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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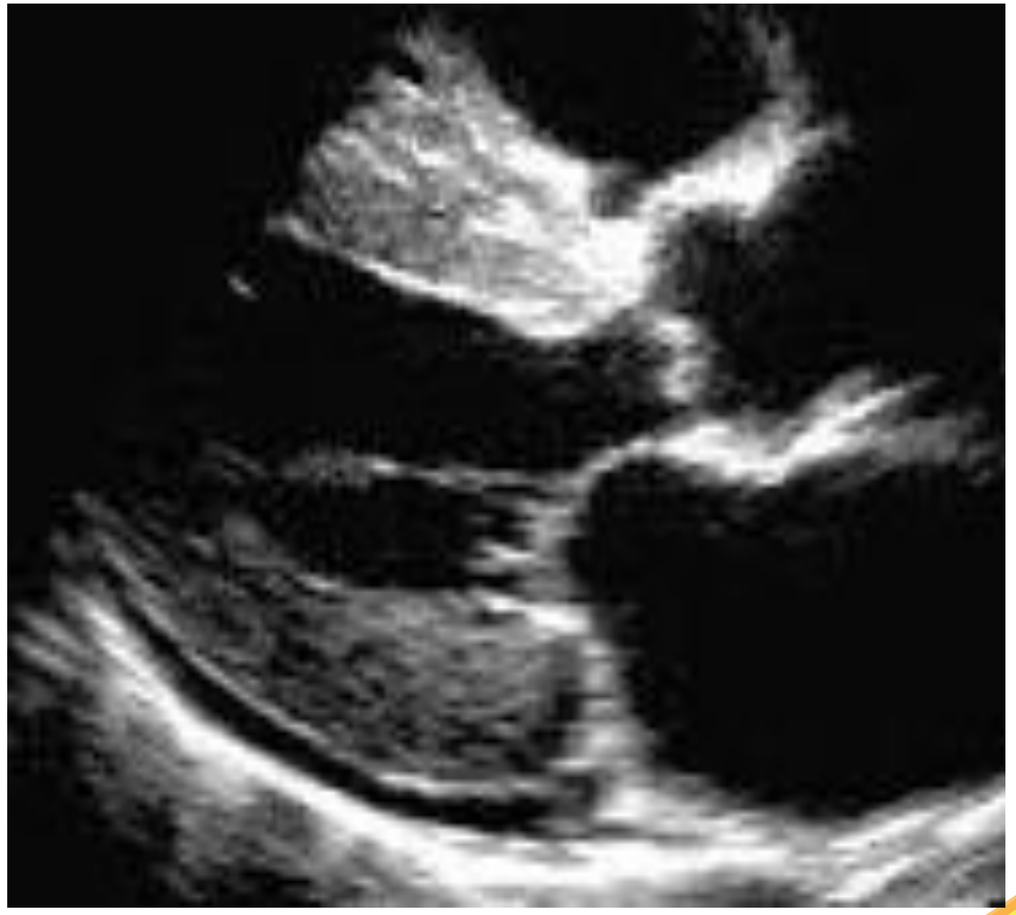
SCIENTIFIC 2018
SESSIONS

Daniel Judge presenting on behalf of the AG10 Phase 2 study investigators

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 patients[1]
  - 16% of patients undergoing TAVR[2]
  - 5% of patients with presumed hypertrophic cardiomyopathy[3]
  - 8% of patients undergoing bilateral carpal tunnel release surgery[4]



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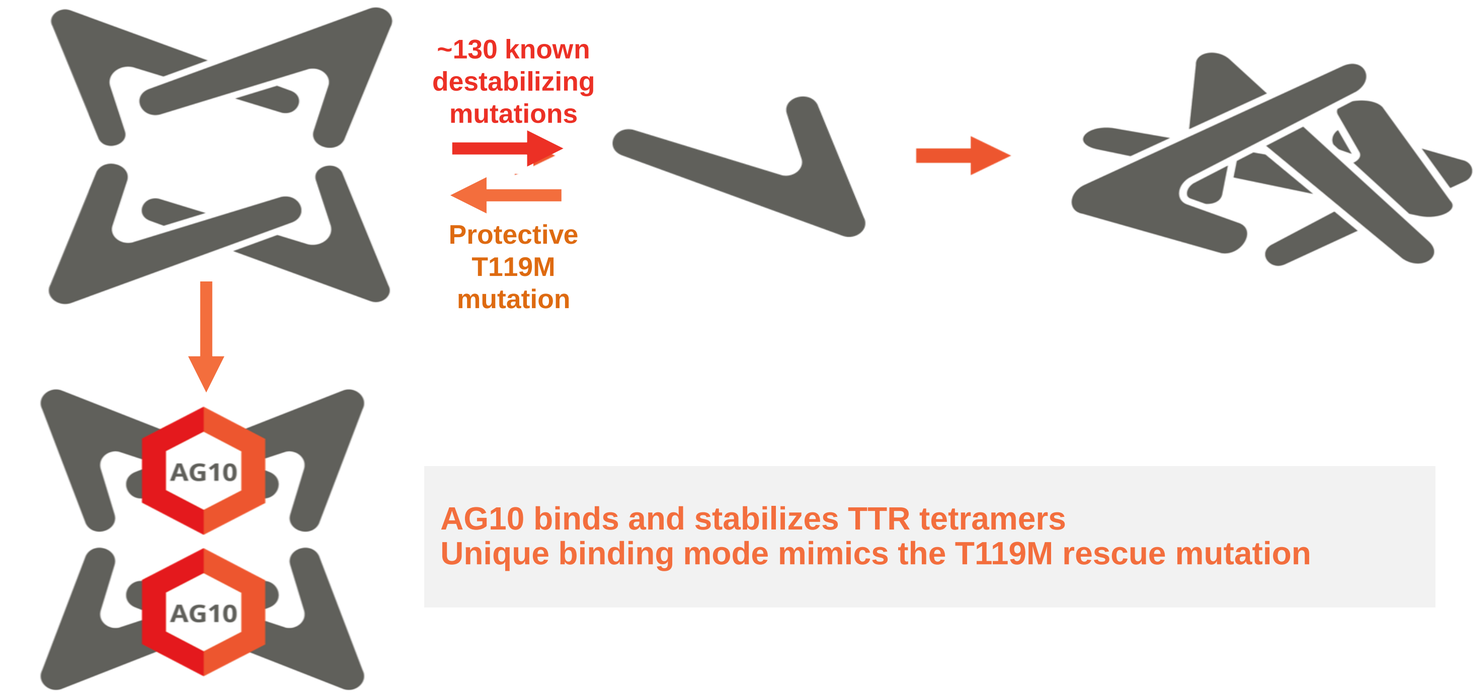
HFpEF = Heart Failure with Preserved Ejection Fraction; TAVR = Transcatheter Aortic Valve Replacement; Tc-PYP = Technetium pyrophosphate

1 Gonzalez-Lopez, E. et al. Eur Heart J., 2015, 36(38):2585-94
2 Castano, A. et al. Eur Heart J., 2017, 38(38):2879–87
3 Damy, T. et al. Eur Heart J., 2015, 37:1826-34
4 Sperry, B.W. et al. JACC, 2018, 72(17):2040-50

ATTR-CM mechanism

Disease mechanism and therapeutic hypothesis



AG10 binds and stabilizes TTR tetramers
Unique binding mode mimics the T119M rescue mutation

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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

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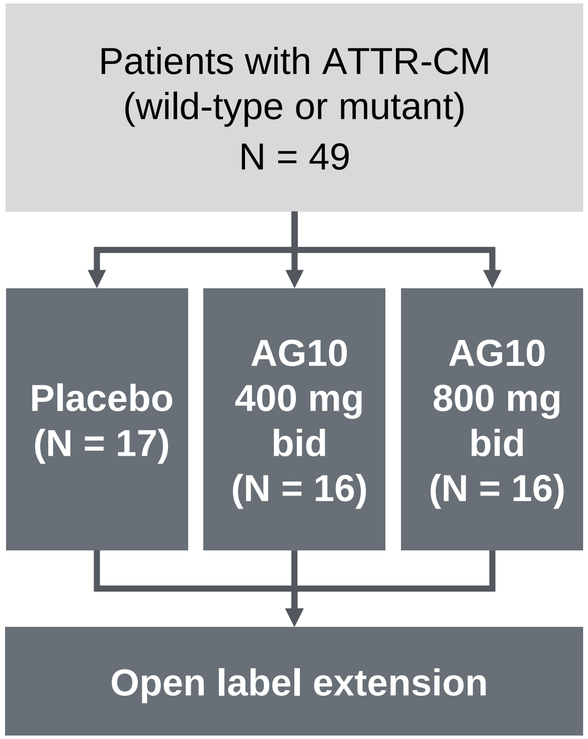
Source: Hellawell J. et al., Heart Failure Society of America, 2018.

Phase 2 study design

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



Key inclusion criteria

- Confirmed ATTR-CM by scan or biopsy, NYHA Class II or III symptoms
- ≥1 prior heart failure hospitalization or clinical evidence of heart failure

Primary endpoint: safety and tolerability

Secondary endpoints:

- Pharmacokinetics (achieving target plasma concentrations)
- Change in serum TTR concentration (biomarker of drug activity)
- TTR stabilization by fluorescent probe exclusion and Western blot

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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)

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1 NT-proBNP normal range = 0 – 449 pg/mL
2 Troponin I normal range = 0 – 0.02 ng/mL
3 TTR normal range = 20-40 mg/dL

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**

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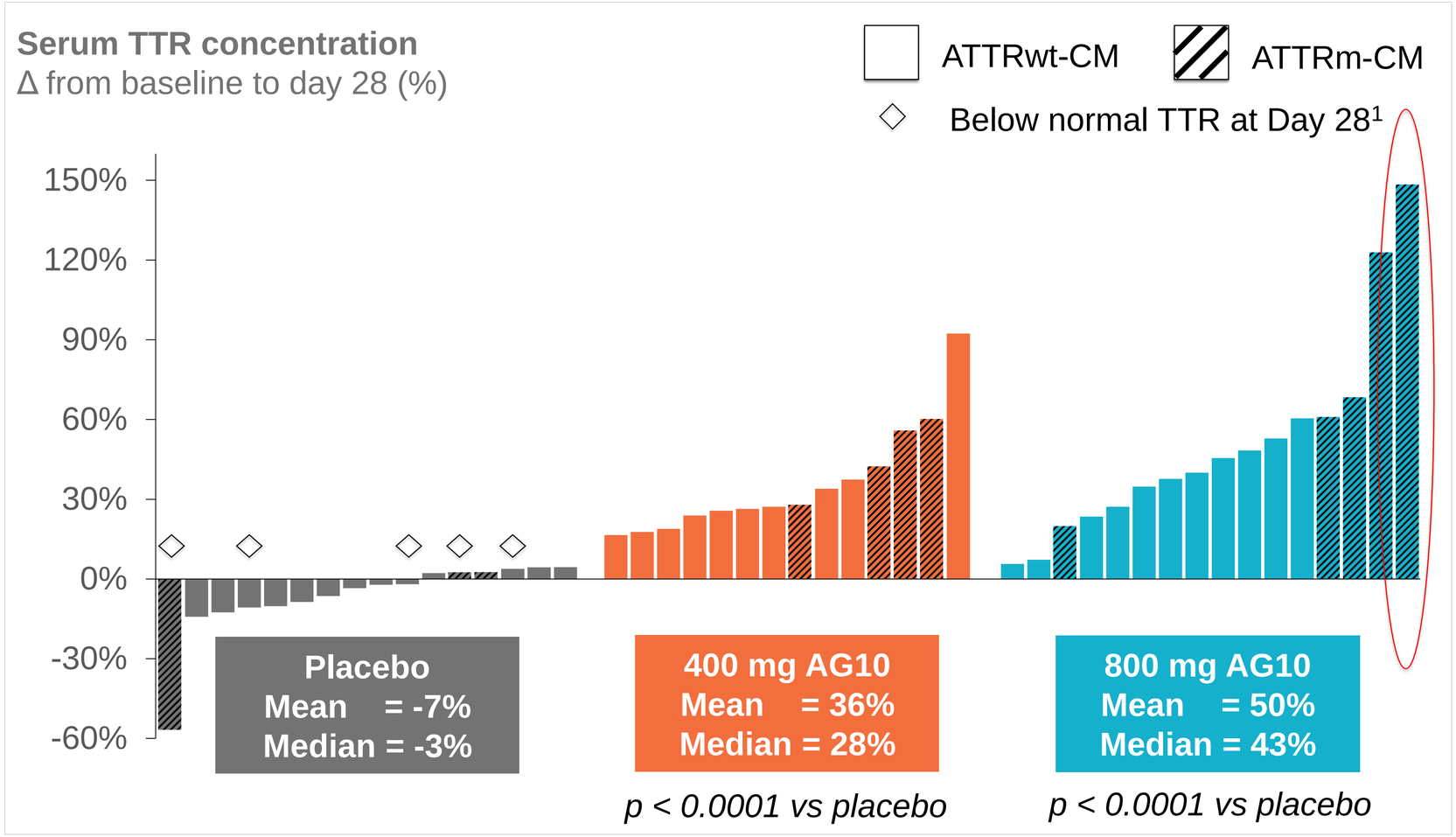
AF = Atrial Fibrillation; CHF = Congestive Heart Failure
* None considered related to study drug
† Acute kidney injury, unlikely related; deafness, neurosensory, unlikely related

Dose-responsive change in serum TTR – subject level data



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

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1 Normal reference range for serum TTR 20-40 mg/dL (3.6-7.3 µM)
Note: Serum TTR concentrations not available at baseline for one 400 mg subject and at Day 28 for one 400 mg and one placebo subject

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

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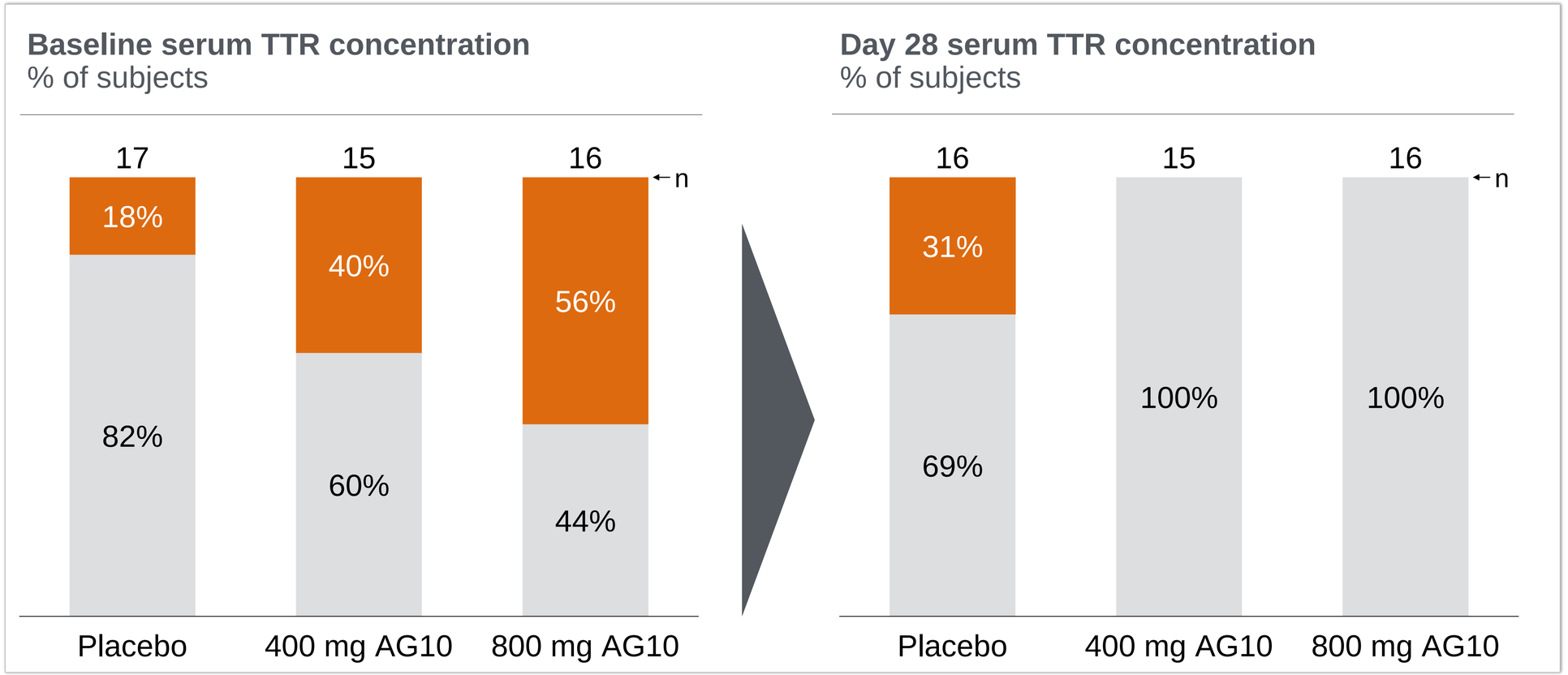
AG10 treatment restores low TTR levels to the normal range in ATTR-CM subjects



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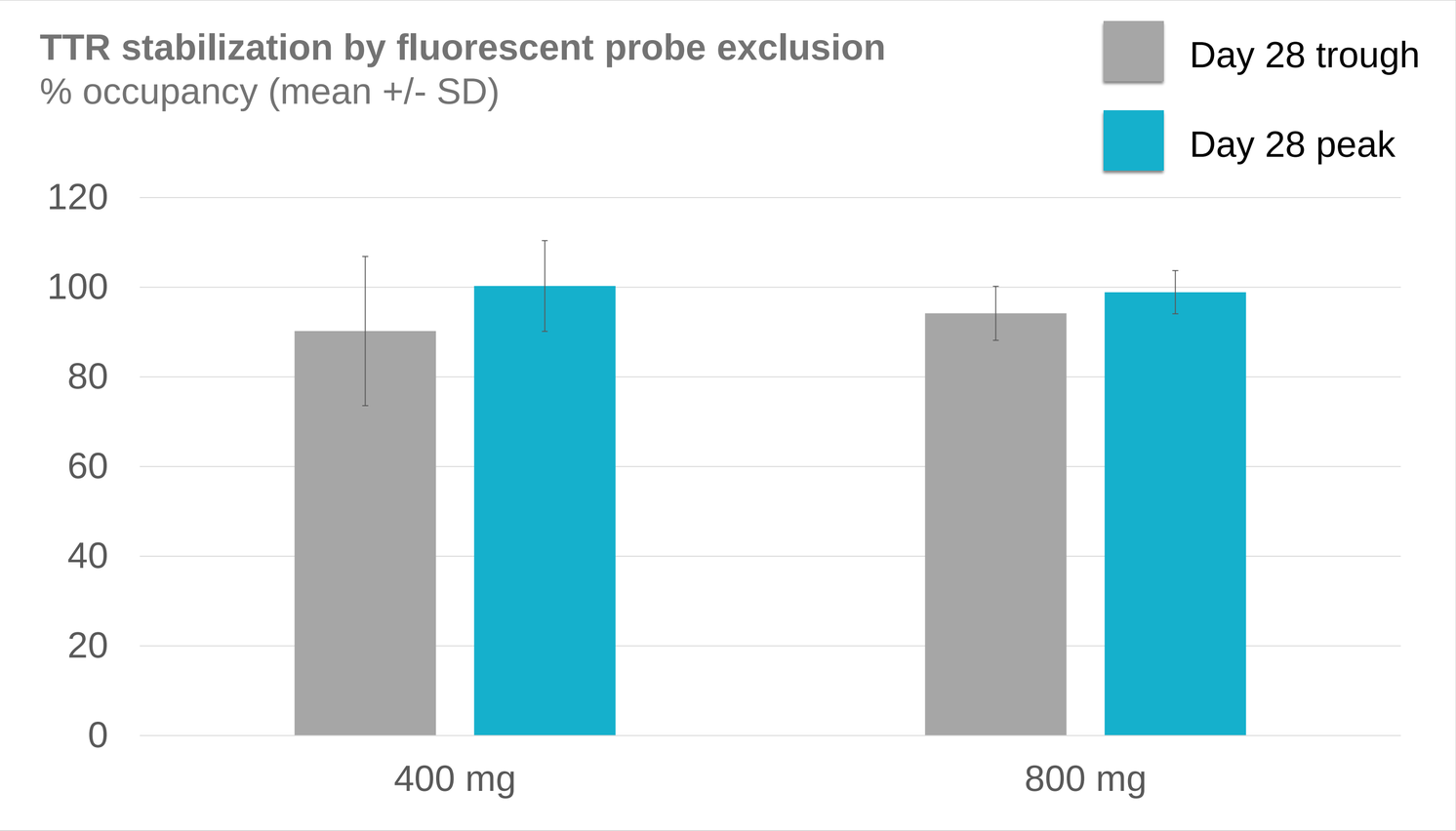
Note: Serum TTR concentrations not available at baseline for one 400 mg patient, at Day 28 for one 400 mg and one placebo patient

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

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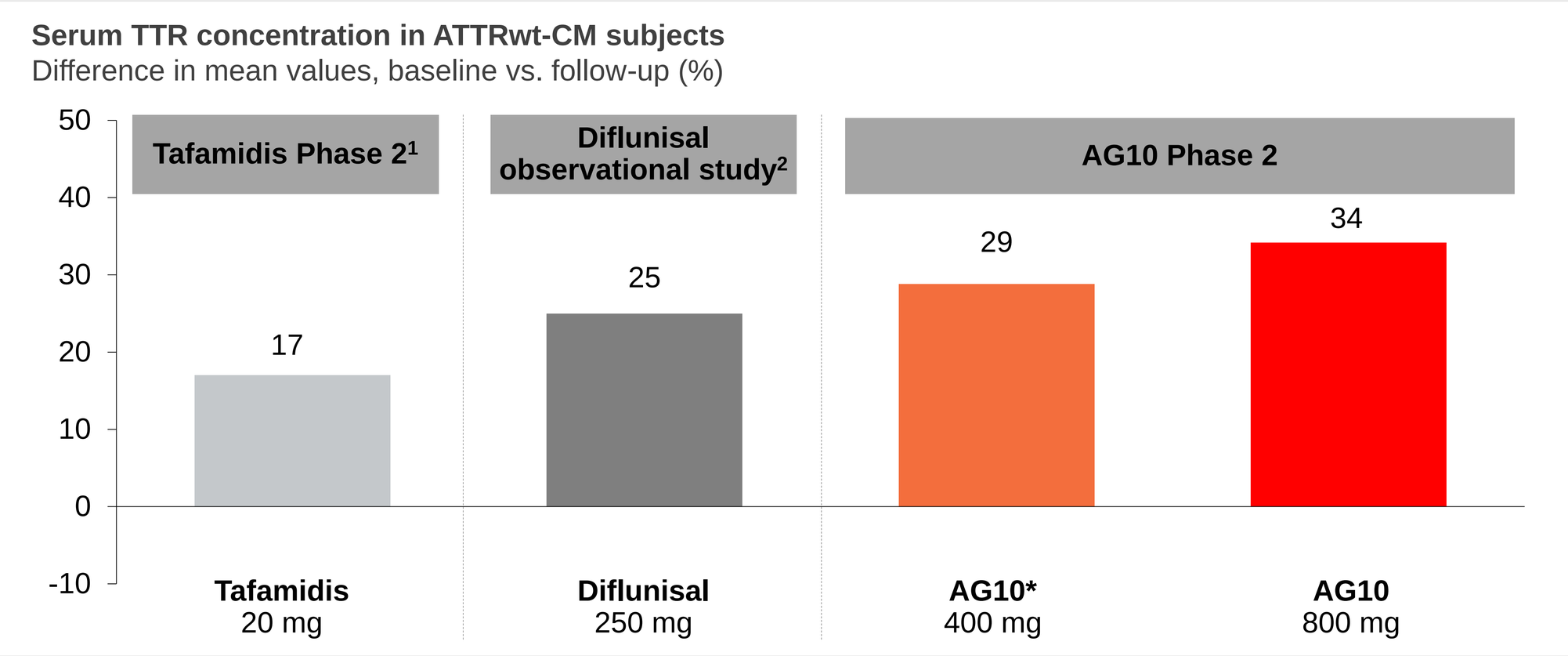
TTR stabilizers increase serum TTR in ATTRwt-CM subjects to varying degrees



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Note: Direct cross-study comparisons may suggest misleading similarities or differences. The values shown are directional and do not report robust comparative analysis.

* Serum TTR concentrations not available at baseline for one 400 mg subject and at day 28 for another 400 mg subject

1 Data shown from 28 day follow-up (FDA CDER Advisory Committee Meeting background package)

2 Data shown from 1 year follow-up (Hanson, J.L.S. et al. Circ Heart Fail 2018 11:e004000)

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

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