

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

- *Primary endpoint shows 74% reduction in disease progression after 12 months compared to placebo control (p-value =0.0506)*
- *Biomarker results demonstrate statistically significant biological response to treatment*
- *Orphazyme to engage with FDA and EMA on path to approval while preparing for filing*

Copenhagen, January 30, 2019 – Orphazyme A/S, a biopharmaceutical company dedicated to developing treatments for patients living with rare diseases, today announced the full data set for its Phase II/III clinical trial of arimoclomol in NPC, a devastating rare genetic disorder. Treatment with arimoclomol adjunct to routine clinical care resulted in a 74% reduction in disease progression (p-value =0.0506) as measured by the primary endpoint, 5-domain NPC Clinical Severity Scale (NPC-CSS). In the predefined subgroup of patients of 4 years and older (44 out of 50 randomized patients in the trial), the treatment difference was statistically significant with a minimal disease progression at month 12 in the arimoclomol-treated group (p-value =0.0219). A highly statistically significant treatment difference was observed in another predefined subgroup analysis, requested by the European Medicines Agency (EMA), that compared arimoclomol to placebo control in patients receiving miglustat as a part of routine clinical care (p-value =0.0071).

In agreement with the US Food and Drug Administration (FDA), treatment response defined as no change or improved on the Clinical Global Impression of Improvement scale (CGI-I) was included as a co-primary endpoint. A responder rate of more than 50% in the placebo control group impeded the ability to show an overall effect on this endpoint. 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.

Anders Hinsby, Chief Executive Officer of Orphazyme, said: *"With this highly compelling data set, we are looking forward to working with regulatory authorities to make arimoclomol available to patients as fast as possible. It has been inspirational to collaborate with the NPC community on this journey and I wish to thank the families for their dedication and patience. Moreover, the positive results from this trial further strengthen our confidence in heat-shock protein amplification as a potential treatment for a range of protein-misfolding diseases."*

Karl-Eugen Mengel, Principal Investigator, Mainz University Hospital, said: *"I am very happy for the patients that may now benefit from our efforts to change the course of this debilitating disease. Achieving such a clinically meaningful response to treatment in this Phase II/III trial with efficacy results for NPC is promising"*.

Several exploratory biomarkers were measured during the trial, demonstrating a clear biological effect of arimoclomol in support of the clinical results. The biomarker data showed a biological response to arimoclomol on key characteristics of its mechanism of action and the disease biology of NPC. This includes the important rescue protein HSP70 and accumulating lipids involved in the disease pathology. HSP70 levels showed a statistically significant increase in patients treated with arimoclomol (p-value =0.0005) demonstrating target engagement. In addition, arimoclomol treatment also led to statistically significant reductions in the accumulation of disease-related lipids such as unesterified cholesterol in skin and blood cells (p-value =0.0450). Furthermore a reduction of the cholesterol metabolite oxysterol was also observed (p-value =0.0613).

As previously reported, overall, baseline characteristics were well-balanced across treatment arms. Arimoclomol was well-tolerated with a similar incidence of adverse events (AEs) for arimoclomol (88.2%) and placebo control (81.3%). Serious AEs occurred less frequently in the arimoclomol group (14.7%) compared to placebo control (37.5%).

The secondary endpoints, NPC Clinical Database (NPC-CDB), Scale for Assessment of Rating of Ataxia (SARA), 9-Hole Peg Test (9HPT), and EQ-5D-Y, did not statistically support a benefit of the arimoclomol group over the placebo control group, albeit directional benefit was observed in the NPC-CDB and the 9HPT assessments. The lack of effect may indicate that these endpoints may not have been appropriate to demonstrate an effect in this patient population over the relatively short 12-month treatment period. Post-hoc analyses are on-going to further the understanding of these results.

Orphazyme understands the urgency of making arimoclomol available to NPC patients as soon as possible. We will immediately initiate filing preparations and seek to meet with the FDA and EMA mid-2019 to discuss the path to approval.

24-month data is expected to become available from the on-going open-label extension of the trial in Q3 2019. Orphazyme plans for submission of filing in the US and EU in H1 2020, with potential approval in H2 2020.

Reported impact of arimoclomol Phase II/III trial on outcome measures

Outcome measures	Arimoclomol	p-values
<i>Primary endpoints</i>		
Mean change from baseline on 5-domain-NPC-CSS (primary)	Arimoclomol: 0.5 pts Placebo control: 1.9 pts Difference: -1.34 pts	0.0506
Treatment response defined as no change or improvement on CGI-I (co-primary in US)	Arimoclomol: 58.8% Placebo control: 56.3% Difference: 2.5%	1.0000
<i>Predefined subgroup analyses 5-domain-NPC-CSS</i>		
Mean change from baseline on 5-domain-NPC-CSS (patients ≥ 4 years)	Arimoclomol: 0.1 pts Placebo control: 2.1 pts Difference: -1.68 pts	0.0219
Mean change from baseline on 5-domain-NPC-CSS (miglustat is part of routine clinical care)	Arimoclomol: -0.2 pts Placebo control: 1.8 pts Difference: -2.00 pts	0.0071
<i>Predefined sensitivity analyses 5-domain-NPC-CSS</i>		
Multiple imputations (MMRM)	Treatment difference: -1.24 pts	0.0587
Additional covariate: Age at study entry	Treatment difference: -1.29 pts	0.0602

Additional covariate: Age at first neurological symptoms	Treatment difference: -1.34 pts	0.0479
Non-parametric analysis	Arimoclomol: 0.00 pts Placebo control: 1.00 pts Difference: -1.00 pts	0.1966
<i>Exploratory biomarker endpoints</i>		
Change in HSP70 level	1815.0 pg/mL	0.0005
Change in unesterified cholesterol level in blood cells	-53433 ng/mg	0.0450
Change in cholesterol metabolite (cholestane-3 β ,5 α ,6 β -triol)	-8.0579 ng/mL	0.0613
<i>Safety & tolerability</i>		
Adverse events	Arimoclomol: 88.2% (3 discontinuations) Placebo control: 81.3%	
Serious adverse events	Arimoclomol: 14.7% Placebo control: 37.5%	

Analysis of the full data set confirms the top-line results announcement (no. 12-2018) on September 28, 2018, while strengthening the significance of the trial results.

This company announcement does not impact the 2018 financial guidance.

About the trial

The trial was a multi-center, prospective, double-blinded, placebo-controlled interventional study with a 12-month duration. In total, 50 patients between the age of 2-18, randomized 2:1 to arimoclomol or placebo control, were enrolled in the US and EU. The purpose of the trial was to assess the efficacy and safety of arimoclomol, compared to placebo control, in the treatment of NPC, administered in addition to the patient's routine clinical care. The primary endpoints, 5-domain NPC-CSS and CGI-I (in the US), evaluated the treatment difference between the arimoclomol-treated and the placebo control group after 12 months of treatment.

Conference call

Orphazyme will be hosting an investor call at which Chief Executive Officer, Anders Hinsby, Chief Medical Officer, Thomas Blaettler, and Chief Scientific Officer, Thomas Kirkegaard Jensen, will be presenting the full clinical trial data set for arimoclomol in NPC. The presentation will be followed by a Q&A session.

The call will be held on: **Wednesday, January 30, 2019 at 11.00 AM CET.**

Dial-in details:

- Denmark: 3272 8042
- France: 01 76 700 794
- Netherlands: 02 07 143 545
- Sweden: 08 50 69 21 80
- United Kingdom: 0844 571 88 92
- United States: 1 631 510 74 95

Event Title: Orphazyme Investor Call

Confirmation code: **8649097**

The presentation will also be available via webcast: <https://edge.media-server.com/m6/p/6bnfvr57>

After the call, the presentation will be available by using the following dial-in details:

- UK (/international): +44 (0)333 300 97 85
- United States: 1 (917) 677 7532

Confirmation code: 8649097

For additional information, please contact

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About Orphazyme A/S

Orphazyme is a biopharmaceutical company focused on bringing novel treatments to patients living with life-threatening or debilitating rare diseases. Our research focuses on developing therapies for diseases caused by misfolding of proteins and lysosomal dysfunction. Arimoclomol, the company's lead candidate, is in clinical development for four orphan diseases: Niemann-Pick disease Type C, Gaucher disease, sporadic Inclusion Body Myositis, and Amyotrophic Lateral Sclerosis. The Denmark-based company is listed on Nasdaq Copenhagen (ORPHA.CO). For more information, please visit www.orphazyme.com.

About arimoclomol

Arimoclomol is an investigational drug candidate that amplifies the production of heat-shock proteins (HSPs). HSPs can rescue defective misfolded proteins, clear protein aggregates, and improve the function of lysosomes. Arimoclomol is administered orally, crosses the blood brain barrier, and has been studied in seven Phase I and three Phase II trials. Arimoclomol is in clinical development for NPC, Gaucher disease, sIBM, and ALS. Arimoclomol has been granted Orphan Drug Designation (EU and USA), Rare Pediatric Disease Designation (USA), and Fast Track designation (USA) for the treatment of NPC.

About NPC

Niemann-Pick disease Type C (NPC) is a genetic, progressively debilitating, and often fatal neurovisceral disease. It belongs to a family known as lysosomal storage diseases and is caused by mutations leading to defective NPC protein. As a consequence, lipids that are normally cleared by the lysosome build-up in tissues and organs, including the brain, and drive the disease pathology. The estimated prevalence of NPC in the USA and Europe combined is 1,000-2,000. There are no approved treatments for NPC in the USA and only one approved product in Europe.

Forward-looking statement

This press release may contain certain forward-looking statements. Although the Company believes its expectations are based on reasonable assumptions, all statements other than statements of historical fact included in this press release about future events are subject to (i) change without notice and (ii) factors beyond the Company's control. These statements may include, without limitation, any statements preceded by, followed by or including words such as "target," "believe," "expect," "aim," "intend," "may," "anticipate," "estimate," "plan," "project," "will," "can have," "likely," "should," "would," "could" and other words and terms of similar meaning or the negative thereof. Forward-looking statements are subject to inherent risks and uncertainties beyond the Company's control that could cause the Company's actual results, performance or achievements to be materially different from the expected results, performance or achievements expressed or implied by such forward-looking statements. Except as required by law, the Company assumes no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.