CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215559Orig1s000

OTHER ACTION LETTERS

NDA 215559

COMPLETE RESPONSE

Ipsen Biopharmaceuticals Inc.
Attention: Andrew Sansone, MS
Vice President, Regulatory Affairs, Quality & Safety, North America
One Main Street, 7th Floor
Cambridge, MA 02142

Dear Mr. Sansone:

Please refer to your new drug application (NDA) dated and received April 29, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for palovarotene capsules.

We also acknowledge receipt of your amendment dated October 19, 2022, which was not fully reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter. We refer you to the ICH guidance for industry *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals*[1] for specific weight of evidence (WoE) criteria and to aid in applying the WoE approach for assessing human carcinogenic risk.

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 have not provided adequate support for the efficacy of palovarotene, thus the anticipated clinical benefit in the treatment of pediatric and adult patients with fibrodysplasia ossificans progressiva (FOP), specifically a benefit of palovarotene to prevent the formation of new heterotopic ossification (HO) (the proposed indication), has not been established.

Major review issues that remain unresolved include:

1) Appropriateness of reliance on post-hoc analyses to support efficacy.

2) Acceptability of the external control group (the Natural History Study, NHS) for evaluation of efficacy of the chronic/flare-up dosing regimen.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3) Uncertain implications of the observed negative new HO volume data.

4) Lack of demonstration of efficacy of flare-up-only dosing the phase 2 studies, and inconsistency in the efficacy data pertaining to chronic/flare-up dosing between phase 2 and phase 3 data.

5) The imbalance in flare-ups between palovarotene-treated patients and non-treated patients in the palovarotene clinical studies. Palovarotene is intended to prevent the formation of new HO, and flare-ups are associated with HO formation. The potential for increased incidence of flare-ups with palovarotene treatment, particularly with higher doses, is a concern regarding both the efficacy and safety of the drug in patients with FOP.

6) Unclear plan for demonstration of substantial evidence of effectiveness as described in guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, e.g., if you intend to rely on a single adequate and well controlled trial, you will need to provide confirmatory evidence of effectiveness.

As a path forward we recommend that the following additional data and data analyses as well as any other available data that may support the efficacy of palovarotene be submitted. Additional data and analyses should include all data out to clinical study close-out:

1) Data pertaining to the number of new sites of HO in Studies PVO-1A-202 B/C (202 B/C) and PVO-1A-301 (301) and the NHS, including whether new HO noted on post-baseline imaging was classified as ‘new lesion’ or ‘enlarged lesion’ or ‘both new and enlarged lesion.’

2) Annualized new HO summary statistics for ‘Pre-pause,’ ‘Interruption,’ and ‘Re-start’ periods in Study 301 and 202B/C.

3) Analyses comparing annualized new HO of treated subjects with untreated subjects from the NHS using all available data. The combined populations of 202B and 202C should be used. Based on the similar protocols for Studies 202C and 301, it would also be acceptable to conduct separate analyses for 202C. The analyses should consider, but not be limited to, the following different combinations of populations, analyses methods and calculation of endpoints.

    a. Analysis population for comparison
        i. Study 202 B/C versus NHS
        ii. Study 301 and Study 202 B/C pooled versus NHS
        iii. Study 301 and Study 202 B/C (like two active arms) versus NHS

b. Analysis method
    i. Generalized estimating equation
    ii. Wilcoxon rank sum test (if applicable)

c. Matching and weighting:
    i. None (not matched or weighted)
    ii. Matching or weighting based on propensity score: For matching, treated subjects should be matched with NHS subjects who share similar baseline characteristics. Subjects should be exactly matched on sex and possibly age group depending on number of subjects that could be exactly matched. Conduct matching using different methods such as nearest neighbor and optimal matching on other covariates. Balances of selected baseline covariates should be assessed before and after weighting or matching. Discuss and interpret the findings from the different matching or weighting analyses.

d. Covariates for analyses, matching and weighting
    i. Baseline age, sex, total HO
    ii. Baseline age, sex, total HO, cumulative analogue joint involvement scale (CAJIS), time since last flare up (may have more missing data)

e. Annualized new HO (use the original study baseline regardless of dosing stop)
    i. Calculated using the last available observation
    ii. Calculated using the 12-month visit window data if available; otherwise using the observation closest to Month 12
    iii. Calculated using the 24-month visit window (applicable to Study 202 B/C vs NHS comparison)
    iv. Calculated using the 36-month visit window (applicable to Study 202 B/C vs NHS comparison)

4) Perform within-subject analyses:

a. Comparing the annualized new HO under palovarotene treatment with the annualized new HO observed in the NHS among NHS subjects who transferred to Study 202 B/C. Plot the average change in total HO from baseline vs visit month by study. The plots should indicate the number of subjects at each visit.

b. Comparing the annualized new HO under palovarotene treatment with the annualized new HO observed in the NHS among NHS subjects who transferred to either Study 202 B/C or Study 301. Plot the average change in total HO from baseline vs visit month by study. The plots should indicate the number of subjects at each visit.

5) Provide a graph depicting the average change in total HO volume by visit month for Study 202 B/C subjects who had a similar dosing regimen and enrollment criteria as Study 301 subjects. Provide an additional graph with average change in total HO volume from baseline further depicted by grouping subjects based on whether the subjects were newly enrolled into Study 202C, or from the NHS directly, or from Study 202B. Provide similar graphs for total HO volume instead of change in total HO volume.

6) For subjects who transferred from the NHS to Study 202, provide the dates and total HO volumes of the end of NHS CT scan and the baseline scan of Study 202, as well as the difference between dates and volumes. For subjects whose end of NHS study CT scans were re-read for the baseline total HO volume for Study 202, perform a simple linear regression analysis of the baseline total volume in Study 202 with the HO volume at the end of the NHS as the independent variable and provide the regression plots and results.

7) Given the different results on WBCT volume from Study 202 B/C and 301, provide an exploration of the differences that may explain the disparate results seen. This should include analyses of differences in age, sex, disease severity and flare-up history. These analyses should also provide information on a potential population in whom palovarotene has clear benefit.

8) In Studies 202 B/C and 301, perform analyses of the relationship between incidence/rate of flare-ups (defined as including Aes of ‘condition aggravated’) and development of new HO, and between the extent of flare-up dosing and development of new HO.

9) For each of the 4 studies (301, 202B, 202C and NHS), populate the following table using “pre-pause” data. For Study 202B, include both treated flare-ups and Aes of ‘condition aggravated.’

Change from baseline at Month 12 in volume of new whole body HO (mm^3) by flare-up location

	Statistics	All subjects	Subjects with no flare-ups	Subjects with ≥1 flare-up cycle	Subjects with 1 flare-up cycle	Subjects with 2 flare-up cycles	Subjects with 3 flare-up cycles	Subjects with 4 flare-up cycles	Subjects with 5 or more flare-up cycles
Overall	N								
	Mean (SD)								
	95% CI								
At flare-up sites	N		X						
	Mean (SD)		X						
	95% CI		X						
At sites of initial flare-up in a cycle	N		X						
	Mean (SD)		X						
	95% CI		X						
At sites of intercurrent flare-up locations	N		X						
	Mean (SD)		X						
	95% CI		X						
Away from flare-up sites	N								
	Mean (SD)								
	95% CI								

10) WBCT images from Study 301 and the NHS were mixed together for blinded image reading following a reader charter; however, it is unclear whether the WBCT images from Study 202 B/C were read using the same process (for example, mixed with the NHS images and read under a similar charter). Elaborate on any differences in the imaging acquisition and reading between Studies 202 B/C, 301 and the NHS.

11) NHS subjects were able to transition into palovarotene interventional Studies 301, 201, or 202 during the NHS follow-up. Statistical analyses for NHS subjects have shown that, with no palovarotene intervention, HO volume measured by WBCT seemed to increase at a slower pace among subjects who transitioned to and potentially throughout the interventional studies, as opposed to subjects who stayed in the NHS. This implicit characteristic of subjects who transitioned to Studies 301, 201, or 202, if present, would not be captured at the study baseline. This self-selection of NHS subjects into interventional studies may potentially impact the results for change in new HO volume measured by WBCT comparing Studies 301 and 202 B/C with the NHS.

Provide an assessment of the potential impact of self-selection of NHS subjects on the results for change in new HO volume by WBCT comparing Studies 301 and 202 B/C with the NHS.

a. Consider a marginal structural model to account for time-varying binary exposure of palovarotene chronic treatment and continuous HO volume by WBCT as time-depending confounder, using all data combined from the NHS, Study 301, and Study 202 B/C populations. Also consider age and stratify by sex in the model.

b. If a marginal structural model is deemed infeasible, based on the limitations of the current data, please provide your assessment of feasibility, and propose sensitivity analyses to address the potential selection bias when comparing Studies 301 and 202 B/C with NHS subjects.

12) Create a dataset for Study 202 B/C subjects with the same structure and variables as the ADHOV4 dataset such that the two datasets can be combined. You should include all available WBCT data in the two datasets regardless of whether the CT scan was obtained after dosing was stopped. Data before dosing stop or any cut-off date should be able to be obtained by simple sub-setting by date. Additionally, add relevant baseline variables such as those listed in 3) d.ii and the following information from CAJIS to the new dataset and the ADHOV4 dataset: whether the subject can walk, uses a wheelchair, needs some help with activities of daily living, needs complete help with activities of daily living. Create an indictor variable for subjects who transferred from the NHS to Study 202 B/C.

13) Submit a guidance document for all programs and datasets used for generating results for this information request. For subjects who participated in multiple studies, a unique subject identification should be provided such that all data for the same subject can be traced across studies.

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.

[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

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We note your submission received October 11, 2022, containing revised carton/container labeling in response to our comments sent on September 27, 2022.

PROPRIETARY NAME

Please refer to correspondence dated, August 11, 2022, which addresses the proposed proprietary name, Sohonos. 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.
- 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 subject 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 drug marketed in other countries.

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

We acknowledge and confirm accepibility of your December 20, 2022, submission containing your safety update proposal.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that if NDA 215559 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of increased palovarotene exposures in subjects with moderate-to-severe hepatic impairment.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased palovarotene exposures in subjects with moderate-to-severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 215559 is approved, you will be required to conduct the following:

Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of palovarotene in subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment relative to healthy adult subjects with normal hepatic function, in accordance with the study design

described in guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Submit the subject-level datasets with the final report.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues: Because the benefits of palovarotene for treatment of patients with FOP have not been established, we are unable to conduct a meaningful benefit risk assessment. The palovarotene related risks identified during our review will be considered in the context of benefit in your future resubmission. Benefits must outweigh risks for us to approve your application.

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.

You may 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 Noreen Cabellon, Regulatory Project Manager, at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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