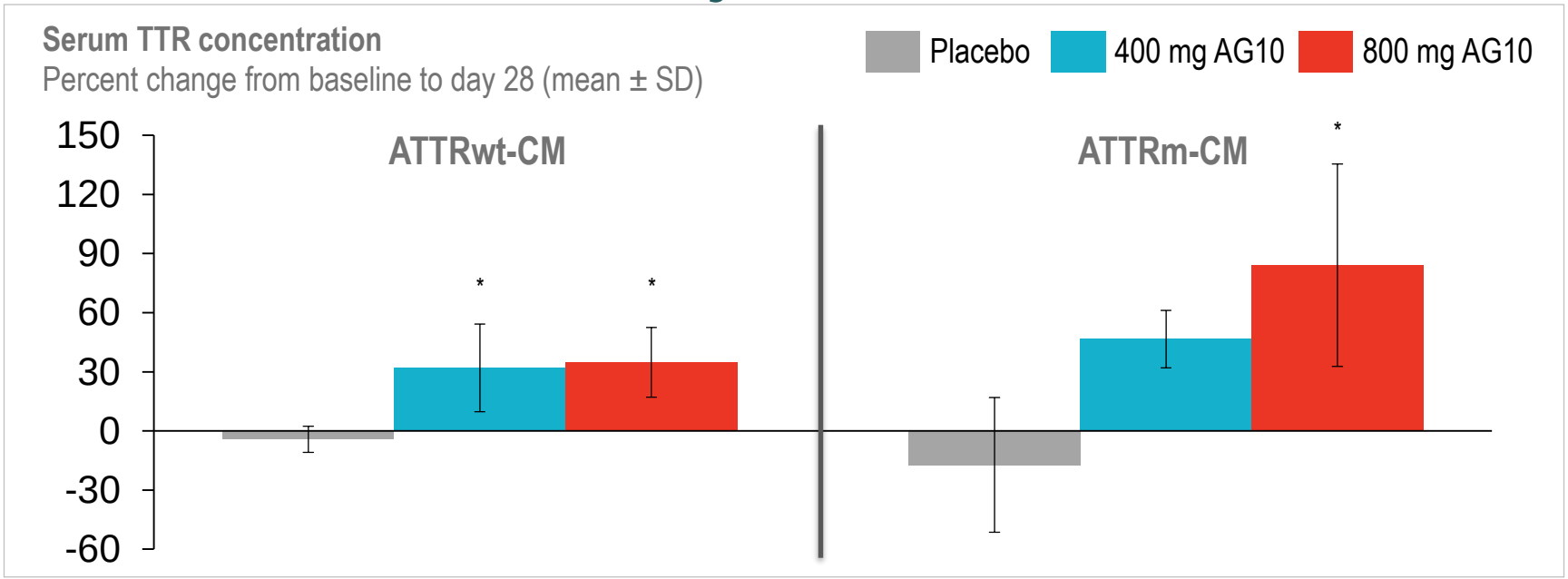


Near-Complete TTR Stabilization Demonstrated by AG10 in Both Wild-Type and Mutant Subjects



* p<0.05 compared to corresponding placebo groups

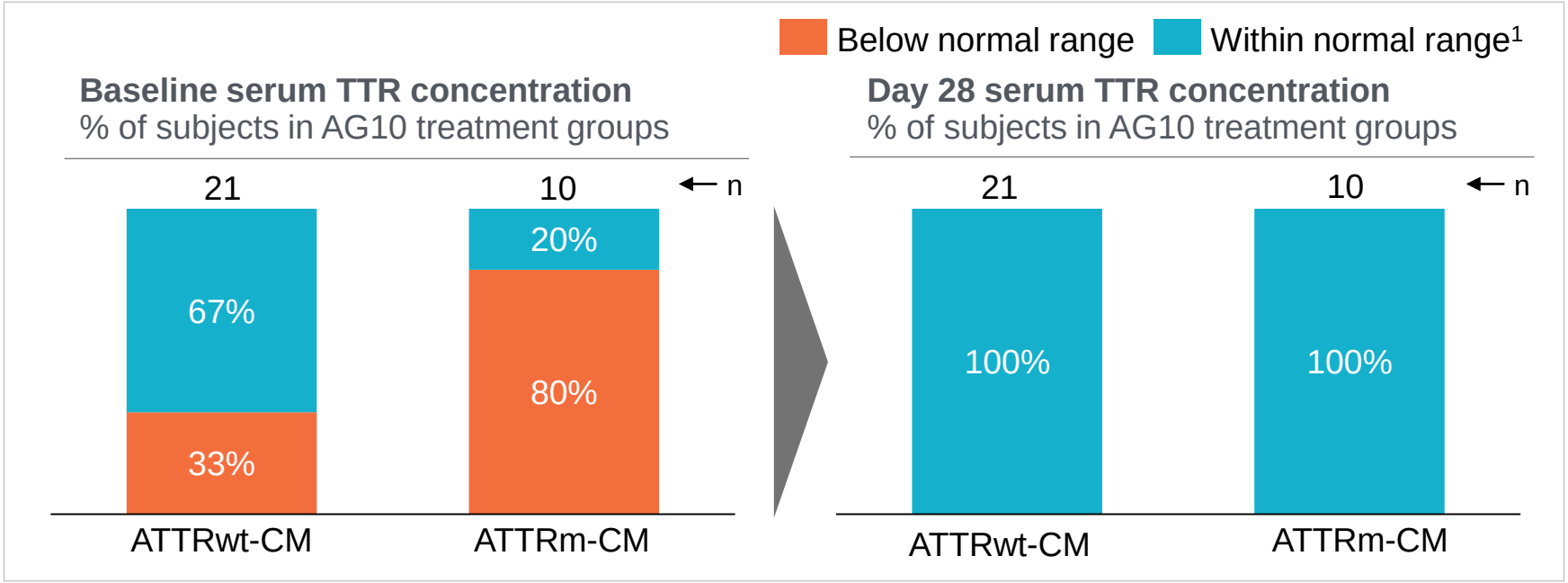
Increase in Serum TTR Concentration Observed in ATTRwt and ATTRm Subjects Treated with AG10



Note: Serum TTR concentration not available at baseline for one ATTRm-CM subject; and at Day 28 for one ATTRwt-CM subject and two ATTRm-CM subjects

* p<0.05 compared to corresponding placebo groups

Treatment with AG10 restored serum TTR concentrations to normal range in all subjects



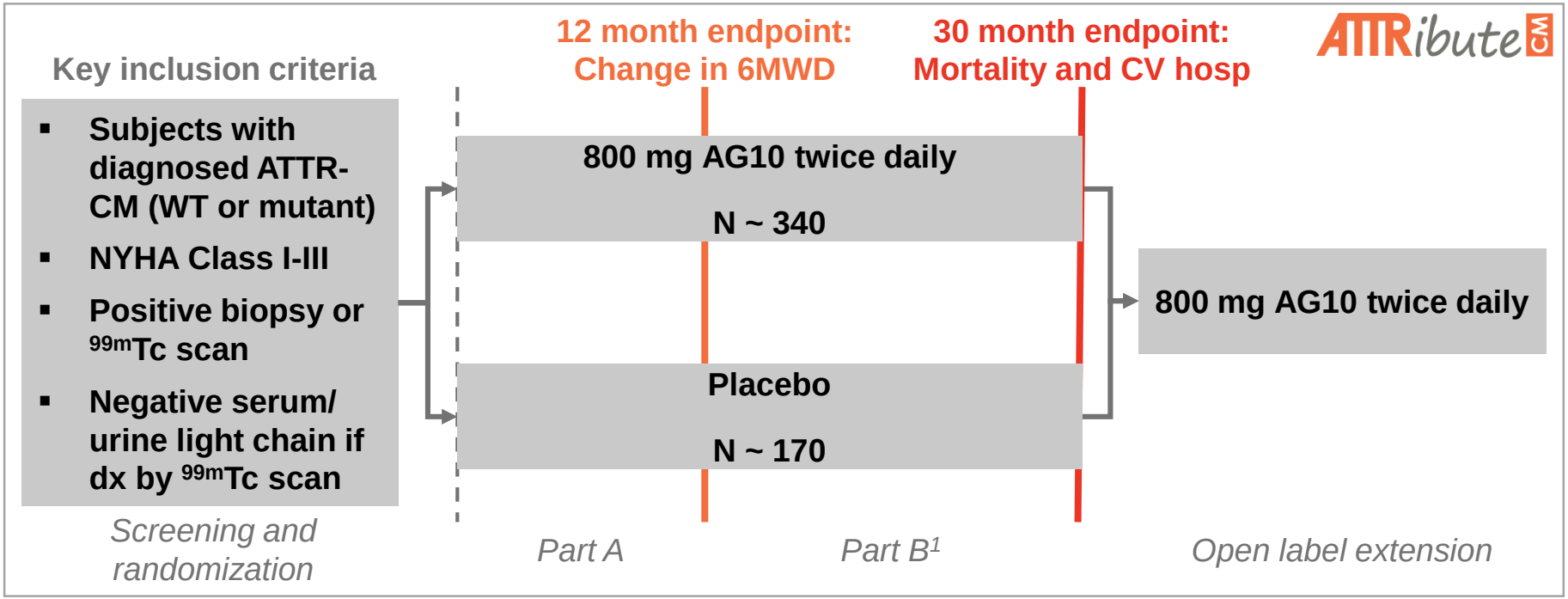
1 Normal reference range for serum TTR 20-40 mg/dL (3.6-7.3 µM)

Note: Serum TTR concentration not available at baseline for one ATTRm-CM subject and at Day 28 for one ATTRm-CM subject

Conclusions

- In a cohort of patients with either mutant or wild-type ATTR-CM, AG10 demonstrated near-complete stabilization of TTR
- At study entry, 33% of ATTRwt-CM and 80% of ATTRm-CM subjects had serum TTR below normal
- Treatment with 800 mg AG10 bid restored serum TTR levels to normal range
  - Increased serum TTR from baseline by 35% and 84% at Day 28 in ATTRwt-CM and ATTRm-CM subjects, respectively
- These results support further development of AG10 in both the ATTRwt-CM and ATTRm-CM populations

ATTRIBUTE-CM Phase 3 Study Schematic



1 As local standard of care evolves, concomitant use of approved, indicated therapies may be allowed

^{99m}Tc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); 6MWD = Six minute walk distance; CV hosp = cardiovascular-related hospitalizations