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

ATTR is a systemic disease

- Central nervous system
- Ocular
- Cardiomyopathy
- Gastrointestinal
- Nephropathy
- Carpal tunnel
- Peripheral neuropathy

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, \(^{99m}\)Tc=Technetium-99m; TAVR=transcatheter aortic valve replacement.

ATTR-CM is a rapidly progressive and fatal disease

50% Survival at Month 36 in untreated ATTR-CM patients

Note: Survival probabilities estimated via plot digitization.
Source: Elliott P. et al, Circulation: Heart Failure 2021
Acoramidis was designed to mimic a naturally occurring TTR variant that protects carriers from ATTR development.

- Native TTR circulates in blood as a tetramer.
- Dissociation into monomers initiates pathogenesis.
- Monomers aggregate, causing disease.

**Disease mechanism**

**Functional protein**

**Disease-causing forms**

**Therapeutic hypothesis**

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

Source: Judge D. et al, JACC 2019
**Acoramidis Phase 2 design**

**Schematic of acoramidis Phase 2 as of August 31, 2021**

<table>
<thead>
<tr>
<th>AG10-201³ (Randomized, 28 days)</th>
<th>49 Patients underwent randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 Placebo</td>
<td></td>
</tr>
<tr>
<td>16 AG10 400mg</td>
<td></td>
</tr>
<tr>
<td>16 AG10 800mg</td>
<td></td>
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<tr>
<td>2 Declined²</td>
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<table>
<thead>
<tr>
<th>AG10-202⁴ (OLE, ongoing)</th>
<th>47 (96%) Continued onto open label extension (OLE)</th>
</tr>
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<tbody>
<tr>
<td>16 discontinued</td>
<td>4 Adverse event (AE)</td>
</tr>
<tr>
<td></td>
<td>3 Deaths</td>
</tr>
<tr>
<td></td>
<td>3 Physician decision</td>
</tr>
<tr>
<td></td>
<td>1 Withdrawal by subject</td>
</tr>
<tr>
<td></td>
<td>5 Other</td>
</tr>
<tr>
<td>31 Continued on study</td>
<td>16 discontinued</td>
</tr>
</tbody>
</table>

**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

**Additional notes**
- **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**

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¹Median 38 months from initial Phase 2 randomization. Median 35 months on open-label acoramidis
²Both declined participation due to geographical constraints regarding study visits.
³Clinicaltrials.gov identifier: NCT03458130
⁴Clinicaltrials.gov identifier: NCT03536767
No safety signals of clinical concern identified in Phase 2 OLE

<table>
<thead>
<tr>
<th>Summary of treatment-emergent adverse events</th>
<th>Summary of serious treatment-emergent adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (%)</td>
<td>Number of participants (%)</td>
</tr>
<tr>
<td><strong>Any treatment-emergent adverse event</strong></td>
<td><strong>Any serious treatment-emergent adverse event</strong></td>
</tr>
<tr>
<td>47 (100)</td>
<td>31 (66.0)</td>
</tr>
<tr>
<td><strong>Most common adverse events (≥ 9)</strong></td>
<td><strong>Most serious common adverse events (≥ 4)</strong></td>
</tr>
<tr>
<td>Fall</td>
<td>Cardiac failure acute</td>
</tr>
<tr>
<td>21 (44.7)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>12 (25.5)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>Cardiac failure congestive</td>
</tr>
<tr>
<td>10 (21.3)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Fall</td>
</tr>
<tr>
<td>9 (19.1)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>9 (19.1)</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Cardiogenetic shock</td>
</tr>
<tr>
<td>9 (19.1)</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Cardiorenal syndrome</td>
</tr>
<tr>
<td>9 (19.1)</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>9 (19.1)</td>
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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)

- **Baseline**: 21.55
- **Month 30**: 30.06

**TTR stabilization by FPE**
Mean +/- SD (%)

- **Month 30**: 102.52

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

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.

1Represents all evaluable data from participants who continued in the study
Safety and tolerability
- Adverse event profile consistent with baseline disease severity and progression
- No signals of concern observed with median participation of 38 months

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

12-month endpoints:
Primary: Change in 6MWD
Key secondary: Change in KCCQ

30-month endpoints:
Primary: Hierarchical composite including all-cause mortality and CV-related hospitalizations
Key secondary: Change in 6MWD, KCCQ

Key inclusion criteria:
- Subjects with diagnosed ATTR-CM (WT or mutant)
- NYHA Class I-III
- ATTR-positive biopsy or $^{99m}$Tc scan
- Light chain amyloidosis excluded if diagnosis by $^{99m}$Tc

- 800 mg acoramidis twice daily
  - N ~ 421
- Placebo twice daily
  - N ~ 211

- Screening and randomization

- Part A
  - Tafamidis usage allowed

- Part B
  - Open-label extension

6MWD = six-minute walk distance; $^{99m}$Tc = Technetium labeled pyrophosphate (PYP); 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
- Positive improvement in KCCQ-OS
- Positive reduction in NT-proBNP
- Positive improvement in serum TTR
- No safety signals of clinical concern

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 m²
A sincere thank-you to the patients and families, investigators, referring physicians, clinical research staff, Eidos employees, and collaborating research partners participating in the study.

### Phase 2 investigators

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Mandar Aras, MD</td>
<td>University of California San Francisco</td>
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<tr>
<td>Rodney Falk, MD</td>
<td>Brigham and Women’s Hospital</td>
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<td>Daniel Judge, MD</td>
<td>Medical University of South Carolina</td>
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<tr>
<td>Cesia Gallegos Kattan, MD</td>
<td>Yale University</td>
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<td>Ahmad Masri, MD</td>
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<td>Mat Maurer, MD</td>
<td>Columbia University</td>
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<tr>
<td>Sanjiv Shah, MD</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Ronald Witteles, MD</td>
<td>Stanford University</td>
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