



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

# Phase 2 Open Label Extension

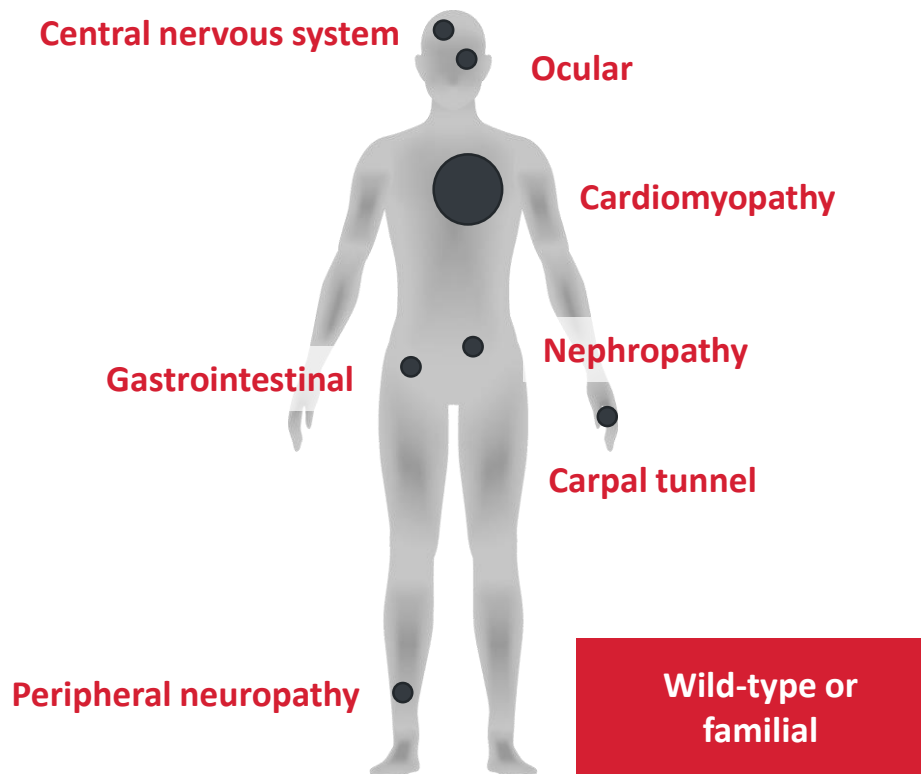
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# Transthyretin (TTR) amyloidosis cardiomyopathy (ATTR-CM) is an emerging diagnostic and treatment priority

ATTR is a systemic disease



Growing awareness of the spectrum of ATTR:

**13-19%** of heart failure with preserved ejection fraction<sup>1,2,3</sup>

**7.1%** of idiopathic bilateral carpal tunnel release<sup>4</sup>

**5%** of suspected hypertrophic cardiomyopathy\*<sup>5</sup>

ATTR pathogenesis and therapeutic strategies:

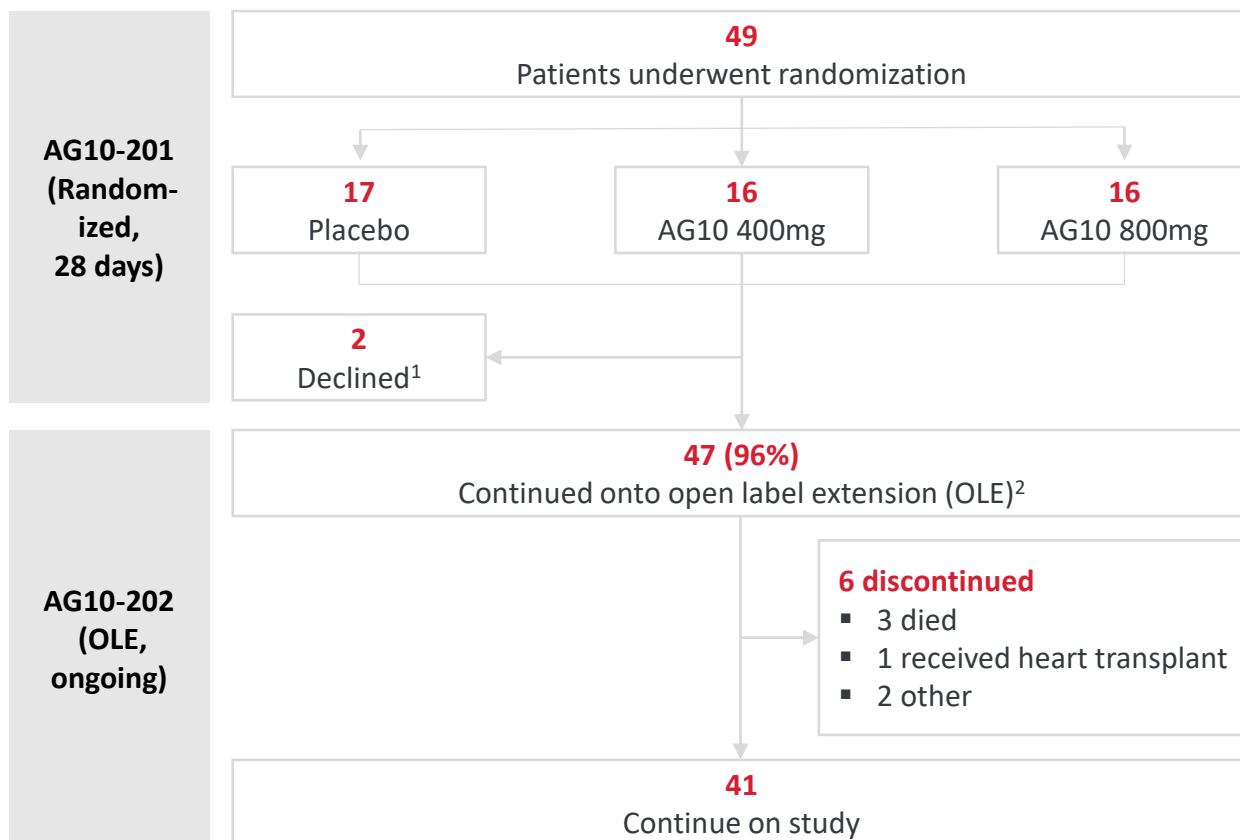
- Instability of the TTR tetramer promotes dissociation and aggregation as amyloid plaques<sup>6</sup>
- Available therapies include TTR tetramer stabilizers, TTR knockdown agents (neuropathy only), and transplant
- Stabilizing mutation (T119M) protects against ATTR and was the basis for development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

\*Mutant TTR only, <sup>99m</sup>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 Failure* 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



1 Both declined participation due to geographical constraints regarding study visits

2 Median rollover period of 72 days (range 41-152 days)

## 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

# 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) <sup>1</sup>	3151 ± 2704	3483 ± 2869	3368 ± 2789
TnI (ng/mL) <sup>2</sup>	0.18 ± 0.33	0.15 ± 0.20	0.16 ± 0.25
TTR (mg/dL) <sup>3</sup>	23.4 ± 5.5	21.3 ± 5.3	22.0 ± 5.4

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

## ATTRm-CM variants (n)

V122I (11)

T60A (2)

V30M (1)

# No safety signals of clinical concern identified in Phase 2 OLE

## Summary of treatment-emergent adverse events

Number of participants (%)

<b>Any Adverse Events</b>	<b>46 (97.9)</b>
<b>Most common Adverse Events (≥ 5)</b>	
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 (%)

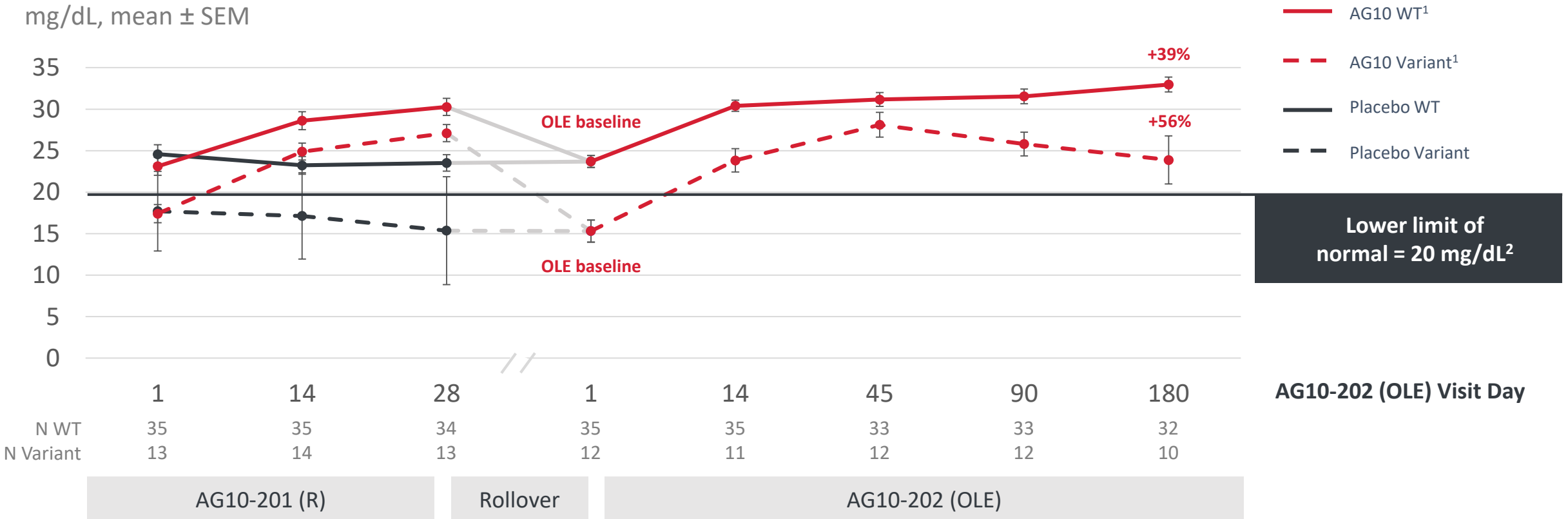
<b>Any Serious Adverse Events</b>	<b>19 (40.4)</b>
<b>Number of subjects who died</b>	<b>3 (6.5)<sup>1</sup></b>
<b>Any Cardiovascular Serious Adverse Events</b>	<b>12 (25.5)</b>
<b>Most common Serious Adverse Events (≥ 2)</b>	
Cardiac failure congestive	5 (10.6)
Acute kidney injury	4 (8.5)
Atrial fibrillation	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

## Serum TTR concentration

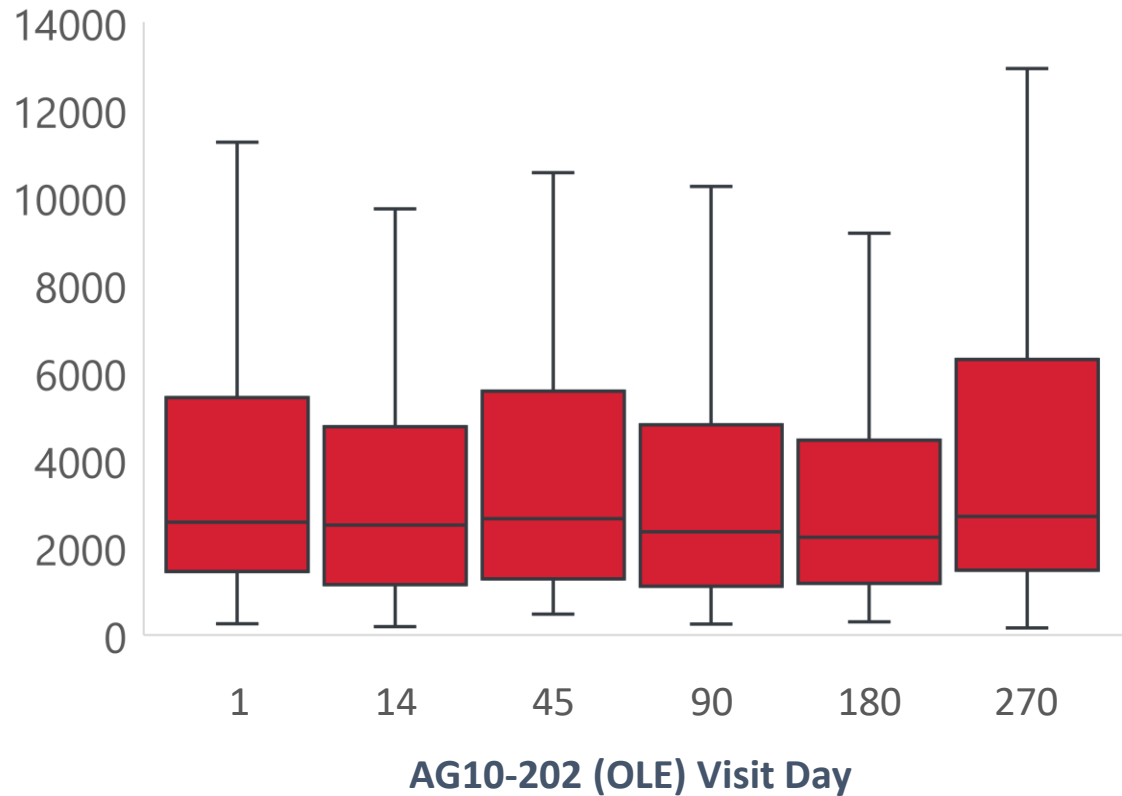


- 400mg and 800mg BID AG10 groups pooled during randomized portion
- Defined as the lower limit of the reference interval for the serum prealbumin (TTR) clinical laboratory assay

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

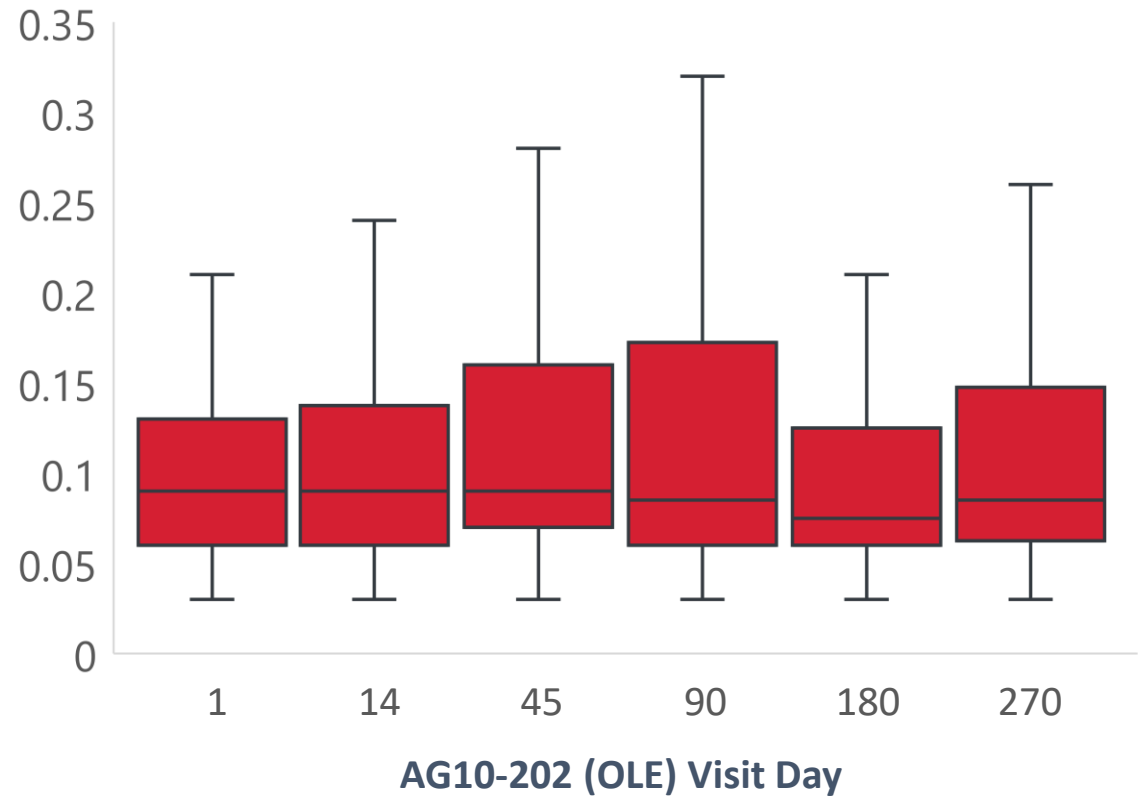
## NT-proBNP

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



## Tnl

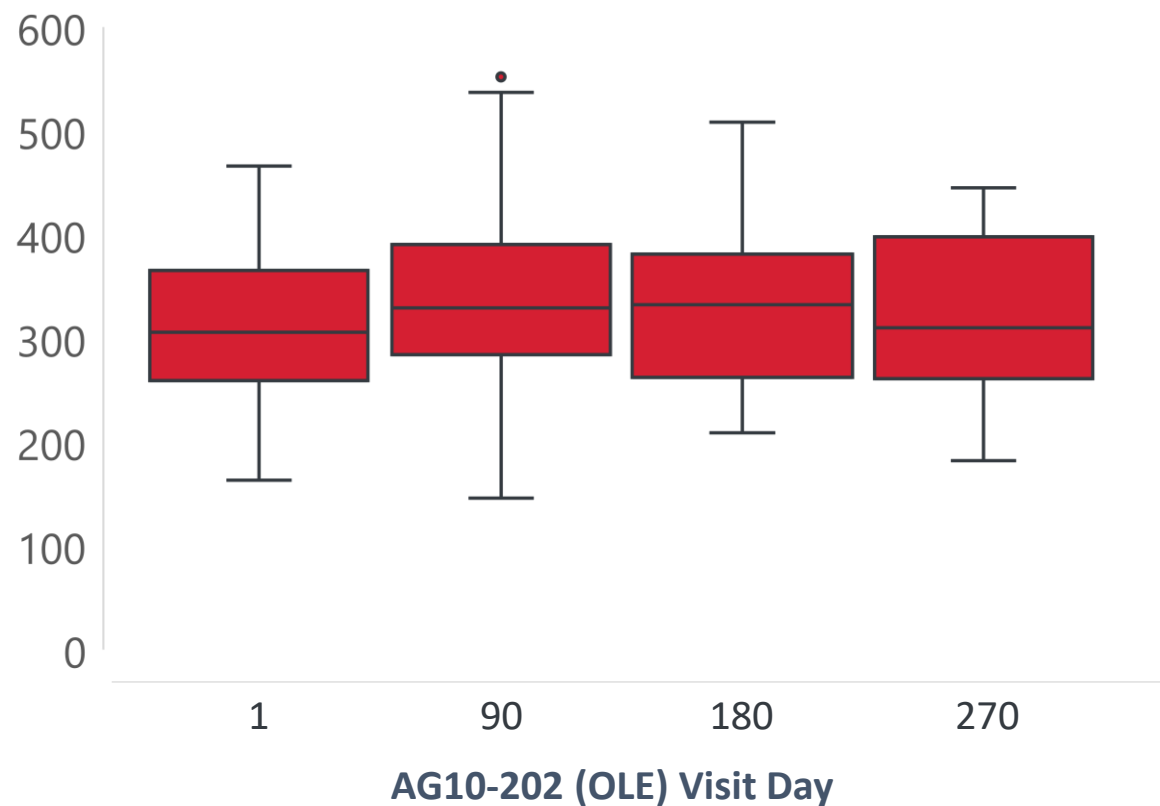
ng/mL; 95% confidence interval, quartiles, median



# Echocardiography parameters were unchanged in AG10-treated participants throughout OLE

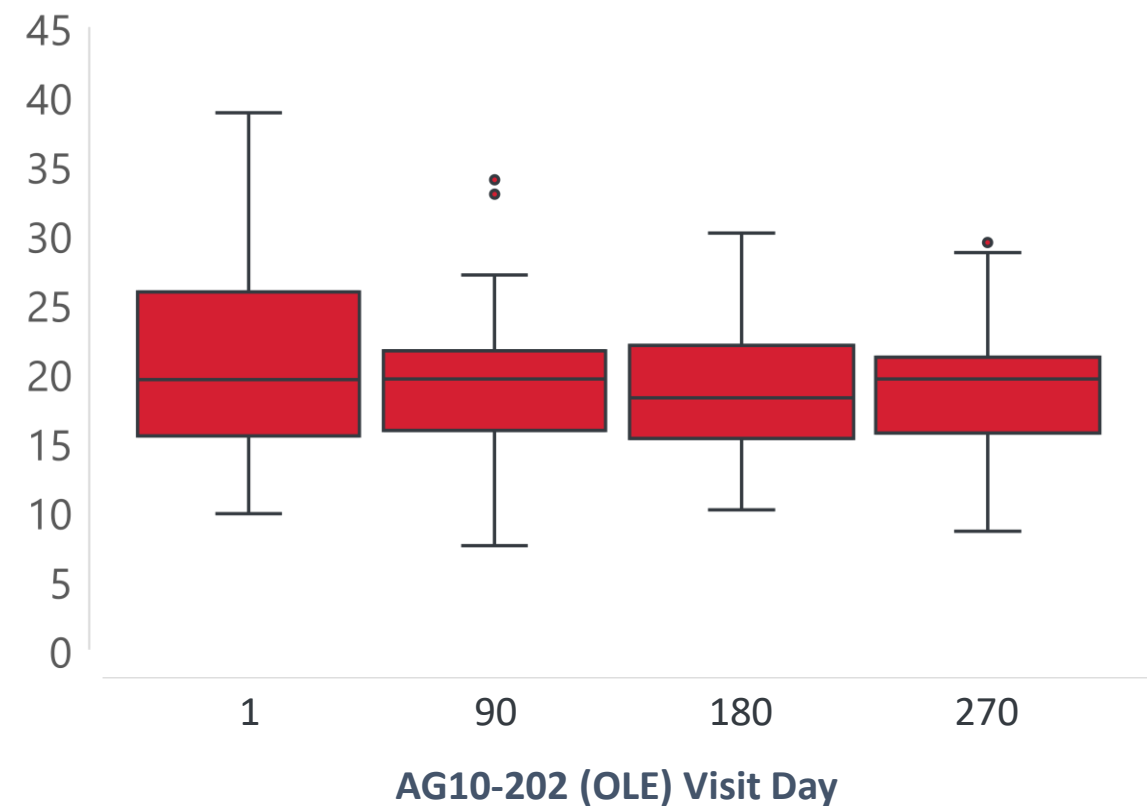
## Left ventricular mass

g; 95% confidence interval, quartiles, median



## Left ventricular stroke volume index

mL/m<sup>2</sup>; 95% confidence interval, quartiles, median





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

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

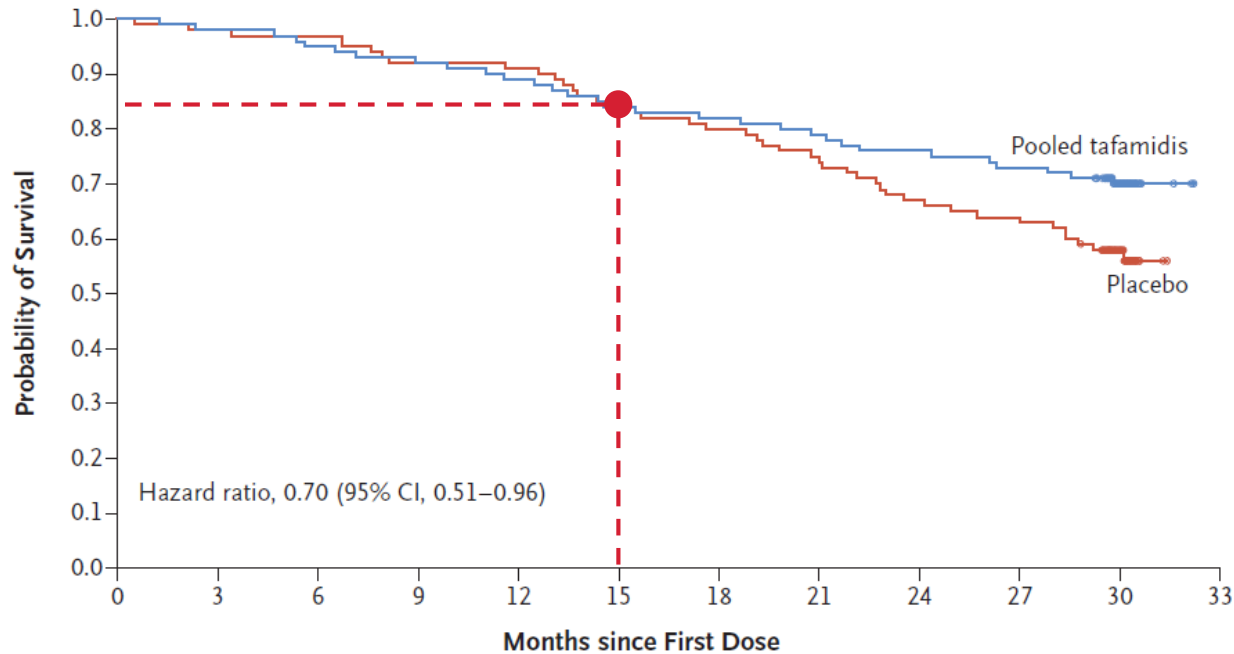
	ATTR-ACT Phase 3 study Tafamidis group <sup>1</sup>	ATTR-ACT Phase 3 study Placebo group <sup>1</sup>	AG10 Phase 2 study All groups <sup>2</sup>
Age, median (range)	75 (46-88)	74 (51-89)	73 (60-86)
Male, n (%)	241 (91%)	157 (89%)	45 (92%)
ATTRm, n (%)	63 (24%)	43 (24%)	14 (29%)
NYHA Class			
Class I, 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%)

<sup>1</sup> Maurer, M.S. et al. N Engl J Med. 2018;379:1007–16

<sup>2</sup> 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%

## All-cause mortality from ATTR-ACT Phase 3 trial



### Mortality at 15 months

Placebo  
**15.3%**

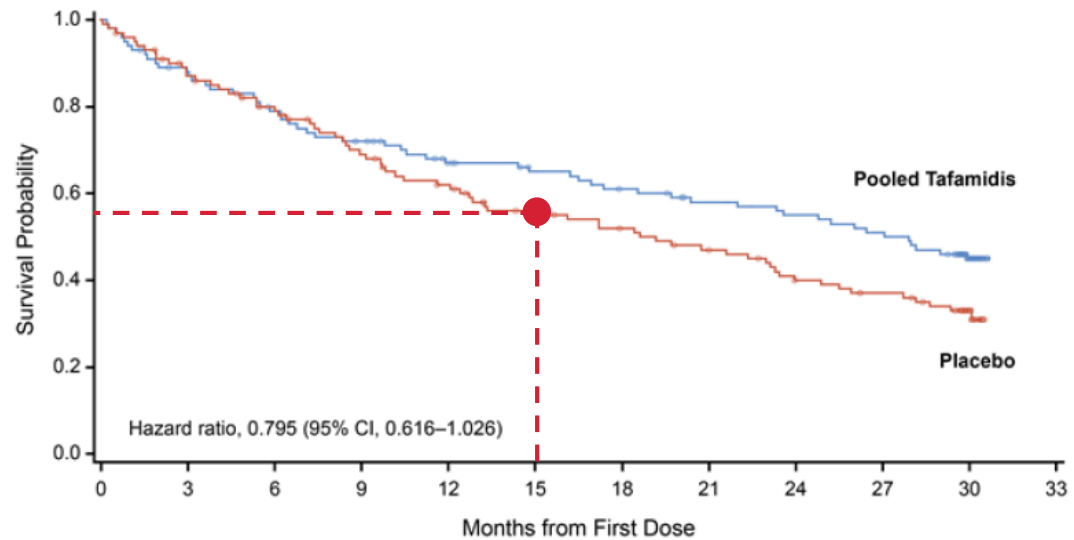
#### No. at Risk (cumulative no. of events)

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)

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

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

## Patients with 1<sup>st</sup> CV hospitalization from ATTR-ACT trial



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

	0	3	6	9	12	15	18	21	24	27	30	33
Tafamidis	264	231	205	187	169	159	147	138	130	120	55	0
Placebo	177	151	133	113	99	83	75	67	55	49	22	0
	0	31	56	73	85	91	102	107	115	125	138	138
	0	22	36	53	64	74	80	86	96	101	106	107

### Proportion of participants with ≥1 CV hospitalization at 15 months

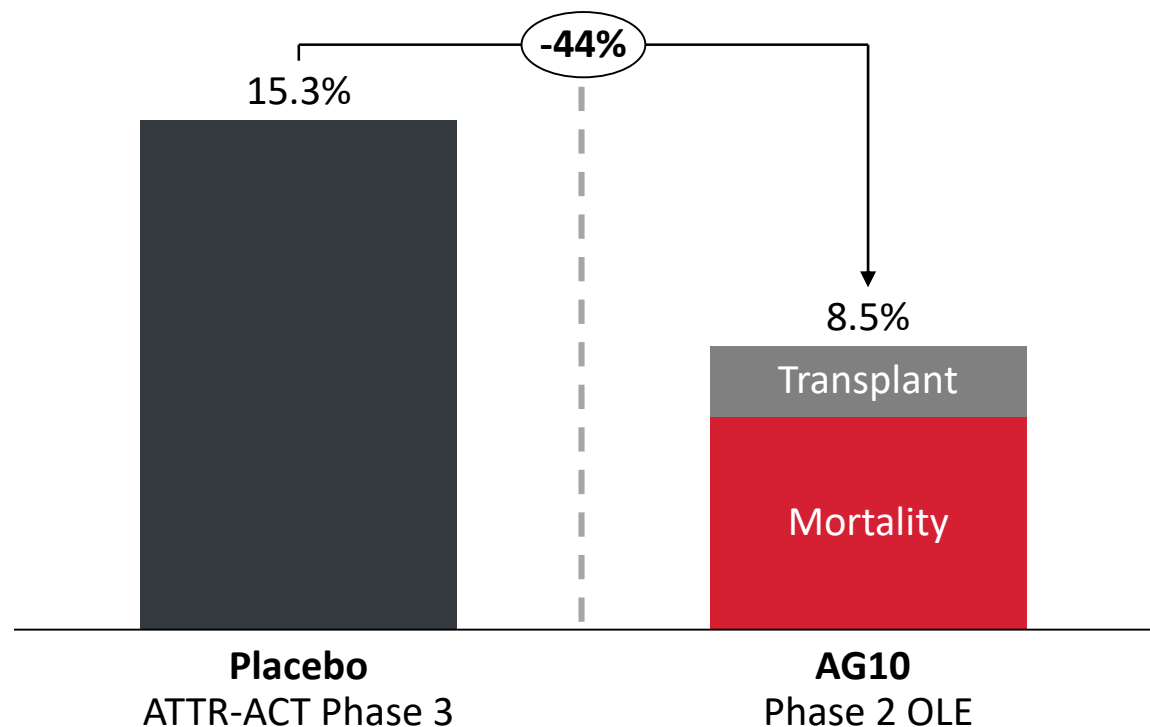
Placebo  
**41.8%**

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

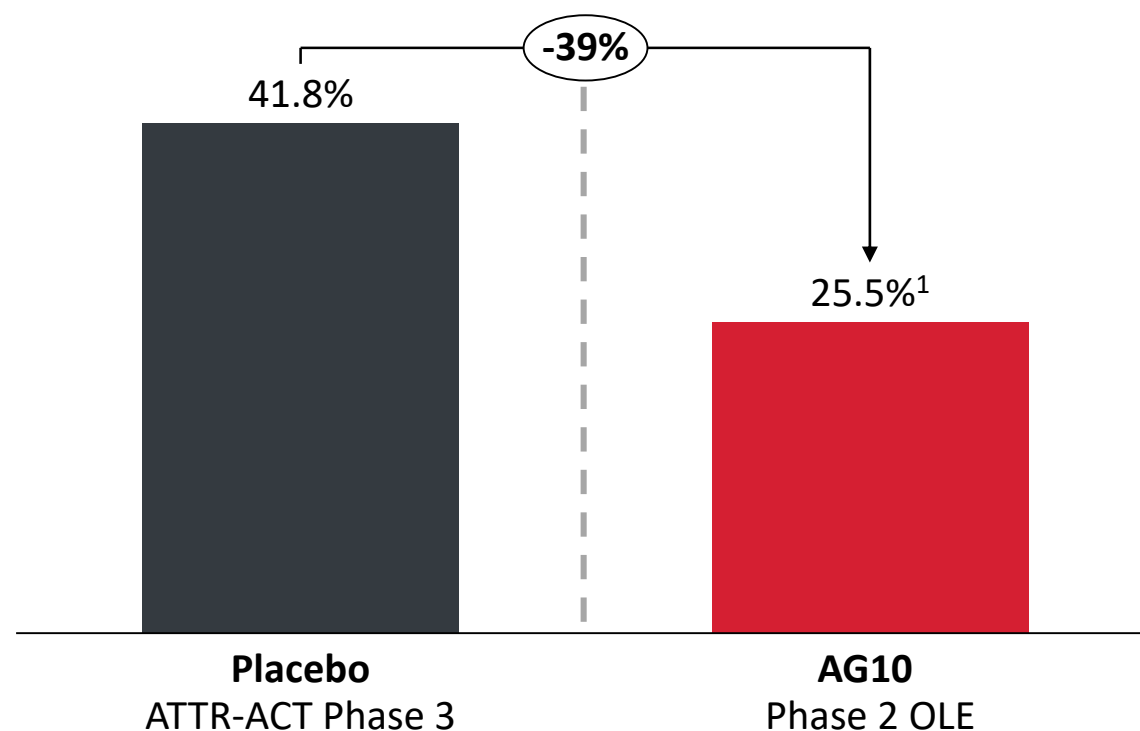
## All-cause mortality at 15 months

Proportion died or receiving transplant (%)



## Cardiovascular hospitalizations at 15 months

Proportion of participants with  $\geq 1$  CV hospitalization (%)



<sup>1</sup> 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

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<sup>1</sup>

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

<sup>1</sup> 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

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## Phase 2 investigators

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*Science Translational Medicine 2011; 3:97ra81*