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

**Masri, Ahmad**¹, Aras, Mandar², Falk, Rodney H.³, Grogan, Martha⁴, Jacoby, Daniel⁵, Judge, Daniel P.⁶, Shah, Sanjiv J.⁷, Witteles, Ronald⁸, Ji, Alan X.⁹, Wong, Paul W.⁹, Cao, Xiaofan⁹, Vanlandingham, Rebecca⁹, Katz, Leonid⁹, Sinha, Uma⁹, Fox, Jonathan C.⁹, Maurer, Mathew S.¹⁰

¹Oregon Health Sciences University, Portland, OR, US ²University of California at San Francisco, San Francisco, CA, US ³Brigham and Women’s Hospital, Boston, MA, US ⁴Mayo Clinic Rochester, MN, US ⁵Yale University Medical Center, New Haven, CT, US ⁶Medical University of South Carolina, Charleston, SC, US ⁷Northwestern University Feinberg School of Medicine, Chicago, IL, US ⁸Stanford University, San Francisco, CA, US ⁹Eidos Therapeutics, Inc., San Francisco, CA, US, ¹⁰Columbia University Medical Center, New York, NY, US

Presented by Dr. Ahmad Masri on behalf of investigators
Disclosures

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

**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
ATTR-CM is a rapidly progressive and fatal disease

![Survival Probability Graph](attachment:SurvivalGraph.png)

- **Gillmore et al., 2018 (n=869)**
- **Grogan et al., 2016 (n=360)**
- **ATTR-ACT placebo (n=177)**

![Note: Survival probabilities estimated via plot digitization.](attachment:Note.png)


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.

Grogan cohort includes wildtype ATTR-CM only.

~60-65% Survival at Month 36 based on ATTR-CM natural history data
Acoramidis was designed to mimic a naturally occurring TTR variant that protects carriers from ATTR development.

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

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 ATTR\(_v\) or ATTR\(_w\).

References:
1. Miller et al., J Med Chem 2018 Sep 13;61(17):7862-7876
Acoramidis Phase 2 design

Schematic of acoramidis Phase 2 as of August 31, 2021

- **AG10-201** (Randomized, 28 days)
  - 49 Patients underwent randomization
  - 17 Placebo
  - 16 AG10 400 mg bid
  - 16 AG10 800 mg bid
  - 2 Declined

- **AG10-202** (OLE, ongoing)
  - 47 (96%) Open-label extension (OLE) AG10 800 mg bid
  - 16 discontinued
    - 4 Adverse event (AE)
    - 3 Deaths
    - 3 Physician decision
    - 1 Withdrawal by subject
    - 5 Other
  - 31 Continued on study

**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

**Other information**
- Median 38 months from initial Phase 2 randomization. Median 35 months on open-label acoramidis
- Both declined participation due to geographical constraints regarding study visits.
- Clinicaltrials.gov identifier: NCT03458130
- Clinicaltrials.gov identifier: NCT03536767

**Additional notes**
- Consent 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
No safety signals of clinical concern identified in Phase 2 OLE

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

### Summary of treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Fall</td>
<td>21 (44.7)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (19.1)</td>
</tr>
</tbody>
</table>

### Summary of serious treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious treatment-emergent adverse event</td>
<td>31 (66.0)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Cardiorenal syndrome</td>
<td>4 (8.5)</td>
</tr>
</tbody>
</table>
Acoramidis increased serum TTR levels and provided near-complete TTR stabilization

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

Baseline

<table>
<thead>
<tr>
<th></th>
<th>Serum TTR concentration</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean +/- SD (mg/dL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>21.55</td>
</tr>
<tr>
<td></td>
<td>Month 30</td>
<td>30.06</td>
</tr>
</tbody>
</table>

+41%

TTR stabilization by FPE\(^1\)
Mean +/- SD (%)

Month 30

<table>
<thead>
<tr>
<th></th>
<th>TTR stabilization by FPE(^1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean +/- SD (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 30</td>
<td>102.52</td>
</tr>
</tbody>
</table>

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.

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

**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

**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

800 mg acoramidis twice daily

N ~ 421

Placebo twice daily

N ~ 211

**Part A**
- Tafamidis usage allowed

**Part B**
- 800 mg acoramidis twice daily

Screening and randomization 2:1

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
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

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>Mandar Aras, MD</th>
<th>Rodney Falk, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of California San Francisco</td>
<td>Brigham and Women's Hospital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daniel Jacoby, MD</th>
<th>Daniel Judge, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale University</td>
<td>Medical University of South Carolina</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Martha Grogan, MD</th>
<th>Ahmad Masri, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic Rochester, Minneapolis</td>
<td>Oregon Health &amp; Science University</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mat Maurer, MD</th>
<th>Sanjiv Shah, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columbia University</td>
<td>Northwestern University</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ronald Witteles, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford University</td>
</tr>
</tbody>
</table>