Long-term safety and efficacy of AG10 in ATTR-CM:

Phase 2 Open Label Extension

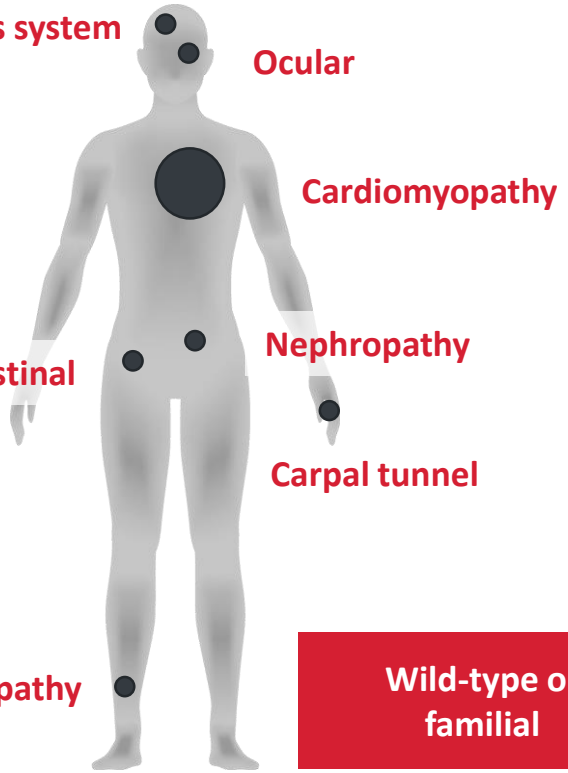
Daniel P. Judge, M.D.
Professor of Medicine/Cardiology
Medical University of South Carolina

MUSC
Medical University of South Carolina

Transthyretin (TTR) amyloidosis cardiomyopathy (ATTR-CM) is an emerging diagnostic and treatment priority

MUSC Medical University of South Carolina

ATTR is a systemic disease



Wild-type or familial

Growing awareness of the spectrum of ATTR:

13-19% of heart failure with preserved ejection fraction[1,2,3]

7.1% of idiopathic bilateral carpal tunnel release[4]

5% of suspected hypertrophic cardiomyopathy*[5]

ATTR pathogenesis and therapeutic strategies:

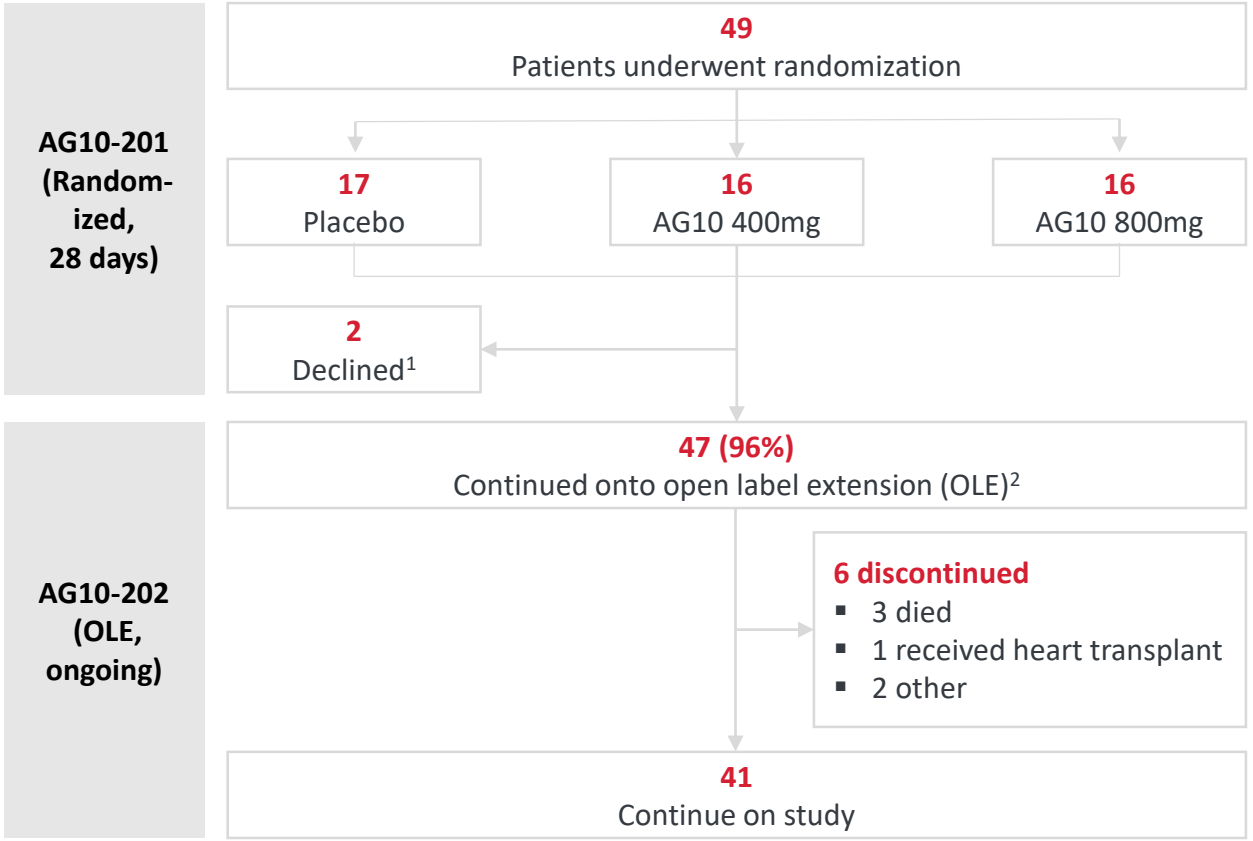
- Instability of the TTR tetramer promotes dissociation and aggregation as amyloid plaques[6]
- Available therapies include TTR tetramer stabilizers, TTR knockdown agents (neuropathy only), and transplant
- Stabilizing mutation (T119M) protects against ATTR and was the basis for development of AG10[7]

*Mutant TTR only, ^{99m}Tc=Technetium-99m; TAVR=transcatheter aortic valve replacement.

References: 1. Gonzalez-Lopez E. et al. *Eur Heart J* 2015. **2.** Mohammed SF, et al. *JACC: Heart F*ailure 2014. **3.** Horvath SA, et al. *Circulation* 2018. **4.** Sperry BW et al. *JACC* 2018. **5.** Damy T, et al. *Eur Heart J* 2015. **6.** Sant'Anna R, et al. Sci Rep. 2017;7(44709):1-15. **7.** Coelho T, et al. Neuromuscul Disord. 1996;6(1):S20.

AG10 Phase 2 Study Objectives and Status

SCHEMATIC OF AG10 PHASE 2 STUDY



AG10-202 (OLE) OUTCOMES

Primary Outcomes

Safety and tolerability

- Adverse events
- Clinical events and vital signs
- Clinical laboratory parameters

Secondary and exploratory outcomes

Pharmacokinetics

Pharmacodynamics

Echocardiographic parameters

Data reported as of 8/31/2019 in conjunction with annual regulatory reporting and review:

- **Median 65 weeks from AG10-201 (Randomized) initiation**
- **Median 53 weeks on open-label AG10**

1 Both declined participation due to geographical constraints regarding study visits
2 Median rollover period of 72 days (range 41-152 days)

Baseline characteristics

	Placebo n = 17	Pooled AG10 n = 32	Total n = 49
Age, median (range)	72 (60-85)	74 (60-86)	73 (60-86)
Male, n (%)	17 (100%)	28 (88%)	45 (92%)
ATTRm, n (%)	3 (18%)	11 (34%)	14 (29%)
NYHA Class II, n (%)	12 (71%)	23 (72%)	35 (71%)
NYHA Class III, n (%)	5 (29%)	9 (28%)	14 (29%)
NT-proBNP (pg/mL)[1]	3151 ± 2704	3483 ± 2869	3368 ± 2789
TnI (ng/mL)[2]	0.18 ± 0.33	0.15 ± 0.20	0.16 ± 0.25
TTR (mg/dL)[3]	23.4 ± 5.5	21.3 ± 5.3	22.0 ± 5.4

ATTRm-CM variants (n)

V122I (11)	T60A (2)	V30M (1)

1 NT-proBNP = N-Terminal pro B-type Natriuretic Peptide, normal range = 0 – 449 pg/mL
2 TnI = troponin I, normal range = 0 – 0.02 ng/mL
3 TTR = transthyretin (prealbumin), normal range = 20 – 40 mg/dL
Judge, D.P. et al. JACC Vol. 74, No. 3, 2019:285 – 95

No safety signals of clinical concern identified in Phase 2 OLE

MUSC Medical University of South Carolina

Summary of treatment-emergent adverse events

Number of participants (%)

Any Adverse Events	**46 (97.9)**
Most common Adverse Events (≥ 5)	
Fall	12 (25.5)
Cardiac failure congestive	7 (14.9)
Dyspnoea	6 (12.8)
Acute kidney injury	6 (12.8)
Fluid overload	5 (10.6)
Gout	5 (10.6)
Pneumonia	5 (10.6)

Summary of treatment-emergent serious adverse events

Number of participants (%)

Any Serious Adverse Events	**19 (40.4)**
Number of subjects who died	**3 (6.5)[1]**
Any Cardiovascular Serious Adverse Events	**12 (25.5)**
Most common Serious Adverse Events (≥ 2)	
Cardiac failure congestive	5 (10.6)
Acute kidney injury	4 (8.5)
Atrial fibrillation	2 (4.3)
Cardiac failure	2 (4.3)
Fall	2 (4.3)
Dehydration	2 (4.3)

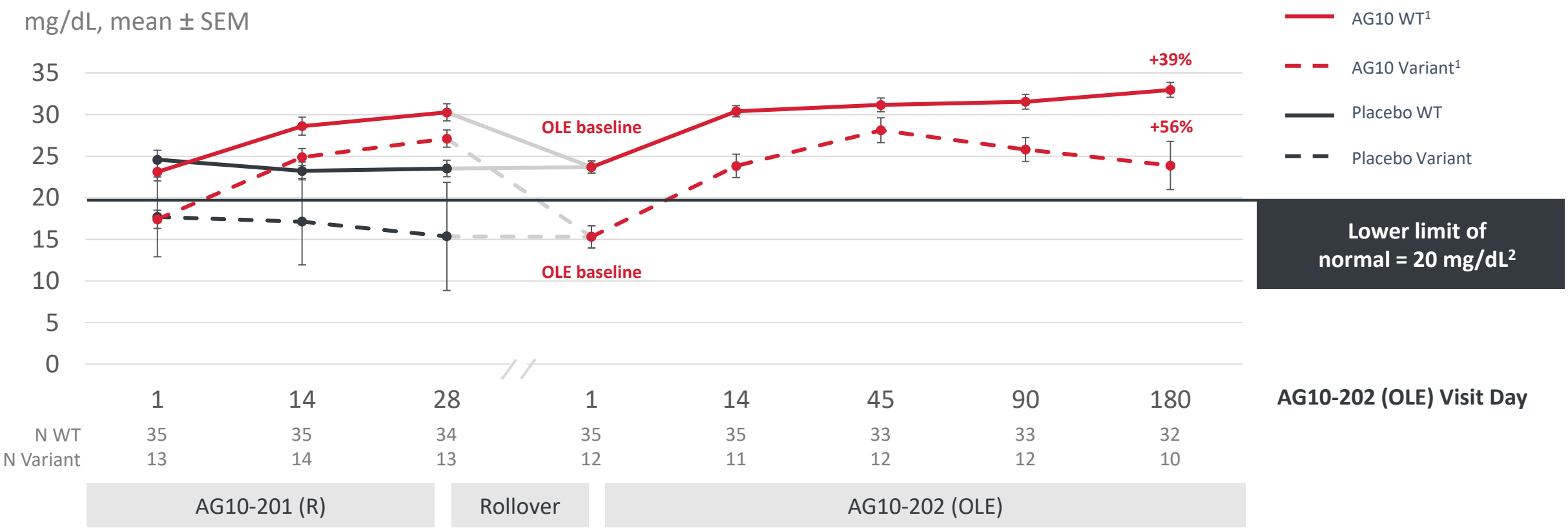
AG10 was generally well tolerated with a pattern of adverse events consistent with underlying disease severity, concurrent illnesses, and age of participants

1. Includes 2 subjects who had SAEs with an outcome of death (1 disease progression; 1 cervix carcinoma); 1 subject died due to heart failure 86 days after the last dose of study drug; Data reported as of 8/31/2019 in conjunction with annual regulatory reporting and review

Serum TTR levels increased upon AG10 treatment and were maintained throughout study duration

MUSC Medical University of South Carolina

Serum TTR concentration



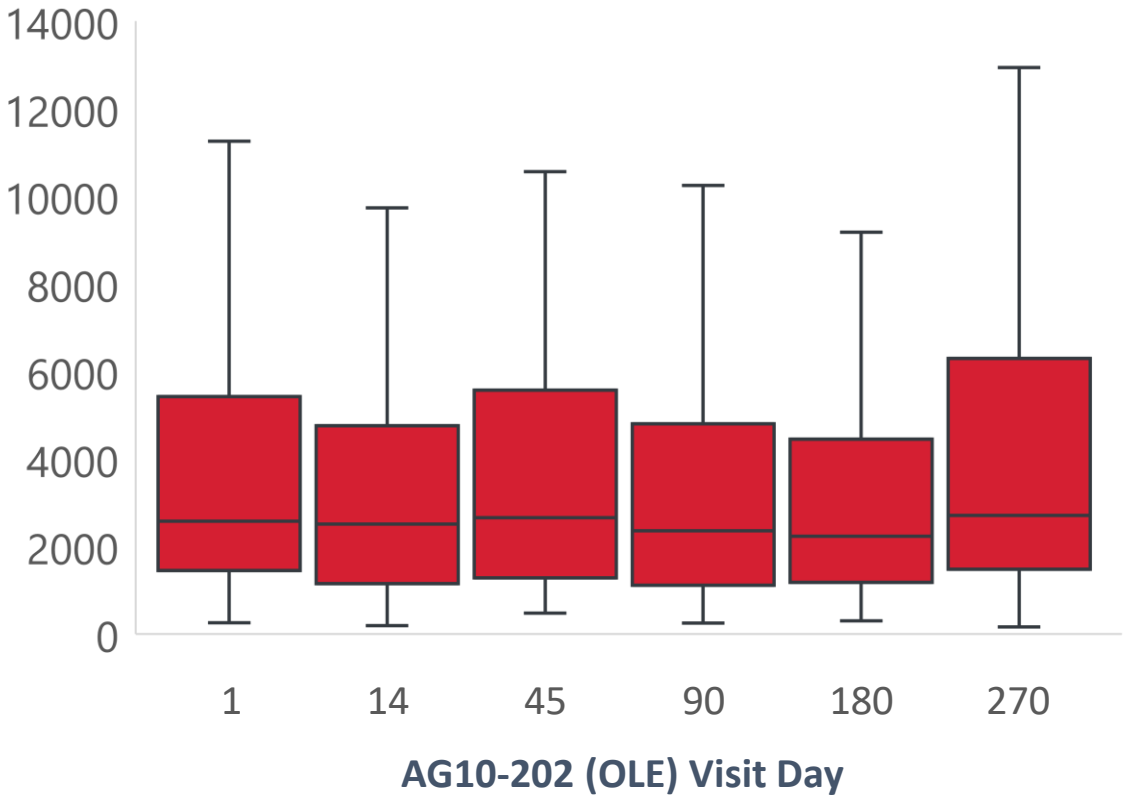
1. 400mg and 800mg BID AG10 groups pooled during randomized portion
2. Defined as the lower limit of the reference interval for the serum prealbumin (TTR) clinical laboratory assay

NT-proBNP and TnI levels were unchanged in AG10-treated participants throughout OLE

MUSC Medical University of South Carolina

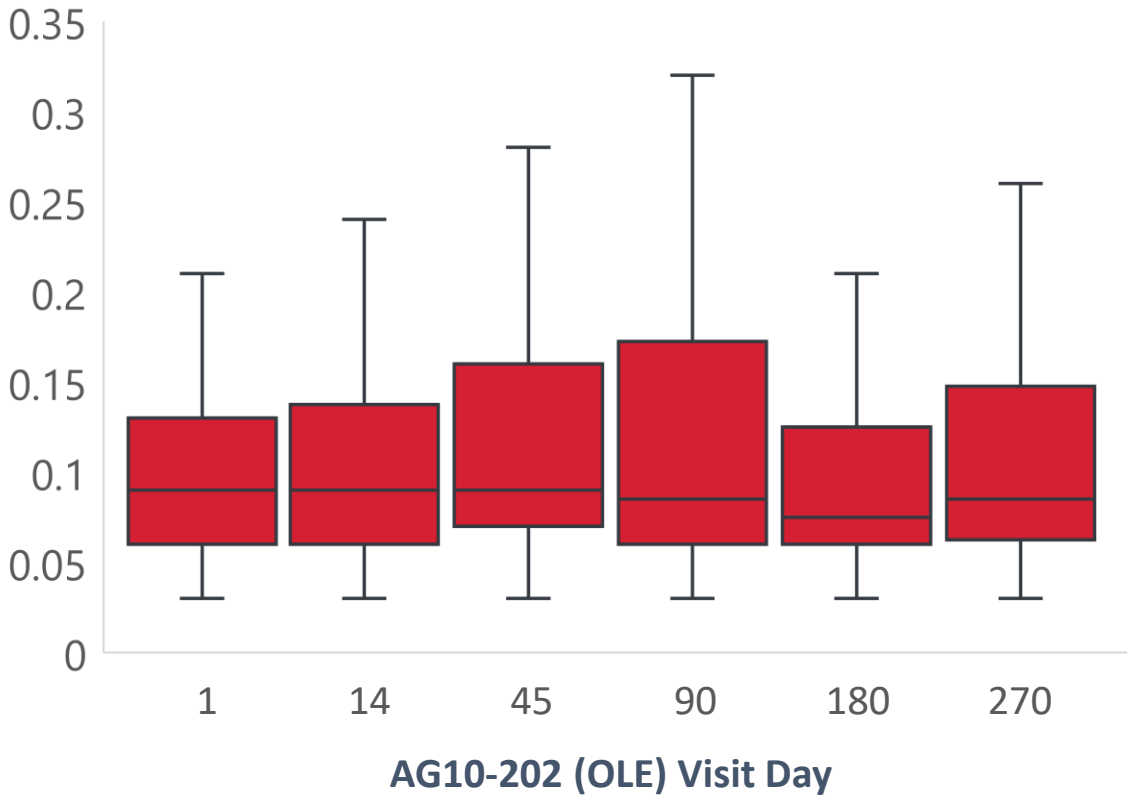
NT-proBNP

pg/mL; 95% confidence interval, quartiles, median



TnI

ng/mL; 95% confidence interval, quartiles, median

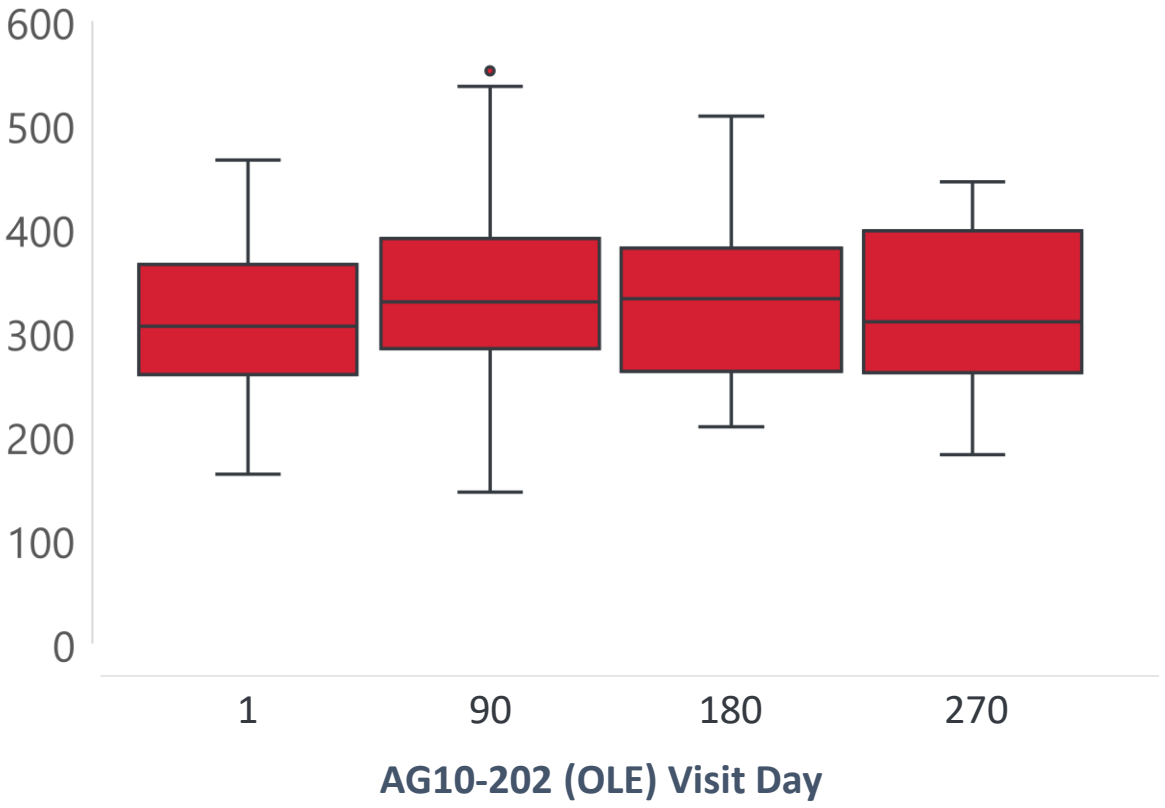


Echocardiography parameters were unchanged in AG10-treated participants throughout OLE

MUSC Medical University of South Carolina

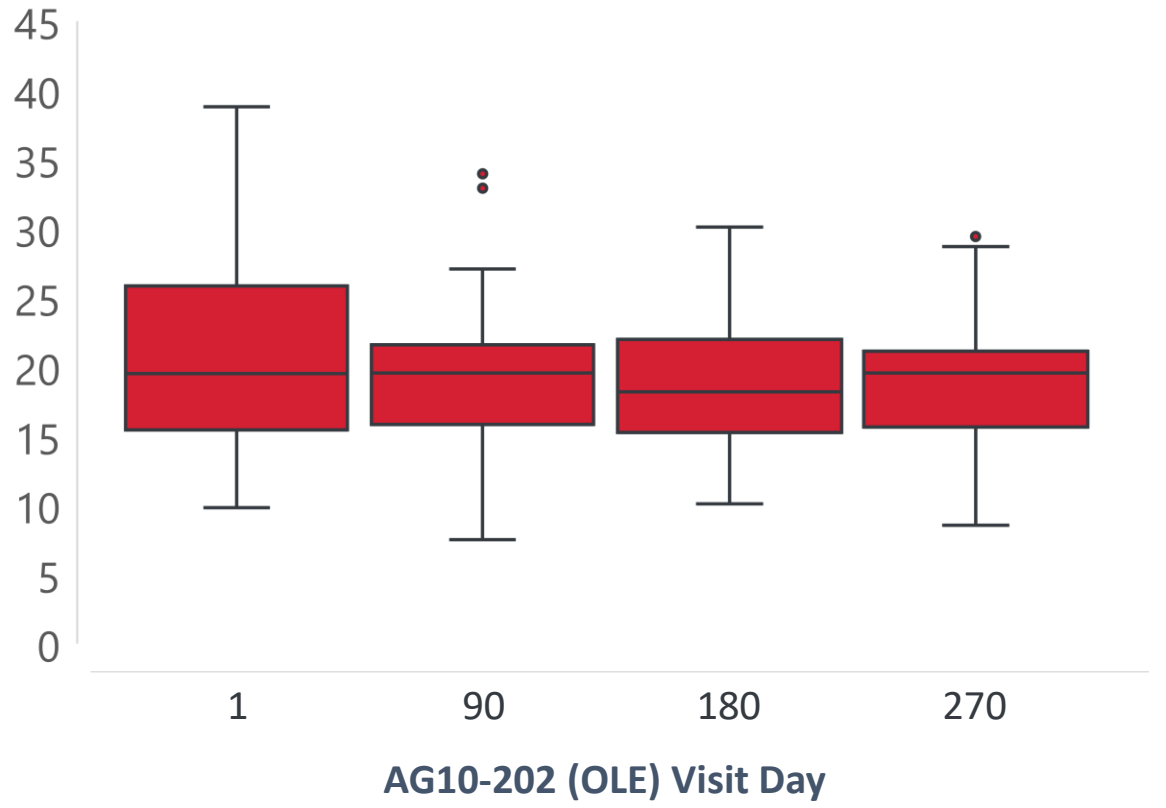
Left ventricular mass

g; 95% confidence interval, quartiles, median



Left ventricular stroke volume index

mL/m^2; 95% confidence interval, quartiles, median



Participants in the AG10 Phase 2 study had similar baseline characteristics as those in the ATTR-ACT study

MUSC Medical University of South Carolina

Baseline characteristics from ATTR-ACT study and AG10 Phase 2 study

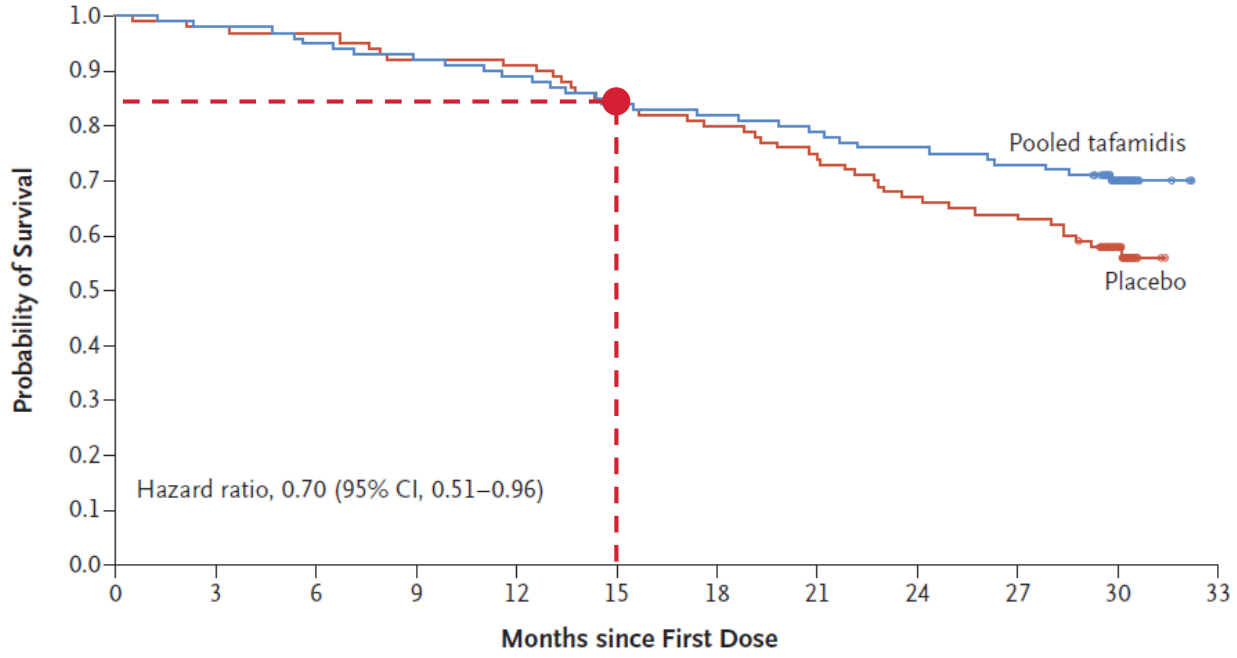
	ATTR-ACT Phase 3 study Tafamidis group[1]	ATTR-ACT Phase 3 study Placebo group[1]	AG10 Phase 2 study All groups[2]
Age, median (range)	75 (46-88)	74 (51-89)	73 (60-86)
Male, n (%)	241 (91%)	157 (89%)	45 (92%)
ATTRm, n (%)	63 (24%)	43 (24%)	14 (29%)
NYHA Class			
Class I, n (%)	24 (9%)	13 (7%)	0 (0%)
Class II, n (%)	162 (61%)	101 (57%)	35 (71%)
Class III, n (%)	78 (30%)	63 (36%)	14 (29%)
Race			
White, n (%)	211 (80%)	146 (83%)	35 (71%)
Black, n (%)	37 (14%)	26 (15%)	10 (20%)
Other, n (%)	16 (6%)	5 (3%)	4 (8%)

1 Maurer, M.S. et al. N Engl J Med. 2018;379:1007–16
2 Judge, D.P. et al. JACC Vol. 74, No. 3, 2019:285 – 95

Mortality in placebo-treated participants at 15 months in the ATTR-ACT study was 15.3%

MUSC Medical University of South Carolina

All-cause mortality from ATTR-ACT Phase 3 trial



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

Mortality at 15 months

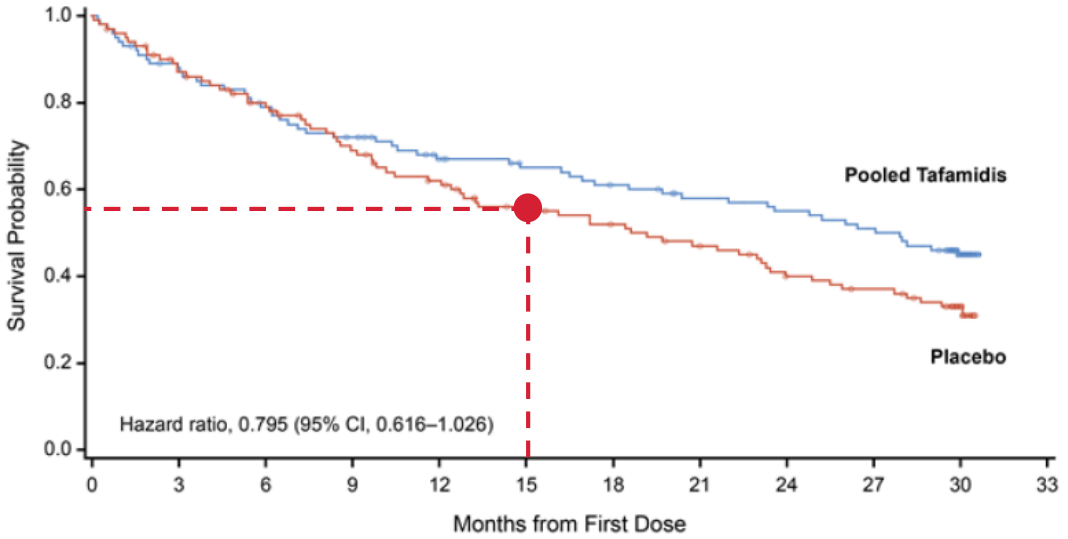
Placebo

15.3%

Adapted from Maurer, M.S. et al. N Engl J Med. 2018;379:1007–16.

Proportion of placebo-treated participants with 1st cardiovascular hospitalization within 15 months in the ATTR-ACT study was 41.8%

Patients with 1st CV hospitalization from ATTR-ACT trial



No. at Risk
Patients Remaining at Risk
(Cumulative Events)

Tafamidis	264	231	205	187	169	159	147	138	130	120	55	0
	0	31	56	73	85	91	102	107	115	125	138	138
Placebo	177	151	133	113	99	83	75	67	55	49	22	0
	0	22	36	53	64	74	80	86	96	101	106	107

Proportion of participants with ≥1 CV hospitalization at 15 months

Placebo

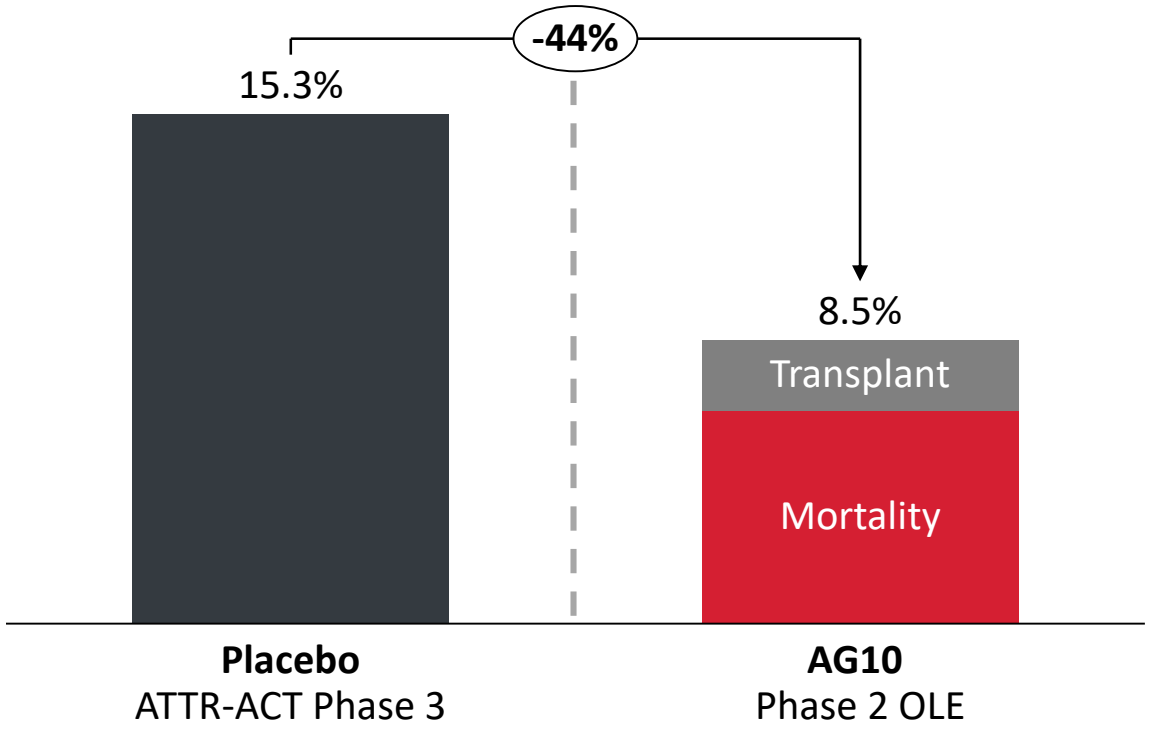
41.8%

Adapted from Maurer, M.S. et al. N Engl J Med. 2018;379:1007–16 Supplement.

Deaths and CV hospitalizations reported in AG10 Phase 2 OLE were lower than those in placebo-treated ATTR-ACT participants

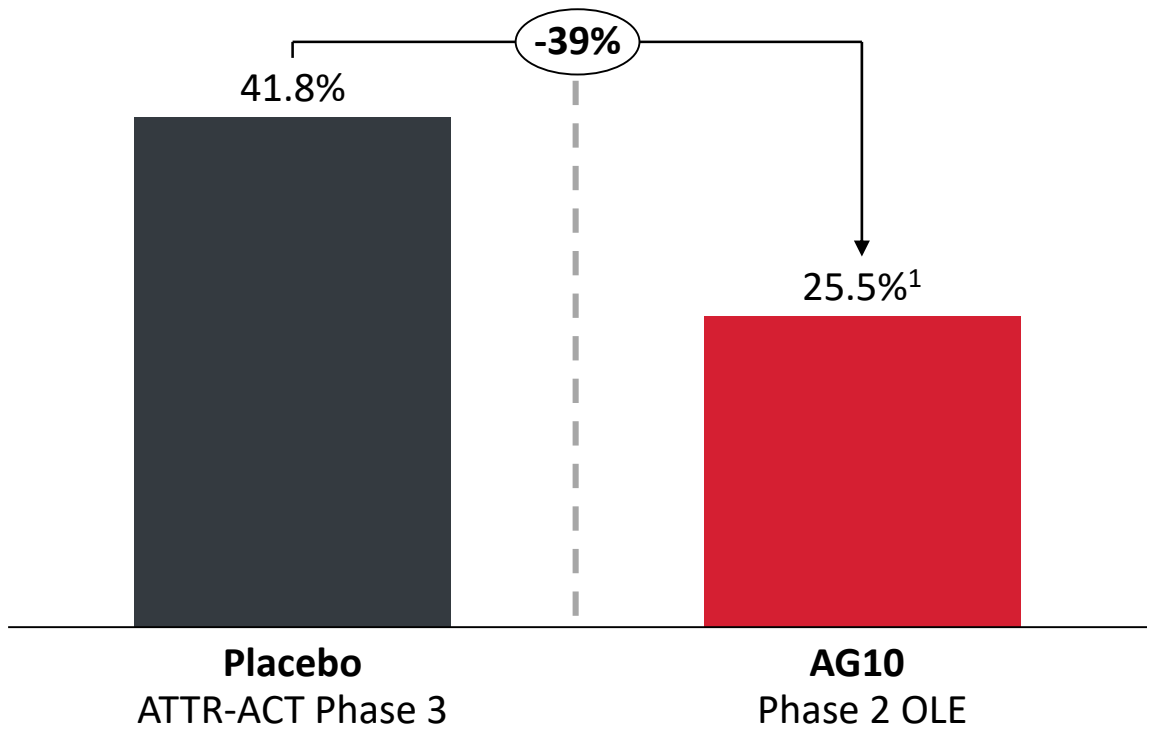
All-cause mortality at 15 months

Proportion died or receiving transplant (%)



Cardiovascular hospitalizations at 15 months

Proportion of participants with ≥1 CV hospitalization (%)



1 Based on routine adverse event reporting

Note: These data are based on a cross-trial comparison and not a randomized clinical trial. As a result, the values shown may not be directly comparable

Summary of AG10 Phase 2 OLE results

MUSC
Medical University of South Carolina

1

Safety and tolerability

Adverse event profile consistent with ATTR-CM disease severity, supportive of continued evaluation in ongoing Phase 3 trial

2

Cardiac biomarkers

Sustained improvement in serum TTR and stability of NT-proBNP, TnI, and echocardiographic parameters

3

Mortality and CV hospitalizations

Mortality and CV hospitalization were lower in AG10 Phase 2 OLE participants than in placebo-treated ATTR-ACT participants at 15 months[1]

These data support further development of AG10 in ATTR-CM. A randomized, placebo-controlled Phase 3 trial is ongoing (NCT03860935)

1 These data are based on a cross-trial comparison and not a randomized clinical trial. As a result, the values may not be directly comparable

Acknowledgements

A sincere thank-you to the patients and families, investigators, referring physicians, clinical research staff, Eidos employees, and collaborating research partners participating in the study.

Phase 2 investigators		
Rodney Falk, MD *Brigham and Women's Hospital*	**Martha Grogan, MD** *Mayo Clinic*	**Mazen Hanna, MD** *Cleveland Clinic*
Stephen Heitner, MD *Oregon Health & Science University*	**Daniel Jacoby, MD** *Yale University*	**Daniel Judge, MD** *Medical University of South Carolina*
Mat Maurer, MD *Columbia University*	**Jose Nativi-Nicolau, MD** *University of Utah*	**Jignesh Patel, MD, PhD** *Cedars-Sinai Medical Center*
Van Selby, MD *University of California San Francisco*	**Sanjiv Shah, MD** *Northwestern University*	**Ronald Witteles, MD** *Stanford University*

Mamoun M. Alhamadsheh, PhD and Isabella A Graef, MD for discovery of AG10.
Science Translational Medicine 2011; 3:97ra81