CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215559Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	August 16, 2023
Reviewer(s):	Po-Yin Chang, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MHS, MPH Division of Epidemiology I
Division Director:	Wei Hua, MD, PhD, MS, MHS Division of Epidemiology I
Subject:	Active Risk Identification and Analysis (ARIA) Sufficiency Assessment for Safety Surveillance of Palovarotene
Drug Name(s):	SOHONOS (palovarotene)
Application Type/Number:	NDA 215559
Submission Number:	57
Applicant:	Ipsen
TTT:	2023-5592

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	Increased flare-up episodes	Alterations in growth	Bone fractures	Pregnancy-related adverse events and birth and development outcomes of infants
-Initial				
-Interim				
-Final	X	X	X	X
Source of safety concern				
-Peri-approval	X	X	X	X
-Post-approval				
Is ARIA sufficient to help characterize the safety concern?				
-Yes				
-No	X	X	X	X
If "No", please identify the area(s) of concern.				
-Surveillance or Study Population	X	X	X	X
-Exposure				
-Outcome(s) of Interest	X	X	X	X
-Covariate(s) of Interest				X
-Surveillance Design/Analytic Tools				X

1. BACKGROUND INFORMATION

1.1. Medical Product

SOHONOS (New Drug Application [NDA] 215559, palovarotene, Ipsen Pharmaceutical Inc.) is an orally bioavailable retinoic acid receptor (RAR) gamma (RARγ) selective agonist (retinoid) that appears to interfere with activin A type I receptor ACVR1 (ALK2)-mediated bone formation indirectly and prevent abnormal endochondral bone formation.[a] The proposed indication is prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). SOHONOS is proposed as an oral capsule. The proposed dosing regimen includes chronic dosing at 5 mg daily and flare-up dosing at 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.

FOP is an ultra-rare, severely disabling disease with approximately 800 confirmed cases in the world and 200 to 300 cases in the United States in 2020.[1,2] FOP is caused by a gain-of-function mutation in the ALK2, with characterizations of malformed big toes and progressive HO in muscles, tendons, and ligaments. HO is often, but not always, associated with painful, recurrent episodes of soft tissue swelling and inflammation (termed "flare-up"). Currently, therapies to prevent the formation of HO are unavailable.

The palovarotene development program consisted of a phase 2, randomized, double-blind, placebo-controlled study in patients with FOP (Study 201), with a phase 2 open-label, single arm extension study (Study 202), and a single arm, open-label, externally controlled phase 3 study (Study 301). The external control group for Study 301 was a 36-month natural history study (NHS), also conducted by the Applicant, in pediatric and adult patients with FOP.

SOHONOS was granted Orphan Drug Designation for the treatment of FOP on July 21, 2014, and Fast Track Designation on November 25, 2014. On July 11, 2017, SOHONOS was designated as a Breakthrough Therapy.

On March 31, 2021, the Applicant submitted NDA 215559, seeking approval for an indication of prevention of HO in adults and children (aged 8 years and above for females and 10 years and above for males) with FOP. On August 21, 2021, the Applicant withdrew NDA 215559 after identifying incomplete imaging data of whole body computed tomography scans. On April 29, 2022, the Applicant re-submitted NDA 215559 for the same proposed indication.

On December 23, 2022, FDA issued a Complete Response Letter, listing major concerns including appropriateness of reliance on post-hoc analyses to support efficacy, acceptability of the external control group for evaluation of palovarotene's efficacy, and imbalance in flare-ups between palovarotene-treated and nontreated patients in the palovarotene clinical studies, among other concerns.[3]

On February 16, 2023, the Applicant re-submitted NDA 215559 for the same proposed indication.

On June 28, 2023, FDA held an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting to discuss:[4] 1a) the use of *post-hoc* analyses to support a demonstration of efficacy, 1b) the interpretability of the results using the external control of NHS; 2) the flare-up events in palovarotene-treated subjects and the relevance to benefit-risk considerations, as well as concerns

[a] In animal models, palovarotene prevents abnormal endochondral bone formation by interfering bone morphogenetic protein signaling, leading to blockade of chondrogenic and osteogenic differentiation, and reprogramming of progenitor cells into non-skeletal lineage.

about other safety issues. The majority of Advisory Committee agreed that evidence in the development program shows palovarotene is effective in patients with FOP, acknowledging limitations of *post-hoc* analyses and use of natural history study as an external control. Given the rarity and disease burden of FOP and the lack of treatment alternatives, most committee members considered the benefits of palovarotene outweigh its risks for the treatment of patients with FOP. The Advisory Committee recommended screening for premature epiphyseal closure (PPC) in pediatric patients, monitoring bone mineral density, and creation of a patient registry to better understand the patient population.

The clinical team recommends the following indication:

- Treatment to reduce the volume of new heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva

1.2. Describe the Safety Concern

Retinoids are associated with numerous class-related adverse effects, including myositis, PPC, bone demineralization, osteoporosis, "slender long bones" in children, and other musculoskeletal adverse effects.[5] These retinoids class-related adverse effects were observed in the palovarotene clinical development program,[6] raising safety concerns of increased flare-up events, alteration in growth, and bone fractures. Systemic retinoids are also known teratogens associated with multiple fetal malformations.[7]

Increased flare-ups: Retinoids have been associated with back pain, arthralgia, and myalgia. There is uncertainty as to whether palovarotene may in some cases trigger flare-ups, or symptoms that could mimic flare-ups. The clinical development program identified a greater proportion of subjects reporting flare-up events in the palovarotene-exposed subjects in the phase 3 Study 301 compared with the unexposed subjects in NHS (0.15 versus 0.07 per month).[6] Within Study 301, new flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 versus 0.12 new events per month during chronic dosing).[6]

Alterations in growth: PPC may lead to significant adverse effects on growth especially in younger age groups. In Study 301, PPC was reported based on scheduled radiograph in multiple pediatric subjects treated with palovarotene, triggering a partial clinical hold in December 2019 for the dosing of any children under age 14 years; dosing was never resumed except for children who subsequently reached age 14.[6] Palovarotene appeared to show a negative impact on growth (Table 1 below).[6]

Table 1. Standing Height Changes at Month 12, Study 301 and NHS

	NHS (Untreated)		Study 301, no PPC		Study 301, With PPC	
Age year in female/male, n	<8/10 n=22	≥8/10 to <14 n=17	<8/10 n=4	≥8/10 to <14 n=24	<8/10 n=11	≥8/10 to <14 n=7
Height mean change from baseline, cm	5.2	4.2	3.6	3.5	3.4	1.2
Growth velocity <4 cm/year	6 (27%)	7 (41%)	2 (50%)	13 (54%)	6 (55%)	6 (86%)
Growth velocity 4-5 cm/year	1 (5%)	4 (24%)	1 (25%)	2 (8%)	0	0
Growth velocity >5 cm/year	15 (68%)	6 (35%)	1 (25%)	9 (38%)	5 (46%)	1 (14%)

Source: M2.7.4 Table 39 (03/31/21 submission) *FOP*, fibrodysplasia ossificans progressiva; *n*, number of subjects; *NHS*, natural history study; *PPC*, premature epiphyseal closure

Bone fractures: The palovarotene development program identified an imbalance in new-onset vertebral fractures that were presented at study baseline (28% of palovarotene-treated subjects in Study 301 and 11% of untreated subjects in NHS).[5,6] The 12-month incidences of at least one new-onset moderate or severe fracture (Grade 2 or 3) were 8.6% (palovarotene) and 4.7% (NHS) overall, or 9.1% (palovarotene) and 4.4% (NHS) in the indicated population (females aged ≥8 years and males aged ≥10 years).[6] These assessments related to vertebral structural integrity were all *post-hoc* and not validated by FDA. An observed increased fracture risk following palovarotene use may also be confounded by multiple factors using NHS as an external control.

Pregnancy-related adverse events and birth and development outcomes of infants: Systemic retinoids are known teratogens associated with multiple fetal malformations, termed "retinoic acid embryopathy," consisting of severe craniofacial, central nervous system, cardiovascular, and thymic malformations.[7] The use of isotretinoin during pregnancy increases the risk of congenital anomalies as well as other adverse pregnancy outcomes, including spontaneous abortions, elective terminations, stillbirths, and extra-uterine pregnancies.[7] In rats exposed to palovarotene during pregnancy, multiple fetal malformations and reduced fetal survival were observed.[b] All FDA approved systemic retinoids have enhanced labeling to warn and help to mitigate the risk of teratogenicity, including a Boxed Warning for embryo-fetal toxicity, a Contraindication for pregnancy, and a Warning and Precaution for embryo-fetal toxicity.[7]

1.3. Labeling

The draft labeling for SOHONOS, as of August 10, 2023, includes Boxed Warning for Embryo-Fetal Toxicity and Premature Physeal Closure in Growing Pediatric Patient. It states that

(b) (4)

In Contraindications (Section 4), it states that

"*SOHONOS is contraindicated in the following patients:*

- During *Pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*
- (b) (4) *a history of allergy or hypersensitivity to retinoids, or to any component of this product [see Description (11)].*"

[b] These fetal malformations including cleft palate, protruding tongue, eye defects, skull abnormalities, blood vessels abnormalities, kidney, ureter, and skeletal malformations, and at higher doses, reduced fetal survival.

The relevant sections of the Warnings and Precautions (Section 5) and Use in Special Populations (Section 8) are provided in Appendix A.

1.4. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	**Increased flare-up episodes**	**Alterations in growth**	**Bone fractures**	**Pregnancy-related adverse events and birth and development outcomes of infants**
Assess a known serious risk				
Assess signals of serious risk	X	X	X	X[c]
Identify unexpected serious risk when available data indicate potential for serious risk				

1.5. Statement of Purpose

The purpose of the registry study of interest is to further characterize the following safety concerns in palovarotene exposed and unexposed patients with FOP. The study intends to collect data for 10 years in a cohort of least 100 patients with FOP. Given FOP is an extremely rare disease, descriptive results are anticipated from the intended registry study.

- Increased flare-up episodes
- Alterations in growth
- Bone fractures
- Pregnancy-related adverse events and birth and development outcomes of infants

1.6. Effect Size of Interest or Estimated Sample Size Desired

A cohort of at least 100 patients with FOP, half of whom will be pediatric (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys) and approximately two-thirds of whom will be exposed to palovarotene.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

[c] Retinoids have a class-wide teratogenic concern, but there was no human data of pregnancy-exposure in the palovarotene development program to inform the teratogenic effect on specific organ systems of infants. There is also a lack of human data on developmental outcomes in infants and pregnancy-related adverse events.

The desired study aims to follow the study population of individuals with FOP for 10 years. FOP is an ultra-rare disease with approximately 800 cases in the world and 200 to 300 cases in the United States in 2020.[1,2]

2.2 Is ARIA sufficient to assess the intended population?

No, ARIA system is likely insufficient to capture the target population of patients with FOP:

- Currently, there is no validated claims-based algorithm using ICD-10 diagnosis code specific for FOP. Indeed, a 2017 study suggests a positive predictive value <10% using ICD-10 code M61.1 (myositis ossificans progressive) to identify patients with FOP in France.[8]
- The current ARIA system lacks molecular genetic test results to confirm FOP. These tests may include specific molecular genetic studies that detect missense mutations or "in frame" deletions in the protein-encoding region of the *ACVR1* gene.[9]

In addition, ARIA is likely insufficient to assess the intended population for 10 years. ARIA typically has only 2-3 years of follow-up. In the Sentinel database, roughly 26% of the patients (56.6 million patients) have cumulative enrollment for over 5 years by July 2022.[10]

3 EXPOSURES

3.1 Treatment Exposure(s)

If approved, exposure to palovarotene will likely be adequately captured via NDC codes.

3.2 Comparator Exposure(s)

Patients with FOP unexposed to palovarotene

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify exposure of palovarotene.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interests include the following:

- Increased flare-up episodes
- Alterations in growth
- Bone fractures
- Pregnancy-related adverse events and birth and development outcomes of infants

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is insufficient to assess flare-up episodes, alterations in growth, bone fractures, and pregnancy-related adverse events and birth and development outcomes of infants.

(1) A **flare-up** event in patients with FOP is painful, recurrent episodes of soft tissue swelling and inflammation. Medical imaging and patient reporting outcomes (e.g., soft tissue swelling, pain, decreased range of motion, stiffness, redness, warmth) are needed to identify a flare-up episode. ARIA capacities currently do not include medical imaging and patient reporting outcomes.

(2) Medical records are needed to assess **alterations in growth** (e.g., a slower-than-expected growth velocity or a lower-than-expected final adult height among subjects with FOP). Currently, ARIA lacks access to standing height or body length across the Sentinel system.

(3) ARIA is insufficient to assess all **bone fractures.** Given the signal observed in the clinical development program, algorithms validated with good performance are needed to ascertain the outcome events and characterize the risk. Validated claims-based algorithms are described in the literature for some fractures associated with osteoporosis,[11] but not for other important fracture sites (e.g., skull, face, fingers, toes).

(4) ARIA lacks access to detailed narratives. Having detailed case narratives are deemed necessary to identify and validate **pregnancy-related adverse events** (e.g., preeclampsia and gestational diabetes) **and birth and developmental outcomes** (e.g., major congenital malformation, spontaneous abortions, stillbirths, and small for gestational age), assess exposure-outcome temporality, and to conduct causality assessments.

5 COVARIATES

5.1 Covariates of Interest

Covariates of interest may include demographics, such as age and gender.

For pregnancy-related and birth and developmental adverse outcomes, covariates of interest may include smoking, alcohol consumption, occupational exposure, and illicit drug use.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA system is insufficient to assess covariates of interest for pregnancy-related adverse events and birth and developmental adverse outcomes because key covariates of interest (e.g., smoking, alcohol use, illicit drug use) are not generally well captured in claims data.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study of interest is a prospective observational registry study intending to collect 10-year safety data from a minimum of 100 subjects.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA tools are insufficient to assess the question of interest for pregnancy-related adverse events and birth and development outcomes of infants. Although retinoids are a class of known teratogen, the teratogenic effect to specific organ systems is unclear and therefore data mining methods are needed. ARIA data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug safety in

pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery. ARIA analytic tools are not available yet for non-live birth pregnancies.

7 NEXT STEPS

We determine that the Sentinel ARIA is insufficient to evaluate the long-term safety profile of SOHONOS due to the inabilities to adequately identify and ascertain the study population, outcomes of interest, and certain covariates of interest.

The proposed PMR language, as of August 14, 2023:

Conduct a prospective observational registry study with safety objectives of comparing palovarotene exposed and unexposed patients with fibrodysplasia ossificans progressiva (FOP). Evaluate risks of increased flare-up episodes, alterations in growth, and bone fractures. The registry should also collect information on women exposed to palovarotene during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant's first year of life. Begin safety data collection within 90 days of protocol agreement. After protocol finalization, the PMR progress report should be submitted annually as part of the NDA annual report that also includes an evaluation of the effectiveness of meeting the registry study's safety objectives. Collect 10-year safety data from a minimum of 100 subjects, approximately half of whom will be pediatric patients (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys), and approximately two-thirds of whom will be exposed to palovarotene.

REFERENCE

1. Fibrodysplasia ossificans progressiva. Updated July 11, 2022. https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva

2. Liljesthröm M, Pignolo RJ, Kaplan FS. Epidemiology of the global fibrodysplasia ossificans progressiva (FOP) community. *J Rare Dis Res Treat*. 2020;5(2):31-6.

3. U.S. Food and Drug Administration. *NDA 215559 Complete Response. Reference ID: 5100155* December 23, 2022.

4. U.S. Food and Drug Administration. Meeting of the Endocrinologic Drugs Advisory Committee Meeting Announcement Accessed July 25, 2023. https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-28-2023-meeting-endocrinologic-drugs-advisory-committee-meeting-announcement-06282023#event-materials

5. U.S. Food and Drug Administration. FDA Briefing Information, June 28, 2023 Meeting of the Endocrinologic Drugs Advisory Committee. Accessed July 25, 2023. https://www.fda.gov/media/169787/download

6. U.S. Food and Drug Administration. Division of General Endocrinology (DGE) Integrated Review for NDA 215559 Sohonos (palovarotene capsules). Reference ID: 2099786. December 23, 2022.

7. Limpert J. Division of Pediatrics and Maternal Health Review of Pregnancy and Lactation Labeling for NDA 215559 Sohonos (palovarotene capsules). Reference ID: 5064429. October 18, 2022.

8. Baujat G, Choquet R, Bouée S, et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in France: an estimate based on a record linkage of two national databases. *Orphanet Journal of Rare Diseases*. 2017/06/30 2017;12(1):123. doi:10.1186/s13023-017-0674-5

9. Tis JE. UpToDate: Fibrodysplasia ossificans progressive. Updated October 3, 2022. Accessed August 4, 2023. https://www.uptodate.com/contents/fibrodysplasia-ossificans-progressiva

10. U.S. FDA Sentinel Initiatives. Key Database Statistics. October 12, 2022. Accessed August 4, 2023. https://www.sentinelinitiative.org/about/key-database-statistics

11. Wright NC, Daigle SG, Melton ME, Delzell ES, Balasubramanian A, Curtis JR. The design and validation of a new algorithm to identify incident fractures in administrative claims data. *Journal of Bone and Mineral Research*. 2019;34(10):1798-1807.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 4, 2023
To:	Noreen Cabellon, MS Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SOHONOS (palovarotene)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 215559
Applicant:	Ipsen Biopharmaceuticals

1 INTRODUCTION

On April 29, 2022, Ipsen Biopharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA)-Resubmission for SOHONOS (palovarotene) capsules, for oral use (NDA 215559). The purpose of this submission is to seek approval of SOHONOS (palovarotene) capsules for the prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressive (FOP).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on March 8, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SOHONOS (palovarotene) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft SOHONOS (palovarotene) MG received on April 29, 2022, and received by DMPP and OPDP on July 21, 2023.
- Draft SOHONOS (palovarotene) Prescribing Information (PI) received on April 29, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on July 21, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 3, 2023

To: Noreen Cabellon, Regulatory Project Manager
Division of General Endocrinology (DGE)

LaiMing Lee, Associate Director for Labeling (DGE)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for SOHONOS (palovarotene) capsules, for oral use

NDA: 215559

Background:
In response to DGE's consult request dated March 7, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the NDA resubmission for SOHONOS (palovarotene) capsules, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 21, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on October 11, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 16, 2023
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 215559
Product Name, Dosage Form, and Strength:	Sohonos (palovarotene) capsules, 1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ipsen Biopharmaceuticals, Inc
FDA Received Date:	April 29, 2022, October 11, 2022, and February 16, 2023
TTT ID #:	2022-603-1
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

Ipsen Biopharmaceuticals, Inc. submitted a Class 2 Resubmission for Sohonos (palovarotene) topical gel (NDA 215559).[a]

As part of the approval process for Sohonos (palovarotene) capsules, the Division of General Endocrinology (DGE) requested that we review the proposed Sohonos Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On March 31, 2021, Ipsen Biopharmaceuticals, Inc. submitted NDA 215559, a 505(b)(1), for palovarotene for the prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressiva (FOP).[b]

On August 12, 2021, Ipsen submitted a request to withdraw the New Drug Application (NDA) 215559. The applicant later resubmitted the application on April 29, 2022.[c, d]

We previously reviewed the proposed labeling submitted and found the labeling could be improved to promote the safe use of this product from a medication error perspective on September 22, 2022.[e] Subsequently, Ipsen submitted revised container labels and carton labeling on October 11, 2022. The revisions are in response to recommendations that we made during the previous label and labeling review.

However, NDA 215559 received a Complete Response (CR) on December 23, 2022.

Ipsen responded to the CR on February 16, 2023. We note Ipsen did not resubmit labels and labeling with the CR response.

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[a] Cover Letter: Class 2 Resubmission – Complete Response for Sohonos NDA 215559. Cambridge (MA): Ipsen Biopharmaceuticals, Inc.; 2023 FEB 16: Available from: \\CDSESUB1\EVSPROD\nda215559\0057\m1\us\12-cover-letter\cover-letter-0057.pdf

[b] Cover letter: Original NDA 215559 for Sohonos. Cambridge (MA): Ipsen Biopharmaceuticals, Inc.; 2021 MAR 31: Available from: \\CDSESUB1\EVSPROD\nda215559\0001\m1\us\12-cover-letter\cover-letter.pdf

[c] Cover Letter: NDA Withdrawal Notice for Sohonos NDA 215559. Cambridge (MA): Ipsen Biopharmaceuticals, Inc.; 2021 AUG 12: Available from: \\CDSESUB1\EVSPROD\nda215559\0028\m1\us\12-cover-letter\cover-letter-0028.pdf

[d] Cover Letter: NDA -Resubmission for Sohonos NDA 215559: Cambridge(MA):Ipsen Biopharmaceuticals, Inc.; 2022 APR 29: Available from: \\CDSESUB1\EVSPROD\nda215559\0029\m1\us\12-cover-letter\cover-letter-0029.pdf

[e] Howard, C. Label and Labeling Review for Sohonos (NDA 215559). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 22.TTT ID# 2022-603.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

We previously recommended to revise the container labels to add the linear barcode. However, per the Applicant, the container label with the blisters cannot be physically detached from the outer carton labeling and thus the container and the carton can be considered as a signal unit; additionally, the product will be distributed to patients through a single specialty pharmacy. We find the rationale acceptable. The Applicant implemented all of our other recommendations for the container labels and the carton labeling and we have no additional recommendations for the container labels and the carton labeling at this time. The proposed Prescribing Information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division.

4 RECOMMEDATIONS FOR DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information and Medication Guide – General Issues			
1.			(b) (4)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.3 (Usual Recommended Dosage and Duration), the statement: (b) (4) is inconsistent with dosing information found in Table 1 in	Inconsistent dosage statements may cause confusion amongst users and potentially cause administration errors.	We recommend clarifying the recommended dosing statement at the beginning of Section 2.3 to specify the weight band or age it applies to and refer to the table for other weight bands. We defer to the clinical team to revise language as appropriate.

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Section 2.3 for patients less than 60 kg as the statement above applies only to patients weighing 60 kg or more.		
2.	In Table 1 in Section 2.3, we note the use of the error prone symbols "≥"and "<". Additionally, we note the lack of a heading for the weight band column as well spacing between the weight and the weight unit (e.g., 60kg)	The symbols '<', '≤', '>', and '≥' are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration section, could lead to medication errors.	Consider replacing the symbols ">" and "≤" with their intended meanings to prevent misinterpretation and confusion. Alternatively, if appropriate, consider revising the body weights to as follows: • Revise "40-<60kg" to "40 kg to 59.9 kg", "20-<40kg" to "20 kg to 39.9 kg", etc. Additionally, we recommend adding a heading to the top of the weight band column for clarity and adding spacing in between the weight and the weight unit (e.g., 60 kg instead of 60kg).

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Sohonos that Ipsen Biopharmaceuticals, Inc submitted on April 29, 2022.

Table 3. Relevant Product Information for Sohonos	
Initial Approval Date	N/A
Active Ingredient	palovarotene
Indication	Prevention of heterotopic ossification in adults and pediatric patients (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)
Route of Administration	oral
Dosage Form	capsules
Strength	1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg
Dose and Frequency	Chronic/Flare-Up Regimen: The recommended dosing consists of 5 mg once daily (chronic treatment), with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment), even if symptoms resolve earlier. Dosing is weight-adjusted (b) (4) (b) (4) If a dose of medication is missed, patients should take a missed dose as soon as possible. If the dose has been missed by more than 6 hours, instruct the patient to skip the missed dose and continue with the next scheduled dose. Instruct the patient to not take two doses at the same time or in the same day.

<table>
<tr>
<td></td>
<td>Dosage Modification for Adverse Reactions:
If the patient experiences adverse reactions that require dose reduction during either the chronic or flare-up (weeks 1-12) SOHONOS treatment, the daily dose should be reduced to the next lower dose as shown in Table 2 at the discretion of the physician; additional dose reduction should occur if adverse reactions do not improve. If the patient is already receiving the lowest possible tolerated dose, then consideration should be given to discontinue therapy temporarily or permanently (b) (4) Subsequent flare-up treatment should be initiated at the same reduced treatment that was tolerated previously.

Table 2:
Dose Reduction of SOHONOS for Flare-Up and Chronic Treatment
<table>
<tr><th>Dose Prescribed</th><th>Reduced Dose</th></tr>
<tr><td>20 mg</td><td>15 mg</td></tr>
<tr><td>15 mg</td><td>12.5 mg</td></tr>
<tr><td>12.5 mg</td><td>10 mg</td></tr>
<tr><td>10 mg</td><td>7.5 mg</td></tr>
<tr><td>7.5 mg</td><td>5 mg</td></tr>
<tr><td>6 mg</td><td>4 mg</td></tr>
<tr><td>5 mg</td><td>2.5 mg</td></tr>
<tr><td>4 mg</td><td>2 mg</td></tr>
<tr><td>3 mg</td><td>1.5 mg</td></tr>
<tr><td>2.5 mg</td><td>1 mg</td></tr>
</table>
(b) (4)</td>
</tr>
<tr>
<td>How Supplied</td>
<td>An opaque white elongated hard-gelatin capsule. SOHONOS is available in size “0”capsule and supplied as a blister strip</td>
</tr>
</table>

<table>
<tr><td></td><td>containing 14 capsules in a child resistant carton. Capsule contains white to off-white powder.

Capsules' strengths, imprints, and NDC numbers
<table><tr><td>Strength (mg)</td><td>Imprint</td><td>NDC</td></tr><tr><td>1</td><td>PVO 1</td><td>15054-0010-1</td></tr><tr><td>1.5</td><td>PVO 1.5</td><td>15054-0015-1</td></tr><tr><td>2.5</td><td>PVO 2.5</td><td>15054-0025-1</td></tr><tr><td>5</td><td>PVO 5</td><td>15054-0050-1</td></tr><tr><td>10</td><td>PVO 10</td><td>15054-0100-1</td></tr></table></td></tr>
<tr><td rowspan="3">Storage</td><td>This package is child-resistant. Keep out of reach of pediatric patients. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room temperature]. Must be kept in the original carton to protect from light.</td></tr>
<tr><td>(b) (4)</td></tr>
<tr><td>SOHONOS capsules may be opened and the contents emptied on a teaspoon of soft food and taken immediately. If not taken immediately, it can be taken after a maximum of one hour after the sprinkling, provided it was maintained at room temperature and not exposed to direct sunlight.</td></tr>
<tr><td>Container Closure</td><td>Blister strip containing 14 capsules in a child resistant carton.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 10, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'palovarotene'. Our search identified previous review[f], and we considered our previous recommendations to see if they are applicable for this current review.

[f] Howard, C. Label and Labeling Review for Sohonos (NDA 215559). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 22. TTT ID No.: 2022-603.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Sohonos labels and labeling submitted by Ipsen Biopharmaceuticals, Inc.

- Container label(s) received on October 11, 2022
- Carton labeling received on October 11, 2022
- Medication Guide and Prescribing Information (Image not shown) received on April 29, 2022, available from \\CDSESUB1\EVSPROD\nda215559\0029\m1\us\114-labeling\114a-draft-label\uspi-final-draft-v1-1-annotated.pdf

F.2 Label and Labeling Images

(b)(4)

4 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

CORWIN D HOWARD
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MADHURI R PATEL
05/16/2023 03:03:24 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Memorandum: Review of Natural History Study

Date:	December 13, 2022
Reviewer:	Po-Yin Chang, PhD Division of Epidemiology I (DEPI-I) Office of Surveillance and Epidemiology (OSE)
Team Leader:	Yandong Qiang, MD, PhD, MPH, MHS DEPI-I, OSE
Acting Deputy Director:	Wei Hua, MD, PhD, MS, MPH DEPI-I, OSE
Drug Name:	SOHONOS (Palovarotene)
Subject:	Assessment of Comparability Between the Natural History Study and the Phase 3, Single-arm, Open-label Clinical Study in the Palovarotene New Drug Application
Application Type/Number:	NDA 215559
Submission Number:	29, 54
Applicant:	Ipsen Biopharmaceuticals Inc
OSE RCM #:	2021-1428

Introduction

This Division of Epidemiology-I (DEPI-I) memorandum provides the Division of General Endocrinology (DGE) with assessments and comments regarding the comparability of subjects with fibrodysplasia ossificans progressiva (FOP) in the Natural History Study (NHS) and subjects with FOP who received palovarotene in the phase 3, single-arm, open-label clinical study (namely, Study PVO-1A-301 -- the MOVE trial).

The NHS was designed specifically for the palovarotene development program during the pre-Investigational New Drug (IND) phase to collect information of natural history of FOP. On August 24, 2021, the Real-World Evidence (RWE) Subcommittee determined that this pre-IND specific NHS was not considered an RWE submission because the study collected natural history data in the same trial setting as the MOVE trial beyond routine medical practice.[a]

DEPI-I reviewed the following study reports submitted on April 29, 2022:

- Clinical Study Report for Protocol PVO-1A-001, titled "A Natural History, Non-Interventional, Two-Part Study in Subjects with Fibrodysplasia Ossificans Progressiva (FOP), Amendment 2," dated March 21, 2022
- Interim Clinical Study Report for Protocol PVO-1A-301, MOVE Trial, titled "A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)," dated April 4, 2022

Background

SOHONOS (New Drug Application [NDA] 215559, palovarotene, Ipsen Pharmaceutical Inc.) is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist. According to the interim clinical study report of the MOVE trial, RARγ agonists impair heterotopic endochondral ossification by redirecting prechondrogenic mesenchymal stem cells to a non-osseous soft tissue fate.

SOHONOS was granted Orphan Drug Designation for the treatment of FOP on July 21, 2014, and Fast Track Designation on November 25, 2014. On July 11, 2017, SOHONO was designated as a Breakthrough Therapy for the prevention of heterotopic ossification (HO) in patients with FOP.

FOP is a rare, severely disabling congenital connective tissue disease with an approximately 800 confirmed cases globally and an estimated prevalence of 0.6–1.3 per million individuals in 2020.[b] FOP is caused by a recurrent heterozygous activating mutation of activin receptor A type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor, with characterizations of malformed big toes and progressive HO in muscles, tendons, and ligaments. HO is often, but not always, associated with painful, recurrent episodes of soft tissue swelling (termed "flare-ups"). Currently, there are no available therapies to prevent the formation of HO.

[a] Real-World Evidence Subcommittee. Presentation, titled "Natural History Studies and the Role of the RWE SC," in CDER Medical Policy-Real World Evidence meeting, August 24, 2021.
[b] Pignolo RJ, Hsiao EC, Baujat G, et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in the United States: estimate from three treatment centers and a patient organization. *Orphanet J Rare Dis.* 2021;16(1):350.

On March 31, 2021, the applicant submitted NDA 215559, proposing an indication of prevention of HO in adults and children (aged 8 years and above for females and 10 years and above for males) with FOP. On August 21, 2021, the applicant withdrew NDA 215559 after identifying incomplete imaging data of whole body computed tomography (WBCT) scans.[c] On April 29, 2022, the applicant re-submitted NDA 215559 for the same indication of palovarotene.[d]

Overview of Natural History Study (NHS) and Study-PVO-1A-301 (MOVE Trial)

Natural History Study (NHS)

NHS was a multicenter, non-interventional, longitudinal, two-part study to investigate the natural disease history in subjects with FOP. NHS aimed to gain insight into disease progression, impacts on subjects' physical function, and relevant clinical features of FOP.[e] NHS included protocol-specified assessments of FOP at prespecified timepoints from December 2014 to April 2020. The first part of NHS enrolled ten subjects aged 18 years or older who received low-dose WBCT excluding head or dual energy x-ray absorptiometry (DEXA) scans, to determine the appropriate modality for assessing the total body HO. The NHS imaging committee determined low-dose WBCT is the preferred modality. The second part of NHS enrolled 117 subjects aged 65 or younger, including the ten subjects in the first part, and followed 114 of the 117 subjects for up to 36 months.[f]

Major study objectives included evaluation of the progression of new bone deposition and change in total body HO burden from baseline; changes in HO burden in relation to functional endpoints and patient-reported outcomes (PROs);[g] number of flare-up events reported by the subject per year; as well as impact of flare-up on FOP outcomes.

NHS assessed HO volume by WBCT scan at baseline, annually at study sites, and within 2 months after study discontinuation; functional endpoints (e.g., range of motion) at baseline and annually at study sites; and PROs every six months by phone and annually at study sites. NHS

[c] In the NDA 215559 resubmission cover letter, the Applicant clarified the NDA was withdrawn because 1) end-of-study WBCT scan data in eight NHS subjects were omitted by vender (that is, these WBCT scans were wrongly read as the MOVE trial baseline, not the end-of-study visit for NHS); 2) incomplete WBCT scan data required re-reads in three subjects of MOVE trial and one subject of phase 2 study PVO-1A-202. All four subjects lacked imaging data of lower legs and one subject lacked data of the shoulders, chest, and upper back.

[d] In the NDA 215559 resubmission cover letter, the Applicant indicated that the resubmission includes 1) all updates from end-of-study NHS scans for the eight NHS subjects who transitioned to MOVE trial, 2) all updates from end-of-study NHS scans for five subjects who transitioned to Study PVO-1A-202 (identified during Applicant's imaging data verification), and 3) WBCT scan re-reads for four subjects who initially had incomplete WBCT data for all anatomy regions.

[e] Clinical features that may be useful for disease diagnosis, monitoring disease progression and potential treatment effects in subsequent interventional studies.

[f] Three subjects were excluded because two did not have R206H mutation and the third did not have FOP.

[g] Functional endpoints may include range of motion assessed by Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP, pulmonary function tests, electrocardiogram, etc. PROs included age-appropriate FOP-Physical Function Questionnaire (PFQ), age-appropriate PROMIS Global Health Scale, and FOP Assistive Devices and Adaptations Questionnaire. FOP-PFQ and Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale were additionally assessed at Study Weeks 1 to 3 during telephone contacts.

collected information of patient-reported flare-up events, concomitant medications, and adverse events (AEs) via telephone (every three months since October 2017) and annually at study sites.

NHS defined a flare-up event as having ≥2 of the six patient-reported symptoms (i.e., pain, swelling, redness, decreased range of motion, stiffness, and warmth). NHS did not require investigators to confirm possible flare-up events. NHS stopped in-person assessments of flare-up events since October 2017 after collecting flare-up related data among 82 of the 114 subjects (71.9%) for analysis.[h]

Statistical analyses were all descriptive, and the results were presented in the overall study population and by prespecified age groups (<8, eight to <15, 15 to <25, and 25 to ≤65 years).

Table 1 below compares the design of NHS and MOVE trial.

Of the 114 NHS subjects with up to 36 months of follow-up, 33 (28.9%) completed the follow-up and 81 (71.1%) discontinued the study. Among the 81 subjects who discontinued NHS, 60 subjects transitioned into interventional studies of palovarotene, including 39 subjects into the MOVE trial (also known as "the transition subjects"), 13 subjects into the phase 2 study PVO-1A-202B, and eight subjects into the phase 2 study PVO-1A-201 at the time of flare-up before their 12-month assessment. Among the remaining 21 subjects who discontinued NHS, nine withdrew consent, six participated into non-applicant-conducted interventional studies, two had protocol noncompliance, one died, one was lost to follow-up, and two discontinued for other reasons.

Study PVO-1A-301 (MOVE trial)

MOVE trial was a phase 3, single-arm, open label study that aimed to evaluate the efficacy and safety of palovarotene among adult and pediatric subjects with FOP during the 24-month follow-up from November 2017 to February 2020.

Subjects received a chronic maintenance dose of palovarotene and a separate flare-up-based regimen[i] for investigator-confirmed flare-up events (i.e., having ≥1 patient-reported flare-up related symptom). At baseline screening and every six months during follow-up, subjects underwent procedures and assessments at study sites, including low-dose WBCT (excluding head), range of motion (assessed by Cumulative Analogue Joint Involvement Scale [CAJIS]), and PROs. MOVE trial collected information of AEs and concomitant medications use at every contact (by phone or at study stie).

The primary objective was to assess the efficacy of palovarotene in reducing new HO volume among 99 subjects[j] who received at least one chronic dose of palovarotene in MOVE trial with the 111 untreated NHS subjects. Primary efficacy endpoint was an annualized change in new HO volume from baseline. Prespecified definition of change in new HO volume was the sum of the increase in HO volume across all body regions for which new HO occurred.

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[h] By October 2017, the Applicant considered flare-up data were sufficient for statistical analyses and discontinued flare-up data collection. During December 2014 and October 2017, 82 of the 114 subjects (71.9%) reported 229 flare-up events and provided information for functional endpoints, PROs, and imaging data.

[i] Maintenance dose: 5 mg once daily (or weight-adjusted 5 mg once daily in skeletally immature subjects). Flare-up-based regimen: 20 mg for four weeks and 10 mg for eight weeks.

[j] These 99 subjects had R206H mutation and were not previously exposed to palovarotene.

The major secondary objectives were to compare the flare-up rate and the proportion of subjects reporting at least one flare-up between MOVE trial and NHS.[k]

For the primary efficacy objective, the Applicant conducted a Bayesian compound Poisson model (referred to as Bayesian model hereafter) that included the change in new HO volume as a function of the number of body regions with non-negative new HO (i.e., change in HO volume >0 mm^3) and the new HO volume (mm^3) per region that incorporated a square-root transformation.[l] If the change in new HO volume per region, or the change in total HO volume from baseline or last measurement, was less than zero, the Applicant set the change in new HO volume to zero in the Bayesian model. The applicant also performed a series of *post-hoc* weighted linear mixed effect (wLME) analyses, with or without square-root transformation of change in new HO volume.[m] For all analyses, body regions with non-evaluable HO volume at a timepoint were presented as having no new HO and the volumes were set to zero.

In all analyses, sex and age at the time of WBCT scans were adjusted for in estimating annual change in new HO volume. To assess the potential impact of differences in baseline characteristics between two studies, the Applicant performed *post-hoc* analyses controlling for baseline HO volume divided by age, baseline age, sex, months since last flare-up, and baseline CAJIS score.

To assess the robustness of analysis results, the Applicant also performed a series of additional sensitivity analyses,[n] including a wLME analysis of the 39 NHS subjects who transitioned to MOVE trial and who had an annualized change in new HO volume in both studies. Among these 39 transition subjects, the mean age (range) was 13 (4-29) years at NHS baseline and 15 (7-32) years at MOVE trial baseline. Baseline HO volume divided by age and origin of study site were the only covariates adjusted for in the analysis for these 39 transition subjects.

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[k] Secondary or exploratory objectives of MOVE trial included evaluation of the effect of palovarotene on 1) flare-up rate and proportion of subjects reporting at least one flare-up; 2) range of motion assessed by the CAJIS for FOP; 3) physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (FOP-PFQ); 4) physical and mental health using age-appropriate forms of the PROMIS Global Health Scale. The secondary objective also included pharmacokinetics evaluation of palovarotene.

[l] In Bayesian model, the increase in new HO volume per region was defined as the square-root of the non-negative volumetric increase in that region.

[m] In wLME analysis without square-root transformation, the annualized change in new HO volume, including negative new HO volumes, was analyzed as reported.

[n] These analyses included analyses restricted to the 39 transition subjects; restricted to subjects with up to 15 or 24 months of follow-up; with imputation methods to address missing data; using generalized estimating equation (GEE); comparing only yearly HO volume data in MOVE trial with NHS; capping the maximum annualized new HO volume at 100,000 mm^3; and using Wilcox rank-sum test.

Table 1. Study Design for Natural History Study and MOVE Trial (DEPI-I Reviewer Summary)

Study Design	Natural History Study (NHS)	Study-PVO-1A-301 (MOVE trial)
Study period	December 18, 2014, to April 9, 2020	November 30, 2017, to February 28, 2020 (data cut-off of the final report Amendment 2)
Subjects	114 subjects, age ≤65 years, with FOP; all with R206H mutation • 33 subjects completed the follow-up of 36 months • 81 subjects discontinued the study	107 subjects, age ≥4 years, with FOP • 99 with the R206H mutation with no previous palovarotene exposure • Eight excluded (other mutations or participated in a phase 2 study)
Design	Multicenter (same study sites as MOVE trial), non-interventional, longitudinal study Part A: Evaluation of imaging modalities for assessing HO Part B: Natural history study for up to 36 months	Phase 3, multicenter, single-arm, open-label study Part A (main part): Efficacy and safety of palovarotene use for up to 24 months (chronic dose and flare-up regimen) Part B**:** 24-month extension of part A
Objectives	Baseline: To investigate • Optimal method of WBCT and DEXA for assessing HO in ten subjects age ≥18 years • Associations between duration of FOP and HO volume, functional endpoints, and PROs • HO volume in relation to functional endpoints and PROs Disease progression: To evaluate • Progression of new bone deposition and change in HO volume by WBCT • Change in HO volume in association with changes in functional endpoints, PROs • Changes in HO status and annualized new HO volume • Extent of HO and functional endpoints at flare-up site among patients with flare-up	Primary objectives: To evaluate • Efficacy of palovarotene in decreasing new HO volume compared with NHS subjects • Safety of palovarotene Secondary objectives: • To evaluate the followings between MOVE trial and NHS o Flare-up rate o Proportion of subjects reporting at least one flare-up o Range of motion, assessed by CAJIS o Physical function, using FOP-Physical Function Questionnaire (FOP-PFQ) o Physical and mental health, assessed by Patient Reported Outcomes Measurement Information System (PROMIS) scale • Pharmacokinetics (PK) of palovarotene.
Efficacy Endpoint	*Post-hoc* analysis of disease progression data, describing: • Annualized change in new HO volume by WBCT • HO volume at annual visit • Number of new HO at annual visit • Number of flare-up events	Primary: • Annualized change in new HO volume by WBCT Other Endpoints • Any new HO at Month 12 • Number of body regions with new HO at Month 12 • Flare-up events at Month 12

Table 1. Study Design for Natural History Study and MOVE Trial (DEPI-I Reviewer Summary)

Study Design	Natural History Study (NHS)	Study-PVO-1A-301 (MOVE trial)
Flare-up Assessment	• Self-reported two of the six symptoms: Pain, swelling, redness, decreased range of motion, stiffness, and warmth • Investigator confirmation not required • Weekly phone contact for flare-up assessment of all patient-reported events, with or without in-clinic evaluation, until flare-up symptoms resolved	• Self-reported one of the following (but not limited to) six flare-up symptoms: Pain, swelling, redness, decreased range of motion, stiffness, and warmth • Investigator confirmed flare-up events and initiated flare-up-based treatment
Follow-up	• Annual visit: Image exams, CAJIS, knee and hand/wrist x-ray, serum chemistry, hematology, range of movement assessment, electronic cardiac echogram (EKG). • Every 3 months by phone: new flare-up occurrence, AEs, concomitant drug use • Every 6 months: PRQs (e.g., FOP-PFQ, PROMIS)	• Every 6 months for 2 years and annually after: Imaging exams, PROs, knee and hand-wrist X-ray, serum chemistry, hematology, EKG • Suicidal ideation and behaviors: every 3 months

DEPI-I Assessment

DEPI-I reviewer has the following comments regarding comparability of NHS and MOVE trial study population.

First, baseline characteristics, FOP disease severity, and HO burden among NHS subjects were likely not comparable to palovarotene-treated subjects in MOVE trial. Compared with MOVE trial subjects, NHS subjects at baseline appeared to be older, experience more flare-up evens within the past 12 months, report more symptoms in the last flare-up event, have a greater prevalence of comorbid conditions, and have a larger baseline HO volume, a greater CAJIS score and a higher FOP-PFQ score. In comparative analyses of change in HO volume between the two studies, baseline disease severity and risk factors for HO formation will need to be carefully considered and properly addressed.

Second, differential loss to follow-up between the two studies may lead to biased results that are not addressable by controlling for baseline characteristics. In NHS, 71% of the subjects discontinued follow-up whereas 17.8% of the MOVE trial subjects discontinued follow-up. NHS subjects may choose to discontinue follow-up prematurely and to enroll in interventional studies because of disease progression or outcome-related factors. Loss to follow-up in MOVE trial subjects may not be similarly related to such factors.

Third, schedules of imaging assessment for HO were different between NHS and MOVE trial (i.e., annual vs 6-month WBCT assessment), resulting in potential bias with uncertain direction. Changes from baseline in HO volume were measured over various time periods in the two studies. Therefore, the primary efficacy endpoint calculation relied on different underlying assumptions (e.g., constant risk, uniform change). For example, the annualized change in new HO volume may be calculated from a period of 12 months, 24 months, or 36 months in NHS, in contrast to a period spanning from 6 months to 24 months in MOVE trial.

Fourth, definition and requirement for confirmation of flare-up events were different between the two studies. Investigators of MOVE trial confirmed patient-reported flare-up events presenting with at least one flare-up related symptom. In contrast, in NHS, patients were required to have at least two self-reported symptoms which may or may not be confirmed by investigators. Therefore, with the requirement for more patient-reported symptoms, flare-ups in NHS may be underestimated when applying the flare-up definition in MOVE trial. On the other hand, without investigators' confirmation, some patient-reported flare-ups in NHS could be misclassified, resulting in an overestimated rate of flare-ups.

Fifth, results from analyses restricted to the 39 transition subjects provided important insights but were subject to bias from time-varying variables. These 39 transition subjects can serve as their own controls, reducing the impact of time-independent variables such as sex, race/ethnicity, and measured or unmeasured genetic factors. However, these transition subjects may potentially have imbalanced baseline factors that change over time, including age, range of motion (CAJIS score), number of flare-ups, HO volume, and number of body region with HO. Applicant's p*ost-hoc* wLME analysis for these transition subjects adjusted only for origin of study site and baseline HO volume divided by age. The results may be impacted by time-varying factors such as disease severity and progression. Furthermore, results for these transition subjects were also subject to bias from various schedules of imaging assessment as well as inconsistent definition and requirement for confirmation of flare-up events.

Sixth, comparative analysis results from the prespecified Bayesian model with square-root transformation did not reach statistical significance. Statistical significance was achieved in a series of *post-hoc* analyses of wLME. DEPI-I reviewer defers to Division of Biometrics (DB)-II to assess the statistical approaches. Notably, age and sex appear to be strong confounding factors or effect modifiers for palovarotene's efficacy in reducing change in new HO volume over time (e.g., no effect in patients age ≥18 years and in female patients). Without exact matching on (or stratification by) age and sex for individual patients, residual cofounding remains an issue in Applicant's *post-hoc* analyses. FDA internal *post-hoc* analyses may consider comparing subjects of the two studies matched on age and sex. If the exact matching approach is deemed infeasible, one alternative may be benchmark analyses using the NHS age-and-sex-specific annualized change in new HO volume as reference. DEPI-I communicated with DB-II in electronic mails regarding the abovementioned exact matching and benchmark analyses. DB-II considers the exact matching analysis a suitable approach.

Conclusion

Given the important concerns about the comparability between NHS and MOVE trial study populations, such as differences in baseline characteristics and HO burden, differential loss to follow-up, various schedules of imaging assessment for HO, and inconsistent definition and requirement for confirmation of flare-up events, NHS might not be adequate to serve as an external control to assess the efficacy of palovarotene. Careful consideration and handling of these issues in *post-hoc* analyses may help improve interpretability of results.

Recommendations to DGE

DEPI-I recommends that DGE consider *post-hoc* analyses with confounding control approaches and comparing the two study populations matched on age and sex.

DGE may also consider additional analyses that use a unified time-period for estimating annualized change in new HO volume and use a consistent definition for flare-up events across the two studies.

These abovementioned recommendations have been discussed during the mid-cycle meeting on July 26, 2022, and via electronic mails to DGE and DB-II on August 3 and 15, 2022. DGE and DB-II are generally in agreement with DEPI-I's recommendations.

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting and FDA Landmark Analyses for Partially Addressing the Abovementioned Concerns

A EMDAC meeting was originally scheduled for October 31, 2022, to discuss the evidence of effectiveness for palovarotene demonstrated in the Study-PVO-1A-301 (MOVE trial), with consideration of the use of *post-hoc* analyses to support a demonstration of efficacy and the interpretability of the results in light of the external NHS control. In preparation for the EMDAC, FDA conducted a series of landmark analyses, aiming to partially address the abovementioned concerns and improve interpretability of the study results. For example, to

reduce the potential bias from different assessment schedules of WBCT imaging between the two studies, the FDA landmark analyses calculated the annualize change in new HO volume by WCBT at month 12 as the primary endpoint. The FDA landmark analyses also analyzed data without square root transformation incorporating methods for causal inference, including propensity score (PS)-matching, PS-weighting, PS-matching with exact match on age and sex, and targeted maximum likelihood estimation methods. In sensitivity analyses, the FDA landmark analyses used a consistent definition of flare-up events. FDA also requested the Applicant to conduct sensitivity analyses for the non-transition subjects incorporating PS-matching and PS-weighting approaches for baseline covariates adjustment. Results from the FDA landmark analyses and the Applicant's sensitivity analyses appeared to be consistent with the conclusion of the Applicant's *post-hoc* wLME analyses.

The FDA landmark analysis basically addressed all DEPI-I comments, except the concern of potential differential loss to follow-up. On October 20, November 5, and November 23, 2022, FDA issued Information Requests (IRs) to the Applicant, requesting additional analyses for NHS subjects who stayed in and who transitioned out of NHS, as well as the Applicant's assessment of the potential impact from differential loss to follow-up on comparative analysis results for HO volume by WBCT between the two studies. The Applicant provided responses to these IRs on October 25, November 7, and November 28, 2022, and plans to provide responses in detail in the future. Appendix I to III document these three IRs and Applicant's responses. DEPI-I will review the full responses from the Applicant once submitted.

In mid-October 2022, FDA became aware of the availability of additional follow-up data from phase 2 Study PVO-1A-202 and phase 3 Study PVO-1A-301 (MOVE trial). On October 21, 2022, FDA informed the Applicant of the FDA's decision to postpose the EMDAC meeting because such data would be required for efficacy assessment before an EMDAC meeting could take place. The EMDAC meeting would be rescheduled tentatively in January 2023.[o]

During the November 23rd, 2022, teleconference, FDA conveyed to the Applicant that taking a complete response (CR) action may be a better approach and would allow the Applicant more time to collect data.[p] FDA also noted that the EMDAC meeting would likely occur in April 2023. The Applicant acknowledged and agreed to FDA's decision.[q]

[o] Noreen C. Memorandum of October 21, 2022 Teleconference for NDA 215559. Palovarotene. DAARTS Reference ID: 5067510

[p] Noreen C. Memorandum of November 23, 2022 Teleconference for NDA 215559. Palovarotene. DAARTS Reference ID: 5091735

[q] Kehoe T. Email Communication. Subject "FDA's new Path Forward with NDA 215559, palovarotene." November 28, 2022.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Review

Date: October 18, 2022 **Date consulted:** June 2, 2022

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Division Director, DPMH

To: Division of General Endocrinology (DGE)

Drug: SOHONOS (palovarotene) capsules

NDA: 215559

Applicant: Ipsen Biopharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)

Materials Reviewed:

- DPMH consult request for NDA 215559 dated April 29, 2022, DARRTS Reference ID 4993390
- Applicant's submitted background package and proposed labeling for NDA 215559

- DPMH labeling review for Absorbica (isotretinoin) and Absorica LD, NDA 021951 and NDA 211913, August 29, 2019, Jane Liedtka, MD, Medical Officer, DARRTs reference ID: 4484673[1]
- DPMH Information Request (IR) response regarding unintended topical exposure, NDA 215559, received August 18, 2022.

Consult Question: "DGE would like DPMH input for decisions on the age cut off for the indication, risk management for the safety risk of teratogenicity, and input on the PLLR sections of the newly proposed labeling for this original NDA application. DGE plans to take the application to an Advisory Committee (AC) which is expected to include discussion of safety in the pediatric population; therefore, additional input from DPMH for the AC preparations may be requested."

INTRODUCTION AND BACKGROUND

On April 29, 2022, Ipsen Biopharmaceuticals, Inc. resubmitted a 505(b)(1) new drug application (NDA) for priority review for SOHONOS (palovarotene) capsules, a new molecular entity (NME), for the prevention of HO in adults and children (aged 8 years and above for females and 10 years and above for males) with FOP. This NDA was originally submitted on March 31, 2021 but withdrawn by the Applicant on August 12, 2021 due to issues related to verification and completeness of the imaging data. On June 2, 2022, DGE consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History[2]

- Palovarotene is an oral retinoic acid receptor gamma (RARγ) selective agonist proposed for the treatment of FOP. (b) (4) There are no FDA-approved therapies for FOP. In January 2022, Palovarotene was approved in Canada for the treatment of FOP.
- Palovarotene was granted Orphan Drug Designation in 2014, Breakthrough Therapy designation in 2017, and Rare Pediatric Disease designation in 2019 for the prevention of heterotopic ossification in patients with FOP. In 2019, FDA issued a partial clinical hold in all subjects younger than 14 years based on the serious identified risk of premature physeal closure (PPC).
- On August 12, 2022, FDA sent an IR to the applicant to request data to support their proposed labeling regarding the risk of unintended topical exposure during pregnancy. On August 18, 2022, the applicant submitted their response.

Drug Characteristics for Palovarotene[3]

- Drug class: retinoic acid receptor gamma (RARγ) selective agonist

[1] The Absorbica/Absorica LD review was part of the materials reviewed but was not a source relied upon for the labeling
recommendations in this consult review.
[2] Applicant's Clinical Overview for NDA 215559 and Draft FDA Integrated Review for Sohonos, NDA 215559
[3]Clinical Pharmacology Mid-Cycle Slides, 7/25/22; Draft FDA Integrated Review for Sohonos, NDA 215559, accessed 8/10/22

- Proposed mechanism of action: selectively activates RARγ receptors expressed in chondrogenic cells and chondrocytes, which interferes with bone-morphogenic protein intracellular signaling to inhibit chondrogenic differentiation.
- Molecular weight: 414.5 g/mol
- Half-life: 8 to 13 hours
- Dosing: Chronic dosing is 5 mg once daily. Flare up dosing regimen is 12 weeks; 20 mg daily during weeks 1 to 4 and then 10 mg daily during weeks 5 to 12.
- Protein binding: 98-99%

Reviewer comment: While palovarotene shows preferential activity towards RARγ receptors, both the Clinical Pharmacology and Pharmacology/Toxicology reviewers consider palovarotene part of the broader systemic retinoid class. The adverse event profile of palovarotene is consistent with other known systemic retinoids, including embryo-fetal toxicity and premature physeal closure.[4] There are no other systemic RARγ selective agonists currently approved. A topical RAR agonist with particular activity towards the gamma subtype (i.e., trifarotene) was approved in 2019 for the treatment of acne.

Class Effects of Systemic Retinoids Relevant to Pregnancy

- Retinoids are a family of compounds derived from vitamin A. Systemic retinoids are known teratogens associated with multiple fetal malformations. A characteristic patten of defects, referred to as "retinoic acid embryopathy," consists of severe craniofacial, central nervous system, cardiovascular, and thymic malformations.[5] The use of isotretinoin during pregnancy includes a risk of congenital anomalies as well as other adverse pregnancy outcomes, including spontaneous abortions, elective terminations, stillbirths, and extra-uterine pregnancies.[6]
- Approved systemic retinoids include isotretinoin for the treatment of severe nodular acne, acitretin for the treatment of severe psoriasis, tretinoin for the treatment of acute promyelocytic leukemia, and bexarotene for the treatment of T-cell lymphoma. All approved systemic retinoids have enhanced labeling to mitigate the risk of teratogenicity, including a Boxed Warning for embryo-fetal toxicity, a Contraindication for pregnancy, and a Warning and Precaution for embryo-fetal toxicity. While bexarotene only contains enhanced labeling, acitretin has a non-REMS risk management plan that includes an education program. Isotretinoin has a Risk Evaluations and Mitigation Strategies (REMS), called the iPLEDGE program, to mitigate the risk of pregnancy.[7] See Appendix A for additional details.

[4] REMS Oversight Committee (ROC) slides for August 29, 2022 meeting
[5] Dunn LK, Gaar LR, Yentzer BA, O'neill JL, and Feldman SRJJODIDJ. Acitretin in dermatology: a review. 2011. 10(7): p. 772.
[6] Altintas Aykan D and Ergun Y. Isotretinoin: Still the cause of anxiety for teratogenicity. Dermatol Ther, 2020. 33(1): p. e13192.
[7] ROC Meeting slides for Sohonos dated August 29, 2022.

REVIEW
PREGNANCY
FOP and Pregnancy

- FOP is an ultra-rare genetic disease characterized by heterotopic ossification (HO) (i.e., bone formation in ligaments, muscles, and tendons) which leads to reduced movement and cumulative disability.[8] There are approximately 900 confirmed patients worldwide with FOP, including 200-300 cases reported in the United States in 2020.[9,10]
- HO is hypothesized to occur in patients with FOP due to dysregulation of bone morphogenetic protein signaling and can occur spontaneously or by soft tissue trauma.[11,12] Most patients have functional ankylosis of all joints by the age of 30. The median life expectancy is 56 years, and patients usually die from complications of thoracic insufficiency syndrome.[13]
- There are no FDA-approved treatments for FOP. Current management includes lifestyle modifications to prevent falls/injuries and supportive care for flare-ups, including short courses of high-dose corticosteroids and non-steroidal anti-inflammatory drugs.[14]
- The severe disability of FOP results in low reproductive fitness. There are fewer than ten multigenerational families known worldwide.[15,16] The current FOP guidelines recommend discussion of contraception and genetic counseling for patients who are sexually active.[17]
- According to the FOP Treatment Considerations from the International Clinical Council on FOP, pregnancy is possible but poses life-threatening risks to both the mother and fetus. The risks described in the guidelines are stated below.[18] Care at a high-risk pregnancy center is recommended. Pregnant patients may require respiratory support due to reduced lung capacity from restrictive chest wall disease. Immobility

[8] Pignolo, R. J. (2020) 2020 Annual Meeting of the American Society for Bone and Mineral Research Virtual Event September 11–15, 2020. *Journal of bone and mineral research : JBMR.* [Online] 35 (SUPPL 1), 301–302.
[9] ROC Presentation Executive Summary for Sohonos (palovarotene)
[10] https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva/
[11] Muglu JA, Garg A, Pandiarajan T, Shore EM, Kaplan FS, Uchil D, Dickson MJ. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med 5:35-38, 2012
[12] Smilde BJ, Botman E, de Ruiter RD, Smit JM, Teunissen BP, Lubbers WD, Schwarte LA, Schober P, Eekhoff EMW. Monitoring and Management of Fibrodysplasia Ossificans Progressiva: Current Perspectives. Orthop Res Rev. 2022 Apr 20;14:113-120.
[13] Muglu JA, Garg A, Pandiarajan T, Shore EM, Kaplan FS, Uchil D, Dickson MJ. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med 5:35-38, 2012
[14] Smilde BJ, Botman E, de Ruiter RD, Smit JM, Teunissen BP, Lubbers WD, Schwarte LA, Schober P, Eekhoff EMW. Monitoring and Management of Fibrodysplasia Ossificans Progressiva: Current Perspectives. Orthop Res Rev. 2022 Apr 20;14:113-120.
[15] Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet*. 2006;38(5):525-527.
[16] Muglu JA, Garg A, Pandiarajan T, Shore EM, Kaplan FS, Uchil D, Dickson MJ. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med 5:35-38, 2012
[17] Kaplan FS, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clin Council FOP 2: 1-127, 2022]
[18] Kaplan FS, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clin Council FOP 2: 1-127, 2022]

also increases the risk of thromboembolism during pregnancy, a known hypercoagulable state. Caesarean section is typically recommended instead of vaginal delivery due to abnormalities in the lumbar spine and pelvis. Both regional and general anesthesia may be technically challenging due to HO. Surgical procedures may also lead to an exacerbation of FOP and new flare-ups. Risks to the fetus include prematurity and fetal distress. There is a 50% chance of inheritance.[19]

- Full-term births have not been reported in the literature. A case series of four pregnant patients with FOP described two spontaneous miscarriages and two cases of premature births with complications.[20]
    - 24-year-old female had a spontaneous miscarriage at 10 weeks' gestation.
    - 22-year-old female had a spontaneous miscarriage at 8 weeks' gestation.
    - 27-year-old female had an emergency caesarean section at 30 weeks' gestation under general anesthesia (reason for delivery unknown). HO subsequently developed at the operative site of the caesarean section.
    - 27-year-old female developed premature labor and delivered via emergency caesarean section at 34 weeks of gestation. The child developed cerebral palsy, possibly due to intrapartum hypoxia.

Nonclinical Experience[21]

In a rat embryo-fetal study, oral palovarotene administered during pregnancy resulted in multiple fetal malformations including cleft palate, protruding tongue, eye defects, skull abnormalities, blood vessels abnormalities, kidney, ureter, and skeletal malformations. At higher doses, effects resulted in reduced fetal survival. The malformations observed with palovarotene are consistent with malformations observed in the retinoid class.[22] Since retinoids as a class are teratogenic and fetal malformations were observed in the rat studies, the Agency agreed there was no benefit in conducting an EFD study of a second species.[23]

The reader is referred to the full Pharmacology/Toxicology review by Lydia Hale, PhD.

Review of Pharmacovigilance Database

Pregnant females were excluded from all clinical studies and no pregnancies were reported. There are no post-marketing data.

[19] Kaplan FS, Al Mukaddam M, Baujat G, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. International Clinical Council on Fibrodysplasia Ossificans Progressiva website. http://www.iccfop.org/dvlp/wp-content/uploads/2020/03/Guidelines_January-2020.pdf. Published March 2019. Updated May 2022. Accessed August 26, 2022.

[20] Muglu JA, Garg A, Pandiarajan T, Shore EM, Kaplan FS, Uchil D, Dickson MJ. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med 5:35-38, 2012

[21] Draft FDA Integrated Review for Sohonos, NDA 215559, accessed 8/10/22.

[22] Draft Integrated Review for NDA 215559, Section 7.1 Reproductive Toxicity, accessed 9/2/22.

[23] Draft Integrated Review for NDA 215559, Section 7.1, Potential Risks or Safety Concerns Based on Nonclinical Data, accessed 8/26/22.

Review of Literature

Applicant's Review of Literature

The applicant searched PubMed and EMBASE to identify published literature relevant to the safety of palovarotene and other systemic retinoids through July 14, 2020. The applicant did not identify published articles describing palovarotene use during pregnancy but identified several articles describing systemic retinoid use during pregnancy and congenital malformations. The applicant also cited the use of systemic retinoids and other adverse pregnancy outcomes, including spontaneous abortions, stillbirths, and extra-uterine pregnancies.[24]

Reviewer comment: In August 2019, DPMH reviewed the literature for isotretinoin use during pregnancy. No new safety information beyond the known teratogenic effects described above was identified.[25]

(b) (4)

Topical retinoids have low systemic absorption and drug-associated risks from topical retinoid exposure during pregnancy have not been identified. The applicant acknowledges that palovarotene would likely result in less dermal absorption compared to topical formulations because it is a dry powder and not formulated for skin absorption.

Reviewer comment: (b) (4)

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,[29] TERIS,[30] REPROTOX,[31] and Briggs[32] to find relevant articles related to the use of palovarotene during pregnancy. Search terms included "palovarotene" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." Palovarotene is not referenced in Micromedex, TERIS, REPROTOX, or Briggs. No relevant literature for palovarotene was identified. DPMH conducted an interim literature search (August

[24] Applicant's submission for NDA 215559, Literature Summary, page 27 and 115.

[25] DPMH labeling review for Absorbica (isotretinoin) and Absorica LD, NDA 021951 and NDA 211913, August 29, 2019, Jane Liedtka, MD, Medical Officer, DARRTs reference ID: 4484673

(b) (4)

[29] https://www.micromedexsolutions.com, accessed 8/10/22

[30] Truven Health Analytics information. Teris, accessed 8/10/22

[31] Truven Health Analytics information. Reprotox, accessed 8/10/22

[32] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 8/10/22

2019-present) regarding systemic retinoids and use during pregnancy. No new safety information was identified.

LACTATION

Nonclinical Experience

There are no animal data regarding lactation.

Review of Pharmacovigilance Database

Lactating females were excluded from all palovarotene clinical studies.

Review of Literature

Applicant's Review of Literature

The applicant did not identify literature relevant to palovarotene and lactation.[33] The applicant cited a review article of systemic retinoids that reported transfer into breastmilk as well as a case report describing the presence of the systemic retinoid acitretin in human milk.[34]

DPMH Review of literature

This Reviewer performed a search in PubMed, Embase, Micromedex,[35] TERIS, [36] Reprotox, [37] and Briggs, [38] *Medications and Mothers' Milk*,[39] and LactMed[40] to find relevant articles related to the use of palovarotene during lactation. Search terms included "palovarotene" AND "breastfeeding" or "lactation." Palovarotene is not referenced in Micromedex, TERIS, Reprotox, LactMed or Hale. Publications relevant to palovarotene use during pregnancy were not identified. No new safety information relevant to systemic retinoids and lactation were identified.

Reviewer comment: Labeling for currently approved systemic retinoids states that breastfeeding is not recommended due to the potential for serious adverse reactions in breastfed infants.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Palovarotene was not genotoxic when tested in the bacterial reverse mutation assay, in an in vitro chromosomal aberration assay in human lymphocytes, or in an in vivo rodent micronucleus assay.

[33] Brown SM, Aljefri K, Waas R, and Hampton PJJODT. Systemic medications used in treatment of common dermatological conditions: safety profile with respect to pregnancy, breast feeding and content in seminal fluid. 2019. 30(1): p. 2-18.

[34] Brown SM, Aljefri K, Waas R, and Hampton PJJODT. Systemic medications used in treatment of common dermatological conditions: safety profile with respect to pregnancy, breast feeding and content in seminal fluid. 2019. 30(1): p. 2-18.

[35] https://www.micromedexsolutions.com, accessed 8/11/22.

[36] Truven Health Analytics information. Teris, accessed 8/11/22.

[37] Truven Health Analytics information. Reprotox, accessed 8/11/22.

[38] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 8/11/22.

[39] https://www.halesmeds.com, accessed 8/11/22.

[40] https://www.ncbi.nlm.nih.gov/books/NBK501922/, Accessed 8/11/22.

Carcinogenicity studies were deferred preapproval because the applicant's weight-of-evidence based assessment indicated minimal carcinogenic concern.[41]

In female rat fertility studies, palovarotene did cause prolonged diestrus, slightly lower ovulation rate and fewer implantation sites at 3 mg/kg/day but did not cause adverse effects on mating, fertility indices or conception. In male rats, no effects on mating, fertility indices, conception, and sperm were observed but evidence of testicular toxicity was seen at daily oral doses at 5 mg/kg in the 4-week study. This dose level produced severe toxicity and deaths, so it is possible that the findings were related to the underlying poor conditions of the animals rather than a direct palovarotene effect. There was no evidence of testicular toxicity in rats or dogs in chronic toxicity studies.

The reader is referred to the full Pharmacology/Toxicology review by Lydia Hale, PhD.

Review of Clinical Studies

In a Phase 1 study, the applicant measured palovarotene levels in human semen as an indirect measure of male mediated embryo and fetal development risk. The maximal amount of palovarotene that was quantified in a single ejaculate was 33 ng (or ~0.00017%) of the daily dose administered. The maximum potential fetal exposure to palovarotene through semen is estimated to be 0.007 ng/mL which is 100-fold lower than exposure at the no adverse effect level (NOAEL) (0.7 ng/mL) for effects on fetal malformations. Thus, palovarotene is unlikely to affect the development of an embryo or fetus carried by a pregnant female partner exposed to palovarotene via the patient's semen.[42]

Reviewer comment: Based on input from Pharmacology/Toxicology, the level of palovarotene in the ejaculate is 100-fold lower than exposure at the NOAEL (0.7 ng/ml) for effect on fetal malformations and would be unlikely to affect the development of an embryo or fetus carried by a pregnancy female partner exposed to palovarotene via the patient's semen.

Review of Literature

Applicant's Review of Literature

The applicant searched PubMed and EMBASE to identify published literature relevant to palovarotene and fertility. No clinical studies for palovarotene were identified. Two small studies suggest increased fertility parameters in males taking isotretinoin. A study of 81 male patients treated with isotretinoin for six months had positive changes from baseline in all semen analysis parameters. Another study in 13 males found increased sperm motility in males treated with 1 mg/kg/day of isotretinoin for 16 weeks. In twenty years of postmarketing surveillance, four cases of isolated fetal defects following paternal exposure to isotretinoin were identified but two reports were incomplete and two had alternative explanations. No other studies have evaluated teratogenicity following paternal exposure to isotretinoin. For acitretin, a small study

[41] Draft Integrated Review for Palovarotene, Section 7.1, accessed 8/11/22.
[42] Draft Integrated Review for Palovarotene, NDA 215559, Section 7.1, accessed 8/17/22.

in 10 males found no impairment in semen parameters.[43] The applicant noted studies that found an association between isotretinoin therapy and decreased ovarian reserve.[44,45]

Reviewer comment: In 2019, DPMH reviewed the publications relevant to systemic isotretinoin treatment and decreased ovarian reserve, an indicator of female fertility. Improvement in ovarian reserve was noted several months following discontinuation of treatment. The reader is referred to the referenced review for additional details.[46]

DPMH Review of literature
This Reviewer performed a search in PubMed, Embase, REPROTOX to find relevant articles related to the use of palovarotene and effects on fertility. Search terms included "palovarotene" AND "fertility," "infertility," "contraception," and "oral contraceptives." No information for palovarotene was identified.

There are limited data regarding potential adverse effects for systemic retinoids in males of reproductive potential. Post-marketing surveillance for acitretin describes thirteen cases of paternal exposure with known pregnancy outcomes, including one infant with malformations that were not consistent with retinoid embryopathy, and six spontaneous abortions which the authors determined these were not significantly higher than the background incidence. For isotretinoin, post-marketing surveillance describes four cases of isolated defects compatible with features of a retinoid-exposed fetus, but two reports were incomplete, and two had alternative possible explanations.[47]

Applicant's Proposed non-REM Risk Management Plan[48]

- Voluntary participation
- Guides for prescribers, pharmacists, and patients on the importance of avoiding pregnancy.
- Pregnancy testing prior to palovarotene initiation, during treatment, and one month after discontinuation of treatment.
- At least one highly effective method of contraception or two effective contraception methods simultaneously at least one month prior to and during SOHONOS treatment
- Discontinuation of palovarotene if the patient becomes pregnant
- Distribution by specialty pharmacies only

[43] Zakhem GA, Motosko CC, Mu EW, and Ho RS. Infertility and teratogenicity after paternal exposure to systemic dermatologic medications: A systematic review. J Am Acad Dermatol, 2019. 80(4): p. 957-969.
[44] Aksoy H, Cinar L, Acmaz G, et al. The effect of isotretinoin on ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with acne. Gynecol Obstet Invest, 2015. 79(2): p. 78-82.
[45] Cozzolino M, Domingo J, and Soares SR. Ovarian stimulation under the effect of isotretinoin. Gynecol Endocrinol, 2018. 34(2): p. 107-109.
[46] DPMH labeling review for Absorbica (isotretinoin) and Absorica LD, NDA 021951 and NDA 211913, August 29, 2019, Jane Liedtka, MD, Medical Officer, DARRTs reference ID: 4484673.
[47] Kumar P, Das A, Lal NR, Jain S, Ghosh A. Safety of important dermatological drugs (retinoids, immune suppressants, anti-androgens and thalidomide) in reproductively active males with respect to pregnancy outcome: A brief review of literature. Indian J Dermatol Venereol Leprol 2018;84:539-546
[48] Applicant's submission, SOHONOS Educational Program for Safe Use of SOHONOS in the Prevention of Heterotopic Ossification in Patients with Fibrodysplasia Ossificans Progressiva

Reviewer comment: On August 29, 2022, reviewers from the Clinical team and the Division of Risk Management (DRM) presented to the REMS Oversight Committee (ROC) with the proposed plan to mitigate the risk of embryo-fetal toxicity through labeling rather than a REMS. Their recommendation to not pursue a REMS is independent of the applicant's non-REMS voluntary education program. The discussion of the risks and benefits included the severe disability of FOP, the rarity of reported pregnancies, and the high-risk of pregnancy. The ROC agreed with the recommendation not to pursue a REMS.

DISCUSSION AND CONCLUSIONS

Pregnancy

FOP is an ultra-rare disease associated with severe disability and early mortality. There are not any currently approved treatments. Rare cases of pregnancy have been reported in the literature, none of which involved palovarotene exposure.[49] There were no cases of pregnancies reported during the palovarotene clinical trials. Based on nonclinical data for palovarotene and human data for the retinoid class, there is a risk of embryo-fetal toxicity for palovarotene use during pregnancy. Similar to the approach taken for other systemic retinoids, DPMH recommends labeling to mitigate the risk of embryo-fetal toxicity, including a Boxed Warning for embryo-fetal toxicity, a Contraindication for pregnancy, and a Warning and Precaution for embryo-fetal toxicity. Labeling will also recommend that patients taking palovarotene should not donate blood during palovarotene therapy and for one week after discontinuation to avoid unintentional palovarotene exposure via blood donation to a pregnant patient.[50]

The review team, in conjunction with ROC, determined that a REMS is not necessary for this population. The applicant also proposed a non-REMS educational program, which is independent of the review team's decision not to pursue a REMS. DPMH concurs with this recommendation. In addition, DPMH also does not recommend a post-marketing pregnancy study because of the known teratogenicity of the retinoid class and the low number of anticipated pregnancies in patients with this ultra-rare disease for the reasons stated above.

Lactation

There are no available data on the presence of palovarotene in human or animal breast milk, the effects of palovarotene on the breastfed infant, or on milk production. The transfer of other systemic retinoids into breastmilk has been reported in the literature.[51] Based on the potential for PPC in breastfed infants exposed to palovarotene, the applicant is proposing (b) (4) that females should avoid breastfeeding for at least one month after the

[49] Kaplan FS, Al Mukaddam M, Baujat G, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. International Clinical Council on Fibrodysplasia Ossificans Progressiva website. http://www.iccfop.org/dvlp/wp-content/uploads/2020/03/Guidelines_January-2020.pdf. Published March 2019. Revised May 2022. Accessed August 26, 2022.

[50] The one week interval was determined with input from Clinical Pharmacology and is based on the metabolite with the longest half-life (i.e., 30 hours) multiplied by five.

[51] Brown SM, Aljefri K, Waas R, and Hampton PJJODT. Systemic medications used in treatment of common dermatological conditions: safety profile with respect to pregnancy, breast feeding and content in seminal fluid. 2019. 30(1): p. 2-18.

final dose based on other systemic retinoids.[52] Since palovarotene is not harmful to the lactating mother, DPMH recommends a statement that breastfeeding is not recommended during treatment with palovarotene and for one week after the last dose (b) (4)[53] The approach not to recommend breastfeeding due to the potential risks of serious adverse reactions in breastfed infants is consistent with other currently approved systemic retinoids. A post-marketing lactation study is not recommended because FOP is an ultra-rare disease, pregnancies in this population are rare, and breastfeeding during palovarotene treatment is not recommended.

Females and Males of Reproductive Potential

There are no data on palovarotene and its effects on fertility in humans. Animal data did not indicate that palovarotene impaired male and female fertility. Based on input from the Pharmacology/Toxicology team, the level of palovarotene transferred into the semen is 100-fold lower than exposure at the NOAEL and, therefore, palovarotene exposure via semen is unlikely to cause adverse effects.

Currently approved systemic retinoids recommend verifying that the patient is not pregnant prior to initiating treatment and at monthly intervals. For bexarotene and isotretinoin, a negative pregnancy test is needed before the next month of treatment is prescribed.[54] DPMH recommends that labeling includes recommendations for verification of a negative serum pregnancy test prior to initiating therapy and to assess pregnancy status at monthly intervals during treatment. Given the severity of disease and disability, DPMH proposes labeling language that allows the health care provider and patient to determine the best method of monthly pregnancy assessment, depending on the patient's particular circumstances and the health care provider's clinical judgement. If a patient is not sexually active, for example, a more restrictive approach for mandatory pregnancy monthly testing in order to receive the next month supply of palovarotene may cause undue burden and have the unintended consequence of decreased or interrupted access to palovarotene. FOP is a serious, progressive disease that leads to disability and early mortality without currently approved therapies. In this case, access to a chronic treatment for a serious disease outweighs the potential benefits of additional measures to mitigate the risk of embryo-fetal toxicity, particularly in light of the rarity and high risk of pregnancy in this population. Upon discussion with the DGE clinical team, the team stated that because pregnancy occurs rarely in the FOP, they disagree with any labeling language recommending the specific type of pregnancy test to use prior to initiating therapy and a specific frequency of pregnancy assessment over the course of treatment.

For females of reproductive potential, DPMH recommends use of effective contraception, unless continuous abstinence is the chosen method. Currently, there is no evidence that use of two contraceptives reduces the incidence of pregnancy. Experts from the December 2012 Drug Safety and Risk Management Advisory (DSaRM) Committee meeting stated that the combined use of two comparatively less effective methods will not be as effective as one contraceptive method with <1% typical use failure rate. If a female of reproductive potential chooses a

[52] Applicant's submission for NDA 215559, Integrated Summary of Safety, page 502.
[53] The interval to avoid lactation following the last dose was determined with input from Clinical Pharmacology and is based on the palovarotene metabolite with the longest half-life (i.e., 30 hours) multiplied by five.
[54] Approved labeling for Targretin (bexarotene) under NDA 021055, last revised 4/30/22; Approved labeling for Absorica (isotretinoin) under NDA 021951, last revised 11/7/2019.

primary contraceptive method with a typical use failure rate <1%, a secondary method may not be required. This thinking, however, has not yet been adopted in other retinoid pregnancy prevention programs. (b) (4)

Therefore, DPMH recommends that labeling advise females of reproductive potential to use effective contraception at least one month prior to treatment, during treatment with SOHONOS and for at least one week after the last dose.

The applicant's proposed recommendation to use contraception at least one month prior to initiating treatment in addition to pregnancy testing prior to initiating treatment will mitigate the risk of palovarotene exposure in the event of an unintended pregnancy. While there is not class labeling for systemic retinoids, all of the approved systemic retinoids include recommendations for contraception and pregnancy testing, though the specifics of pregnancy testing and contraception vary between labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 2.1, 4, 5.x, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on October 3, 2022. DPMH recommendations are below. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
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MEMORANDUM TO FILE

Version Date:	August 31, 2022
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH
NDA Number:	215,559
Applicant:	Ipsen Biopharmaceuticals, Inc
Drug:	Sohonos (palovarotene [an RAR gamma (γ) agonist])
Proposed Indication:	Prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressiva (FOP)
Dosage Form and Route of Administration:	1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg capsules for oral (PO) administration
Proposed Regimen:	Adult and Pediatric patients 14 years and older Chronic: 5 mg/day Flare up: 20 mg/day x 4 weeks, then 10 mg/day x 8 weeks. Flare up regimen may be initiated for flare up or high-risk traumatic event likely to cause flare-up. Females 8 to < 14 years and males 10 to 14 years: See text.
Division Consult Request:	The Division of General Endocrinology (DGE) requests assistance with establishing the lower age bounds for the indication, labeling review, and Advisory Committee preparation for this new molecular entity.

Background

Sohonos (hereafter, palovarotene or PVO) is an orally available retinoic acid receptor gamma (RARγ) selective agonist submitted for premarket review for prevention of heterotopic ossification in patients with fibrodysplasia ossificans progressive (FOP; previously referred to as myositis ossificans progressiva). On July 21, 2014, palovarotene was granted orphan drug designation for the treatment of FOP, breakthrough therapy designation granted on July 11, 2017, and rare pediatric disease designation on February 7, 2019. This NDA was initially received on March 31, 2021, withdrawn on August 12, 2021, and was resubmitted on April 29, 2022.

The Applicant intends to indicate the drug for adults and children (females 8 years and older, and males 10 years and older) with FOP. The Applicant withdrew the application in August 2021 in order to prepare responses to multiple information requests.

The following disease summary is taken from the Online Mendelian Inheritance in Man website (OMIM entry number: 135,100).[1] FOP is an autosomal dominant disorder caused by any of several mutations of the bone morphogenetic protein (BMP) type 1 receptor ACVR1 gene located at chromosome 2q24. The mutation leads to downstream activation of BMP bone-signaling pathways. Worldwide prevalence is approximately 1 per 2 million people. Penetrance is 100% but with some variation in expression (age at presentation and severity).

Patients almost universally present with malformation of the great toes noticed a birth. However, given the rarity of the condition, subtle great toe malformations may only be recognized retrospectively as the herald sign of FOP. Typically, patients first develop inflammatory lesions after several years of uncomplicated development, though several patients first presented in their late teens or early twenties. Inflammatory lesions most commonly occur after minor (e.g., including intramuscular injections) or major insults (surgeries); however, lesions may also begin without reported trauma. Inflammatory lesions progress to heterotopic ossification, development of morphologic bone, in soft tissues including tendon and muscles. Accumulation and progression of lesions leads to severe disfigurement, progressive limitation of movement leading to whole body immobility, cardio-pulmonary compromise secondary to mechanical compromise, difficulty of speaking and eating, and premature death.

Palovarotene and other RARγ agonists have been shown to dampen BMP signaling and inhibition of chondrogenesis and osteogenesis. Treatment of *ex vivo* wholly or partially differentiated cells show short term effects only. In animal models, exposure to retinoid agonists demonstrated short-term inhibition of chondrogenesis and osteogenesis. These findings suggest that repeat dosing of RARγ agonists would be needed for long-term treatment.

Development of manipulated stem cell transplants for preventive treatment appears unlikely because native abnormal progenitor cells are seeded throughout the body prior to birth.

[1] OMIM Entry #: 135,100. Fibrodysplasia Ossificans Progressiva (FOP); https://www.omim.org/entry/135100?search=fop&highlight=fop. Website accessed July 7, 2021.

Regulatory History

On December 23, 2019, FDA issued a partial clinical hold (PCH) on under 21 CFR 312.42(b)(2)(i) (unreasonable and significant risk of illness or injury, and insufficient information to assess the risk in the patient population) for studies of FOP for patients younger than 14 years because premature physeal/growth plate closure (PPC).[2] Additional clinical information and radiographic information was requested to established if the PCH could be lifted (e.g., radiographic definitions for growth plate closure, specification of all growth plates assessed in all patients, the estimated bone age at each assessment, and whether dose modification for PCH were undertaken).

As noted in the FDA clinical review of the Applicant's reply,[3] 33 of 51 treated children experienced PPC after 12 to 24 months of treatment. The group with PPC had lower mean change in standing and knee height, and shorter femur and tibial length compared to the group without PC. Comparison to an untreated natural history study (NHS) cohort (N=39) showed that untreated patients had greater mean changes in standing height and greater femur and tibial length compared to treated patients, irrespective of PPC.

When patients with MO were excluded, FDA concluded that in FOP patients treated with PVO, PPC was found in four of 19 boys (21%) aged 10 to13 years and four of 23 girls (17%) aged 8 to 13 years. Additionally, FDA subgroup efficacy analysis showed limited inhibition of new HO volume in palovarotene treated patients. FDA concluded that the submitted data did not support a favorable benefit and risk assessment for the Applicant's proposal to lower the age limit for clinical hold to 8 years for girls and 10 years for boys.[4]

At the subsequent pre-NDA meeting, the Applicant again sought FDA input on the possibility use in males at least 10 years old and females at least 8 years. The Applicant proposed the clinical ramifications would be lessened compared to PPC in younger patients because most children would have already completed pre-Tanner stage II (pre-adolescent) growth, and the time to onset for PPC would likely allow most of these patients to achieve normal adolescent growth acceleration prior to onset of PPC which would hopefully allow attainment of near normal adult height. FDA deferred analysis of the data and comment on the acceptability of the proposed lower age bounds for males and females pending review of safety information in the NDA

Clinical studies intended to support the indication are listed in the appendix of this review.

The DGE consult requests DPMH input for the age cut-off (i.e., lower age bounds for males and females), risk management for the safety risk of teratogenicity, and input on the PLLR sections of newly proposed labeling. Teratogenicity, and the pregnancy and lactation sections of labelling will be addressed in a separate maternal health consult.

[2] IND 120,181; PCH Letter December 23, 2019.
[3] IND 120,181 and IND 135,403; May 15, 2020.
[4] IND 120.181; Continue Partial Clinical Hold letter; May 15, 2020.

Benefit/Risk Discussion

The two most significant issues if the drug were to be approved would be 1) the youngest indicated ages, and 2) appropriate post-market monitoring; potentially including postmarketing studies to further explore the incidence and clinical ramifications of PPC, such as asymmetric growth plate closure. DGE previously informed the Applicant that interim data suggested the incidence and potential clinical ramifications of PPC would preclude labeling for the youngest patients (younger than 8-years for female and younger than 10 years for males) and possibly for younger adolescents (< 14 years).

Comprehensive review of the growth-related safety data (height, growth velocity, and their z-score transformations) is deferred to DGE; however, DPMH makes the following observations.

1. The Applicant assessed effect of palovarotene-exposure in on height. Characteristics reported include mean, median, standard deviation (SD) and z-scores derived from those parameters.
2. The small size of the two studies and the sub-groups [< 8 years old (yo) F/<10 yo M, ≥8 yo F/10 yo M to < 14 yo F/M, and ≥14 yo F/M] limits interpretability and generalizability of the data [mean (SD), median, and z-score analyses]; however, rare disorders such as FOP, are not amenable to larger datasets even in the post-market setting.
3. Z-scores can be applied to quantitative characteristics (e.g., height or height velocity, or cardiac ejection fraction), rather than qualitive characteristics (e.g., eye color). The reported z-score is a unitless characteristic defined as the number of standard deviations of a subject's (or group's) measurement from the median measurement of a comparable sample population. Unless the comparator groups are defined (healthy person to matched healthy group, or affected person to an unaffected group, or affected group to unaffected group), the score cannot be appropriately interpreted. Increasing positive height z-scores over time indicate attainment of greater height over time than expected for age in relation to the comparator population. Increasingly negative height z-scores over time indicate slower linear growth over time (and slowed height velocity) for age in relation to the comparator population. There is no universally accepted definition for clinically meaningful change in z-score; however, a loss of 0.5 or 1 indicates loss of 0.5 to 1 standard deviation (SD) compared to the reference population.

   The comparator for the reported z-scores for both the NHS and FOP groups appears to be a demographically matched unaffected population which is appropriate.
4. Data for standing height, standing growth velocity, and knee length are reported in in Section 2.5.1.4.1 of Module 2.7.4 of the Summary of Clinical Safety. The summary of that section states "all but one of the PPC SAEs was observed first in the knee, showing that PPC preferentially affects the lower extremities. When contralateral growth plate evaluations were available, growth plate closure was symmetric." (b) (4) angular deformity, should asymmetric physeal fusion occur, would likely take a longer amount of time to manifest than the time periods of study.

5. At the August 23, 2022, team meeting, DGE reported that interim review of the safety data showed no strong trend toward limb length discrepancy or height between the PVO and NHS groups; however, a response to an information request for additional data regarding unilaterality or bilaterality of PPC is still pending.
6. DGE's efficacy analyses remain ongoing; however, DGE commented that while the study may have failed to reach the prespecified primary endpoint, post hoc analyses may suggest a trend toward effectiveness.
7. While labeling (section 2.4) states that temporary dose suspension or reduction may be considered for patients with signs of adverse events (e.g., PPC), I found no summary data to support the effectiveness of the strategy in the application and conclude that, in relation to PPC, the recommendation is ad hoc.

Discussion

Even if effective, a strong signal for PPC in critical joints (around the knee for example) might preclude approval for a subset of patients if it were to lead to substantial limb-length discrepancies or substantially decreased adult height. If that same concern were not present (adults) or were less (mid-adolescents whose adolescent growth spurt had commenced or had been completed) in other subpopulations, approval with appropriate safety labeling could be acceptable. It is therefore encouraging that DGE's interim safety analysis, while acknowledging several outliers, suggests unremarkable differences in end of study height between PVO-treated and the NHS patients.

While acknowledging the gravity of the condition, that no treatments are currently available, and strong safety signal for PPC, DPMH concludes the treatment effect would have to be clinical meaningful and statistically persuasive to support indicating the drug for growing children.

Therefore, DPMH believes analyses of safety and effectiveness by DGE and FDA Statistics, and input from FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) are required prior to making definitive recommendations on approvability and the lowest indicated ages.

If approved, post market studies may be required to establish if dose modification can ameliorate risk of PPC since there are no currently recognized treatments or reversal agents for PPC.

Labeling

The following labeling recommendations are based on the presumption of drug approval.

DPMH's labeling recommendations focus on the proposed boxed warning, and sections 1 (Indications and Usage), 2.3 (Dosage and Administration; limited to the sub-section for children younger than 14 years), 4 (Contraindications), 5 (Warnings and Precautions), and 8.4 (Pediatric Use). Discussion of section 2 remains pending while Clinical Pharmacology and DGE complete their review.

Descriptions of retinoid class-related safety issues from other approved retinoid labeling will be used to inform safety recommendations in this review (e.g., NDA 21,951 Absorica and Absorica LD; labeling date November 11, 2019).

Text which DPMH recommends being deleted is noted by a ~~strike out~~. DPMH recommendations are indicated by **bold red** font. Changes recommended by other disciplines (DGE, other consultants) are noted by **bold blue** font.

The reader is reminded that pediatric labeling for drugs intended, primarily or significantly, for children is distributed throughout labeling, and the responsibility for such labeling resides with other disciplines. Therefore, the reader is directed to final labeling for additional edits not described in this document.

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[5] Muglu JA, Garg A, Pandiarajan T, et al. Pregnancy in fibrodysplasia ossificans progressive. Obstet Med. 2012 Mar;5(1):35-38.

(b) (4)

Reviewer comment: The edits above are recommended for clarity and are consistent with current labeling guidance. The deleted paragraphs are move to section 5.2 of labeling where they are more appropriate as warnings/precautions. Additional edits to those paragraphs, such as replacing summary comments with data will, are deferred to DGE.

Appendix

Table 1: Clinical studies intended to support the indication (source: pages 15 and 16 of the clinical summary of efficacy)

Study Name	Design	Population	Dose/Treatment	Subjects per Dose
PVO-1A-001 Completed	Non-interventional natural history study (NHS)	Subjects with the R206H mutation aged 0-65 years	NA (non-interventional study); 3-year follow-up.	114 subjects: 0 to <8 years (n=17) 8 to <15 years (n=36) 15 to <25 years (n=34) 25 to ≤65 years (n=27)
PVO-1A-301 (Phase 3) Ongoing	Multicenter, open-label study evaluating the efficacy and safety of PVO in decreasing HO in subjects with FOP versus untreated subjects in the NHS	Palovarotene treatment naïve FOP subjects with the R206H mutation or other FOP mutations	Oral 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4 week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve	107 subjects (99 with R206H mutation, and 8 with other mutations)
PVO-1A-201 (Phase 2) Completed	Multicenter, R, DB, PC adaptive dose finding/Proof of concept	Cohort 1: FOP subjects with active flare-ups; age ≥15 years Cohort 2: FOP subjects with active flare-ups age ≥6 years	Cohort 1: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks, or placebo Cohort 2: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks; oral QD 5 mg for 2 weeks, then 2.5 mg for 4 weeks; or placebo. Weight-based dosing implemented in Cohort 2 across three categories (20 to <40 kg, 40 to <60 kg, ≥60 kg)	Cohort 1: 12 active; 4 placebo Cohort 2: 18 active; 6 placebo Total of 40 subjects
PVO-1A-202 Part A (Phase 2) Completed	Multicenter, OLE of PVO-1A-201	FOP subjects who completed Study PVO-1A-201.	Oral QD 10 mg for 2 weeks, then 5 mg for 4 weeks for the next two subsequent treatment-qualifying flare-ups. Weight-based dosing when children 6+ years of age enrolled in Study PVO-1A-201.	40 subjects from PVO-1A-201
PVO-1A-202 Part B (Phase 2) Completed Corresponds to PVO-1A-204 in France	Multicenter, OLE of PVO-1A-201	FOP subjects from Part A and new FOP subjects with at least 90% skeletal maturity regardless of age.	Adult Cohort (chronic/PVO 20/10 mg): oral 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4-week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve). Pediatric Cohort (flare-up only treatment): same as flare-up dosing in the Adult Cohort except dosing is weight-adjusted.	54 subjects: 36 subjects from Part A and 18 new Adult Cohort subjects (13 subjects from the NHS and five new subjects).
PVO-1A-202 Part C (Phase 2) Ongoing Corresponds to PVO-1A-204 in France	Multicenter, OLE of PVO-1A-201	FOP subjects from Study PVO-1A-202/Part B	All subjects (chronic/ PVO 20/10 mg treatment): oral QD administration 5 mg for up to 24 months, with dose escalation for flare-up treatment to oral QD 20 mg for 4 weeks, then 10 mg for 8 weeks (total of 12 weeks; may be extended by 4-week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve). Dosing is weight-adjusted in skeletally immature subjects.	48 subjects from Part B

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Clinical Inspection Summary

Date	August 08, 2022
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., M.P.H., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Stephen Voss, M.D., Clinical Reviewer Theresa Kehoe, M.D., Clinical Team Leader/Division Director Noreen Cabellon, Regulatory Project Manager Division of General Endocrinology
NDA #	215559
Applicant	Ipsen Biopharmaceuticals Inc.
Drug	Sohonos (palovarotene) capsules
NME (Yes/No)	Yes
Review Priority	Priority
Mission Critical	Yes (Orphan Drug, Breakthrough Designation)
Proposed Indication(s)	Prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva
Submission Date	Original submission: March 31, 2021 Re-submission: April 29, 2022
Consultation Request Date	May 3, 2021
Summary Goal Date	September 15, 2021; extended to September 29, 2022
Action Goal Date	December 01, 2022
PDUFA Date	December 29, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a natural history study (PVO-1A-001), two Phase 2 studies PVO-1A-201 and PVO-1A-202 (Parts A, B and C) and a Phase 3 study (PVO-1A-301) were submitted to the Agency in support of this New Drug Application (NDA) 215559 for Sohonos (palovarotene) capsules for the proposed indication. Three clinical investigators (CIs): Drs. Mona Mukaddam (Site #21 for Study PVO-1A-001; Site #1 for Study PVO-1A-202 and Site #1004 for Study PVO-1A-301), Edward Hsiao (Site #22 for Study PVO-1A-001; Site #2 for Studies PVO-1A-201 and PVO-1A-202; and Site #1001 for Study PVO-1A-301), and Edna Mancilla (Site #1003 for Study PVO-1A-301) were inspected for the submitted four studies in this NDA.

Based on the overall results of these CI inspections, the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist, which was granted orphan drug designation for the treatment of fibrodysplasia (b) (4) ossificans progressiva (FOP) on 07/21/2014, the fast track designation on 11/25/2014, and breakthrough therapy designation on 07/11/2017. Ipsen submitted NDA 215559 for Sohonos (palovarotene) capsules on 03/31/2021 for the proposed indication of prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with FOP.

Data from a natural history study (PVO-1A-001), two Phase 2 studies PVO-1A-201 and PVO-1A-202 (Parts A, B and C) and a Phase 3 study (PVO-1A-301) were submitted to support the application.

During the NDA review process, it was identified that the end-of study (EOS) Whole Body CT (WBCT) scans for 8 subjects were missing in Study PVO-1A-001 (NHS). Other review issues included 1) delayed recognition of radiologic changes in a pediatric subject (# (b) (6)) leading to a Premature Physeal Closure (PPC) safety signal, which was reported to FDA as a serious adverse event (SAE) that led to a partial clinical hold of the study on 12/2019 that dosing in all subjects < 14 years old were put on hold; and 2) processing error whereby multi-acquisition of WBCT scans resulted in missed anatomy for review in the dataset.

The sponsor, Ipsen, withdrew NDA 215559 for additional image data verification and quality review on 08/21/2021. The sponsor conducted an independent third party (FDAQRC) audit of the imaging vendor (b) (4) and consulted (b) (4), an external regulatory compliance consulting group, on the study data quality analysis and protocol deviations related to (b) (4) image reading issues. The sponsor determined that the causes for the incomplete data were the upload processes in data reconciliation steps for WBCT scans and failures to adequately assess and monitor the risks presented required to upload WBCT into the image vendor (b) (4) system. The quality investigation identified a total of 13 subjects' WBCT scans were incompletely submitted. NDA 215559 was re-submitted on 04/29/2022. The resubmission includes a "Data Integrity Quality Review Report", which consists of the sponsor's analysis of quality issues with the causes and the improvement actions with new QC processes implemented, trainings and re-trainings provided, and the effectiveness of the actions assessed. The sponsor concluded that the re-submission included all scans and all verified data.

During the original NDA review process, three CIs: Drs. Mona Mukaddam, Edward Hsiao, and Edna Mancilla were selected for clinical inspections for the submitted four studies. The inspections conducted did not identify significant good clinical practice (GCP) issues or regulatory non-compliance. A discussion with the Division on 05/10/2022 decided that no new inspections are needed for the re-submission.

Study PVO-1A-001

PVO-1A-001 was a natural history, non-interventional, two-part study in subjects with FOP. The study objective was to describe FOP disease characteristics by age, disease progression, and to illuminate the impact of flare-ups on FOP outcomes.

The primary efficacy endpoints were 1) new whole-body HO as measured by WBCT scan and 2) new HO at flare-up sites as measured by CT of flare-up sites.

After enrollment, subjects were followed for up to 36 months. Evaluations were at Weeks 1-3 and at Months 6, 18, and 30.

The study enrolled 114 subjects at 7 study sites in 6 countries: US (2) and 1 site each in France, Italy, Argentina, Australia, and the United Kingdom (UK). The first subject was enrolled on 12/18/2014 and the last subject's last visit was on 04/09/2020.

Study PVO-1A-201

PVO-1A-201 was a multicenter, randomized, double-blind, placebo-controlled, adaptively designed study in subjects with FOP. The primary study objective was to evaluate the ability of different doses of palovarotene to prevent HO at the flare-up site as assessed by plain radiographs.

The primary efficacy endpoint was the percentage of subject with no or minimal new HO at the flare-up site compared with baseline by plain radiographs at Week 6.

The study consisted of 2 Cohorts:

- Cohort 1: 8 subjects were randomly assigned at a 3:1 ratio to either palovarotene (10 mg daily for 14 days followed by 5 mg daily for 28 days) or placebo daily for 42 days. When the 8th subject completed Week 6, safety and efficacy data were reviewed by a Data Monitoring Committee, which provided a recommendation on the appropriate dosing regimens to be evaluated in Cohort 2.
- Cohort 2: 24 additional subjects ≥ 6 years old were randomized at a 3:3:2 ratio to two weight-based dose regimens of palovarotene (10 mg for 14 days and 5 mg for 28 days; or 5 mg for 14 days and 2.5 mg for 28 days) or placebo daily for 42 days. Subjects in the weight-range categories of 20-40 kg and 40-60 kg had weight-adjusted doses of palovarotene estimated to achieve exposures equivalent to 10, 5, and 2.5 mg. Subjects were evaluated at Weeks 2, 4, 6, 9 and 12.

The study screened a total of 44 subjects and enrolled 40 subjects in 4 study sites: US (2), France (1) and UK (1). All 40 subjects completed the study. The first subject was enrolled on 07/14/2014 and the last subject's last visit was on 05/23/2016.

Study PVO-1A-202

Study PVO-1A-202 was a Phase 2, open-label study that explored different dosing regimens of palovarotene in adult and pediatric subjects with FOP. The study had three parts: Part A, B and C.

Part A: Effects of palovarotene 10/5 mg were evaluated in subjects who experienced additional flare-ups that qualified for treatment.

The primary study objectives were 1) to evaluate the long-term (up to 12 months) safety and efficacy of prior palovarotene treatment in FOP subjects who completed Study PVO-1A-201; and 2) to evaluate the safety and efficacy of palovarotene in FOP subjects who experienced up to two new distinct flare-ups for up to 36 months.

The primary efficacy endpoint was the percentage of subject who had no or minimal new HO at the original flare-up site compared with baseline (Study PVO-1A-201 data) as assessed by plain radiographs at the follow-up visit; and the percentage of subject who had no or minimal new HO at up to two new distinct flare-up sites compared with baseline (Day 1) as assessed by low-dose CT scan (or plain radiographs for subjects unable to undergo CT scan) at Flare-up Week 6 (Day 42).

The study had two components:
The Follow-up Component:

- Subjects completed Study PVO-1A-201 were enrolled and followed for up to 36 months.
- A screening visit (the last day of Study PVO-1A-201) and a follow-up visit at Month 12.

The Flare-up Component:

- Two, new, distinct flare-ups were assessed and treated with palovarotene 10 mg daily for 14 days, followed by 5 mg daily for 28 days.
- Three periods (12 weeks): 1) Screening Period that occurred within 7 days of a new, distinct flare-up and the 1st dose of study drug was taken within 7 days. 2) Treatment Period with palovarotene 10/5 mg for 6 weeks, and 3) Follow-up Period of 6 weeks (42 days).
- Subjects who completed the Flare-up Component for two, new, distinct flare-ups and met the eligibility requirements were eligible to enroll into Part B.

The study enrolled a total of 40 subjects (all from Study PVO-1A-201) in 3 sites: US (2) and France (1). The first subject was enrolled on 10/09/2012 and the study was completed in 07/2017 with a total of 36 subjects enrolled into Part B.

Part B:
The primary study objective was to evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP.

The primary efficacy endpoint was the proportion of flare-ups with no new HO at Week 12 as assessed by low-dose CT scan (or plain radiographs for subjects unable to undergo CT scan).

Chronic Treatment:
All subjects received 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects) for up to 24 months.

Flare-up Treatment:

- Eligible flare-ups were defined as comprising of at least two of the six most common flare-up symptoms, similar to the subject's previous flare-ups, confirmed by the Investigator, with symptom initiation within 7 days.
- Flare-ups were treated with palovarotene 20 mg daily for 28 days followed by 10 mg daily for 56 days (or exposure-equivalent doses based on weight). Any new flare-ups (intercurrent flare-up) that occurred during the 12-week flare-up assessment period (including treatment extensions) could not be treated were captured as adverse events (AEs).

The study enrolled a total of 54 subjects with 36 subjects from Part A and 18 new subjects, at 8 study sites in 5 countries: US (3), France (1), Germany (1), Australia (2) and Argentina (1). The study was completed in October 2018, with 48 subjects enrolled into Part C.

Part C (ongoing with the study report cut-off date of 02/28/2020): subjects were followed for up to additional 36 months.

The primary objective was to evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP.

The primary efficacy endpoint was the annualized change in new HO volume as assessed by low-dose WBCT scan, excluding head, as compared to data collected from the natural history study PVO-1A-001.

Chronic Treatment:

- All subjects received 5 mg palovarotene once daily (or weight-adjusted doses) for up to 36 months.
- Subjects who began chronic treatment during Part B, continued the same visit schedule and received chronic treatment for up to an additional 36 months. Thus, subjects may undergo chronic treatment for up to 60 months over the entire study (24 months in Part B and 36 months in Part C).

Flare-up Treatment:

- The presence of only one symptom was required for initiation of treatment.
- Upon flare-up confirmation, subjects were immediately treated with palovarotene 20 mg daily for 28 days, followed by 10 mg daily for 56 days (or exposure-equivalent doses based on weight). Based on clinical signs and symptoms, treatment may be extended in 4-week intervals while on-treatment with 10 mg palovarotene and continued until the flare-up resolved and 4-week extension treatment had been completed. If a subject experienced a new intercurrent flare-up (a new flare-up or marked worsening of the original flare-up), or the presence of a substantial high-risk traumatic event likely to lead to a flare-up, during flare-up based treatment, the 12-week dosing regimen restarted upon new intercurrent flare-up confirmation by the Investigator (i.e., 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]).
- Once all flare-ups in a cycle had resolved and flare-up based treatment had been completed, subjects resumed the chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

The study enrolled a total of 48 subjects from Part B at 8 study sites in 5 countries: US (3), France (1), Germany (1), Australia (2) and Argentina (1). The study was ongoing with the study report cut-off date of 02/28/2020.

Study PVO-1A-301

PVO-1A-301 was an ongoing Phase 3, multicenter, single-arm, open label study in pediatric subjects ≥ 4 years and adult with FOP to evaluate the efficacy and safety of chronic 20/10 mg palovarotene dosing in preventing new HO as assessed by low-dose WBCT compared to data from untreated

subjects in PVO-1A-001. Of note, dosing in all subjects < 14 years old was put on hold by FDA started on 12/04/2019, following reports of a premature physeal closure SAE.

The primary study objectives were 1) to evaluate the efficacy of palovarotene in decreasing HO in adult and pediatric subjects with FOP as assessed by low-dose WBCT, excluding head, as compared to untreated subjects from the natural history study PVO-1A-001; and 2) to evaluate the safety of palovarotene in adult and pediatric subjects with FOP.

The primary efficacy endpoint was the annualized change in new HO volume as assessed by low-dose WBCT, excluding head.

The study had two parts:
Part A: Subjects received chronic treatment of palovarotene 5 mg once daily (weight-adjusted for subjects < 18 with < 90% skeletal maturity on hand-wrist radiography at screening) for up to 24 months. Remote visits occurred at Week 6 and at Months 3, 9, 15, and 21.

Part B: Palovarotene was taken for an additional 24 months with the chronic/flare-up dosing regimen to all subjects until commercial availability, and to obtain long-term safety data.

Flare-up-Based Treatment:
- If the symptom(s) were consistent with flare-ups and confirmed by the Investigator (the presence of only one symptom was required for initiation of treatment), or the Investigator confirmed the presence of a substantial high-risk traumatic event likely to lead to a flare-up, subjects immediately began flare-up-based treatment.
- Treatment: palovarotene 20 mg daily (or weight-based equivalent) for 28 days and followed by palovarotene 10 mg daily (or weight-based equivalent) for 56 days, for a total flare-up treatment duration of 84 days.
- Once all flare-ups or traumatic events in a cycle had resolved and flare-up-based treatment had been completed, subjects resumed chronic treatment with 5 mg palovarotene once daily (or weight-based equivalent).

The study enrolled 107 subjects in 16 study sites in 11 countries: US (4), Western Europe (5), Canada (2), Australia (2), Japan (1) and Latin America (2). Site #5001 in Australia was closed due to the CI's departure and all subjects (6) were transferred to Site #5002 (Australia). The first subject was enrolled on 11/30/2017 and the last subject was enrolled on 07/31/2018. The study was ongoing as the study report cut-off date on 02/28/2020 with 88 subjects remained in the study.

Rationale for Site Selections
Three CIs: Drs. Mona Mukaddam (Site #21 for Study PVO-1A-001; Site #1 for Study PVO-1A-202 and Site #1004 for Study PVO-1A-301), Edward Hsiao (Site #22 for Study PVO-1A-001; Site #2 for Study PVO-1A-201 and Study PVO-1A-202; and Site #1001 for Study PVO-1A-301), and Edna Mancilla (Site #1003 for Study PVO-1A-301) were requested for clinical inspection in support of the application. These sites were selected based on enrolling a high number of subjects to the study treatment arms that may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. Mona Mukaddam, M.D.

3737 Market Street, 3rd Floor
Philadelphia, PA 19104

This CI was inspected on 06/24-07/14/2021 as a data audit for Studies PVO-1A-001, PVO-1A-202 (Parts A, B and C) and PVO-1A-301. This was the initial FDA inspection for Dr. Mukaddam. The inspection reviewed 100% of the Informed Consent Forms (ICFs) for each of the study. Table 1 below is the reviewer's summary of the inspection information.

Table 1: Summary of Dr. Mona Mukaddam's Inspection Information

Study	Site #	Number of Subjects Screened	Number of Subjects Enrolled	Number of Subjects Completed	Date of First Subject Enrolled	Date of Last Subject Completed	Number of Subject Records Reviewed
PVO-1A-001	21	22	22	Month 36: 12 (4 entered 301)	03/12/20 15	3/12/2020	22
PVO-1A-202A	1	11	9	6	10/25/20 14	6/06/2021	21
PVO-1A-202B	1	8 (new)	14 (including from Part A)	9			
PVO-1A-202C	1	8 (new)	21 (13 from Part B)	13			
PVO-1A-301	1004	8	8	Month 24: 1 Month 18: 6 Month 12: 1	02/21/20 18	Ongoing	8

Source records reviewed during the inspection included the studies protocols and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including laboratory tests, imaging studies and AEs), visit data, paper subjects' diaries, paper Case Report Forms (CRFs) and electronic data capture (EDC) data entry, record retention, investigation product (IP) accountability records, protocol deviations and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training logs, monitoring logs, ClinicalTrials.gov registration, financial disclosures and delegation of authority].

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary endpoint HO data were centrally read, calculated, and evaluated and were not available at the clinical site for verification. The inspection verified that the site conducted and uploaded WBCT scans to the central reader per the protocols. There was no evidence of underreporting of AEs or SAEs.

At the end of the inspection, a Form 483 (Inspectional Observations) was not issued. There were no discussion items. In general, this clinical site appeared to be in compliance with GCP.

2. Edward Hsiao, M.D., Ph.D.
513 Parnassus Ave., HSE901G
San Francisco, CA 94143

This CI was inspected on 06/10-29/2021 as a data audit for Studies PVO-1A-001, PVO-1A-201, PVO-1A-202 (Parts A, B and C) and PVO-1A-301. This was the first FDA inspection for Dr. Hsiao. The inspection reviewed 100% of the ICFs for each of the study. Table 2 below is the reviewer's summary of the inspection information.

Table 2: Summary of Dr. Edward Hsiao's Inspection Information

Study	Site #	Number of Subjects Screened	Number of Subjects Enrolled	Number of Subjects Completed	Date of First Subject Enrolled	Date of Last Subject Visited	Number of Subject Records Reviewed
PVO-1A-001	22	23	20	4	03/19/2015	04/09/2020	7
PVO-1A-201	2	16	14	12	07/14/2014	05/23/2016	5
PVO-1A-202A	2	14	14	3	10/09/2014	08/17/2016	6
PVO-1A-202B	2	19	16	2	06/10/2016	05/07/2018	8
PVO-1A-202C	2	14	14	Ongoing	01/12/2018	Ongoing	6
PVO-1A-301	1001	22	19	Ongoing	11/30/2017	Ongoing	7

Source records reviewed during the inspection included the study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, imaging studies, AEs and SAEs), paper subjects' diary, paper CRFs with eCRFs and EDC data entry, record retention, protocol deviations, IP accountability records and related regulatory documents (e.g., IRB approvals and communications, staff training logs, monitoring logs, ClinicalTrials.gov registration, financial disclosures and delegation of authority).

The inspection found adequate source documentation for the study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary endpoint HO data were centrally calculated and evaluated and were not available at the clinical site for verification. The inspection verified that the site conducted and uploaded the WBCT scans to the central reader.

At the end of the inspection, a Form 483, Inspectional Observations, was issued with the observation that "an investigation was not conducted in accordance with the investigational plan". Specifically, not all SAEs were reported to the IRB within the required 5 working days, as shown in Table 3 below.

Table 3: SAEs Reported to the IRB Over Required 5 Business Days

Study PVO-1A-202: 7 of 17 SAEs				
Subject #	**SAE**	**Date PI Awareness**	**Date Received by IRB**	**Days Late**
(b) (6)	Hospitalization for epidural hematoma		(b) (6)	55
	Hospitalization for pneumonia			8
	Hospitalization for			14

(b) (6)	dehydration, GI illness	(b) (6)	
	Hospitalization for hypoxia and fever		3
	Hospitalization for severe knee pain		5
	Hospitalization for seizures		306
	Hospitalization for leg pain and edema		40
Study PVO-1A-301: 1 of the 3 SAEs			
(b) (6)	Hospitalization for severe iron deficiency anemia	(b) (6)	52

Reviewer's Comments*: All of the above listed SAEs were reported to the sponsor and FDA, although they were reported to the IRB over the required 5 days. The delated reporting of SAEs to IRB would not have an impact on the safety profile of the study drug. The CI responded to the FDA 483 on 07/13/2021, acknowledged the issues and submitted an action plan that included additional trainings to improve communications with the IRB, and implemented a SAE reporting SOP with a tracking system. The CI's response is acceptable.*

Discussion items were:

1) Six SAEs (shown in the Table 4 below) were reported to the sponsor later than the protocol required "within 24 hours" reporting period.

Table 4: SAEs Reported to the Sponsor Over 24 Hours

Study PVO-1A-202:					
Subject #	**SAE**	**SAE Onset**	**Date PI Awareness**	**Date Sponsor Notification**	**Days Late**
(b) (6)	Right knee flare			(b) (6)	2
	Left neck flare				1
	Neck myoclonus				1
	Back myoclonus				1
	Abdominal myoclonus				1
Study PVO-1A-301:					
(b) (6)	Worsening right leg pain			(b) (6)	9

Reviewer's Comments: *All of the above listed SAEs were reported to the sponsor and FDA, although they were reported to the sponsor over the required 24 hours. The delated reporting of SAEs to the sponsor would not have an impact on the safety profile of the study drug.*

2) For Study PVO-1A-301, two subjects completed consenting on 11/02/2017 prior to the site activation on 11/27/2017.

***Reviewer's Comments**: The above incidents were identified by the CI on 11/03/2017 and was reported as protocol violations to the IRB on 11/03/2017. No study-related procedures were conducted for the two subjects. The subjects were reconsented after the site activation. However, these should be submitted as minor protocol deviations. The CI responded to the above item on 07/13/2021, acknowledged the issues and submitted an action plan that included additional trainings to improve communications with the Sponsor/CRO/IRB.*

In general, this clinical site appeared to be in compliance with GCP, except the items noted above. These findings appear unlikely to have significant impacts on the overall efficacy and safety results.

3. Edna Mancilla, M.D./Site 1003
3500 Civic Center Blvd.
Philadelphia, PA 19104

This CI was inspected on 06/30-07/02/2021, 07/06/2021 and 07/12-13/2021 as a data audit for Study PVO-1A-301. This was the first FDA inspection for Dr. Mancilla.

For the inspected study, the site screened and enrolled a total of 11 subjects. The first subject was enrolled on 04/26/2018. The study was ongoing with 7 subjects completed the study at the study report cut-off date of 02/24/2020. Source records of all of the 11 enrolled subjects were reviewed.

Source records reviewed during the inspection included the ICFs, documentation of eligibility criteria, study protocol and amendments, medical records (including visit reports, laboratory tests, radiology studies, AEs/SAEs, concomitant medication use), protocol deviations, IP accountability records, paper subject diaries, paper CRFs with eCRFs and EDC data entries, record retention, sponsor audit and monitoring logs and related regulatory documents (e.g., IRB approvals and communications, staff training records, ClinicalTrials.gov registration, financial disclosures and delegation of authority).

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary endpoint HO was centrally analyzed by the sponsor. The inspection verified that the site conducted and submitted the required imaging scans with documentation.

At the end of the inspection, a Form 483, Inspectional Observations, was not issued.

Discussed items were the four under-reported AEs: Subject # (b) (6)'s abnormal urinalysis result was increased calcium oxalate crystals that was referred to a nephrologist (the subject was diagnosed with kidney stone in (b) (6) that was listed as an AE) and abnormal audiology results at Month 12. Subject # (b) (6)'s abnormal urinalysis result of increased calcium oxalate crystals; and Subject # (b) (6)'s abnormal audiology results on (b) (6) that was noted with a referral to the ENT were not reported.

***Reviewer's Comment**: The CI considered that these four AEs were non-serious and unrelated to the study drug. According to the protocol, all AEs including clinically significant lab abnormalities*

should be reported. The review Division may consider including the above AEs in the safety evaluation.

In general, this clinical site appeared to be in compliance with GCP except the items noted above.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-215559
Submission Number	001 (New NDA)
Submission Date	3/31/2021
Date Consult Received	4/7/2021
Drug Name	Palovarotene
Indication	Prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressiva (FOP).
Therapeutic Dose	5 mg once daily (chronic treatment), with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment).
Clinical Division	DGE

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 4/7/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-120181 dated 01/28/2019 in DARRTS (link);
- Previous IRT review under IND-120181 dated 04/16/2019 in DARRTS (link);
- Sponsor's clinical study protocol # PVO-1A-103 (SN0000 / SDN001; link);
- Sponsor's clinical study report # PVO-1A-103 (SN0000 / SDN001; link);
- Sponsor's statistical analysis plan # PVO-1A-103 (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; link).

1 SUMMARY

No significant QTcF prolongation effect of palovarotene was detected in this QT assessment.

The effect of palovarotene was evaluated in a thorough QT study (Study # PVO-1A-103). This was a randomized, partially double-blind, placebo- and positive-controlled, 4-way crossover study. The highest dose that was evaluated was 50 mg (as single dose), which covers the worst-case exposure scenario (CYP3A inhibition, Section 3.1). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest

that palovarotene is associated with significant QTc prolonging effect (refer to 4.5) – see Table 1 for overall results. The assay sensitivity was established by the moxifloxacin arm.

The findings of this analysis are further supported by the available nonclinical data (Section 3.1.2), the by-time analysis (Section 4.3) and categorical analysis (Section 4.4).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Concentration** (pg/mL)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Palovarotene 50 mg	315386.1	1.0	(-0.5 to 2.4)

For further details of the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the CSS-IRT. Our changes are highlighted (addition, ~~deletion~~). Each Section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At a dose 2.5 times the maximum recommended dose, <Sohonos> does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Clementia Pharmaceuticals Inc. is developing palovarotene for the prevention of heterotopic ossification (in adults and children) with fibrodysplasia (b) (4) ossificans progressiva. Palovarotene (Sohonos, CLM-001, RO3300074, R667, AMC09; MW: 414.54 g/mol) is a retinoic acid receptor gamma (RARγ) agonist.

The product is formulated as an immediate release capsule containing 1, 1.5, 2.5, 5, and 10 mg palovarotene for oral administration. Recommended dosage includes 5 mg once daily (chronic treatment), with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment). Weight-base dosing is proposed in the pediatric population targeting plasma levels similar to adults. The peak concentrations of 133 ng/mL (Tmax: ~5 h; half-life: ~9 h) are expected at steady-state with the anticipated therapeutic dose (Study # PVO-1A-102). The peak concentrations of 138 to 202 ng/mL are expected at steady-state with the maximum proposed dose in target population (POP-PK Predicted).

The product exhibits a slightly positive food effect with a 16% increase in exposure (Cmax: ~16% and AUC: 40%; for 20 mg single dose) was observed following its administration with a high-fat and high-calorie meal compared to that under fasting condition (Study # PVO-1A-102). The sponsor proposed to administer palovarotene under fed conditions. The studies indicate that palovarotene is mainly metabolized by CYP3A4 and to lesser extent by CYP2C8 and CYP2C19. Concomitant administration of palovarotene with a strong inhibitor of CYP3A4 is expected to result in increased exposures of palovarotene (Cmax: 2-fold & AUC: ~3-fold). The human mass balance study indicates that ~97% of the drug is excreted in feces, and 3.2% in urine. However, the sponsor has not conducted clinical studies evaluating the impact of organ impairment (likely hepatic impairment) on the pharmacokinetics of palovarotene and claims that liver dysfunction is not a known complication of fibrodysplasia ossificans progressiva.

Previously, the sponsor proposed to conduct a dedicated thorough QT study (PVO-1A-103) evaluating the potential effects of a therapeutic (20 mg single dose) and a supratherapeutic dose (60 mg single dose) of palovarotene on electrocardiogram parameters in healthy subjects (n=24/28) using a randomized, partially double-blind, placebo- and positive-controlled, 4-way crossover design (with 12 treatment sequences and ≥ 5-day washout period between doses). Refer to previous IRT review under IND-120181 dated 04/16/2019 in DARRTS (link). Palovarotene was administered orally under the fed condition using 10-mg powder-filled, hard gelatin capsules. The study was performed using 20 mg single dose (therapeutic exposures) and 50 mg single dose (supratherapeutic exposures).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

Potential effects on cardiovascular system function were evaluated directly in an in vitro hERG assay, an in vitro action potential assay in canine Purkinje fibers, two dedicated

safety pharmacology studies in surgically instrumented male dogs given single oral doses and monitored continuously by telemetry, and by way of ECG evaluations in repeat-dose toxicity studies in dogs.

In the hERG assay, palovarotene inhibited potassium current by 5%, 10%, 15%, 18%, and 33% at concentrations of 0.3, 1, 3, 10, and 30 μM, respectively (approximately 124, 415, 1244, 4146, and 12,437 ng/mL, respectively) and so an IC50 could not be calculated.

In the Purkinje fiber assay, palovarotene had no effect on resting membrane potential, depolarization rate, upstroke amplitude, or action potential duration at concentrations of up to 10 μM (approximately 4146 ng/mL), the highest concentration tested.

In the two safety pharmacology studies, groups of four male conscious dogs were given single oral doses of vehicle or palovarotene at 0.04, 0.2, 1, or 10 mg/kg and heart rate, blood pressure, and ECG data were recorded continuously from 30 minutes before dosing through 8 hours after dosing. Palovarotene did not affect heart rate, heart rhythm, blood pressure, or ECG parameters (including QTc interval) at any dose level. Palovarotene also did not affect heart rate, heart rhythm, or ECG parameters in dogs given repeated daily oral doses at up to 0.2 mg/kg/day for 4 weeks and up to 0.04 mg/kg/day for 9 months or 0.025 mg/kg/day for 13 weeks followed by 0.120 mg/kg/day for 9 months.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for Palovarotene was based on exposure-response analysis, please see Section 3.2.3 for additional details.

Reviewer's comment: *FDA reviewer's by-time analysis results are similar to the sponsor's by-time analysis results. FDA reviewer also performed by-time analysis for HR, PR and QRS. Please see Section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Exposure-response analysis was the primary analysis for the assay sensitivity.

Reviewer's comment: *FDA reviewer's and sponsor's exposure-response analysis as well as by-time analysis show that the assay sensitivity was established by the moxifloxacin arm.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), PR, and QRS.

Reviewer's comment: *FDA reviewer's categorical analysis results are similar to the sponsor's results. Please see Section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

As primary analysis, the sponsor performed PK/PD analysis to explore the relationship between plasma concentration of palovarotene and ΔΔQTcF (placebo-corrected change from baseline in QTcF) using a linear mixed-effects approach (Garnett et al. 2018). The estimated slope of palovarotene plasma concentration in the concentration-QTc relationship was -0.000087 ms per ng/mL [90% CI: -0.0058, 0.0056; not statistically significant] with a positive and not statistically significant intercept of 1.0 ms. The model predicted ΔΔQTcF (upper confidence interval) values of 0.95 (2.89) msec at the mean peak concentrations for the highest studied dose (50 mg; geomean Cmax ~314 ng/mL) following single oral administration. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the maximum proposed dose.

Reviewer's comment: *Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

No AEs leading to death, SAEs, or AEs resulting in discontinuation of the study or study drug withdrawal were reported.

No episodes of ventricular tachycardia, flutter, or fibrillation, syncope, and seizure, AEs resulting in the subject discontinuing from the study, and deaths or other SAEs.

Additionally, no subject had AEs during the study captured by standardized MedDRA query analysis performed for torsade de pointes/QT prolongation (narrow) and PT seizure.

No AEs in the standardized Medical Dictionary for Regulatory Activities query analysis for torsade de pointes/QT prolongation (narrow) and preferred term seizure were identified for subjects in this study.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

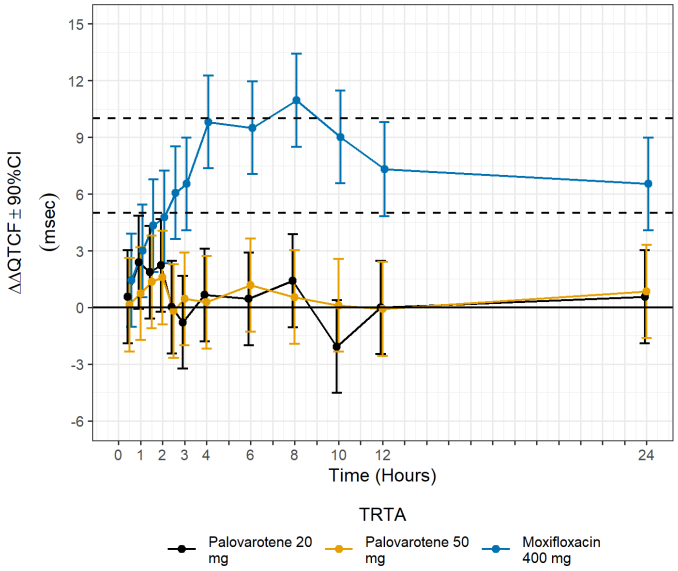


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Treatment	N_{act} / N_{pbo}	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Palovarotene 20 mg	31 / 31	1.0	2.4	(-0.1 to 4.8)
Palovarotene 50 mg	30 / 31	2.0	1.6	(-0.9 to 4.1)

4.3.1.1 Assay Sensitivity

FDA reviewer used the same model for the assay sensitivity. The time-course of changes in ΔΔQTcF is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 3).

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see Section 4.5.1 for details.

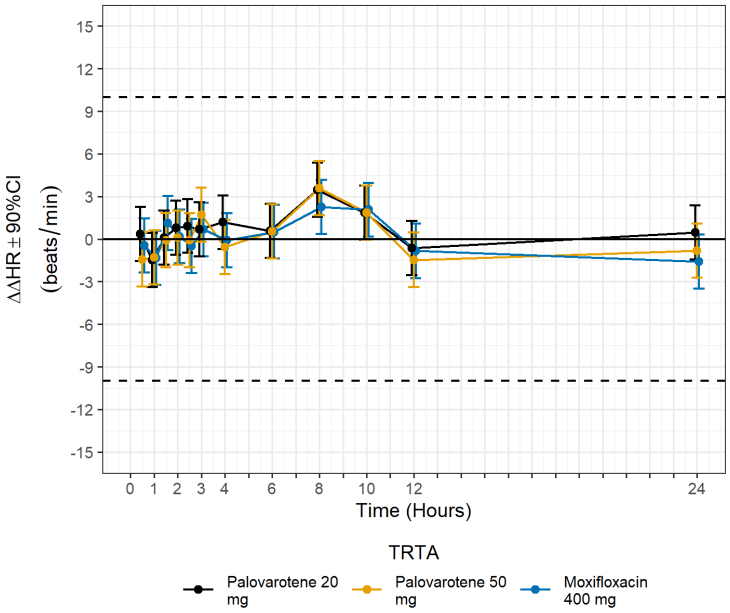
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Treatment	Nact/Npbo	Time (hours)	ΔΔQTcF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	31 / 30	8.0	11.0	(8.5 to 13.4)	(7.6 to 14.3)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

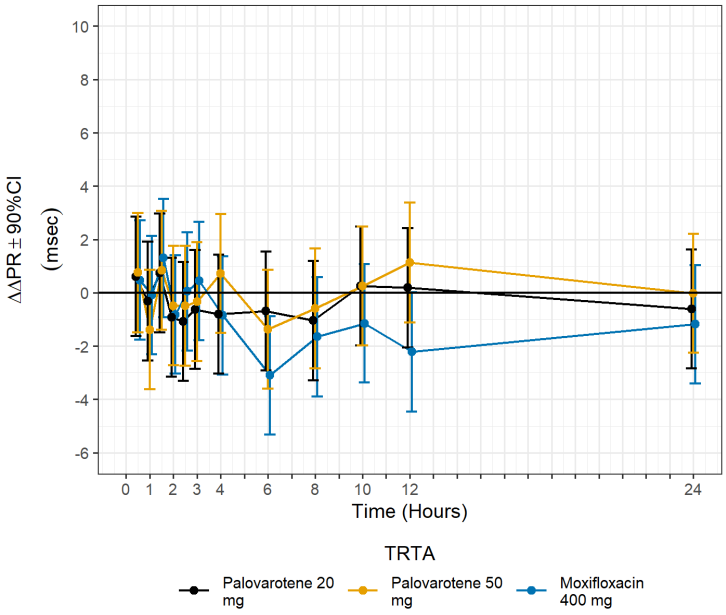
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

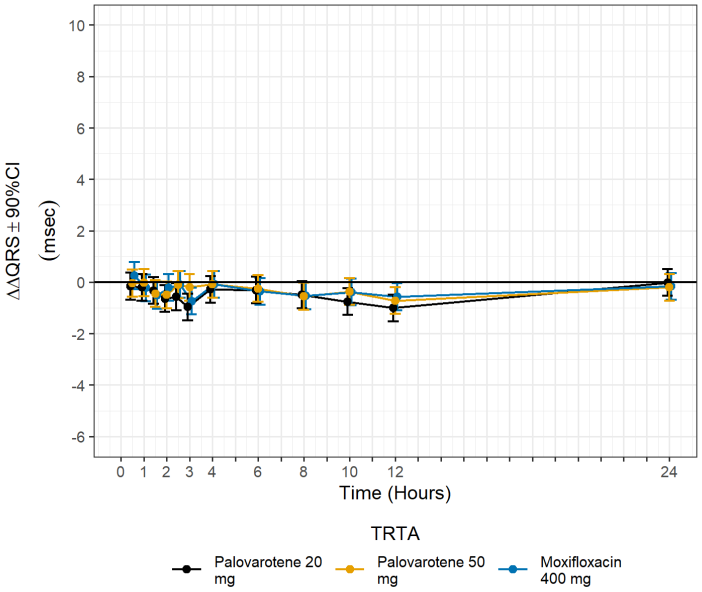
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the

following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF greater than 500 msec or ΔQTcF greater than 60 msec in both treatment arms.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in palovarotene 50 mg group experienced HR greater than 100 beats/min.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palovarotene 20 mg	31	372	31 (100.0%)	372 (100.0%)	0 (0%)	0 (0%)
Palovarotene 50 mg	31	369	30 (96.8%)	368 (99.7%)	1 (3.2%)	1 (0.3%)
Placebo	31	369	31 (100.0%)	369 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

None of the subjects experienced PR greater than 220 msec in any of the treatment arms.

4.4.4 QRS

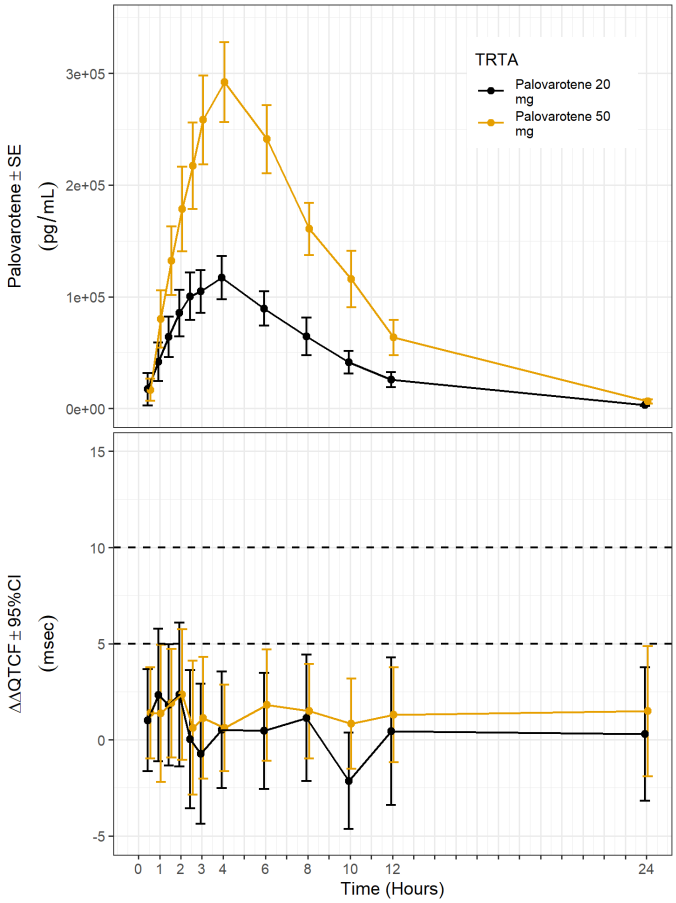
None of the subjects experienced QRS >120 msec with 25% increase over baseline in any of the treatment arms.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of palovarotene and ΔΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between palovarotene concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between palovarotene concentration and ΔΔQTc and 3) a non-linear relationship. An evaluation of the time-course of palovarotene concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of palovarotene indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 6 bpm (Sections 4.3.2 and 4.4.2).

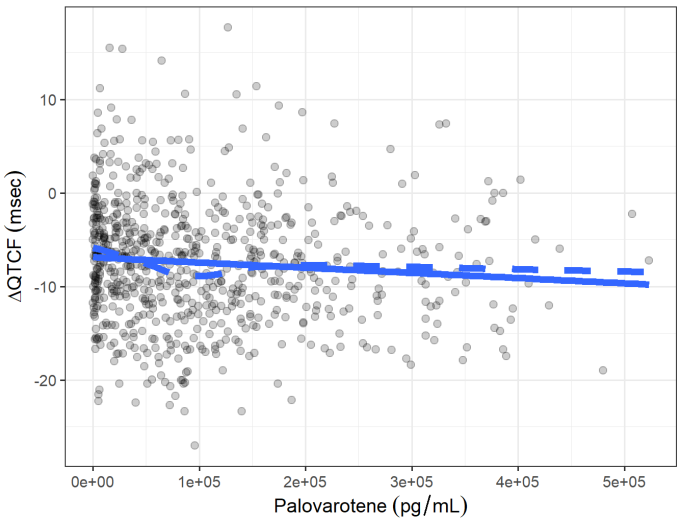
Figure 5: Time-course of palovarotene Concentration (top) and QTcF (bottom)[1]



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between palovarotene concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between palovarotene concentration and ΔQTc and supports the use of a linear model.

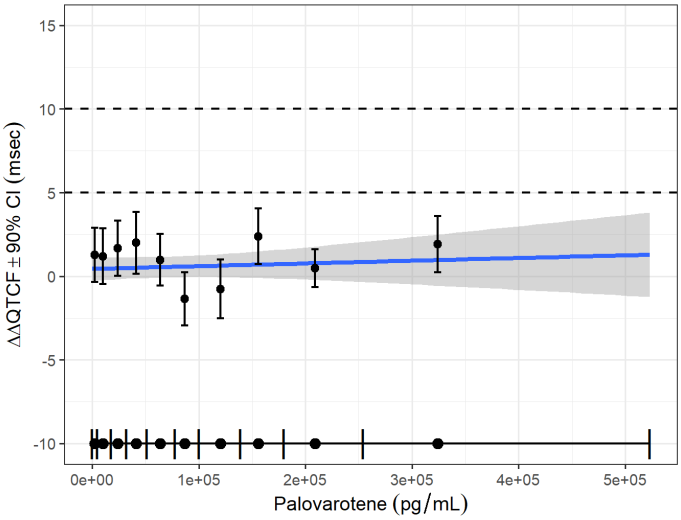
[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 1.

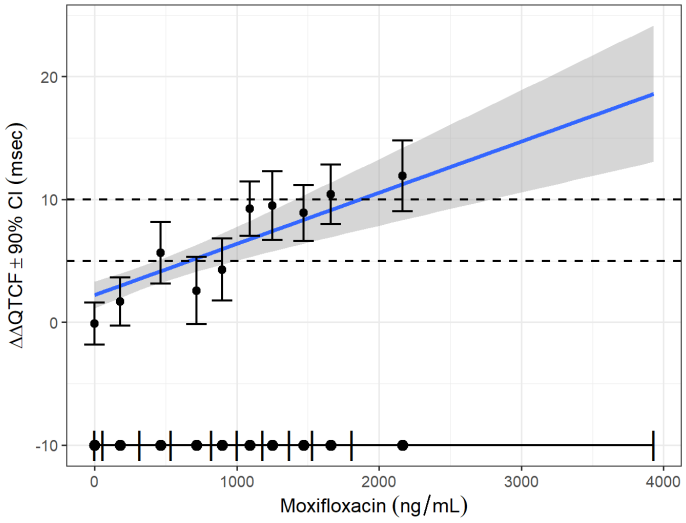
Figure 7: Goodness-of-fit Plot for QTcF



4.5.1 Assay Sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control detecting small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group was generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*).

Figure 8: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin



Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 msec. Therefore, assay sensitivity is established. The goodness-of-fit plot for moxifloxacin is shown in **Error! Reference source not found.** and the predicted QTc at the geometric mean Cmax is listed in Table 5. Assay sensitivity was also established using by time analysis. Please see Section 4.3.1.1 for additional details.

Table 5: Predictions from Concentration-QTcF Model for Moxifloxacin

Treatment	Moxifloxacin (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400mg	1892	10.1	(7.6 to 12.7)

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