CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214927Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 214927

COMPLETE RESPONSE

Orphazyme A/S
c/o Orphazyme US Inc.
Attention: Abhijit Pangu, RAC
Senior Director, US Regulatory Affairs
180 N La Salle Street, Suite 3475
Chicago, IL 60601

Dear Mr. Pangu:

Please refer to your new drug application (NDA) dated July 17, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for arimoclomol capsules.

We acknowledge receipt of your major amendment dated December 22, 2020, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

You submitted data from a 12-month, randomized, double-blind, placebo-controlled trial together with confirmatory evidence from in vitro, animal and clinical pharmacology data to establish substantial evidence of effectiveness of arimoclomol for the treatment of Neimann-Pick disease Type C (NPC).

We recognize NPC as a rare, serious and life-threatening disease with a high unmet need and no approved therapies. In situations such as this one, we must incorporate regulatory flexibility, while still ensuring there is substantial evidence of effectiveness.

Based upon our review of your submitted data, we are unable to conclude that there is substantial evidence of effectiveness. This conclusion is based on concerns with your 5 domain NPC Clinical Severity Scale (5DNPCCSS) and the weak and contradictory confirmatory evidence of effectiveness, as explained below, which is in the context of a numerically small treatment effect in your trial (treatment difference of about 1 point on a 25 point scale), problematic “hypothetical estimand”, and the lack of statistical significance at the conventional level ($p<0.05$) on our analysis of the 5DNPCCSS using a while-on-treatment estimand.

TRIAL NPC-002:

Primary Efficacy Results:

As discussed at the pre-NDA meeting, we have concerns with your hypothetical estimand targeted by your primary efficacy analysis for the 5DNPCCSS endpoint, which yielded a treatment difference of -1.4 points (95% confidence interval -2.8, 0.0; p=0.046). Hypothetical 5DNPCCSS scores after early escape or premature study discontinuation due to adverse events are not clinically plausible (that is, it is not reasonable to assume a hypothetical treatment effect for patients who stopped treatment for a clinical reason, because the expectation in this situation is that, for the same clinical reason, treatment would not be resumed). We also question the appropriateness of the underlying missing at random assumption based on derived estimated means of the missing hypothetical scores conditional on the observed trajectories using your Mixed Model Repeated Measures (MMRM) analysis. Therefore, our main efficacy evaluation focused on the while-on-treatment estimand, where the treatment effect was quantified by the difference between the two treatment arms in the mean change from baseline to 12 months or last visit prior to study treatment discontinuation. In this analysis, the estimated treatment difference was -1.2 (95% confidence interval -2.7, 0.3; p=0.12), which does not meet the conventional threshold for statistical significance ($p<0.05$) and is numerically small relative to the 0 to 25 range for the 5DNPCCSS score. In this context, we have identified the following concerns with the 5DNPCCSS, many of which were communicated at several time points during your IND development, as summarized below.

5DNPCCSS Regulatory History:

In our September 2, 2016, advice letter we indicated that certain domains of the NPCCSS (specifically speech, ambulation, fine motor skills, cognition, memory, and seizures) were either not well-defined or likely insensitive to change, and recommended performance-based assessments to standardize the evaluation of specific domains (cognition, ambulation, fine motor, memory). We restated in an advice letter dated January 19, 2017 that the NPCCSS, in its current form, was not well-defined and reliable, and requested evidence demonstrating that the measurement of the domains of the NPCCSS (i.e., those intended to be included as a primary endpoint) are standardized across patients and sites (e.g., by inclusion of performance tests such as the Scale for the Assessment and Rating of Ataxia or SARA, 9-hole peg test, and neurological examinations), and demonstrating that the NPCCSS scoring was reliable and reproduceable. In a meeting dated July 20, 2017, we reiterated that our earlier advice communicated on September 2, 2016 and January 19, 2017 had not been fully incorporated, and indicated that establishing the validity and standardization of all five domains was needed, especially performance tests for swallowing, cognition, and speech. In a meeting dated July 10, 2019, given that we had not assessed the measurement properties of the 5DNPCCSS prior to trial completion and data

unblinding, we conveyed that the adequacy of the 5DNPCCSS score would be an NDA review issue.

5DNPCCSS Validity Concerns:

- Despite our advice during the IND phase, the NDA did not include data that compares the 5DNPCCSS domains with other measures (e.g., performance-based assessment of neurocognitive functioning, SARA speech and gait subdomains) to help establish the validity of the instrument, with the exception of the American Speech-Language-Hearing Association National Outcomes Measurement System (ASHA-NOMS) Swallow Scale and the Penetration-Aspiration Scale (PAS), discussed below.

- We have several concerns with the swallow domain (which together with speech and fine motor skills accounts for the numerical difference in the 5DNPCCSS endpoint between arimoclomol and placebo). These concerns, described below, raise questions as to whether the swallow score reflects the patient's level of swallowing dysfunction, whether no change in the swallow score reflects a true delay in swallowing dysfunction progression, and whether improvement or worsening of the swallow score reflects actual improvement or worsening of swallowing. Because the 5DNPCCSS total score is calculated by adding the swallow domain score to other scores we are concerned that the issues identified with the swallow domain impact interpretability of the 5DNPCCSS total score.

    - The same swallow score is given for situations that may not be equivalent, such as a "3" for patients who report "coughing while eating + intermittent dysphagia with liquids and solids," "coughing while eating + dysphagia with liquids," or "coughing while eating + dysphagia with solids". A "4" is given for patients who report "nasogastric tube or gastric tube for supplemental feeding," "cough while eating + intermittent dysphagia with liquids + dysphagia with solids," or "cough while eating + intermittent dysphagia with solids + dysphagia with liquids." A score of "5", which represents the most severe presentation could indicate "cough while eating plus dysphagia with solids plus dysphagia with liquids" or "nasogastric tube or gastric tube feeding only." While higher scores are intended to reflect increased disease severity, it is not clear that the scores are ordered to reflect clinical progression in severity.

    - It is uncertain whether the identified issues with the swallow domain will bias results toward the null or away from the null, particularly because this small randomized trial had differences between treatment arms in baseline swallow scores with differential opportunities to show apparent worsening or improvement even if such changes reflected construct-irrelevant variance due to shortcomings with the instrument. For example, there were five arimoclomol patients who improved on their swallow scores, four

with a two-point improvement and one with a one-point improvement. However, the placebo arm had less opportunity to show improvement because 44% of placebo-treated patients had a non-zero score at baseline, with only 38% having high enough baseline scores to allow for a two-point improvement compared to 65% of arimoclomol-treated patients with a non-zero score at baseline. It is also unclear whether the differences in baseline swallowing scores may have led to differential behavioral advice (e.g., to cut food into smaller pieces) across the two treatment arms that could have also impacted the scoring.

- Use of the NIH natural history study to quantitatively evaluate the validity of NPCCSS swallow scores through comparison with scores on the ASHA-NOMS Swallow Scale and the PAS showed positive correlations between the NPCCSS swallow scores and scores on these other scales at baseline and Month 12. However, there was poor alignment between baseline swallow scores on the NPCCSS vs. ASHA-NOMS and PAS (with a considerable number of patients having a normal score on the ASHA-NOMS and PAS but having non-zero scores of 1-4 on the NPCCSS swallow domain). In addition, there was poor alignment between NPCCSS swallow scores in the 0-3 range with the ASHA-NOMS and PAS, which is the region of the response scale in which improvement in swallowing was seen with arimoclomol in Study NPC-002.

- Regarding the other 5DNPCCSS domains, there are several response options that appear problematic. For example, two response options for the ambulation domain involve retrospective reports of early childhood development (e.g., ataxic unassisted gait or not walking by 18 months) that would not be able to change in a drug trial of older patients and do not measure what matters to patients, which is current ambulation ability. For the cognition domain, some of the response options may reflect the patient environment rather than a drug effect (e.g., access to services). Also, cognition is a broad concept and cannot adequately be evaluated using a single item clinician-reported scale. For the fine motor skills domain, the difference between “slight” dysmetria and “mild” dysmetria is unclear.

CONFIRMATORY EVIDENCE:

The confirmatory evidence of effectiveness for arimoclomol appears weak and contradictory, as summarized below:

- In eight cell lines derived from NPC patients, incubation with increasing concentrations of arimoclomol (50 to 400 µM) increased NPC1 protein expression. These in vitro concentrations are 16-fold to more than 130-fold maximal plasma concentrations (~1.5-3 µM) observed with the clinical doses. The clinical relevance of the in vitro findings at these high exposures is unclear.

- There are two non-GLP studies and one GLP study in an (Npc-/-) mouse model of NPC disease. One of the non-GLP studies showed improved ataxia at the low dose but not at the high dose of arimoclomol. This paradoxical finding related to dose is unexpected for a drug effect. In addition, improvement in ataxia was not seen with arimoclomol in the other non-GLP mouse study or in the GLP mouse study. The second non-GLP study showed improved survival with an unexpected increase in brain glycosphingolipid with arimoclomol. You hypothesize that arimoclomol may benefit patients with NPC by upregulating heat shock proteins that could improve intracellular trafficking of cholesterol and glycosphingolipids in patients with NPC. The observed increase in brain glycosphingolipids in this study does not appear consistent with the intended effect of the drug. In addition, there was no improvement in survival with arimoclomol in the GLP study. GLP studies are the gold standard for nonclinical work in terms of documentation and reproducibility, and the lack of any reproducibility in the GLP study is a concern.

- You included your peer-reviewed publication by Kirkegaard et. al.[1] to provide additional nonclinical support for arimoclomol's effectiveness, but it is unclear whether this publication is an aggregation of previous work already included in the NDA, a post-hoc analysis of previous work, independent studies, or a combination of these approaches.

- In Trial NPC-002 eight pharmacodynamic biomarkers were assessed and only one (Lyso-SM-509 at 6 months) demonstrated a significant treatment difference. Although the Lyso-SM-509 data may suggest a possible pharmacologic effect of arimoclomol in NPC patients, the data were not consistent across the 6 and 12 month timepoints and none of the other pharmacodynamic biomarker data showed statistically significant differences between arimoclomol and placebo. Therefore, the submitted biomarker data are not considered adequate to serve as confirmatory evidence. We have outlined several concerns with the data below.

    - HSP70 concentrations in peripheral blood mononuclear cells significantly increased from baseline in the 11 arimoclomol treated patients with available data (nominal p=0.001), but a similar numerical increase was also observed in the four placebo treated patients. The missing data in a significant number of patients limits conclusions.

    - While there appeared to be numerical mean reductions from baseline with arimoclomol compared to placebo on unesterified cholesterol in peripheral blood mononuclear cells and on serum cholestane-triol, there was

[1] Kirkegaard T, Gray J, Priestman DA, et al. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses, Sci Transl Med. 2016: 8(355): 355ra118.

substantial variability in the measurements, and differences between treatment arms were not statistically significant.

- An exploratory analysis of Lyso-SM-509, a novel lipid that is elevated in the plasma of NPC patients showed a significant reduction from baseline at 6 months (p=0.05) that was less pronounced at 12 months (p=0.40). However, the clinical relevance of the reduction in Lyso-SM-509 in NPC patients is not well-understood, and no evidence is provided to demonstrate that reduction in Lyso-SM-509 corresponds with clinical efficacy. In addition, the LC-MS/MS bioanalytical assay used to determine plasma Lyso-SM-509 concentrations has not been fully validated due to lack of sample stability testing.

In summary, we have concerns that the available data do not meet the evidentiary standard for substantial evidence of effectiveness based on the weak and contradictory confirmatory evidence and validity concerns with the 5DNPCCSS in the context of a numerically small treatment effect that was not statistically significant (p=0.12) at the conventional level when using a while-on-treatment estimand.

INFORMATION NEEDED TO RESOLVE THE DEFICIENCIES:

Provide substantial evidence of effectiveness for arimoclomol for the treatment of NPC.

1. Address point-by-point each of the issues identified in this letter regarding the 5DNPCCSS domains and swallow scores, including:

    a. Whether the NPCCSS swallow scores and other domain scores can be improved by rescoring.

    b. The alignment concerns in the NIH natural history study between NPCCSS swallow scores in the 0-3 range with the ASHA-NOMS and PAS, with an explanation for the considerable number of patients in the NIH natural history study who are reported to have a normal ASHA-NOMS and PAS score but who reported dysphagia, with scores of 1-4 on the NPCCSS swallow domain.

    c. When responding to the 5DNPCCSS concerns, include analyses and rationale that addresses whether bias in each of the domain scores and the total score would be towards the null or away from the null.

2. We recommend additional quantitative and qualitative evidence to support the interpretation and use of 5DNPCCSS scores to evaluate arimoclomol's treatment effects. Examples include, but are not limited to, showing that clinicians can clearly and consistently interpret and differentiate the response options within each domain of the 5DNPCCSS (e.g., using a qualitative cognitive interview

study with NPC clinical experts and/or clinical exerts with sufficiently related expertise to address validity questions about the 5DNPCCSS). Additional data providing quantitative validity evidence for each of the 5DNPCCSS domains using established performance-based or clinician-reported outcome measures administered longitudinally concomitantly with the 5DNPCCSS could also be useful.

3. Consider whether there are additional analyses and/or other data that you can provide from Trial NPC-002 that may be able to address any of the identified concerns. Examples include, but are not limited to:

    - Data and analyses of the skin biopsies performed at baseline, month 6, and month 12 of the trial

    - Clinically meaningful changes at the patient level in the trial based on comparisons of Much Improved or Very Much Improved on the Global Impression of Change to the 5DNPCCSS

    - Additional in vitro, nonclinical and/or clinical data that provide a scientific basis for some of the subgroup findings (e.g., whether arimoclomol is ineffective in patients with double-null mutations, and whether there is a pharmacodynamic interaction between arimoclomol and miglustat)

4. We recommend that you bolster the confirmatory evidence of effectiveness to help establish that there is a true drug effect. Examples include, but are not limited to:

    - A short-term, cross-over pharmacodynamic study using sufficiently validated assays in a reasonable number of patients to clearly establish arimoclomol's effects on biomarkers related to its mechanism of action in NPC

    - Other data from Trial NPC-002 (e.g., findings from skin biopsies performed at baseline, 6 months and 12 months in the trial).

This application may need discussion at an advisory committee meeting during the next review cycle.

ADDITIONAL COMMENTS

We also have the following comment that is not an approvability issue:

- Trial NPC-002 only enrolled patients with NPC type 1 but you are seeking approval for all patients with NPC, including those with NPC type 2. Provide a scientific rationale for extending the indication to those with NPC type 2.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[4]

PROPRIETARY NAME

Refer to correspondence dated October 16, 2020, which addresses the proposed proprietary name, Miplyffa. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

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[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drugmarketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

We strongly recommend that you request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
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