X-Linked Myotubular Myopathy (XLMTM) ASPIRO Phase 1/2 Gene Therapy Trial In XLMTM: Interim Safety And Efficacy Findings

Audentes Therapeutics, Inc.
Agenda

- Audentes Team
- Overview of Some Recent Achievements
- Overview of Interim Data Findings from the ASPIRO Study
- Frequently Asked Questions
- Next Steps
- Question & Answer Session
Audentes Team Represented Today

- Kim Trant
  - Head of Patient Advocacy and Engagement

- Bree Martin
  - Vice President of Development Operations

- Jennifer Chu
  - Senior Project Manager, Development Operations

- Suyash Prasad
  - MD, Paediatrician, Senior Vice President and Chief Medical Officer
What have we been doing since we last met?
We have been growing as a company...
Audentes Company Growth and Development

**XLMTM (AT132)**

- **Aug 2015**: XLMTM Orphan Designation
- **Apr 2017**: IND approved (FDA)
- **Jun 2018**: Priority Medicines (PRIME) designation (EMA)

**Initial proof of concept (POC) established in mouse and dog models at Genethon**

**Additional POC studies in mouse and dog models**

**Year** | **Event**
--- | ---
2012 | Company founded, 1 employee
2013 | Open corporate office, San Francisco
2014 | AAV vectors for gene transfer therapy, ongoing research
2015 | R&D labs open
2016 | Large-scale in-house manufacturing and QC facilities open
2017 | Expand offices, SF Expand lab ops
2018 | 168 employees

**2012**
- First patient in RECENSUS

**2013**
- Open corporate office, San Francisco

**2014**
- AAV vectors for gene transfer therapy, ongoing research

**2015**
- R&D labs open

**2016**
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**2017**
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**2018**
- 168 employees

**European Family Conference**

- Jan 2016: Crigler-Najjar Orphan Designation
- Nov 2015: CPVT Orphan Designation
- Jan 2016: Pompe Orphan Designation

**European Family Conference**

- Jan 2016: Pompe Orphan Designation

**European Family Conference**

- Feb 2018: First patient dosed in VALENES Phase 1/2 Study

**Lawlor et al.**: Comparative Pathology of XLMTM Review. JNEN 2016

**Beggs et al.**: RECENSUS. Muscle & Nerve 2018

**Kuntz et al.**: First ASPIRO data. ASGCT 2018
We have been contributing to the body of scientific knowledge about XLMTM...
Scientific Publications and Presentations

Beggs et al. First RECENSUS publication. Muscle & Nerve, 2018

Lawlor, Schoser, Sewry et al. Comparative Pathology of XLMTM Review. JNEN 2016

ASGCT Oral Presentation
16 May 2018
We continue to discuss emerging data and new insights with the scientific and medical community...
Respiratory Therapy and Pulmonology Meeting
Audentes Board of Scientific and Clinical Advisors
We continue our engagement with and learning from the patient community...
When asked the question ‘What result would you like to see in your child’ - the mothers answered...

**General**
- “Cure”
- Able to put son in car & drive independently
- More robust

**Respiratory**
- Independence from machines
- Improved communication
- No respiratory medicines
- Breathe independently
- Able to swallow
- Improved speech
- Able to sing
- Stability: fewer infections

**Motor**
- Able to walk
- Able to raise arms above head
- Hold head up more
- Sit independently
- Reposition independently
- Increase fine motor skills
XLMTM Patient Advocacy Leader - Physician Advisory Board
We dosed the first patient in the ASPIRO study!
AT132 for XLMTM Clinical Development Program

**RECENSUS**
Retrospective Medical Chart Review of Patients with XLMTM
N=140
- Characterize aspects of the disease and medical management of XLMTM
- Identify potential outcome measures for ASPIRO
- Initial presentation Q1:17; First publication Q4:17

**INCEPTUS**
Prospective Natural History Run-in Study in XLMTM Patients
N=25
- Longitudinal baseline and within-patient control for ASPIRO
- Facilitates enrollment in and operational aspects of ASPIRO
- Prelim. data shared Q4:17

**ASPIRO**
A Phase 1/2 Clinical Study in XLMTM Patients
N=12
- Assessment of safety and tolerability and preliminary efficacy
- Focus on neuromuscular & respiratory measurements
- First patient dosed Q3:17; Positive interim data reported for Cohort 1 in Q1:18
ASPIRO Phase 1/2 Clinical Study

Open-label, ascending-dose, safety and preliminary efficacy study

**Inclusion Criteria**
- Subject is male
- <5 yrs old, or enrolled in INCEPTUS
- Genetically confirmed XLMTM
- Requires ventilator support

**Key Efficacy Assessments**
- **Neuromuscular**
  - CHOP INTEND
  - MFM-20
  - Muscle biopsy
  - Developmental milestones
- **Respiratory**
  - Max Inspiratory Pressure (MIP)
  - Ventilator use

**Enrollment Plan**
- N=12, roll-over from INCEPTUS
- Cohort 1: 1x10^{14} vg/kg dose, 6 treated patients plus a randomized, delayed-treatment, concurrent control patient
- Dose escalation TBD

**GT administration**

**Assessments**
- Neuromuscular
- Respiratory
- Developmental milestones
- Muscle biopsy

**Weeks 1 - 8**
- Prednisolone 1mg/kg/day

**Weeks 9-16 taper**
- Weeks 9 - 16 taper
ASPIRO Clinical Study Sites
ASPIRO Cohort 1 - $1 \times 10^{14}$ vg/kg

Seven patients have been transitioned from INCEPTUS into ASPIRO

- Ventilator status at screening / baseline (hours per day):
  - Patient 1: 12 h of BiPAP
  - Patient 2: 22 h of invasive ventilation
  - Patient 3: 24 h of invasive ventilation
  - Patient 4: 12 h of BiPAP
  - Patient 5: 22.7 h of invasive ventilation
  - Patient 6: 24 h of invasive ventilation
  - Patient 7: 23.5 h of invasive ventilation
Preliminary Data from the first 6 dosed patients in ASPIRO
Before I start, some important things to remember

- Regulatory agencies have not approved the Audentes investigational gene therapy product as safe or effective, as it is still undergoing formal assessment in clinical trials.

- This is interim data
  - We cannot make any firm conclusions on the interim findings of the clinical trial until after all enrolled subjects are dosed and evaluated for the duration of the study, and the full scope of data is collected and analyzed.

- We are a public company, and certain information may not be disclosed until done so in a public setting.
Safety and Tolerability from ASPIRO
Safety Findings to Date

- Ongoing safety assessments are critical to proper determination of potential safety issues and adverse events.

- There have been a total of 24 adverse events (AEs) reported in ASPIRO, which have been managed with medical treatment.
  - Six of these adverse events were classified as serious adverse events (SAEs)
    - five (5) occurred in one participant (4 of them possibly related to drug)
    - one occurred in the the delayed treatment control participant who has not been dosed
  - Seven (7) non-serious adverse events that were possibly or probably related to the investigational product occurred in a total of two participants.
Efficacy Data - Neuromuscular Function

CHOP-INTEND and Developmental Milestones
Significant Improvements in Neuromuscular Function as Assessed by the CHOP-INTEND Scale

Interim data as of May 12, 2018
Multiple Motor Developmental Milestones Achieved

<table>
<thead>
<tr>
<th>First-year developmental milestones in healthy children</th>
<th>Patient 1 (0.8y)</th>
<th>Patient 2 (4.1y)</th>
<th>Patient 3 (2.6y)</th>
<th>Patient 4 (Control-4.0y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 24</td>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>Rolling over</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Head Control</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Sitting unassisted &gt;5 sec</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Additional observations</td>
<td>• Oral feeding • Standing w/ support • Loudness</td>
<td>• Standing w/ support • Scooting &amp; crawling • Loudness</td>
<td>• Increased trunk strength • Loudness</td>
<td></td>
</tr>
</tbody>
</table>

Interim data as of May 12, 2018
Efficacy Data - Respiratory Function

Maximal Inspiratory Pressure and Ventilator Dependence
Significant Improvements in Respiratory Function as Assessed by Maximal Inspiratory Pressure (MIP)

Estimated normal minimal pressures in healthy children

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Baseline Pressure in ASPIRO</th>
<th>Most recent Pressure (Wk)</th>
<th>Change from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>89 (Wk 24)</td>
<td>56 (170%)</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>104 (Wk 24)</td>
<td>60 (136%)</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>48 (Wk 12)</td>
<td>22 (85%)</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>46 (Wk 24)</td>
<td>-12 (-21%)</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>33 (Wk 4)</td>
<td>19 (136%)</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>63 (Wk 4)</td>
<td>28 (80%)</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interim data as of May 12, 2018
Ventilator Dependence Within the Previous 24 Hours
First treated patient has reached ventilator independence

Interim data as of May 12, 2018
Clinical Assessment Videos
ASPIRO Key Findings and Program Next Steps

- Well tolerated during administration and manageable safety profile to date
- Improvements in neuromuscular and respiratory function have been seen
- Progressive qualitative improvements in disease severity observed in all treated patients
- Plan to review muscle biopsy data in conjunction with all safety and efficacy data to inform further dosing decisions and ongoing conduct of the study

It is important to understand that regulatory agencies have not approved the Audentes investigational gene therapy product as safe or effective, as it is still undergoing formal assessment in clinical trials. The investigational gene therapy product is not approved for commercial sale and is only being used in clinical trial settings.
Frequently Asked Questions

There are many “unknowns”

- Will the number of participants in the clinical trial increase? What would determine that?

- In the SMA clinical trials, they were stopped early due to positive results, do you anticipate that happening for the XLMTM clinical trial?

- Will the clinical trial results in young children translate to older children? How would the impact on older children be measured?

- What is the expanded access (early access, compassionate use) policy?

- What happens next?
We would like to acknowledge the many contributors that have gotten us to this point!

Anna Buj Bello  
*Genethon*

Martin K. (Casey) Childers  
David Mack  
*University of Washington, USA*

Alan H. Beggs  
*Children’s Hospital Boston, USA*

Michael Lawlor  
*Children’s Hospital and Medical College of Wisconsin, USA*

- Audentes team members
- Audentes Board of Scientific and Clinical Advisors
- Principal investigators and their teams
  - Nancy Kuntz
  - Perry Shieh
  - Barbara Smith and Barry Byrne
  - James Dowling
  - Carsten G Bönnemann
  - Wolfgang Müller-Felber
  - Laurent Servais
  - Francesco Muntoni
- Study expert trainers

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  - The Myotubular Trust
  - ZNM - Zusammen Stark!
  - The Joshua Frase Foundation
  - MTM-CNM Family Connection
  - Where There’s a Will There’s A Cure Foundation for Myotubular Myopathy

The children, families and the entire XLMTM patient community for their cooperation and participation in these studies
Questions???