Long-Term Safety and Tolerability of Acoramidis (AG10) in Symptomatic Transthyretin Amyloid Cardiomyopathy: 4-Year Update From an Ongoing, Phase 2, Open-Label Extension Study

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BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a chronic, progressive, fatal disease caused by transthyretin (TTR) destabilization and subsequent TTR amyloid fibril deposition in the myocardium, leading to progressive heart failure, significantly impaired quality of life, hospitalization, and death.[1]
- Destabilization of the TTR tetramer and the resulting generation of unstable monomers is the root cause of ATTR amyloidosis, with an association between the extent of TTR destabilization and disease severity.[2]
- Acoramidis (AG10) is a next-generation, oral, potent, highly selective, small molecule, near-complete TTR stabilizer that offers a unique binding mode by mimicking the stabilizing properties of the T119M variant and is being investigated for the treatment of ATTR-CM.[1]
- The safety and tolerability of acoramidis in patients with ATTR-CM was investigated in a phase 2, randomized, double-blind, placebo-controlled, 28-day trial that enrolled 49 participants (AG10-201; NCT03458130).
  - Participants were required to have New York Heart Association (NYHA) class II or III symptoms and ≥1 prior hospitalization for heart failure or clinical evidence of heart failure.
- Acoramidis has been further evaluated in the prospective, placebo-controlled, randomized, double-blind, multicenter, phase 3 ATTRibute-CM trial, which met its primary endpoint with high statistical significance.[3]
- This open-label extension (OLE) study (NCT03536767) is investigating the long-term safety of acoramidis in this patient population with advanced disease, enrolling participants who completed the phase 2 AG10-201 study.

OBJECTIVE

- To report a 4-year update of the long-term safety and biomarker data collected in the OLE for participants who completed the phase 2 AG10-201 study.

METHODS

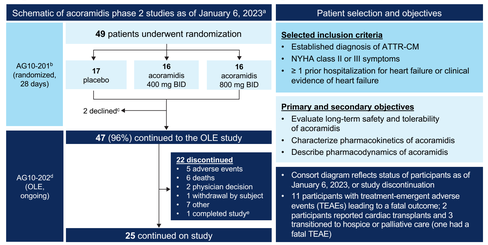
- Participants who completed the phase 2 study and enrolled in the OLE (n = 47) received oral acoramidis HCl 800 mg twice daily.
- Clinical, safety, and laboratory assessments were performed on days 1, 14, and 45, and at 3-month intervals thereafter.
- The primary endpoint was long-term safety and tolerability, and secondary endpoints included pharmacokinetic and pharmacodynamic assessment of TTR stabilization.
  - TTR stabilization was assessed through ex vivo assays fluorescent probe exclusion (FPE; measures binding site occupancy) and western blot (WB; quantifies tetrameric TTR persistence under conditions of accelerated dissociation) and through the in vivo measure of serum TTR levels.
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, a biomarker of heart failure due to cardiac wall stress,[4] were also evaluated.

RESULTS

Participants

- As of January 6, 2023, 25/47 participants (53.2%) remained on study (**Figure 1**) and completed the Month 45 visit.
- The median (25th-75th percentile) time since phase 2 enrollment was 55 (18.56-55.29) months.

Figure 1. Participant Disposition With Long-term Follow-up



[a]Median 55 months from initial phase 2 randomization. Median 50.5 months on open-label acoramidis. [b]ClinicalTrials.gov identifier: NCT03458130. [c]Both declined participation due to geographical constraints regarding study visits. [d]ClinicalTrials.gov identifier: NCT03536767. [e]Status incorrectly entered in the database as "completed;" participant discontinued treatment due to "participant decision."

Safety

- Acoramidis was generally well tolerated. All participants experienced a TEAE; 5 participants (10.6%) experienced a treatment-related TEAE, and 1 participant (2.1%) had a serious treatment-related TEAE (**Table 1**).

Table 1. Safety Summary

Summary of TEAEs, n (%)	N = 47
Any TEAE	47 (100.0)
Treatment-related TEAE	5 (10.6)
Serious TEAE	37 (78.7)
Serious treatment-related TEAE	1 (2.1)
Severe TEAE	30 (63.8)
TEAE leading to treatment discontinuation	9 (19.1)
TEAE leading to death	11 (23.4)

- Adverse events were consistent with disease severity, concurrent illness, and age (**Table 2** and **Table 3**). No new safety signals were identified with additional follow-up.

Table 2. TEAEs Occurring in >15% of Participants

TEAE by preferred term, n (%)	N = 47
Fall	22 (46.8)
Acute kidney injury	13 (27.7)
Cardiac failure, acute	12 (25.5)
Atrial fibrillation	11 (23.4)
Fatigue	11 (23.4)
Insomnia	11 (23.4)
Arthralgia	10 (21.3)
Constipation	10 (21.3)
Dyspnea	10 (21.3)
Back pain	9 (19.1)
Cough	9 (19.1)
Epistaxis	9 (19.1)
Hypervolemia	9 (19.1)
Cardiac failure, congestive	8 (17.0)
Diarrhea	8 (17.0)
Hypokalemia	8 (17.0)
Nausea	8 (17.0)
Pain in extremity	8 (17.0)

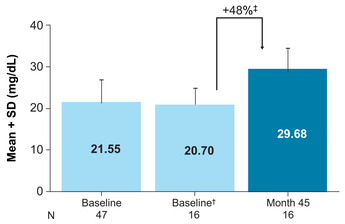
Table 3. Serious TEAEs Occurring in >5% of Participants

TEAE by preferred term, n (%)	N = 47
Cardiac failure, acute	12 (25.5)
Acute kidney injury	8 (17.0)
Fall	6 (12.8)
Atrial flutter	5 (10.6)
Cardiac failure	5 (10.6)
Cardiac failure, congestive	5 (10.6)
Cardiorenal syndrome	5 (10.6)
Atrial fibrillation	4 (8.5)
Cardiogenic shock	4 (8.5)
Pneumonia	3 (6.4)

Biomarker Data

- Consistent with prior analysis, acoramidis treatment resulted in a 48% increase in the mean percent change of serum TTR concentrations from baseline at Month 45 in participants with available baseline and Month 45 data (**Figure 2**).

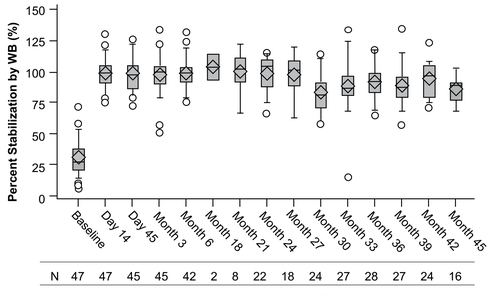
Figure 2. Serum TTR Change From Baseline at Month 45



†Mean + SD for the 16 participants with TTR concentration at Month 45.
‡Mean percent change of serum TTR concentrations from baseline to Month 45.

- Western blot confirmed high TTR stabilization with acoramidis treatment at Month 45 (mean [SD]: 85.97% [9.757%]), representing a mean (SD) difference of 55.59% (16.221%) compared with baseline.
  - High TTR stabilization was observed in participants with both wild-type (mean [SD]: 87.63% [8.965%]) and variant TTR (mean [SD]: 78.75% [11.645%]).
  - High TTR stabilization was maintained over time through to 4-year follow-up (**Figure 3**).

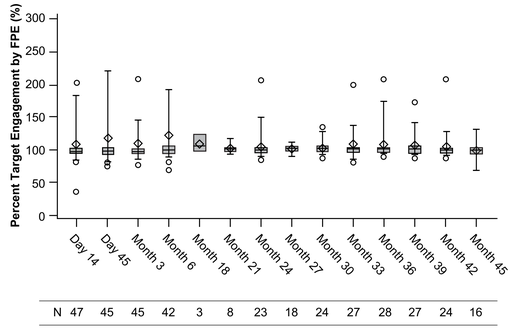
Figure 3. Percent TTR Stabilization With Acoramidis Treatment Over Time by Western Blot



Note: Boxes represent median value and the interquartile range (IQR). Diamonds represent the mean value. Percent stabilization at each visit was defined as 100 times the mean of 72-hour acidification duplicates on each visit divided by the mean of the 0-hour acidification duplicates at each visit.

- The FPE assay showed near-complete TTR engagement (mean [SD]: 99.25% [11.984%]) with acoramidis treatment at Month 45 (**Figure 4**).
  - High TTR engagement was observed in participants with both wild-type (mean [SD]: 99.34% [13.375%]) and variant TTR (mean [SD]: 98.89% [1.881%]).
  - Near-complete TTR engagement was maintained over time (**Figure 4**).

Figure 4. Percent TTR Engagement With Acoramidis Treatment Over Time by FPE



Note: Boxes represent median value and the IQR. Diamonds represent the mean value. Percent target engagement at each visit was defined as 100 times [(the mean of FPE at 60 minutes duplicates at Day 1 minus preprobe measurement FPE duplicates on Day 1) minus (the mean FPE at 60 minutes duplicates at each visit minus pre-probe measurement duplicates on each visit) divided by (the mean of FPE at 60 minutes duplicates at Day 1 minus preprobe measurement duplicates on Day 1). A total of 6 high outlying values (during first 6 months due to interference by hemolysis leading to artificially elevated values) were removed.

- NT-proBNP levels continued to be reduced from baseline with acoramidis treatment, with median (25th-75th percentile) change from baseline to Month 45 of −307 (−679 to 204) pg/mL (**Figure 5**).
  - Reductions in NT-proBNP were observed in 17/25 participants at Month 45 (**Figure 6**).

Figure 5. Median Percentage Change in NT-proBNP by Visit

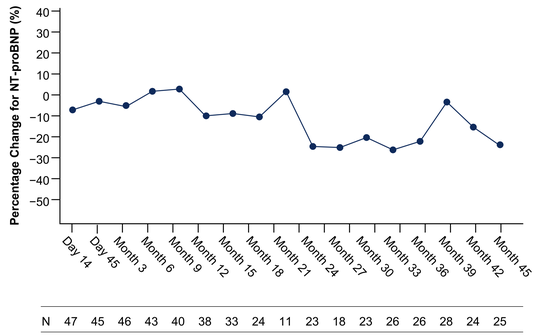
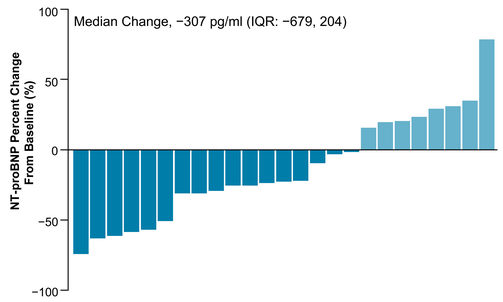


Figure 6. Change From Baseline to Month 45 in NT-proBNP by Participant



CONCLUSIONS

- Long-term treatment with acoramidis remained generally well tolerated and was associated with sustained increases in TTR stabilization, TTR occupancy, and sustained reduction in median NT-proBNP levels in a population of patients with advanced symptomatic ATTR-CM (NYHA class II or III at entry to the phase 2 study)
  - The pattern of NT-proBNP and TTR stabilization in this study are consistent with that observed in the ATTRibute-CM trial
- At least 53% of this enrolled patient population has survived for a median follow-up of 4.6 years with acoramidis.
- Acoramidis has been further evaluated in the prospective, placebo-controlled, randomized, double-blind, multicenter, phase 3 ATTRibute-CM trial, which met its primary endpoint with high statistical significance.[3]
- These data further reinforce the long-term safety of acoramidis and complement the emerging favorable benefit-risk profile that has been demonstrated in the phase 3 ATTRibute-CM trial.

ACKNOWLEDGMENTS

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ABBREVIATIONS

AE, adverse event; ATTR-CM, transthyretin amyloid cardiomyopathy; BID, twice daily; FPE, fluorescent probe exclusion; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; TEAE, treatment-emergent adverse event; TTR, transthyretin; WB, western blot.

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