

Safety, Tolerability and Transthyretin Stabilization by AG10: A Phase 2, Randomized, Double-blind, Placebo-controlled Clinical Trial in Patients with Transthyretin Amyloid Cardiomyopathy and NYHA Class II/III Heart Failure

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**SCIENTIFIC 20
SESSIONS 18**

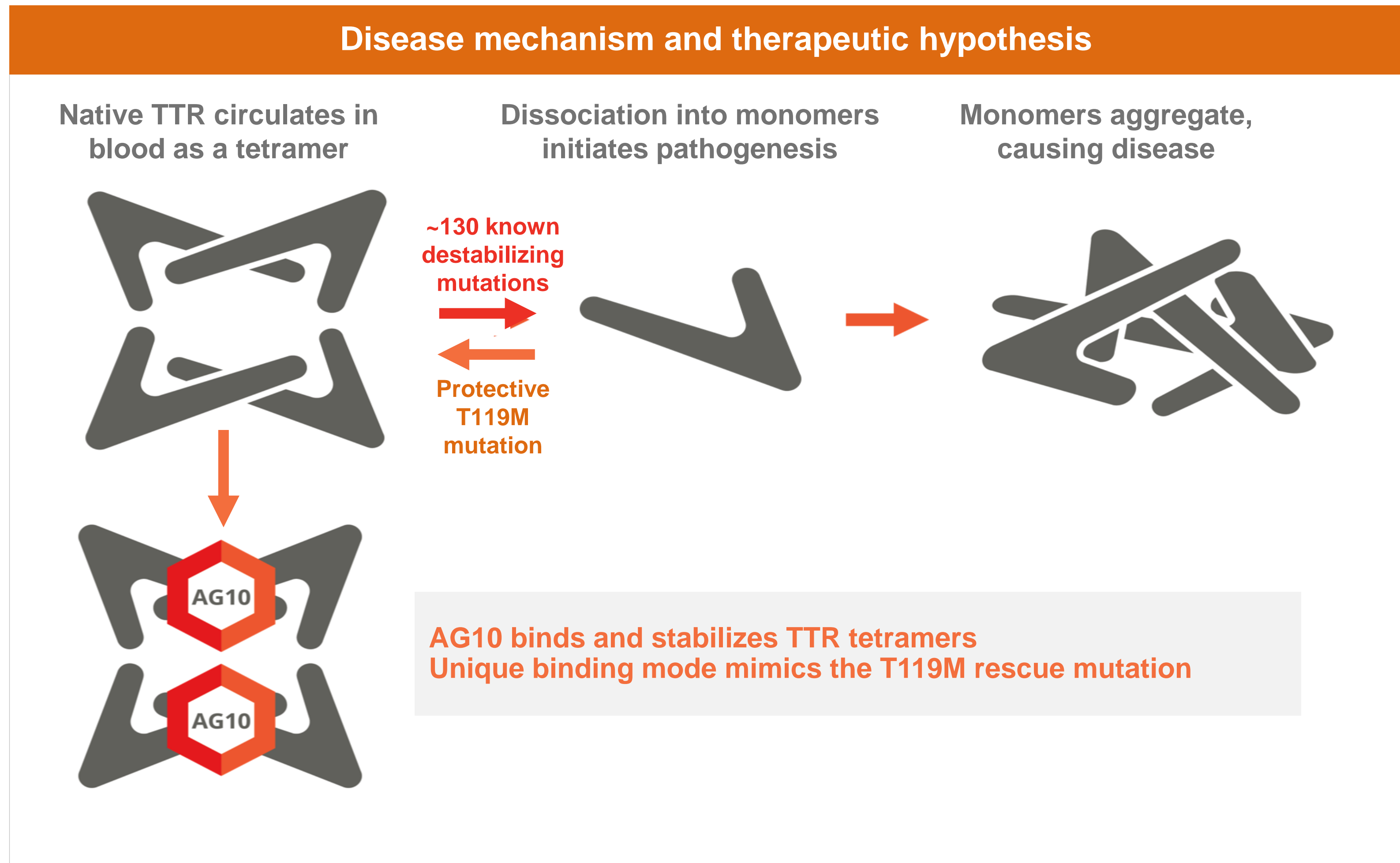
ATTR-CM clinical presentation

Clinical presentation

- ATTR-CM: an infiltrative, restrictive cardiomyopathy
- Non-invasive diagnosis by Tc-PYP scans: increasingly finding ATTR-CM patients “hiding in plain sight”:
 - 10-15% of HFpEF patients¹
 - 16% of patients undergoing TAVR²
 - 5% of patients with presumed hypertrophic cardiomyopathy³
 - 8% of patients undergoing bilateral carpal tunnel release surgery⁴



ATTR-CM mechanism

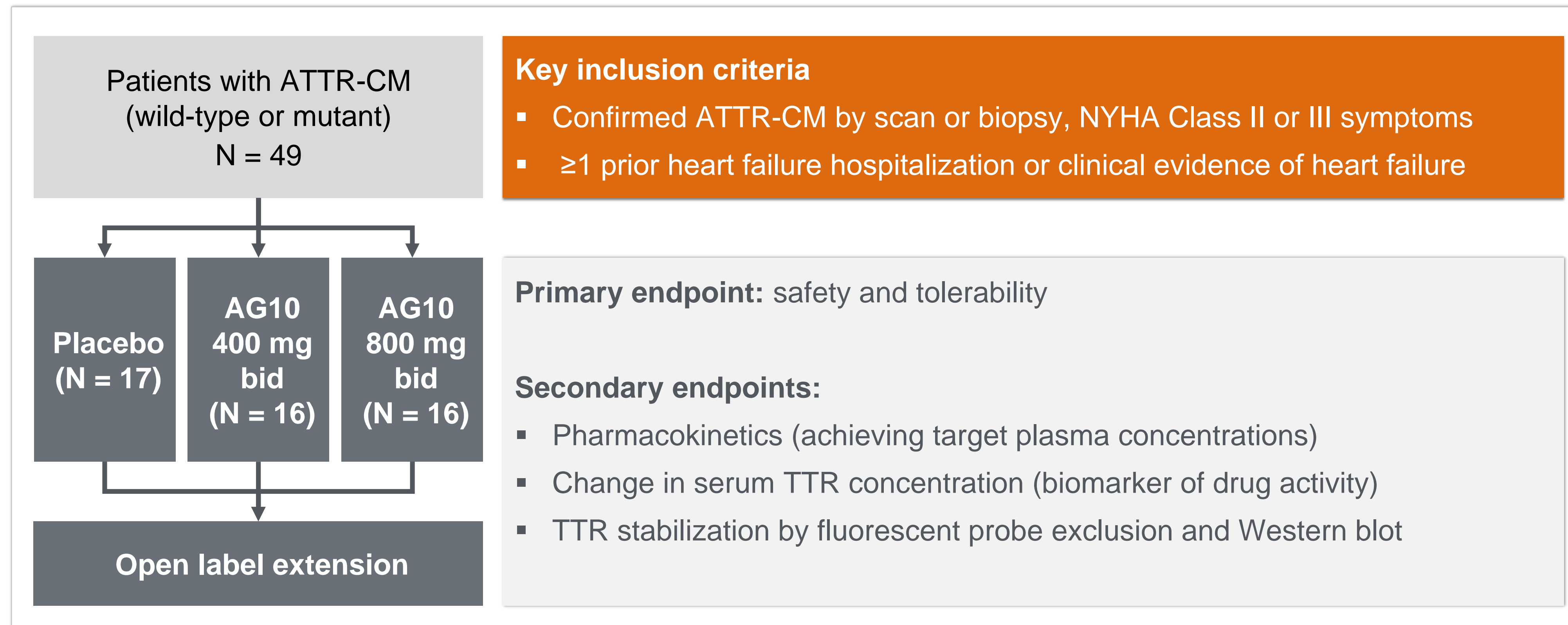


Positive Phase 1 results provided evidence of AG10 clinical activity

- All doses of AG10 were well-tolerated without any serious adverse events and no safety findings of clinical concern
- Target steady-state concentration achieved near-complete, sustained TTR stabilization of >95% across the dosing interval when dosed at 800 mg q12h
- Serum TTR concentration increased by 59% in AG10-treated subjects, demonstrating in vivo evidence of clinical activity

Phase 2 study design

Randomized, double-blind, placebo controlled, 28-day multi-center study of AG10 in ATTR-CM



Baseline characteristics

Characteristic	Placebo N = 17	AG10 400 mg N = 16	AG10 800 mg N = 16	Total N = 49
Age, mean (range)	73.2 (60-85)	73.8 (60-83)	75.4 (67-86)	74.1 (60-86)
Male, n (%)	17 (100%)	14 (88%)	14 (88%)	45 (92%)
ATTRm, n (%)	3 (18%)	6 (38%)	5 (31%)	14 (29%)
NYHA Class III, n (%)	5 (29%)	6 (38%)	3 (19%)	14 (29%)
Race, n (%)				
White	13 (76%)	10 (62%)	12 (75%)	35 (72%)
Black	3 (18%)	4 (25%)	3 (19%)	10 (20%)
Other	1 (6%)	2 (13%)	1 (6%)	4 (8%)
NT-proBNP (pg/mL) ¹	3151 ± 3705	3589 ± 3020	3377 ± 2806	3368 ± 2789
Troponin I (ng/mL) ²	0.17 ± 0.30	0.22 ± 0.24	0.10 ± 0.06	0.16 ± 0.22
TTR (mg/dL) ³	23.4 ± 5.5	23.2 ± 5.7	19.5 ± 4.2	22.0 ± 5.4

ATTRm-CM variants (n)

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



Safety and tolerability

Summary of adverse events, n (%)

	Placebo N = 17	AG10 400 mg N = 16	AG10 800 mg N = 16
Any Adverse Event	15 (88%)	10 (63%)	11 (69%)
Mild	6 (35%)	8 (50%)	3 (19%)
Moderate	8 (47%)	2 (13%)	7 (44%)
Severe	1 (6%)	0	1 (6%)
Any Serious Adverse Event*	2 (12%)	1 (6%)	0
AF and CHF	1 (6%)	0	0
Leg cellulitis	1 (6%)	0	0
Dyspnea	0	1 (6%)	0

No lab safety signals of potential clinical concern attributed to study drug

Most frequent AEs: (n≥4 subjects)

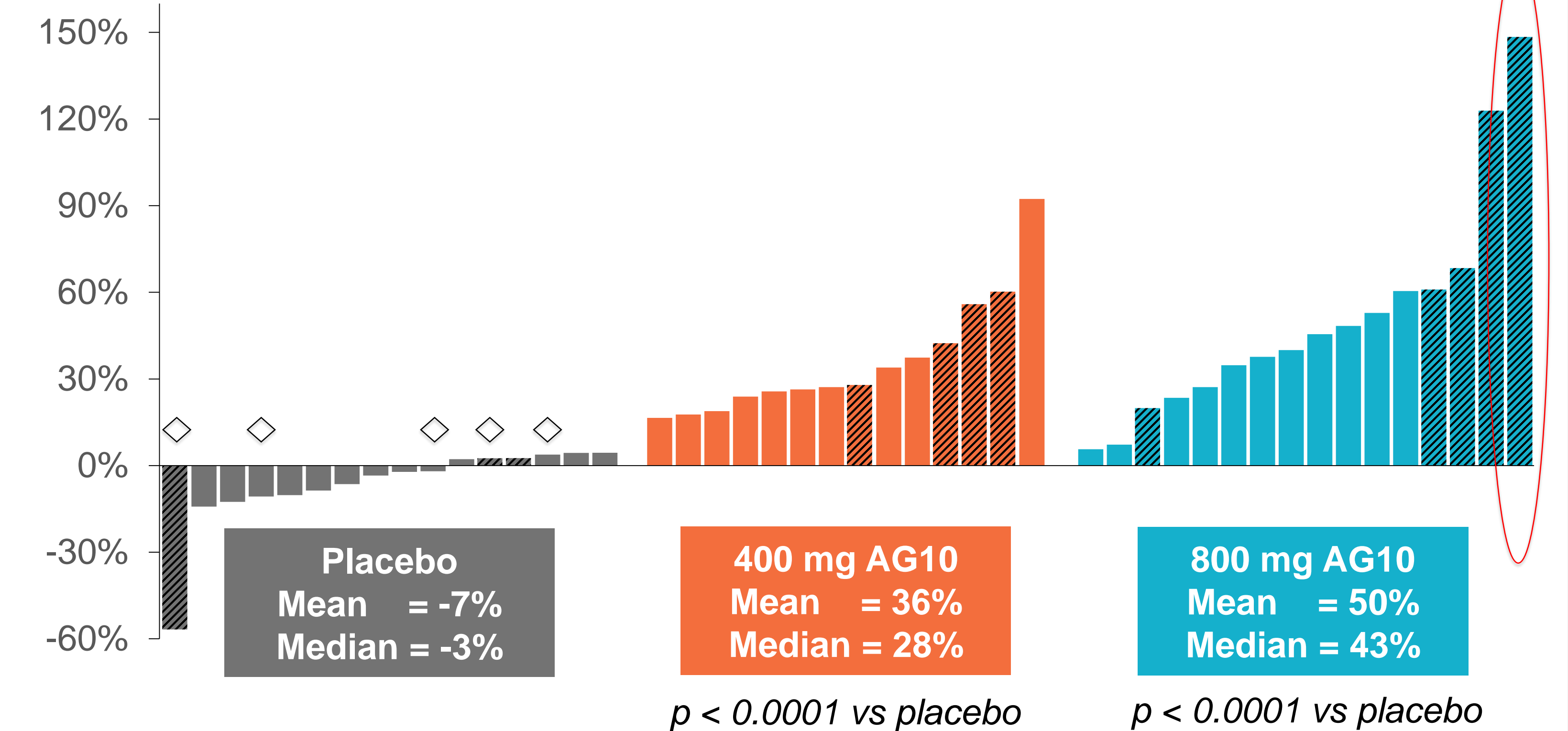
- AF
- Constipation
- Diarrhea
- Muscle spasms



Dose-responsive change in serum TTR – subject level data

Serum TTR concentration
Δ from baseline to day 28 (%)

ATTRwt-CM ATTRm-CM
Below normal TTR at Day 28¹



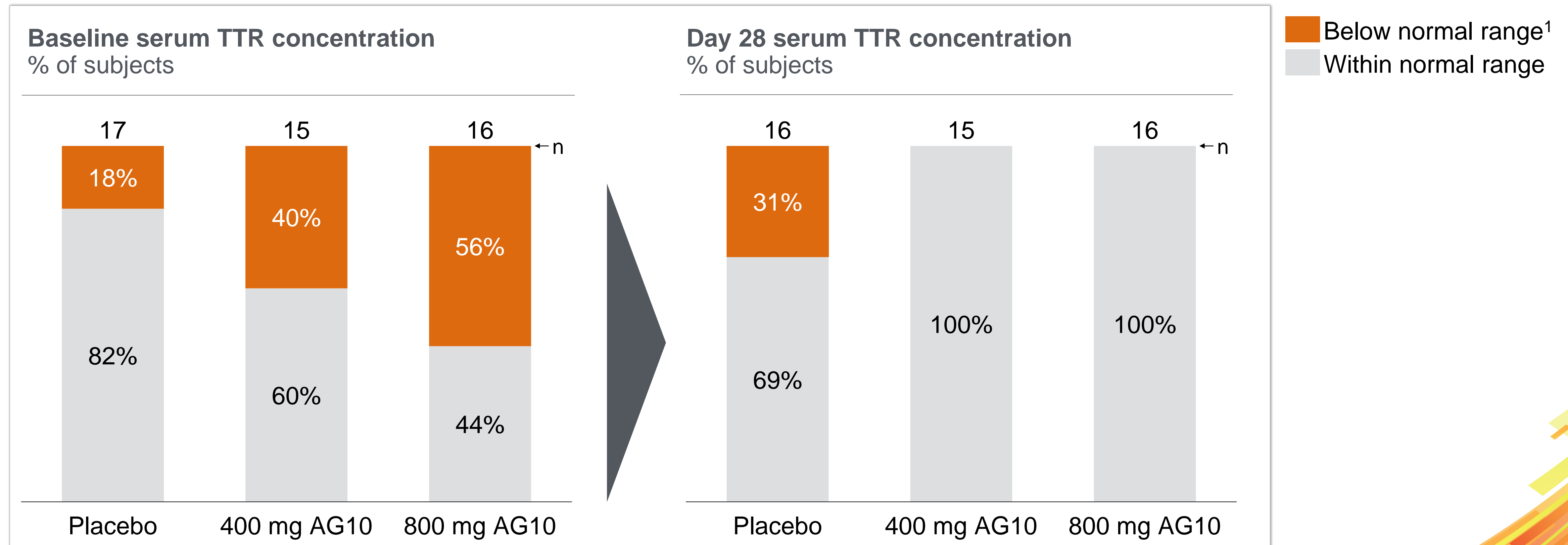
- Dose-dependent increase in serum TTR level with AG10 treatment
- Greater on-treatment effect observed in subjects with ATTRm-CM

Details for the participant with greatest improvement in serum TTR during the trial:

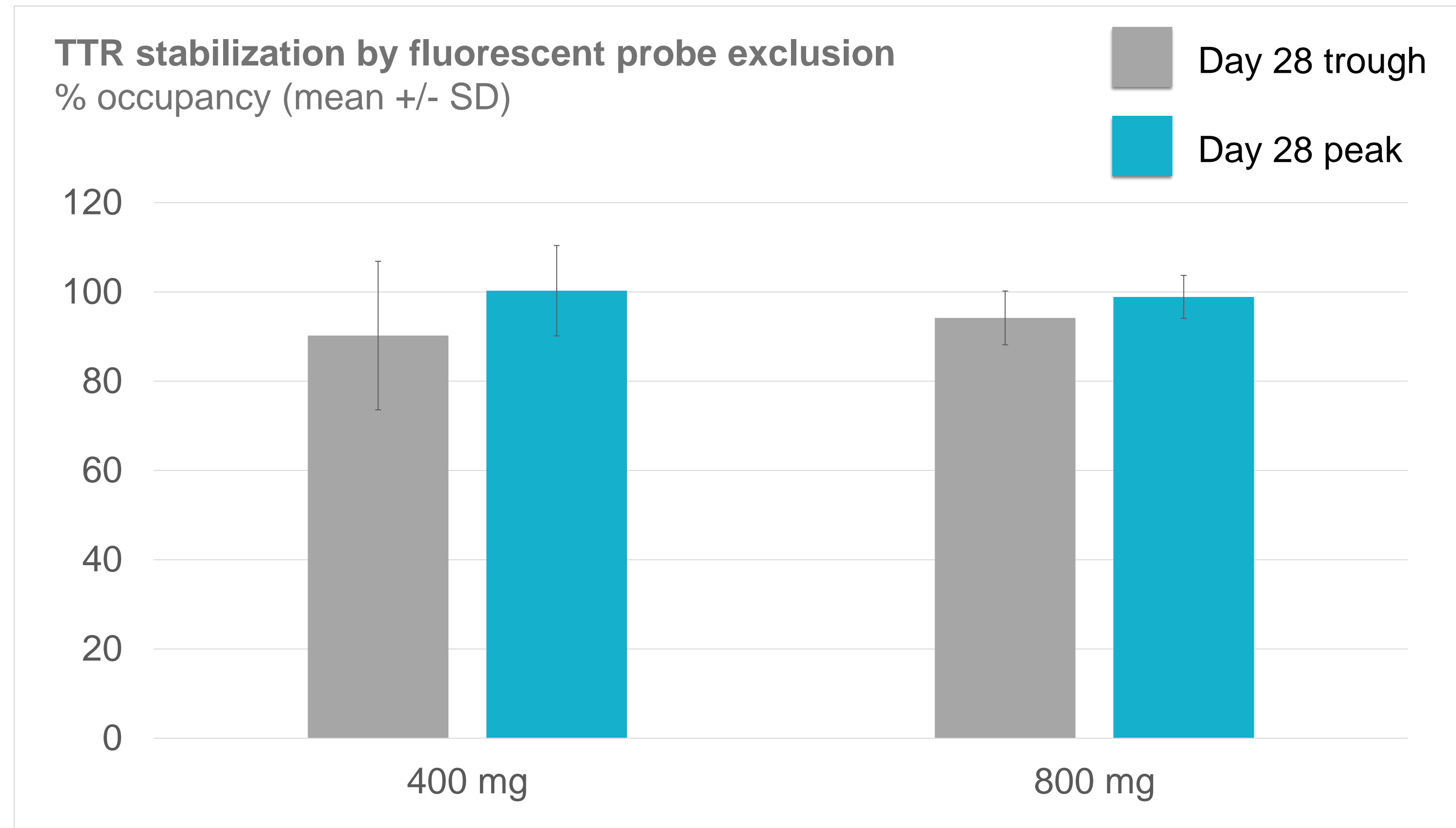
AG10 800 mg

- **86 year old African American female with ATTRm-CM (V122I, NYHA II)**
- **Baseline serum TTR level far below normal (9.5 mg/dL), increased 148% at Day 28**
- **Baseline NT-proBNP above normal (8059 pg/mL), dropped 22% at Day 28**
- **Experienced no moderate/severe AEs during treatment period**

AG10 treatment restores low TTR levels to the normal range in ATTR-CM subjects



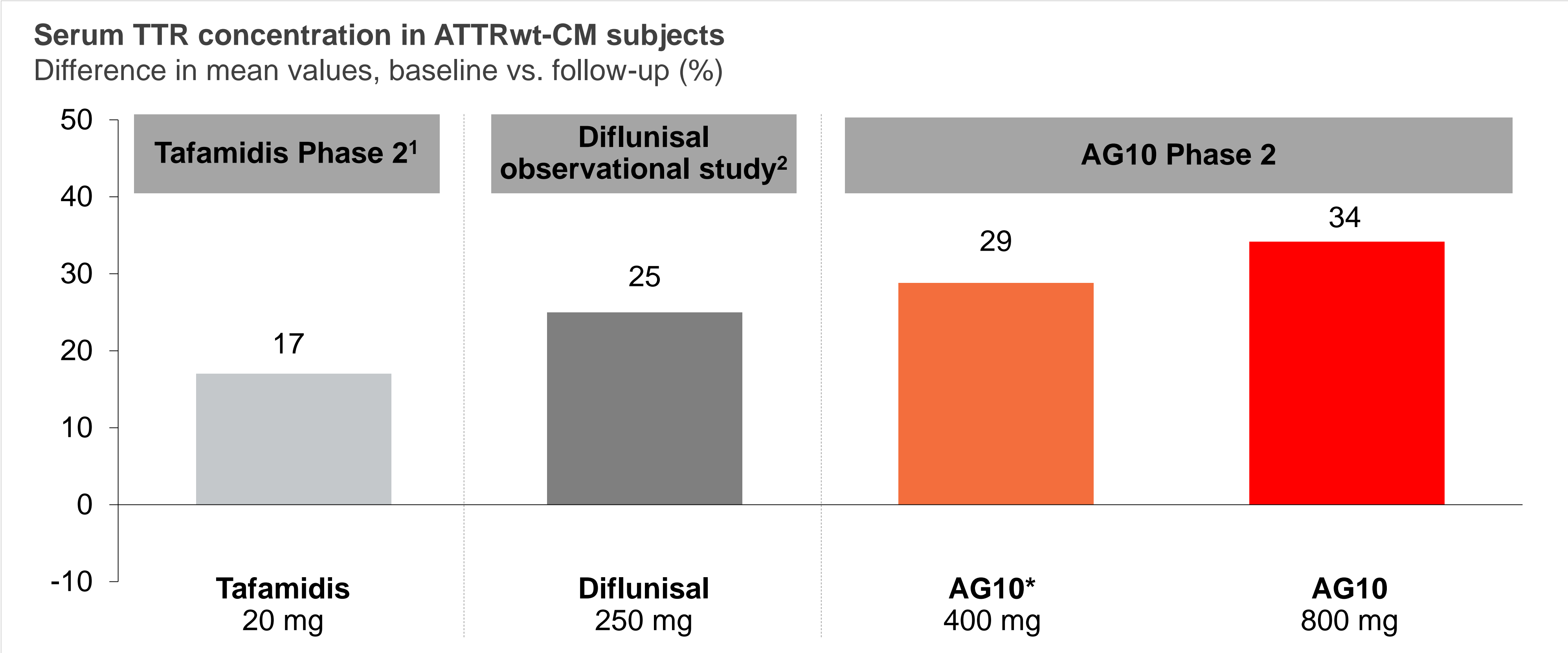
Ex vivo stabilization of TTR by AG10



Near-complete stabilization of TTR confirmed using ex vivo Western blot assay

- >90% average tetramer stabilization at Day 28 in AG10-treated subjects
- Response consistent across both wild-type and mutant TTR carriers

TTR stabilizers increase serum TTR in ATTRwt-CM subjects to varying degrees



Conclusions

- AG10 was well tolerated in symptomatic (NYHA II-III) ATTR-CM patients for 28 days without clinical or laboratory signals of potential clinical concern
- AG10 shown to be a potent, highly selective stabilizer of tetrameric TTR
 - AG10 mimics the T119M rescue mutation
 - AG10 400 mg and 800 mg stabilize TTR at >90% on average at day 28
- At day 28, AG10 400 mg and 800 mg increase serum TTR concentrations by 36% and 50%, respectively, and restore low TTR levels to normal in all ATTR-CM patients
- These results support the best-in-class potential of AG10 and its further clinical development in ATTR



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