AG10 in patients with transthyretin amyloid cardiomyopathy (ATTR-CM): Further analyses of 15-month follow-up of Phase 2 open label extension

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Background

- Transthyretin (TTR) amyloidosis (ATTR) is an under-diagnosed cause of heart failure driven by TTR destabilization due to pathogenic mutations and/or aging.[1]
- ATTR-CM occurs when TTR fibrils aggregate and deposit in the myocardium, resulting in an infiltrative, restrictive cardiomyopathy characterized by both right and left heart failure.[2,3]
- AG10 is a highly selective and potent oral stabilizer of TTR under development for the treatment of patients with either mutant or wild-type ATTR cardiomyopathy.[4,5]
- In a randomized, double-blind Phase 2 study in patients with symptomatic ATTR cardiomyopathy (ATTR-CM), AG10 was well tolerated, demonstrated near-complete stabilization of TTR, and increased serum TTR levels to normal in all treated subjects.[5]
- Results of the open-label extension (OLE) of that Phase 2 study are shown here, reported as of August 31st, 2019 in conjunction with annual regulatory reporting and review.

AG10 Phase 2 Program

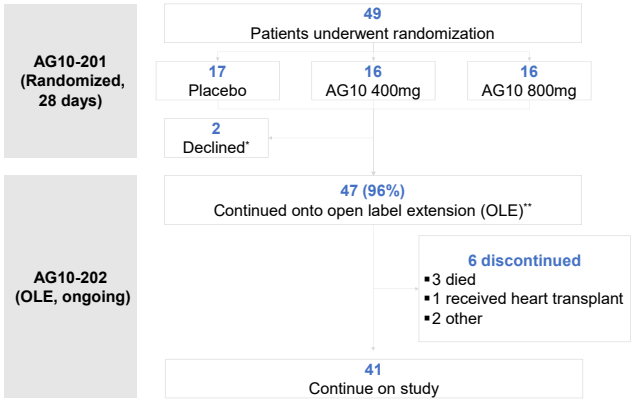

Figure 1. Schematic of AG10 Phase 2 Program

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

AG10 Phase 2 OLE Study Overview

Primary Outcomes

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

Secondary and Exploratory Outcomes

- Pharmacokinetics
- Pharmacodynamics
- Echocardiographic parameters

Length of Observation through August 31, 2019

- Median 65 weeks from AG10-201 (randomized study) initiation
- Median 53 weeks on AG10

Baseline Characteristics of Phase 2 Program

	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)*	3151 ± 2704	3483 ± 2869	3368 ± 2789
TnI (ng/mL)**	0.18 ± 0.33	0.15 ± 0.20	0.16 ± 0.25
TTR (mg/dL)†	23.4 ± 5.5	21.3 ± 5.3	22.0 ± 5.4

* NT-proBNP = N-Terminal pro B-type Natriuretic Peptide, normal range = 0 – 449 pg/mL
** TnI = troponin I, normal range = 0 – 0.02 ng/mL
† TTR = transthyretin (prealbumin), normal range = 20 – 40 mg/dL

Safety and Tolerability of AG10

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 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)

Select Pharmacodynamic Measures

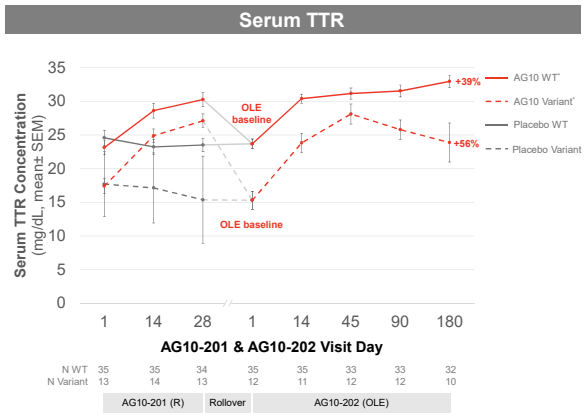

Figure 2. Serum TTR levels increased upon AG10 treatment and maintained throughout Phase 2 program

* 400mg and 800mg BID AG10 groups from randomized component of Phase 2 program shown as pooled

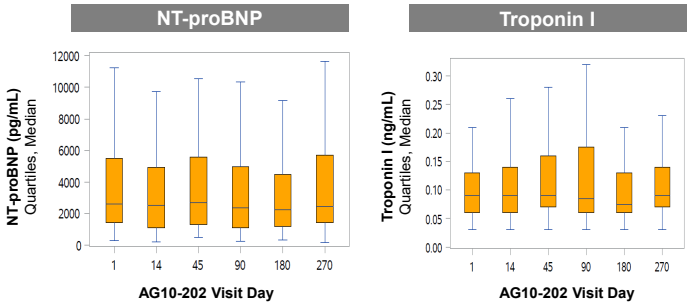

Figure 3. NT-proBNP and Troponin I levels remained unchanged in AG10-treated subjects throughout OLE

Note: Outliers (observations >1.5 x IQR away from the nearest quartile) are not included in the plot.

Observed Mortality and Cardiac Transplants

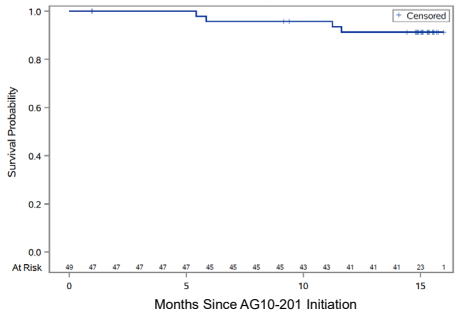

Figure 4. 8.5% of subjects who initiated the OLE study either died or received a heart transplant as of August 31st, 2019 based on adverse event reporting

Conclusions

- Adverse event profile of AG10 is consistent with ATTR-CM disease severity.
- Durable treatment-dependent increase in serum TTR observed throughout Phase 2 program.
- Stabilization of disease biomarkers including NT-proBNP and troponin I.
- Observed event rate during the open label extension of the Phase 2 study provides encouraging early evidence of disease-modifying potential of AG10.
- Collectively, these data support continued evaluation of AG10 in ATTR-CM, in an ongoing randomized, placebo-controlled, global Phase 3 clinical trial [ClinicalTrials.gov Identifier: NCT03860935].

References

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4. Penchala S, et al. AG10 Inhibits Amyloidogenesis and Cellular Toxicity of the Familial Amyloid Cardiomyopathy-Associated V122I Transthyretin. Proc Natl Acad Sci. 2013;110:9992-7.
5. Judge DP et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285-295.