ATTRibute-CM Phase 3 Topline Results

July 17, 2023
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Discussion topics

1. Introduction & Overview
   - Neil Kumar, PhD
   - Chief Executive Officer

2. ATTRibute-CM Phase 3 Topline Results
   - Jonathan Fox, MD, PhD
   - Chief Medical Officer, Cardiorenal

3. Next Steps
   - Uma Sinha, PhD
   - Chief Scientific Officer

4. Commercial Launch Plans
   - Matt Outten, MBA
   - Chief Commercial Officer

5. Q&A Session
A sincere THANK YOU to patients and families, advocates, physicians, clinical research staff, and collaborating research partners.
Program context

- ATTR-CM: Idea → Phase 3
- Achondroplasia: Idea → Phase 3
- ADH1: Idea → Phase 3
- LGMD2i: Idea
- CAH: Idea
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
- Dose-dependent improvements in both TTR stabilization and clinical outcomes demonstrated by tafamidis in ATTR-CM
- Extent of TTR stabilization or knockdown associated with degree of clinical benefit in ATTR-PN
- TTR has been highly conserved throughout evolution
- TTR is an abundant plasma protein with relatively rapid turnover requiring sustained metabolic energy expenditure

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

Disease mechanism

~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

Therapeutic hypothesis

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

% Stabilization

<table>
<thead>
<tr>
<th></th>
<th>DSMO</th>
<th>TAF 16(\mu)M</th>
<th>TAF 26(\mu)M</th>
<th>Acoramidis 10(\mu)M</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Stabilization</td>
<td>27%</td>
<td>57%</td>
<td>66%</td>
<td>~100%</td>
</tr>
</tbody>
</table>

% Increase in Serum TTR

<table>
<thead>
<tr>
<th></th>
<th>ATTR-ACT Month 12 Data(^3)</th>
<th>ATTRibute-CM Month 12 Data(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tafamidis 20 mg</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Tafamidis 80 mg</td>
<td>66%</td>
<td>39%</td>
</tr>
<tr>
<td>Acoramidis HCl 800 mg</td>
<td>~100%</td>
<td>39%</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.
**Unprecedented and consistent benefit on survival and morbidity**

<table>
<thead>
<tr>
<th>Best Case Target Clinical Profile</th>
<th>Outcome Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Achieve statistical significance on primary endpoint:</strong> p-value &lt;0.04</td>
<td>✓ Primary endpoint met (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Unprecedented survival:</strong> Highest ever 30-month survival rate on drug (&gt;80%) with clinically meaningful separation from placebo</td>
<td>✓ 81% 30-month survival on acoramidis&lt;br&gt;✓ 6.4% absolute &amp; 25% relative risk reduction compared to placebo</td>
</tr>
<tr>
<td><strong>Best-in-class CVH data:</strong> Profound reduction in event rates</td>
<td>✓ 50% relative risk reduction for cumulative frequency of CVH (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Win Ratio better than 1.7:</strong> Significant impact on mortality and morbidity</td>
<td>✓ Win Ratio = 1.8</td>
</tr>
<tr>
<td><strong>Best-in-class treatment effect on serum biomarkers:</strong> NT-proBNP, serum TTR, TTR stabilization</td>
<td>✓ Clinically and statistically significant (p&lt;0.0001) benefit on NT-proBNP and serum TTR; sustained impact on TTR stabilization</td>
</tr>
</tbody>
</table>

CVH = Cardiovascular-related hospitalization; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.
**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**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
<th>Tafamidis usage allowed after Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg acoramidis HCl twice daily</td>
<td>N = 421</td>
<td></td>
</tr>
<tr>
<td>Placebo twice daily</td>
<td>N = 211</td>
<td></td>
</tr>
</tbody>
</table>

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

**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

**Open-label extension**

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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.

Highly statistically significant result achieved on primary and select secondary endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchical analysis consisting of:</td>
<td></td>
</tr>
<tr>
<td>• All-cause mortality</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>• Cumulative frequency of CVH</td>
<td></td>
</tr>
<tr>
<td>• Change from baseline in NT-proBNP</td>
<td></td>
</tr>
<tr>
<td>• Change from baseline in 6MWD</td>
<td></td>
</tr>
<tr>
<td>Win Ratio</td>
<td>1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Select secondary endpoints</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative frequency of CVH</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Change from baseline in 6MWD</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Change from baseline in KCCQ-OS</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Change from baseline in serum TTR</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Change from baseline in NT-proBNP</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>p=0.057</td>
</tr>
</tbody>
</table>

KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.

1Primary analysis assessed using the Finkelstein-Schoenfeld method. 2Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis. 3Negative binomial regression with treatment group, stratification factors and the offset term is used to analyze the cumulative frequency of adjudicated CV-related hospitalization. 4Least squares mean difference change from baseline at 30 months. 5Ratio of adjusted geometric mean fold change from baseline at 30 months. 6Assessed by Cochran-Mantel-Haenszel test; p=0.15 as assessed by Cox Proportional Hazard Model.

58% of ties broken by first two components of Win Ratio analysis
No safety signals of potential clinical concern identified

<table>
<thead>
<tr>
<th>Subjects with one or more event(s)</th>
<th>Acoramidis N=421 N (%)</th>
<th>Placebo N=211 N (%)</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.
Exploratory post hoc analysis: serum TTR levels

-1 0 1 2 3 4 5 6 7 8 9 10

Serum TTR Level

Mean Change from Baseline\(^1\)

Placebo + Tafamidis\(^2\)

Placebo

Acoramidis

Acoramidis + Tafamidis\(^2\)

\(N = 100\)

\(N = 35\)

\(N = 234\)

\(N = 49\)

\(+42\%\)

Mean change from baseline in serum TTR at Month 30 in mITT population. \(^2\)Mean exposure on tafamidis = 11 months in mITT population.
Exploratory post hoc analysis: median NT-proBNP

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change from Baseline (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>98</td>
</tr>
<tr>
<td>Placebo + Tafamidis(^2)</td>
<td>35</td>
</tr>
<tr>
<td>Acoramidis</td>
<td>232</td>
</tr>
<tr>
<td>Acoramidis + Tafamidis(^2)</td>
<td>48</td>
</tr>
</tbody>
</table>

1 Median change from baseline in NT-proBNP at Month 30 in mITT population. 2 Mean exposure on tafamidis = 11 months in mITT population.
Summary of topline results

- Unprecedented **30-month survival of >80%** for a targeted intervention in ATTR-CM
- Achieved primary endpoint with highly statistically significant result with **Win Ratio of 1.8**
- **6.4% ARR & 25% RRR** in all-cause mortality
- **50% RRR** for cumulative frequency of CVH
- Well-tolerated with no safety signals of potential clinical concern

ARR = Absolute risk reduction. RRR = Relative risk reduction.
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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
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Commercial launch plans

We have a world-class commercial team and we are prepared to go to market
  • 20+ FTEs (Pharmacyclics, Vertex, and Schering Plough alumni) and a distinctive commercial advisory board, inclusive of Fred Hassan, Jennifer Cook and Jim Robinson
  • Have initiated discussions with key partners (payers and distributors) to bring this drug to patients

Our goal is to continue working closely with current and future partners to bring this next generation stabilizer to as broad a patient and provider community as possible
  • Access
  • Global reach

More details on commercial execution to come
ATTRibute-CM Phase 3
Topline Results
Q&A Session