Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Results of the ATTRibute-CM Trial

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Disclosures

Advisor/consultant for BridgeBio, Alnylam, Ionis, AstraZeneca, Intellia, Pfizer, ATTRalus, Lycia

Acoramidis is an investigational molecule. The safety and efficacy have not been fully evaluated by regulatory authorities.
**ATTRibute-CM: Study Design**

**Key eligibility criteria**
- Subjects with diagnosed ATTR-CM (WT or variant)
- NYHA Class I-III
- ATTR-positive biopsy or 99mTc scan
- Light chain amyloidosis excluded if diagnosis by 99mTc

**Screening and randomization**

**30-month primary endpoint:**
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD

**Efficacy assessment included 611 participants in the pre-specified mITT population (eGFR ≥30 mL/min/1.73 m²)**

**Tafamidis usage allowed after Month 12**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg acoramidis HCl twice daily</td>
<td>N = 421</td>
</tr>
<tr>
<td>placebo twice daily</td>
<td>N = 211</td>
</tr>
</tbody>
</table>

**6MWD = Six-minute walk distance; NYHA = New York heart association; 99mTc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); mITT = Modified intent-to-treat. eGFR = Estimated glomerular filtration rate. ClinicalTrials.gov identifier: NCT03860935.**
## ATTRibute-CM: Baseline Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acoramidis (N=421)</th>
<th>Placebo (N=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>77.4 (6.5)</td>
<td>77.1 (6.8)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>384 (91.2)</td>
<td>186 (88.2)</td>
</tr>
<tr>
<td>ATTRwt-CM, n(%)</td>
<td>380 (90.3)</td>
<td>191 (90.5)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL), median (IQR)</td>
<td>2326 (1332, 4019)</td>
<td>2306 (1128, 3754)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²), mean (SD)</td>
<td>60.9 (18.2)</td>
<td>61.0 (18.7)</td>
</tr>
<tr>
<td>TTR (mg/dL), mean (SD)</td>
<td>23.2 (5.6)</td>
<td>23.6 (6.1)</td>
</tr>
<tr>
<td>KCCQ-OS, mean (SD)</td>
<td>71.5 (19.4)</td>
<td>70.3 (20.5)</td>
</tr>
<tr>
<td>6MWD (m), mean (SD)</td>
<td>361.2 (103.7)</td>
<td>348.4 (93.6)</td>
</tr>
<tr>
<td>Concomitant tafamidis use, n (%)*</td>
<td>61 (14.5)</td>
<td>46 (21.8)</td>
</tr>
</tbody>
</table>

ATTRwt-CM = Transthyretin amyloidosis wild-type cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = interquartile range; TTR = transthyretin; KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.

*Tafamidis usage allowed after Month 12.
## ATTRibute-CM: Primary Outcome Overall and by Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Win Ratio [95% CI]</th>
<th>FS test P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>611(100.0)</td>
<td>1.772 [ 1.417, 2.217 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ATTR-CM Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRm-CM</td>
<td>59(9.7)</td>
<td>2.529 [ 1.303, 4.911 ]</td>
<td>0.0061</td>
</tr>
<tr>
<td>ATTRwt-CM</td>
<td>552(90.3)</td>
<td>1.756 [ 1.396, 2.208 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 3000</td>
<td>401(65.6)</td>
<td>1.787 [ 1.373, 2.325 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>210(34.4)</td>
<td>1.678 [ 1.160, 2.426 ]</td>
<td>0.0060</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>94(15.4)</td>
<td>1.410 [ 0.849, 2.341 ]</td>
<td>0.1841</td>
</tr>
<tr>
<td>&gt;= 45</td>
<td>517(84.6)</td>
<td>1.797 [ 1.452, 2.226 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 78</td>
<td>299(48.9)</td>
<td>2.052 [ 1.489, 2.829 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;= 78</td>
<td>312(51.1)</td>
<td>1.499 [ 1.098, 2.045 ]</td>
<td>0.0107</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>512(83.8)</td>
<td>1.892 [ 1.479, 2.419 ]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>III</td>
<td>99(16.2)</td>
<td>1.150 [ 0.652, 2.030 ]</td>
<td>0.6292</td>
</tr>
</tbody>
</table>

FS = Finkelstein-Schoenfeld; CI = Confidence interval.

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ATTRibute-CM: All-Cause Mortality

ARR = 6.4%
RRR = 25%

Separation observed at Month 19

ARR = Absolute risk reduction; RRR = Relative risk reduction.
All-cause mortality includes heart transplant, implantation of cardiac mechanical assist device, and all-cause death.
ATTRibute-CM: Cardiovascular-Related Mortality

CV-related: Cardiovascular-related.

1 Heart transplant and implantation of cardiac mechanical assistance device (CMAD) were treated as death for this analysis. N = 1 heart transplant & N = 1 CMAD implantation in placebo group.

2 CV-related mortality includes all adjudicated CV-related and undetermined cause of death.

ARR = 6.4%
RRR = 30%

CV-related mortality\(^1\,^2\) at Month 30

Acoramidis (N=409)

Placebo (N=202)

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**ATTRibute-CM: Frequency of CVH; P<0.0001 on overall analysis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>611(100.0)</td>
<td>0.496 [0.355, 0.695]</td>
</tr>
<tr>
<td>ATTR-CM Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRm-CM</td>
<td>59(9.7)</td>
<td>0.377 [0.139, 1.027]</td>
</tr>
<tr>
<td>ATTRwt-CM</td>
<td>552(90.3)</td>
<td>0.514 [0.360, 0.734]</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 3000</td>
<td>401(65.6)</td>
<td>0.456 [0.299, 0.695]</td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>210(34.4)</td>
<td>0.576 [0.330, 1.003]</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>94(15.4)</td>
<td>0.594 [0.250, 1.415]</td>
</tr>
<tr>
<td>&gt;= 45</td>
<td>517(84.6)</td>
<td>0.481 [0.334, 0.692]</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 78</td>
<td>299(48.9)</td>
<td>0.437 [0.275, 0.696]</td>
</tr>
<tr>
<td>&gt;= 78</td>
<td>312(51.1)</td>
<td>0.576 [0.353, 0.940]</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>512(83.8)</td>
<td>0.447 [0.310, 0.645]</td>
</tr>
<tr>
<td>III</td>
<td>99(16.2)</td>
<td>0.721 [0.313, 1.660]</td>
</tr>
</tbody>
</table>

Negative binomial regression with treatment group, stratification factors, and subgroup of interest was used to analyze the cumulative frequency of adjudicated CV-related hospitalization.
ATTRibute-CM: Change from Baseline in NT-proBNP & 6MWD

1Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values.

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ATTRibute-CM: Change from Baseline in KCCQ-OS & Serum TTR

Change from Baseline in KCCQ-OS\(^1\)

Change from Baseline in Serum TTR\(^2\)

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\(^{1}\)Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values.

\(^{2}\)Observed measurements without any imputation. No adjustment was made for early discontinuation for any reason, including death.
**ATTRibute-CM: Improvements in Disease Measures**

**Improvement from baseline in NT-proBNP**

- **Acoramidis** (N=280): 45%
- **Placebo** (N=133): 9%

**Improvement from baseline in 6MWD**

- **Acoramidis** (N=268): 40%
- **Placebo** (N=121): 22%

mITT population. Improvement is defined as <0 pg/mL change from baseline to month 30 for NT-proBNP; >0 meter change from baseline to month 30 for 6MWD. In both cases, among subjects with both baseline and month 30 values.
### ATTRibute-CM: Patient Safety

Acoramidis was generally well-tolerated with no findings of potential clinical concern.

<table>
<thead>
<tr>
<th>Subjects with one or more event(s)</th>
<th>Acoramidis N=421</th>
<th>Placebo N=211</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent adverse events (TEAEs)</td>
<td>413 (98.1%)</td>
<td>206 (97.6%)</td>
</tr>
<tr>
<td>TEAE with fatal outcome</td>
<td>60 (14.3%)</td>
<td>36 (17.1%)</td>
</tr>
<tr>
<td>TEAE leading to hospitalization</td>
<td>212 (50.4%)</td>
<td>128 (60.7%)</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>39 (9.3%)</td>
<td>18 (8.5%)</td>
</tr>
<tr>
<td>Any treatment-emergent serious adverse events (SAEs)</td>
<td>230 (54.6%)</td>
<td>137 (64.9%)</td>
</tr>
<tr>
<td>Treatment-emergent SAEs leading to study drug discontinuation</td>
<td>21 (5.0%)</td>
<td>15 (7.1%)</td>
</tr>
<tr>
<td>Severe TEAEs$^1$</td>
<td>157 (37.3%)</td>
<td>96 (45.5%)</td>
</tr>
</tbody>
</table>

All Adverse Events (AEs) occurring during the treatment period are considered treatment-emergent adverse events (TEAEs). Serious Adverse Event (SAE) meets seriousness criteria.

$^1$Severity as assessed by the investigator.
ATTRibute-CM: Conclusions

• Primary endpoint analysis (Finkelstein-Schoenfeld hierarchy of ACM, CVH, NT-proBNP, 6MWD) highly statistically significant
  • Win ratio 1.8; p<0.0001; 58% of win ratio ties broken by ACM + CVH

• Consistent treatment effect across secondary endpoints
  • Better preservation of functional capacity (6MWD) and QoL (KCCQ-OS)
  • Reduced progressive increase in NT-proBNP; 45% of patients improved

• 81% survival rate on acoramidis approaches survival rate in age-matched US database (~85%)\(^1,2\)

• 0.29 mean annual CVH frequency on acoramidis approaches annual hospitalization rate observed in broader US Medicare population (~0.26)\(^3\)

• Reassuring safety profile

\(^1\)ssa.gov. \(^2\)Miller et al., Am J Card 2021 \(^3\)US Department of Health & Human Services, Jan 2018.
ATTRibute-CM: Acknowledgements

• Patients, caregivers
• Investigators, research staff
• Steering Committee, Data Monitoring Committee, Clinical Events Committee, Data Reporting Center
• Patient advocacy organizations
• BridgeBio scientists and supporting employees