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ADISINSIGHT REPORT

Palovarotene: First Approval

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Abstract
Palovarotene (Sohonos™) is an orally bioavailable selective retinoic acid receptor (RAR)γ agonist being developed by Ipsen for the reduction of heterotopic ossification (HO) formation in patients with fibrodysplasia ossificans progressiva (FOP). By binding to RARγ, palovarotene inhibits bone morphogenetic protein and SMAD 1/5/8 signalling: interfering with these pathways prevents chondrogenesis and ultimately HO by permitting normal muscle tissue repair or regeneration to occur. Palovarotene received its first approval on 21 January 2022 to reduce the formation of HO in adults and children aged 8 years and above for females and 10 years and above for males with FOP in Canada. This article summarizes the milestones in the development of palovarotene leading to this first approval.

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Palovarotene (Sohonos™): Key Points

A selective RARγ agonist is being developed by Ipsen for the reduction of HO formation in patients with FOP

Received its first approval on 21 January 2022 in Canada

Approved to reduce the formation of HO in adults and children aged 8 years and above for females and 10 years and above for males with FOP

1 Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare (incidence of ≈ 1 in 2 million individuals) autosomal dominant disorder characterized by the formation of endochondral bone in ligaments, joints, muscles and tendons [i.e. heterotopic ossification (HO)] [1–3]. HO is often preceded by painful and recurrent soft-tissue swellings (i.e. flare-ups) [4]. FOP is most commonly caused by a gain-of-function missense mutation in the *ACVR1/ALK2* gene [2]. *ACVR1/ALK2* encodes activin receptor type 1A (ACVR1)/activin receptor-like kinase 2 (ALK2), a bone morphogenetic protein (BMP) type I receptor that is involved in controlling bone and muscle growth and development, including the gradual replacement of cartilage by bone that occurs during normal skeletal maturation [1–3, 5]. The presence of mutations in *ACVR1/ALK2* results in aberrant signalling through the receptor and over-activation of the SMAD 1/5/8 pathway, which is thought to trigger HO [2, 3]. There is no curative therapy for FOP and therapeutic options are limited [1, 2].

Retinoids play a crucial role in the embryonic development and postnatal functioning of various tissues and organs, including the skeleton, for which they are essential for chondrogenesis and proper skeleton formation [2]. Retinoic acid signalling is mediated via three retinoic acid receptors (RARs): α, β and γ [2]. These receptors form heterodimers with retinoic X receptors (RXRs); the resultant heterodimeric RAR–RXR complexes act as transcriptional activators in the presence of their endogenous ligand (all-*trans* retinoic acid) and as transcriptional repressors in their unbound form [2, 4]. Upon the discovery that retinoid signalling is a strong inhibitor of chondrogenesis and that transcriptional repression elicited by unliganded RAR receptors was required for chondrogenic differentiation, synthetic retinoid agonists were suggested as potential pharmacological agents to inhibit HO [4]. Indeed, at pharmacologic doses,

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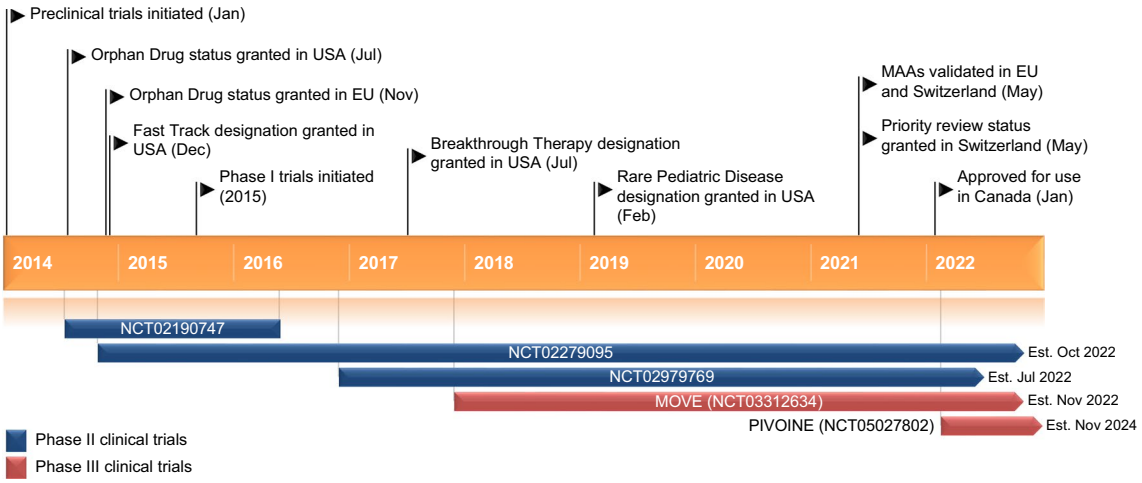


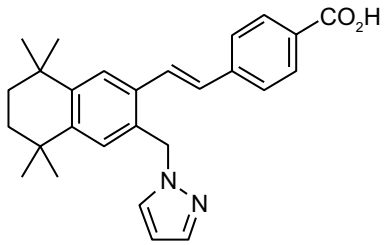
Key milestones in the development of palovarotene, focusing on its use in reducing heterotopic ossification formation in patients with fibrodysplasia ossificans progressiva. *Est.* estimated, *MAA* Marketing Authorisation Application

RAR agonists can potently impede skeletogenesis and endochondral ossification by redirecting the differentiation of prechondrogenic mesenchymal stem cells [4].

RAR-γ is expressed in chondrogenic cells and chondrocytes [5]. Palovarotene (Sohonos™) is an orally bioavailable selective RARγ agonist [5]. Developed by Ipsen, it was approved in January 2022 by Health Canada to reduce the formation of HO in adults and children aged 8 years and above for females and 10 years and above for males with FOP [5, 6].

Palovarotene should be taken with food and preferably at the same time each day [5]. It may be swallowed whole, or the capsules (1 mg, 1.5 mg, 2.5 mg, 5 mg or 10 mg) may be opened and the contents emptied onto a teaspoon of soft food. For chronic therapy, the recommended dosage of palovarotene is 5 mg once daily. For flare-up episodes, the recommended dosage of palovarotene is 20 mg once daily for 4 weeks, then 10 mg once daily for 8 weeks. If flare-up symptoms persist, therapy may be extended in 4-week intervals with palovarotene 10 mg once daily. Flare-up episode treatment should commence (under the guidance of a healthcare professional) at the onset of the first symptom indicative of an FOP flare-up, or following a substantial high-risk traumatic event likely to result in a flare-up. The chronic regimen should be stopped when the flare-up regimen is started, and reinitiated following completion of flare-up treatment. For both regimens, a weight-adjusted dosage is required for children aged < 14 years; the product monograph should be consulted for information regarding dose modification recommendations, including for children aged < 14 years and the management of adverse reactions [5].

The Health Canada product monograph for palovarotene carries a boxed warning regarding the risk of teratogenicity, and premature physeal closure (PPC) in growing children [5]. Contraindications thus include patients who are pregnant, and



Chemical structure of palovarotene

those of childbearing potential (unless all conditions for pregnancy prevention are met, or they are not at risk of pregnancy due to physical limitations as assessed by the physician). Periodic (every 3 months) monitoring of physeal growth plates is recommended in growing children [5] (see Sect. 2.4). The clinical development of palovarotene for the treatment of chronic obstructive pulmonary disease and multiple osteochondromas has been discontinued.

1.1 Company Agreements

Palovarotene was originally developed by Roche Pharmaceuticals for the treatment of chronic obstructive pulmonary disease before being licensed to Clementia Pharmaceuticals before January 2014 [7]. Under the terms of the agreement with Roche, Clementia acquired the global rights to palovarotene and is solely responsible for its development in any indication. In addition to an upfront payment to Roche, Clementia is responsible for additional payments upon achieving certain clinical and regulatory milestones, as well as royalties on product sales [7]. In April 2019, Clementia was acquired by Ipsen [8].

2 Scientific Summary

2.1 Pharmacodynamics

By binding to RARγ, palovarotene inhibits BMP and SMAD 1/5/8 signalling: interfering with these pathways prevents chondrogenesis and ultimately HO by permitting normal muscle tissue repair or regeneration to occur [5]. Palovarotene inhibited BMP-mediated SMAD 1/5 signalling in human FOP fibroblasts carrying the gain-of-function R206H mutation [5]. It inhibited mineralized tissue formation in a subcutaneous mouse model of HO [9] and reduced HO in juvenile FOP mice [10] and a blast-associated rat model of combat-related extremity injury [11]. The use of palovarotene in the juvenile FOP mice was associated with aggressive synovial joint overgrowth and long bone growth plate ablation [10].

In a blast-associated rat model of combat-related extremity injury, palovarotene significantly ($p < 0.05$) reduced systemic (e.g. IL-6, TNFα and IFNγ) and local (via reduced cellular infiltration) inflammatory responses, osteogenic connective tissue progenitor colonies and the expression of osteo- and chondrogenic genes [12].

Single therapeutic (20 mg) and supratherapeutic (50 mg) doses of palovarotene had no effect on corrected QT interval, QRS duration, PR interval or heart rate in healthy adults [5].

2.2 Pharmacokinetics

Food increases the oral absorption of palovarotene [5] (see Sect. 1). The pharmacokinetics of palovarotene were linear and dose proportional over a dose range of 0.02–50 mg, according to a population pharmacokinetic analysis. Steady-state concentrations of palovarotene were achieved by day 3; at steady-state, the maximum concentration of palovarotene (5 mg, 10 mg and 20 mg) was achieved 3 h post-dose in patients with FOP [5].

Palovarotene was 99.0% (mean value) bound to proteins in vitro [5]. It is extensively metabolized by CYP3A4 and to a minor extent by CYP2C8 and CYP2C19. There are five metabolites of palovarotene: M1, M2, M3, M4a and M4b. The parent drug and its four known major metabolites (M2, M3, M4a and M4b) represent 40% of the total plasma exposure; in vitro, M3 and M4b have ≈ 1.7% and ≈ 4.2% the pharmacological activity of the parent drug. Following the administration of a 1 mg dose of palovarotene to healthy individuals, 97.1% and 3.2% of the dose was recovered in the faeces and urine; over 92% of the dose was recovered in the first 6 days post-dose. At steady state, the half-life of palovarotene 5 mg, 10 mg and 20 mg was 4.9 h, 4.3 h and 4.4 h, respectively, in patients with FOP [5].

The pharmacokinetics of palovarotene do not appear to be affected by age, sex, race, smoking status, health status, mild hepatic impairment, or mild or moderate renal impairment [5]. However, bodyweight has a significant effect, with the exposure of palovarotene increasing with a decreasing weight (see Sect. 1). Caution is advised when using palovarotene in patients with moderate hepatic impairment; palovarotene is not recommended in patients with severe hepatic impairment, or those with severe renal impairment (in whom it has not been studied). The coadministration of palovarotene with strong CYP3A4 inducers and inhibitors, tetracycline derivatives, and vitamin A and/or other oral retinoids should be avoided [5]; see product monograph for further details.

Features and properties of palovarotene

Alternative names	Clm-001; IPN-60120; R-667; RAR-gamma; RG-667; RO-3300074; Sohonos
Class	Benzoic acids; eye disorder therapies; naphthalenes; pyrazoles; small molecules
Mechanism of action	Retinoic acid receptor gamma agonists
Route of administration	Oral
Pharmacodynamics	Binds to retinoic acid receptor γ, inhibiting bone morphogenetic protein and SMAD1/5/8 signalling, thereby preventing chondrogenesis and ultimately heterotopic ossification by permitting normal muscle tissue repair or regeneration to occur
Pharmacokinetics	Food increases the oral absorption of the drug; linear and dose proportional over a dose range of 0.02–50 mg; maximum concentration reached in 3 h
Most frequent adverse events	Dry skin, dry lip, pruritus, alopecia, rash, erythema, skin exfoliation, dry eye, skin reaction and skin abrasion
ATC codes	
WHO ATC code	M09AX11 (Palovarotene)
EphMRA ATC code	M5X (All Other Musculoskeletal Products)
Chemical name	4-[2-[5,5,8,8-tetramethyl-3-(1H-pyrazol-1-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]vinyl]benzoic acid

2.3 Therapeutic Trials

Oral palovarotene is currently being evaluated in a 48-month, open-label, multinational, phase III study (MOVE; NCT03312634) in patients with FOP [5, 13]. MOVE is divided into three parts: Part A (the main part of the study), Part B (the extension) and Part C (which is assessing longer-term safety in patients who were skeletally immature at the time of study treatment discontinuation). Patients in this study are receiving palovarotene 5 mg once daily for up to 48 months, with the dosing adjusted based on bodyweight (10 to < 20 kg, 20 to < 40 kg, 40 to < 60 kg and ≥ 60 kg) in skeletally immature children [i.e. those who had not reached ≥ 90% skeletal maturity (defined as a bone age of ≥ 12 years 0 months for girls and ≥ 14 years 0 months for boys)]. Dose escalation (20 mg once daily for 4 weeks, then 10 mg once daily for 8 weeks; 20/10 mg regimen) for flare-up episodes is permitted, with therapy extended in 4-week increments for persistent symptoms. Flare-up episodes were defined as ≥ 1 symptom (e.g. pain, swelling, redness) consistent with a previous flare-up, or a substantial high-risk traumatic event likely to lead to a flare-up. The primary endpoint is the annualized change in new HO volume [as assessed by low-dose, whole body computed tomography (excluding the head)] compared with untreated patients from a longitudinal natural history study (NHS; NCT02322255). Using a Bayesian compound Poisson model with square-root transformation, futility was prespecified as a < 5% posterior probability of a ≥ 30% reduction in square-root transformed annualized new HO volume [5, 13].

Palovarotene reduced HO formation in patients with FOP in MOVE [5, 13]. At a planned interim analysis at month 12, the boundary for futility had been crossed according to a prespecified analysis using a Bayesian compound Poisson model with square-root transformation. However, post hoc analyses of the month 12 data revealed that the square-root transformation of the data in the Bayesian model had moved the statistical conclusion from a significant therapeutic benefit with palovarotene to demonstrating futility. Moreover, a planned post hoc interim analysis when all patients had reached their month 18 visit using Bayesian and weighted linear mixed effects (wLME) models of annualized new HO volume without square-root transformation (including all raw data) demonstrated the efficacy of palovarotene. Treatment was associated with a 62% reduction in the mean annualized rate of new HO volume compared with no treatment (8821 vs 23,318 mm^3) [$n = 97$ and 98 from MOVE and NHS], and the post-hoc wLME model yielded a treatment difference of −11,611 mm^3 (nominal two-sided p-value of $p = 0.0292$) in MOVE compared with no treatment [5, 13].

In a subgroup of female patients aged ≥ 8 years and male patients aged ≥ 10 years (i.e. the target population) in which all patients had reached their month 18 visit, a 57% reduction in the mean annualized rate of new HO volume was seen with palovarotene ($n = 77$) compared with no treatment ($n = 76$) [10,655 vs 24,777 mm^3) [5].

The findings of MOVE are supported by efficacy data from patients aged ≥ 6 years with FOP participating in a randomized, double-blind, placebo-controlled, multinational phase II study (NCT02190747) and its multinational, phase II extension (NCT02279095) [5, 14]. In NCT02190747, patients received palovarotene 10 mg once daily for 2 weeks then 5 mg once daily for 4 weeks (10/5 mg regimen), palovarotene 5 mg once daily for 2 weeks then 2.5 mg once daily for 4 weeks (5/2.5 mg regimen), or placebo. NCT02279095 is divided into four parts. In Part A (total follow-up: 36 months), patients experiencing a flare-up received the palovarotene 10/5 mg regimen. In Part B (total follow-up: 24 months), patients who had reached ≥ 90% skeletal maturity received the chronic palovarotene regimen (i.e. 5 mg once daily), with permitted dose escalation to the 20/10 mg regimen for flare-up episodes; those who were skeletally immature received a weight-adjusted 20/10 mg palovarotene flare-up regimen. In Part C (total follow-up: ≤ 48 months), which is ongoing, patients (from Part B) are receiving the palovarotene chronic regimen (i.e. 5 mg once daily) in addition to the flare-up regimen; dosing is weight adjusted for skeletally immature patients. Part D is assessing longer-term safety in patients who were skeletally immature at the time of study treatment discontinuation. The duration of Parts C and D will not exceed 48 months [5, 14]. Only data for the palovarotene flare-up regimens are currently available [5].

In an analysis of flare-up episodes (15 and 47 flare-ups assessed in the palovarotene and placebo/untreated groups, respectively) during the phase II studies, there was a nominally significant ($p = 0.02$) 72% reduction in new HO volume seen with the palovarotene 20/10 mg regimen compared with placebo/no treatment (3045 mm^3 vs 10,780 mm^3) [5]. When data were derived from the target population, an analysis of flare-up episodes (14 and 43 flare-ups assessed in the palovarotene and placebo/untreated groups, respectively) found that there was a nominally significant ($p = 0.04$) 72% reduction in new HO volume with palovarotene compared with placebo/no treatment (3262 vs 11,715 mm^3). Moreover, 72% and 76% reductions in new HO volume were seen with the palovarotene 10/5 mg flare-up regimen compared with placebo/no treatment in the total population and the target population, respectively [5].

Key clinical trials of palovarotene in patients with fibrodysplasia ossificans progressiva

Drug(s)	Phase	Status	Location(s)	Identifier	Sponsor
Palovarotene	III	Not yet recruiting	Multinational	NCT05027802 (PIVOINE)	Ipsen
Palovarotene	III	Active, not recruiting	Multinational	NCT03312634 (MOVE)	Clementia Pharmaceuticals, Ipsen
Palovarotene	II	Active, not recruiting	Multinational	NCT02279095	Clementia Pharmaceuticals, Ipsen
Palovarotene	II	Active, not recruiting	France	NCT02979769	Clementia Pharmaceuticals, Ipsen
Palovarotene, placebo	II	Completed	Multinational	NCT02190747	Clementia Pharmaceuticals, Ipsen
Palovarotene	II	Discontinued	USA	NCT02521792	Clementia Pharmaceuticals, Ipsen

2.4 Adverse Events

Unless otherwise stated, data in this subsection are from female patients aged ≥ 8 years and male patients aged ≥ 10 years with FOP who have received palovarotene for a maximum of 3.8 years in phase II and III studies [5]. Patients ($n = 139$) received either a chronic/flare-up regimen of palovarotene [i.e. 5 mg once daily (chronic), or 20 mg once daily for 4 weeks then 10 mg once daily for 8 weeks (flare-up regimen)] or a flare-up regimen [the 20/10 mg dose for 12 weeks, a 10/5 mg dose for 6 weeks (10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks) or a 5/2.5 mg dose for 6 weeks (5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks)] [5].

The most frequently reported adverse reactions (occurring in > 20% of patients) with palovarotene were dry skin (78% of patients), dry lip (55%), pruritus (55%), alopecia (41%), rash (39%), erythema (32%), skin exfoliation (31%), dry eye (26%), skin reaction (24%) and skin abrasion (21%), with most being mild or moderate in severity [5].

The Health Canada product monograph for palovarotene carries a boxed warning regarding PPC in growing children [5]; see Sect. 1. In clinical studies, serious adverse reactions of PPC were reported in 24 (24%) of 102 patients aged < 18 years, and were more common in younger (age < 8/10 years) than older (≥ 8/10 to < 14 years) patients [14 (56%) of 25 patients versus 10 (26%) of 39 patients]. Of the eight patients with severe PPC, five were aged ≤ 7 years. Palovarotene is thus not indicated for use in female patients aged < 8 years and male patients aged < 10 years [5]; see Sect. 1.

In MOVE, all of the patients experienced ≥ 1 adverse event (AE), with the AEs considered to be mild, moderate or severe in 32.3%, 45.5% and 22.2% of patients, respectively [13]. Most (97%) patients experienced ≥ 1 retinoid-associated (e.g. mucocutaneous) AE. At least one serious AE, including PPC or epiphyseal disorder in 19 of 70 patients aged < 18 years, occurred in 29.3% of patients [13].

2.5 Ongoing Clinical Trials

The multinational phase III MOVE study (NCT03312634) is currently ongoing, as are two phase II extension studies (NCT02279095 and NCT02979769). The multinational, phase III PIVOINE study (NCT05027802) has yet to start enrolling patients.

3 Current Status

Palovarotene received its first approval on 21 January 2022 to reduce the formation of HO in adults and children aged 8 years and above for females and 10 years and above for males with FOP [5, 6].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01709-z.

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Semler O, Rehberg M, Mehdiani N, et al. Current and emerging therapeutic options for the management of rare skeletal diseases. Paediatr Drugs. 2019;21(2):95–106.

2. Wentworth KL, Masharani U, Hsiao EC. Therapeutic advances for blocking heterotopic ossification in fibrodysplasia ossificans progressiva. Br J Clin Pharmacol. 2019;85(6):1180–7.
3. US National Library of Medicine. Genetics Home Reference: fibrodysplasia ossificans progressiva. 2021. https://medlineplus.gov/genetics/condition/fibrodysplasia-ossificans-progressiva/. Accessed 24 Feb 2022.
4. Pignolo RJ, Pacifici M. Retinoid agonists in the targeting of heterotopic ossification. Cells. 2021;10(11): 3245.
5. Ipsen Biopharmaceuticals Canada Inc. PrSOHONOS™ (palovarotene capsules 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg): Canadian product monograph. 2022. https://pdf.hres.ca/dpd_pm/00064435.PDF. Accessed 1 Feb 2022.
6. Health Canada. Notice of compliance information: SOHONOS. 2022. https://health-products.canada.ca/noc-ac/info.do?lang=en&no=27451. Accessed 22 Mar 2022.
7. Clementia Pharmaceuticals Inc. Clementia Pharmaceuticals Inc. announces closing of $22.5 million Series A financing with preeminent U.S. and Canadian healthcare venture capital funds [media release]. 10 Jan 2014. https://finance.yahoo.com/news/clementia-pharmaceuticals-inc-announces-closing-133000560.html.
8. Ipsen. Ipsen completes acquisition of Clementia Pharmaceuticals [media release]. 18 Apr 2019. https://www.ipsen.com/press-releases/ipsen-completes-acquisition-of-clementia-pharmaceuticals/.
9. Sinha S, Uchibe K, Usami Y, et al. Effectiveness and mode of action of a combination therapy for heterotopic ossification with a retinoid agonist and an anti-inflammatory agent. Bone. 2016;90:59–68.
10. Lees-Shepard JB, Nicholas SE, Stoessel SJ, et al. Palovarotene reduces heterotopic ossification in juvenile FOP mice but exhibits pronounced skeletal toxicity. Elife. 2018;7(e40814):1–20.
11. Pavey GJ, Qureshi AT, Tomasino AM, et al. Targeted stimulation of retinoic acid receptor-γ mitigates the formation of heterotopic ossification in an established blast-related traumatic injury model. Bone. 2016;90:159–67.
12. Wheatley BM, Cilwa KE, Dey D, et al. Palovarotene inhibits connective tissue progenitor cell proliferation in a rat model of combat-related heterotopic ossification. J Orthop Res. 2018;36(4):1135–44.
13. Pignolo RJ, Al Mukaddam M, Baujat G, et al. Palovarotene (PVO) for fibrodysplasia ossificans progressiva (FOP): data from the phase III MOVE trial [abstract no. 1046]. J Bone Miner Res. 2020;35(Suppl 1):16–7.
14. US National Institutes of Health. ClinicalTrials.gov identifier NCT02279095. 2022. https://clinicaltrials.gov/. Accessed 1 Mar 2022.