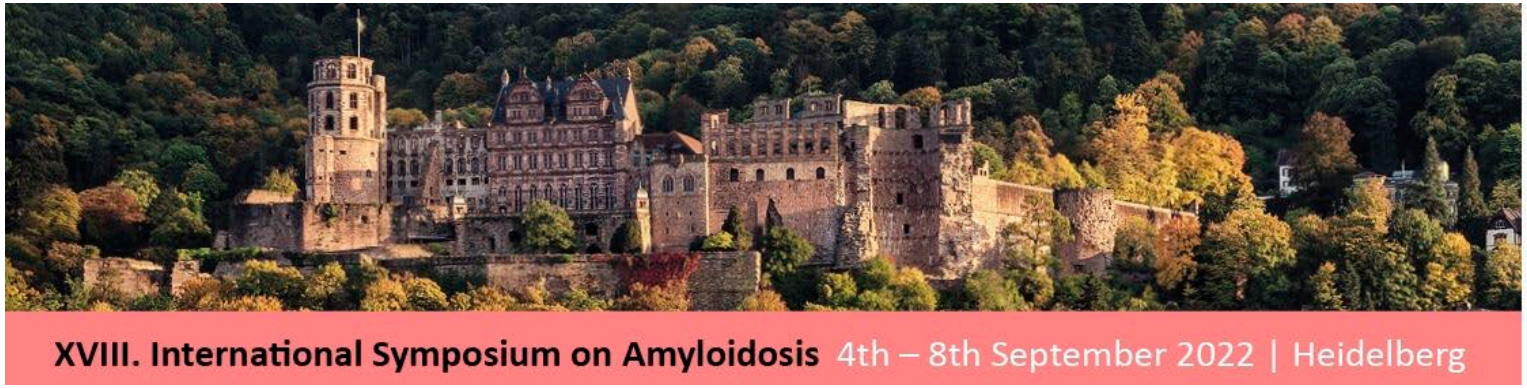

ISA 2022

Long-term safety and tolerability of acoramidis (AG10) in symptomatic transthyretin amyloid cardiomyopathy: Updated analysis from an ongoing phase 2 open-label extension study

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Presented by Dr. Ahmad Masri on behalf of investigators

Disclosures

- Research Grants from: Pfizer, Akcea, Ionis, Ultromics, and the Wheeler Foundation.
- Consulting fees and/or honoraria from: Eidos, Pfizer, Ionis, BMS, Attralus, Tenaya, Alnylam and Cytokinetics.

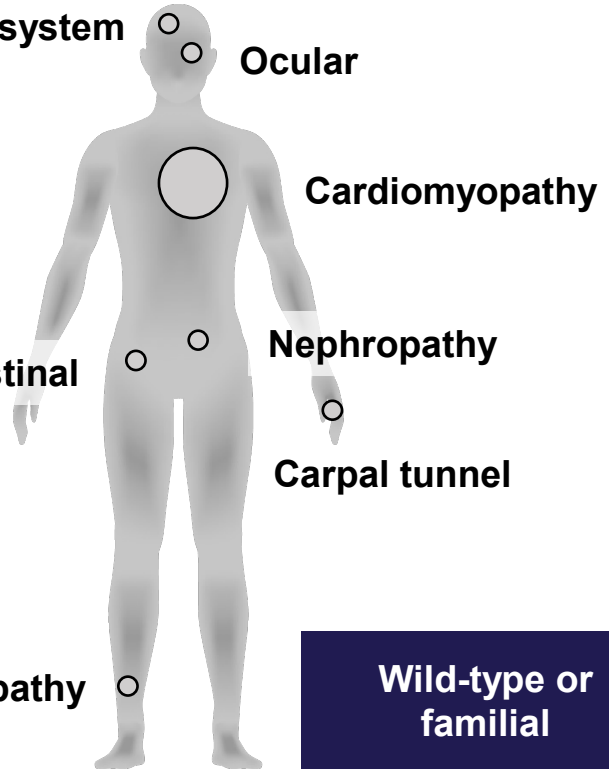
- ENCORE abstract presentation. Data first presented at ACC 2022.

- The presentation includes several slides on the phase 2 and phase 3 program of acoramidis which were provided by Eidos/BridgeBio.

- Acoramidis is an investigational agent that is not approved for use by any regulatory agency as efficacy and safety have not been established.

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

ATTR is a systemic disease



Wild-type or familial

Growing awareness of undiagnosed ATTR:

10-13% of heart failure with preserved ejection fraction[1,2,3]

7% of idiopathic bilateral carpal tunnel release[4]

5% of suspected hypertrophic cardiomyopathy[5*]

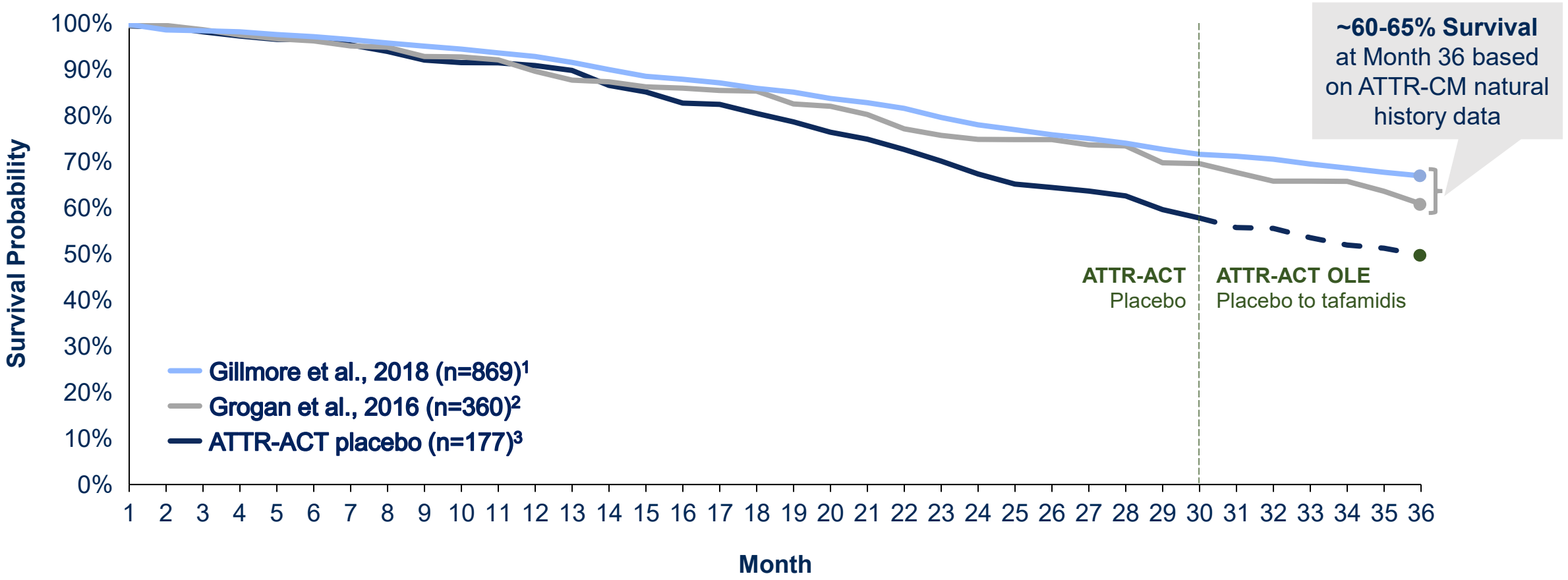
ATTR pathogenesis and therapeutic strategies:

- 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 acoramidis[7]

*Mutant TTR only

References: 1. Gonzalez-Lopez E. et al. *Eur Heart J* 2015 Oct. 7;36 (38): 2585-94. 2. Mohammed SF, et al. *JACC: Heart F*ailure 2014 Apr 2 (2):114-22 3. Hahn VS, et al. J*ACC Heart Failure* 2020 Sept 8 (9):712-724. 4. Sperry BW et al. 2018 JACC Oct 23;72 (17):2040-2050. 5. Damy T, et al. *Eur Heart J* 2016 Jun 14;37(23): 1826-34. 6. Sant'Anna R, et al. 2017 Sci Rep. March 24:7:44709. 7. Miller et al., J Med Chem 2018 Sep 13;61(17):7862-7876.

ATTR-CM is a rapidly progressive and fatal disease



Note: Survival probabilities estimated via plot digitization.

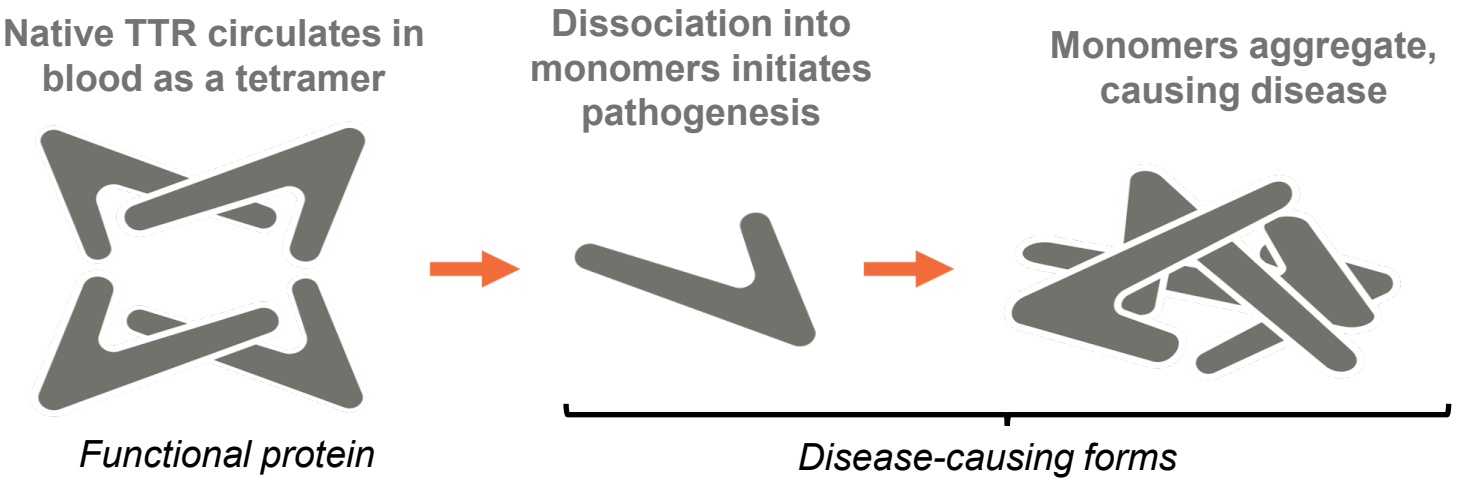
1. Gillmore JD et al. *Eur Heart J*. 2018;39(30):2799-2806 2. Grogan M. et al., *JACC* 2016; 68:1014–1020 3. Elliott P. et al, *Circulation: Heart Failure* 2022; 15(01):e008193

[1]Survival data digitized using NT-proBNP subgroups plots (>3,000 pg/mL or ≤3,000 pg/mL). Blended survival curve forecasted based on the patient distribution across NT-proBNP strata at baseline.

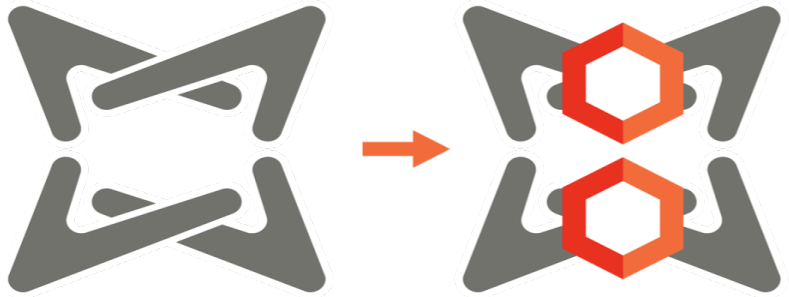
[2]Grogan cohort includes wildtype ATTR-CM only.

Acoramidis was designed to mimic a naturally occurring TTR variant that protects carriers from ATTR development

Disease mechanism



Therapeutic hypothesis

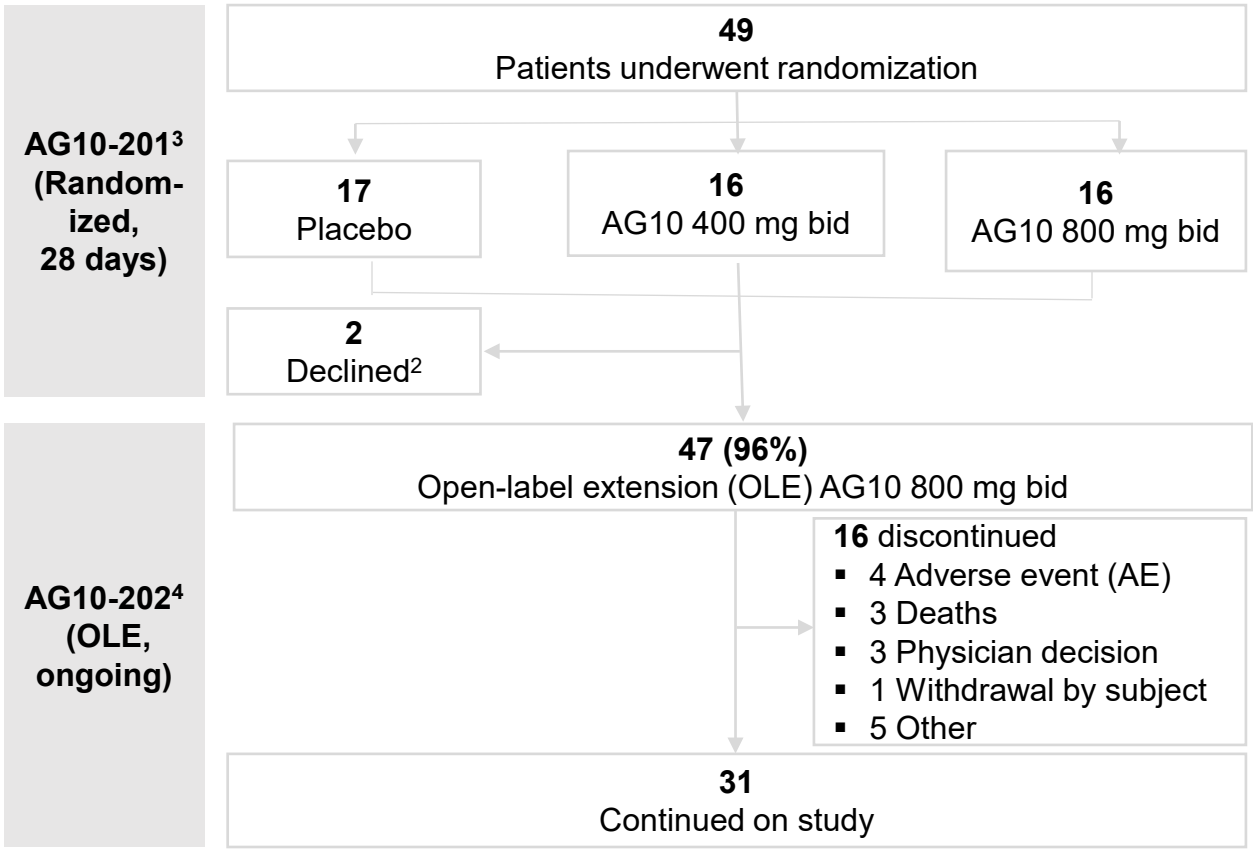


- **Acoramidis is an investigational, highly selective, and potent stabilizer of TTR that was designed to mimic the T119M rescue mutation[1,2]**
- **Acoramidis has the potential to become a disease-modifying treatment for patients with either ATTRv or ATTRwt**

References: 1. Miller et al., J Med Chem 2018 Sep 13;61(17):7862-7876 2. Hammarstrom P, et al. Proc Natl Acad Sci U S A. 2002;99:16427-16432

Acoramidis Phase 2 design

Schematic of acoramidis Phase 2 as of August 31, 2021[1]



Patient selection and objectives

Selected inclusion criteria

- **Established diagnosis of ATTR-CM**
- **NYHA class II or III symptoms**
- **≥1 prior hospitalization for heart failure or clinical evidence of heart failure**

Primary and secondary objectives

- **Safety and tolerability**
- **Pharmacokinetics**
- **Pharmacodynamics**

- **Consort diagram reflects status of participants as of August 31, 2021 or study discontinuation**
- **Overall, AEs with an outcome of death, cardiac transplant or transition to hospice were reported for 11 participants**

[1]Median 38 months from initial Phase 2 randomization. Median 35 months on open-label acoramidis
[2]Both declined participation due to geographical constraints regarding study visits.
[3]Clinicaltrials.gov identifier: NCT03458130
[4]Clinicaltrials.gov identifier: NCT03536767

No safety signals of clinical concern identified in Phase 2 OLE

Summary of treatment-emergent adverse events
Number of participants (%)

Any treatment-emergent adverse event	**47 (100)**
Most common adverse events (≥ 9)	
Fall	21 (44.7)
Acute kidney injury	12 (25.5)
Cardiac failure congestive	10 (21.3)
Arthralgia	9 (19.1)
Cardiac failure acute	9 (19.1)
Constipation	9 (19.1)
Dyspnea	9 (19.1)
Fatigue	9 (19.1)

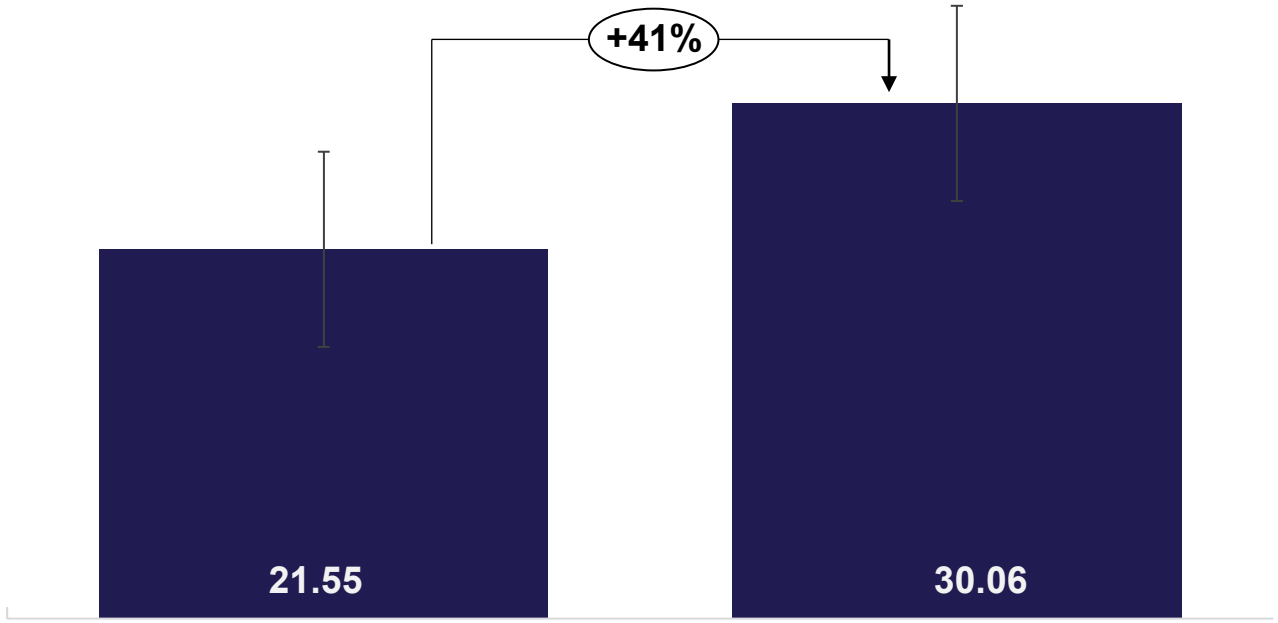
Summary of serious treatment-emergent adverse events
Number of participants (%)

Any serious treatment-emergent adverse event	**31 (66.0)**
Most common serious adverse events (≥ 4)	
Cardiac failure acute	9 (19.1)
Acute kidney injury	7 (14.9)
Cardiac failure congestive	5 (10.6)
Fall	5 (10.6)
Cardiac failure	4 (8.5)
Cardiogenic shock	4 (8.5)
Cardiorenal syndrome	4 (8.5)

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

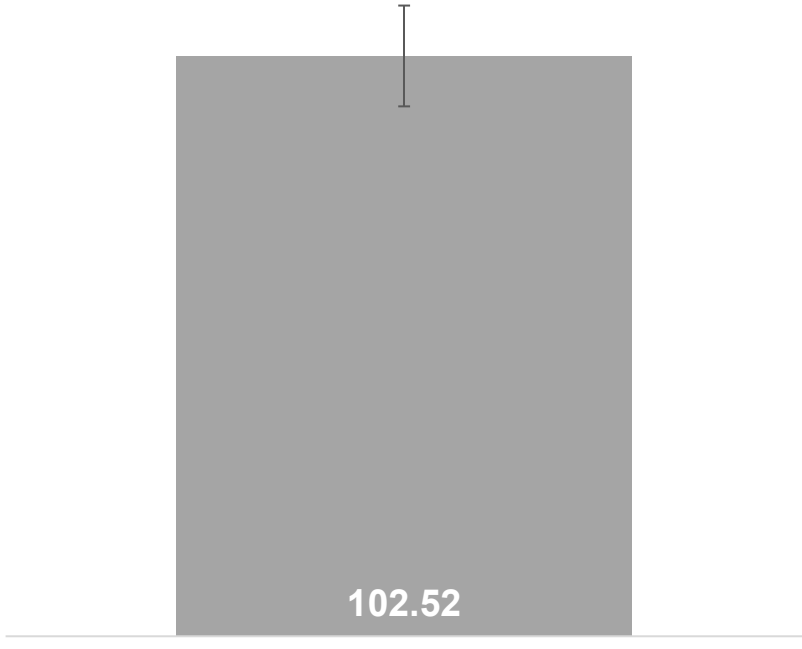
Acoramidis increased serum TTR levels and provided near-complete TTR stabilization

Serum TTR concentration
Mean +/- SD (mg/dL)



N	47	21

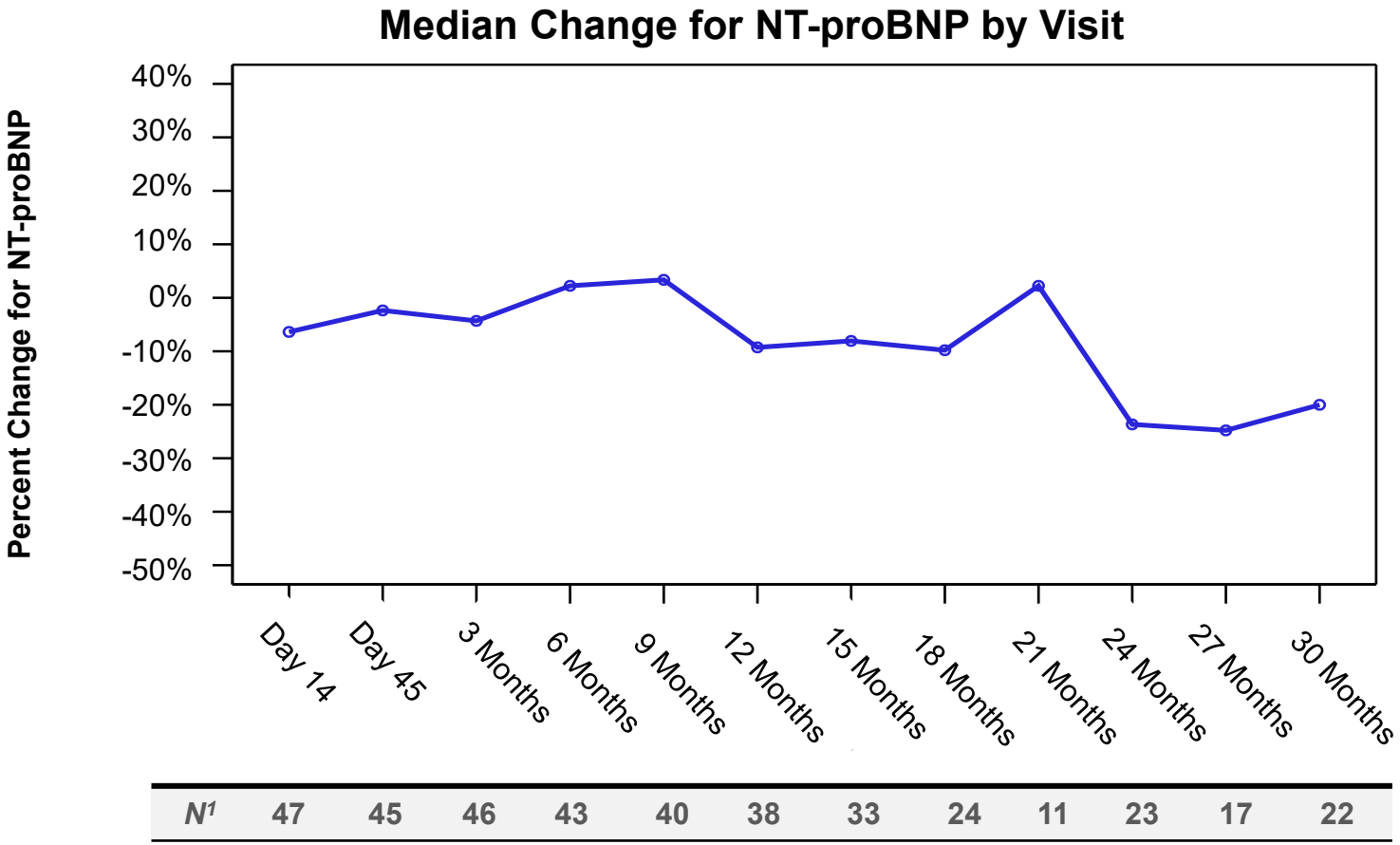
TTR stabilization by FPE[1]
Mean +/- SD (%)



N	23

Serum TTR concentration reference range: 20-40 mg/dL
[1]Fluorescent Probe Exclusion; percent target engagement at baseline is zero

Median NT-proBNP was stable or improving at all time points beyond Month 12



- **At Month 30, median change from baseline was -437 pg/mL [-950, 316]**
- **At Month 30, 15/22 (68%) participants had NT-proBNP levels below their baseline[1]**

Note: Based on Study AG10-202 data cut on Aug. 31, 2021.
Baseline defined as the date of the first dose of acoramidis.
NT-proBNP was a reported laboratory parameter, not a pre-specified safety endpoint.
[1]Represents all evaluable data from participants who continued in the study

Summary of acoramidis Phase 2 OLE results

1 **Safety and tolerability**

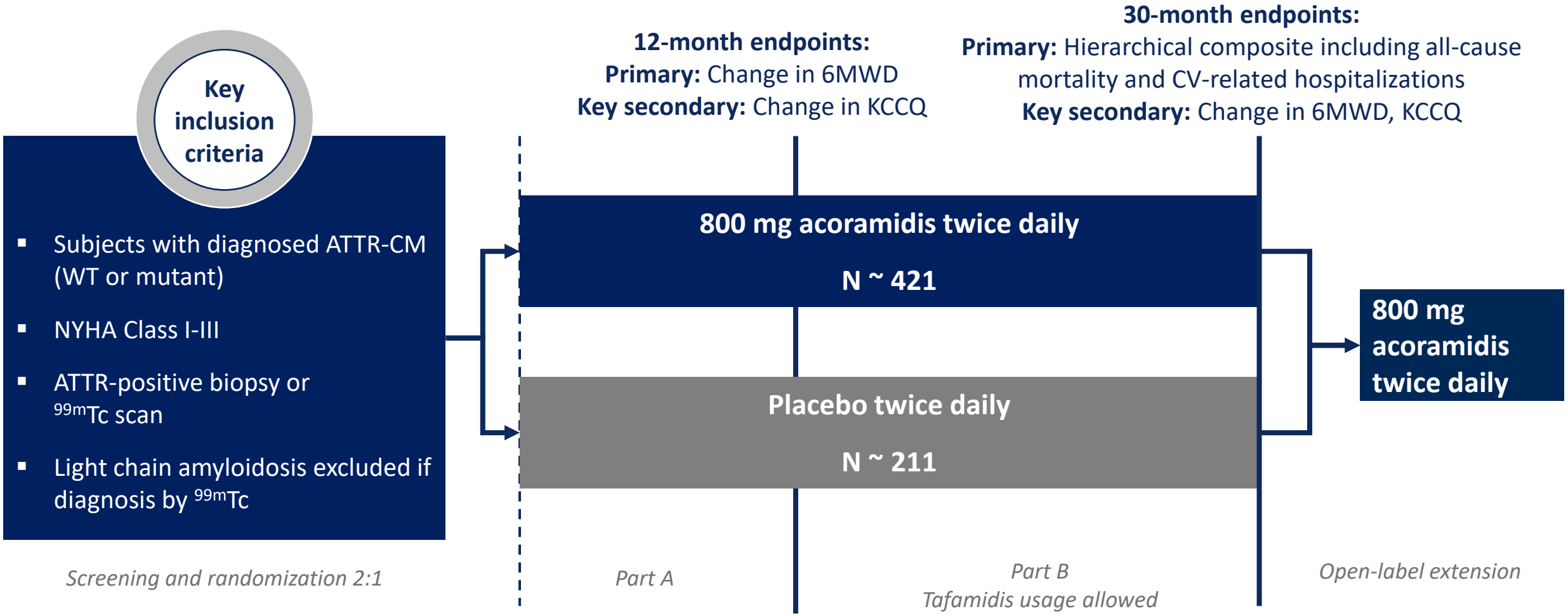
- Adverse event profile consistent with baseline disease severity and progression
- No signals of concern observed with median participation of 38 months

2 **Cardiac biomarkers**

- Sustained stabilization of TTR demonstrated by increased serum concentrations and ex vivo assays
- Median NT-proBNP was stable or declining at all time points beyond Month 12

Phase 2 OLE data and ongoing participation through 3 years support further development of acoramidis in ATTR-CM; evaluation in a Phase 3 trial is ongoing (ATTRibute-CM)

ATTRibute-CM Phase 3 design includes primary endpoints at Month 12 and Month 30



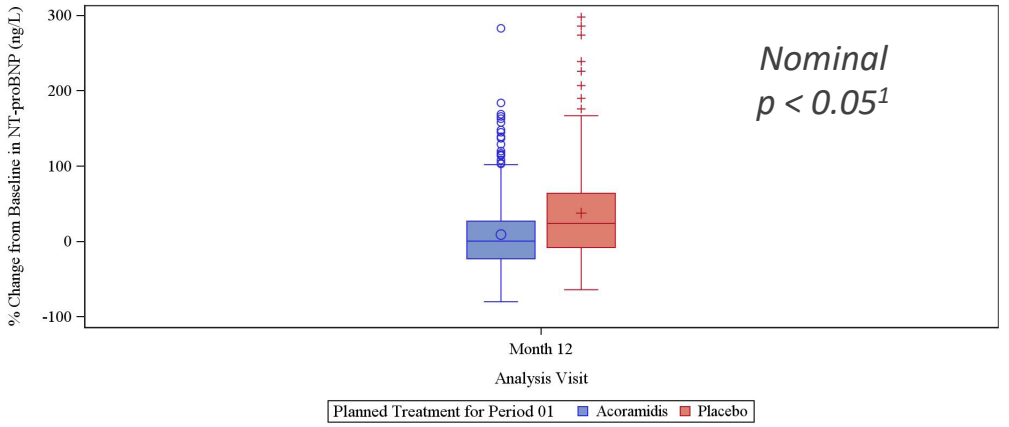
6MWD = six-minute walk distance; ^{99m}Tc = Technetium radiolabel; CV= cardiovascular; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.
Source: Clinicaltrials.gov identifier: NCT03860935

Summary of Month 12 results

Based on data available at Month 12, acoramidis demonstrated relative to placebo:

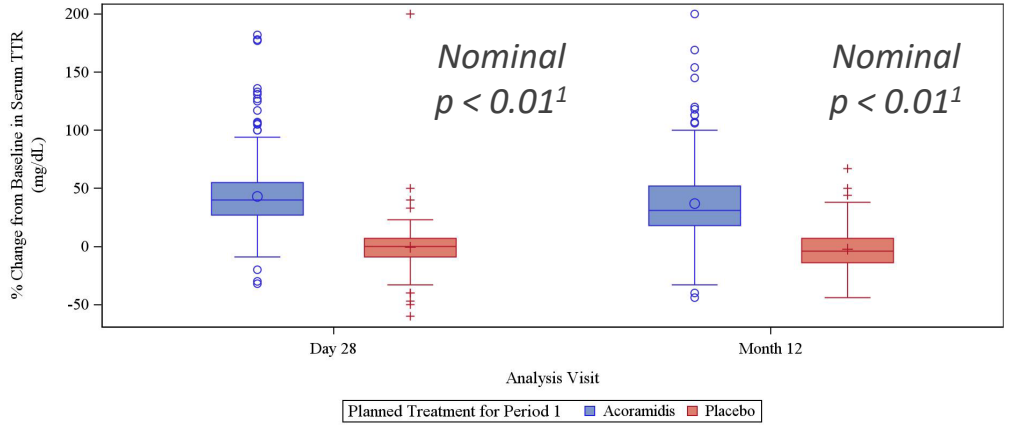
- ▪ No improvement in 6MWD
- ✓ Improvement in KCCQ (nominal p < 0.05)
- ✓ Improvement in NT-proBNP (nominal p < 0.05)
- ✓ Increased serum TTR levels (nominal p < 0.01)
- ✓ No safety signals of clinical concern

Percent change from baseline in NT-proBNP [2]



Note: to facilitate a focused review of the vast majority of the data, outliers greater than 300% change from baseline are not included in this plot.

Percent change from baseline in serum TTR[2]



Note: to facilitate a focused review of the vast majority of the data, outliers greater than 200% change from baseline are not included in this plot.

Source: BridgeBio press release published 12/27/2021

[1]Inference analysis (p-value) based on absolute change from baseline between groups

[2] Modified intent-to-treat (mITT) population defined as all randomized subjects who have received at least one dose of IMP and have at least one post baseline efficacy evaluation. mITT population pre-specified to exclude subjects with baseline eGFR < 30 mL/min/1.73 m^2

Acknowledgements

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Phase 2 investigators	
Mandar Aras, MD *University of California San Francisco*	**Rodney Falk, MD** *Brigham and Women's Hospital*
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Mat Maurer, MD *Columbia University*	**Sanjiv Shah, MD** *Northwestern University*
Ronald Witteles, MD *Stanford University*	