Detailed Results of the ATTRibute-CM Phase 3 Study

August 28, 2023
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Discussion topics

1. Molecular hypothesis
2. ATTRibute-CM Phase 3 results
3. Context for clinical findings
4. Next steps
5. Q&A session
Acoramidis was designed to achieve maximal stabilization and preserve native TTR

**Design Objectives**

1. Maximize TTR stabilization/minimize toxic monomer

2. Preserve circulating native TTR

**Rationale**

- Strong genotype/phenotype correlation between TTR instability and disease severity\(^1\)
- Dose-dependent improvements in both TTR stabilization and clinical outcomes demonstrated by tafamidis in ATTR-CM\(^2\)
- Extent of TTR stabilization or knockdown associated with degree of clinical benefit in ATTR-PN\(^3-6\)
- TTR has been highly conserved throughout evolution\(^7\)
- TTR is an abundant plasma protein with relatively rapid turnover requiring sustained metabolic energy expenditure

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We plan to enter the ATTR-CM market with acoramidis, a next generation, more potent TTR stabilizer

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TTR = Transthyretin; ATTR-CM = TTR amyloid cardiomyopathy.

Acoramidis is a next generation stabilizer that employs multiple strategies to maximize potency

Native TTR circulates in blood as a tetramer

Dissociation into monomers initiates pathogenesis

Monomers aggregate, causing disease

~130 known destabilizing mutations

Protective T119M mutation

Acoramidis was designed to mimic protective T119M mutation. Acoramidis sees more target (superior free fraction), binds more target (superior kd2), and glues the target together stronger (enthalpic binding mode).\(^1,2\) Phase 3 results confirm differential stabilization via effects on serum TTR.

Acoramidis is an investigational molecule. The safety and efficacy have not been established by regulatory authorities.

Data supporting more potent TTR stabilization

Superior Binding to TTR in vitro\(^1\)
facilitated by enthalpic interactions

Near-Complete TTR Stabilization\(^2\)
at target trough clinical concentrations

Rapid, durable increases in serum TTR
an in vivo marker of native tetramer stability

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Note: Direct cross-study comparisons may suggest misleading similarities or differences. The values shown are directional and do not report robust comparative analysis.
Acoramidis demonstrated pan-variant TTR stabilization to a greater extent than tafamidis

Source: Ji A. X. et al., ESC 2023: “Acoramidis Produces Near-Complete TTR Stabilization in Blood Samples from Patients with Variant Transthyretin Amyloidosis that is Greater than that Achieved with Tafamidis”

Note: SD shown for measurements with two or more samples
Exploratory post hoc analysis: serum TTR levels

Mean change from baseline in serum TTR at Month 30 in mITT population.

1Mean change from baseline in serum TTR at Month 30 in mITT population. 2Mean exposure on tafamidis = 11 months in mITT population.
Discussion topics

1. Molecular hypothesis
2. ATTRibute-CM Phase 3 results
3. Context for clinical findings
4. Next steps
5. Q&A session
Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Results of the ATTRibute-CM Trial

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ATTRibute-CM study design\textsuperscript{1,2}

**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**

- 800 mg acoramidis HCl twice daily
  - N = 421
  - Efficacy assessment included 611 participants in the pre-specified mITT population (eGFR ≥30 mL/min/1.73 m\(^2\))

- Placebo twice daily
  - N = 211
  - Tafamidis usage allowed after Month 12

**30-month primary endpoint\textsuperscript{3}:**
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD

**Open-label extension**

800 mg acoramidis HCl twice daily

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Acoramidis is an investigational molecule. The safety and efficacy have not been fully evaluated by regulatory authorities.

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.

\textsuperscript{1}ClinicalTrials.gov identifier: NCT03860935. \textsuperscript{2}Gillmore JD et al. Circulation. 2019;140(1):14214. Oral poster presented at AHA. \textsuperscript{3}Primary analysis assessed using the Finkelstein-Schoenfeld method.
## 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/1.73m$^2$), 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; 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</th>
<th>Win Ratio [95% CI]</th>
<th>FS test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>611(100.0)</td>
<td></td>
<td>1.772 [1.417, 2.217]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>ATTR-CM Genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRn-CM</td>
<td>59(9.7)</td>
<td></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></td>
<td>1.756 [1.396, 2.208]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 3000</td>
<td>401(65.6)</td>
<td></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></td>
<td>1.678 [1.160, 2.426]</td>
<td>0.0060</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73m2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>94(15.4)</td>
<td></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></td>
<td>1.797 [1.452, 2.226]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 78</td>
<td>299(48.9)</td>
<td></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></td>
<td>1.499 [1.098, 2.045]</td>
<td>0.0107</td>
</tr>
<tr>
<td><strong>NYHA Class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>512(83.8)</td>
<td></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></td>
<td>1.150 [0.652, 2.030]</td>
<td>0.6292</td>
</tr>
</tbody>
</table>

FS = Finkelstein-Schoenfeld; CI = Confidence interval.
ATTRibute-CM: All-Cause Mortality

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.

1Heart 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.

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

CV-related mortality at Month 30:

- Acoramidis (N=409): 14.9%
- Placebo (N=202): 21.3%

ARR = 6.4%
RRR = 30%
## 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>NYHHA 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**

**Change from Baseline in NT-proBNP**

- 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.

**Change from Baseline in 6MWD**

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

Change from Baseline in KCCQ-OS

Change from Baseline in Serum TTR

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**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of subjects improving from baseline at M30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acoramidis</td>
<td>45%</td>
</tr>
<tr>
<td>Placebo</td>
<td>9%</td>
</tr>
</tbody>
</table>

Acoramidis (N=280) vs Placebo (N=133)

**Improvement from baseline in 6MWD**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of subjects improving from baseline at M30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acoramidis</td>
<td>40%</td>
</tr>
<tr>
<td>Placebo</td>
<td>22%</td>
</tr>
</tbody>
</table>

Acoramidis (N=268) vs Placebo (N=121)

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

<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></td>
<td></td>
<td></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>

\(^1\)Severity as assessed by the investigator.

**Acoramidis was generally well-tolerated with no findings of potential clinical concern**
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; 148:146-150.  \(^3\)US Department of Health & Human Services, Jan 2018.
Discussion topics

1. Molecular hypothesis
2. ATTRibute-CM Phase 3 results
3. Context for clinical findings
4. Next steps
5. Q&A session
Surviving more and going to the hospital less

A. Dramatic risk reduction
B. Biomarker & functional improvement
C. Connecting the dots between extent of TTR stabilization and outcomes
Observed effect of acoramidis approaches rates of mortality and hospitalization in similarly aged US cohorts

<table>
<thead>
<tr>
<th>Rate of Survival at Month 30</th>
<th>Mean Annual Hospitalization Frequency$^5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural History$^1$</td>
<td>Acoramidis (ATTRibute-CM)</td>
</tr>
<tr>
<td>85%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Note: Direct cross-study comparisons may suggest misleading similarities or differences. The values shown are directional and do not report robust comparative analysis.


$^5$Natural history reflects US Medicare non-neonatal, non-maternal inpatient stays. ATTRibute-CM and ATTR-ACT data reflect cardiovascular hospitalizations.
>40% of participants experienced improvement in laboratory and functional measures of disease progression on acoramidis.

**NT-proBNP (pg/mL)**

<table>
<thead>
<tr>
<th>ATTRibute-CM</th>
<th>Acoramidis</th>
<th>% improvement from baseline at M30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=409</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTR-ACT</th>
<th>Tafamidis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=264</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

**6MWT (m)**

<table>
<thead>
<tr>
<th>ATTRibute-CM</th>
<th>Acoramidis</th>
<th>% improvement from baseline at M30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=409</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTR-ACT</th>
<th>Tafamidis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=264</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Direct cross-study comparisons may suggest misleading similarities or differences. The values shown are directional and do not report robust comparative analysis. N represents number of patients at baseline. ATTRibute-CM data reflects 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.

Molecular hypothesis for a second generation TTR stabilizer translated to observed benefit on measures of disease progression

1. Acoramidis was designed to mimic the protective T119M mutation

2. % Increase in Serum TTR at M12

   - Tafamidis 20 mg: 22%
   - Tafamidis 80 mg: 30%
   - Acoramidis HCl 800 mg: 39%

3. Near-complete TTR stabilization results in higher serum TTR levels on acoramidis

4. Higher serum TTR concentrations correlated with benefit on morbidity and quality of life with high statistical significance (correlation coefficient p<0.0001)

   - CVH Rate
   - NT-proBNP
   - KCCQ

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1Estimated from Damy, T., et al., Eur J Heart Fail. 2021;23(2):277-285. 2Mean change from baseline in serum TTR at Month 30 in mITT population. 3Mean exposure on tafamidis = 11 months in mITT population.
Discussion topics

1. Molecular hypothesis
2. ATTRibute-CM Phase 3 results
3. Context for clinical findings
4. Next steps
5. Q&A session
First regulatory submission planned for year-end 2023

- Present ATTRibute-CM Primary Results
  European Society of Cardiology 2023
  August 27th, 2023

- File New Drug Application (NDA) with FDA
  End of 2023

- Submit additional regulatory filings (EMA & others)
  2024

- Execute lifecycle management
  Initiate primary prevention study (ACT-EARLY)
  2024
Ongoing and planned studies of acoramidis aim to expand evidence base and addressable patient population.

**Today**
- **ATTR-CM**
  - WT and hereditary
  - Primary results

**2H 2023**
- **ATTR-CM**
  - WT and hereditary
  - Continued analysis of Ph. 3 data
  - In vitro TTR stabilization
  - Acoramidis vs. Tafamidis
  - Acoramidis Ph. 2 OLE
  - 4+ years safety and efficacy data

**2024+**
- **ATTR-CM**
  - WT and hereditary
  - Open-label extension
  - Expanded safety and efficacy

**Multi-prong evidence generation plan in progress to strengthen acoramidis’ differentiated clinical profile**

- actearly
  - ATTR-CM
  - Hereditary
  - Prevention study
  - Additional real-world evidence generation
  - Imaging Study
  - Longitudinal CMR monitoring

**CMR** = Cardiac magnetic resonance.
Discussion topics

1. Molecular hypothesis on stabilization
2. ATTRibute-CM Phase 3 results
3. Context for clinical findings
4. Next steps
5. Q&A session