January 30, 2019

Orphazyme reports positive results from full data set of Phase II/III arimoclomol trial in Niemann-Pick disease Type C (NPC)
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Niemann-Pick Disease Type C (NPC)

**WHAT IS NPC?**

NPC is a rare, inherited, progressive, and often fatal neurodegenerative disease.

NPC is a lysosomal storage disorder caused by genetic mutations that often lead to misfolded variants of NPC proteins. Misfolded NPC protein does not function properly and is subject to rapid degradation.

**1-2000 people are diagnosed with NPC in the USA and EU**

**MANIFESTATIONS**

- The disease affects the brain, liver, spleen, and lungs. Often patients succumb to the disease before reaching the end of their teens.
- The disease is progressive and patients gradually lose:
  - Motor function and coordination
  - Speech
  - Cognition
  - Memory

**20 years is the average life expectancy**

**95% have mutations in the NPC1 gene**

**ONLY 1 DRUG**

is currently approved to treat NPC (Zavesca).

**DIAGNOSIS**

Difficult to diagnose, NPC is often diagnosed by ruling out other diseases, which may take years.

There is **NO CURE for NPC**
Key Results

- **Baseline demographics and characteristics**: Comparable between treatment arms
- **Pharmacokinetics (PK)**: Preliminary assessment of population PK indicates good compliance
- **Safety**: Arimoclomol was safe and well-tolerated
- **Efficacy**:
  - Primary endpoint 5-domain NPC-Clinical Severity Scale (NPC-CSS) shows -1.34 treatment effect in favor of arimoclomol over placebo, p=0.0506
  - Signal enhancement in:
    - Patients ≥4 years: -1.68 treatment effect in favor of arimoclomol over placebo, p=0.0219
    - Patients on background miglustat treatment: -2.00 treatment effect in favor of arimoclomol over placebo control, p=0.0071
  - Clinical Global Impression of Improvement (CGI-I) responder endpoint (no change or improved) not met, however further analysis of CGI-I indicates supportive evidence
- **Biomarkers**: Demonstrate statistically significant biological effect
Arimoclomol prospective double-blind, randomized, placebo-controlled trial in patients diagnosed with NPC

Throughout the trial, patients stay on their on-going prescribed incl. best Routine Clinical Care (RCC), miglustat, and symptom management.
Selection of 5 Domains out of Full 17-Domain NPC-CSS for Primary Endpoint

5-Domain NPC-CSS
- Captures key aspects of disease important to patients and clinicians
- Range:
  - Individual domain 0 (normal) – 5 (worst)
  - Total score range 0 (normal) - 25 (worst)
- Correlation between total score of 5-domain NPC-CSS and full NPC-CSS is 0.93
- Sensitive to change
  - In observational trial annualized mean change: 1.5 points/year
Safety and Tolerability

- Overall incidence of AEs similar for arimoclomol (88.2%) and placebo (81.3%)
- 3 patients withdrew due to AEs – all in the arimoclomol group (n=3, 8.8%)
- SAEs occurred less frequently in arimoclomol group (14.7%) compared to placebo (37.5%)
  - 1 patient died due to cardiopulmonary arrest assessed as not related to arimoclomol
Primary Endpoint: 5-Domain NPC-CSS Mean Change from Baseline – Full Analysis Set

Overall Population (2 years – 18 years)

General Linear MMRM Treatment Effect: -1.34 (-2.69, 0.00) p=0.0506

Patients 4 years – 18 years

General Linear MMRM Treatment Effect: -1.68 (-3.11, -0.26) p=0.0219

Patients receiving miglustat as part of routine clinical care

General Linear MMRM Treatment Effect: -2.00 (-3.42, -0.58) p=0.0071
Individual Domains on NPC-CSS

- Generally, most change observed on 4 out of 5 Domains from primary endpoint over 12 months, changes in placebo control arm comparable to NPC-001 observational study

<table>
<thead>
<tr>
<th>Domain</th>
<th>Arimoclomol</th>
<th>Placebo control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulation</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Speech</td>
<td>-0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Swallow</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>
• In agreement with FDA, treatment response defined as no change or improved on the Clinical Global Impression of Improvement scale (CGI-I) included as a co-primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Arimoclomol (N=34)</th>
<th>Placebo (N=16)</th>
<th>Total (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder at 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (58.8%)</td>
<td>9 (56.3%)</td>
<td>29 (58.0%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>No</td>
<td>14 (41.2%)</td>
<td>7 (43.8%)</td>
<td>21 (42.0%)</td>
<td></td>
</tr>
</tbody>
</table>

• However, when considering patients who severely progressed during the trial, only 10.7% of the arimoclomol treated patients got ‘much worse’ or ‘very much worse’ compared to 26.7% in the placebo control group supporting an effect of arimoclomol in preventing severe progression over a 12-months observation period
CGI-I Cumulative Distribution

Figure 2.2.2 Cumulative Distribution Curve of CGI-I at 12 Months (Full Analysis Set)

1 = Very much worse; 2 = Much worse; 3 = Minimally worse; 4 = No change; 5 = Minimally improved; 6 = Much improved; 7 = Very much improved
Biomarker Analysis – What Are We Measuring and Why?

- Skin cells
- Peripheral blood mononuclear cells (PBMCs)
- Serum

**Target engagement/PD**
- HSP70 (in PBMCs)

**Disease pathology-relevant biomarkers**
- UE Cholesterol (in PBMCs)
- UE Cholesterol (in skin cells)
- Oxysterol (in serum)
Biomarker Analysis: Target Engagement – HSP70 Levels Increase

HSP70 levels increase over time in arimoclophil-treated patients

HSP70 levels in blood cells (PBMCs)

$p=0.0005$
Biomarker Analysis: Reduced Accumulation of Cholesterol in Blood and Skin Cells

Reduction of Unesterified Cholesterol in blood and skin cells

Cholesterol accumulation in blood cells

UE Cholesterol accumulation in blood cells

$\text{ng/mg protein}$

$\text{p}=0.0450$

Skin biopsies, $N=19$

N.B.

Biomarker Analysis: Reduced Accumulation of Cholesterol in Blood and Skin Cells
Biomarker Analysis: Reduction of Oxysterol in Blood

Reduction of Oxysterol in serum

Reduction of Unesterified Cholesterol in blood and skin cells

Oxysterol in Serum

Ari Pb

\( p = 0.0613 \)
Conclusions

• **Baseline demographics and characteristics**: Comparable between treatment arms
• **Pharmacokinetics (PK)**: Preliminary assessment of population PK indicates good compliance
• **Safety**: Arimoclomol was safe and well-tolerated
• **Efficacy**:
  o Primary endpoint 5-domain NPC-CSS shows -1.34 treatment effect in favor of arimoclomol over placebo, \( p=0.0506 \)
  o Signal enhancement in:
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  o CGI-I responder endpoint (no change or improved) not met, however further analysis of CGI-I indicates supportive evidence
• **Biomarkers**: Demonstrate statistically significant biological effect
Next Steps

• Initiate filing preparations and seek to meet with US Food and Drug Administration and European Medicines Agency mid-2019 to discuss path to approval
• 24-month data will become available from on-going open-label extension of the trial in Q3 2019
• Orphazyme expects filing in the US and EU in H1 2020, with potential approval in H2 2020