Indication

- Ritlecitinib is indicated for the treatment of severe AA in adults and adolescents 12 years and older.

Pharmacology

- Ritlecitinib is a kinase inhibitor. It irreversibly inhibits JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family by blocking the ATP binding site.
  - In cellular settings, ritlecitinib inhibits cytokine induced STAT phosphorylation mediated by JAK3-dependent receptors. Ritlecitinib inhibits signaling of immune receptors dependent on TEC kinase family members. The relevance of inhibition of specific JAK or TEC family enzymes to therapeutic effectiveness is not currently known.

Clinical Efficacy

- A 48-week, double-blind (DB), placebo-controlled (PC), multicenter (MC), Phase 2b/3 randomized controlled trial (RCT), ALLEGRO, evaluated various dosing regimens of ritlecitinib vs placebo in 718 patients ≥ 12 years of age with severe AA (*King et al 2023*); 50 mg once daily subsequently became the FDA-approved dose. The primary endpoint, the proportion of patients with a SALT score ≤ 20 at week 24, was greater in the ritlecitinib 50 mg group (23%) vs the placebo group (2%), with a difference of 21.85 (95% confidence interval [CI],14.65 to 30.23; $p < 0.0001$). Differences also favored ritlecitinib in the key secondary endpoint of SALT score ≤ 10 response at week 24, which was achieved by 14% of patients in the ritlecitinib 50 mg group vs 2% of patients in the placebo group.
- Based on a subgroup analysis of ALLEGRO, ritlecitinib treatment demonstrated clinician-reported efficacy, patient-reported improvement, and an acceptable safety profile through week 48 in adolescents with AA. In total, 105 adolescents were randomized (14.6% of the initial ALLEGRO study population). In the ritlecitinib 50 mg group, the primary endpoint of a SALT score ≤ 20 was achieved by 25% and 50% of patients at week 24 and week 48, respectively, and the secondary endpoint of SALT score ≤ 10 was achieved by 13% and 33% of patients at these respective time points (*Hordinsky et al 2023*).

Place in Therapy

- Ritlecitinib is the second FDA-approved systemic therapy for the treatment of severe AA, and the first FDA-approved therapy for patients with this condition who are ages 12 through 17 years.
- Topical corticosteroids are recommended as first-line agents for AA, and several topical, intralesional, and oral treatments have been used off-label. Although there are no current United States (U.S.) clinical guidelines for management of AA, an international consensus of experts stated that JAK inhibitors were their preferred systemic treatment (*Meah et al 2020*).

Safety

- Ritlecitinib is generally well tolerated. It has a Boxed Warning shared with other JAK inhibitors for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. There are also warnings for decreases in lymphocytes and platelets, and elevations in liver enzymes and creatinine phosphokinase (CPK).
- Routine monitoring of absolute lymphocyte count (ALC), platelets, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) is recommended. Treatment interruption or discontinuation are recommended based on ALC, platelet count, and liver enzyme abnormalities.
- The most common adverse events (AEs) with ritlecitinib, occurring at an incidence of ≥ 1% in the treated groups and at a higher rate than placebo, are headache, diarrhea, acne, rash, urticaria, folliculitis, pyrexia, atopic dermatitis, dizziness, blood CPK increased, herpes zoster, red blood cell count decreased, and stomatitis.

Dosing

- The recommended dosage of ritlecitinib is 50 mg orally once daily with or without food.
  - The full prescribing information provides guidance for missed doses, considerations before initiation, and drug interactions.

Conclusion

- JAK enzymes have been identified as a therapeutic target of interest in the pathogenesis of AA. Prior to the approvals of baricitinib and ritlecitinib, treatments for AA have been used off-label.
- Baricitinib, an oral JAK inhibitor, was the first FDA-approved systemic treatment for AA.
- The availability of ritlecitinib expands systemic treatment options for patients with AA to include patients who are 12 through 17 years of age, and provides another treatment option for adult patients with AA.

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Background

- AA is a chronic autoimmune disease of the hair follicle characterized by partial or complete hair loss and episodes of spontaneous disease flares and hair regrowth (*Gupta et al 2023*). AA affects 6.7 million Americans (*National Alopecia Areata Foundation 2023[a]*. In a cohort study of nationwide U.S. employer-sponsored insurance, AA prevalence was 0.199% to 0.222%, and AA incidence was 91.46 to 92.90 cases per 100,000 patient-years from 2016 to 2019. Rates of AA and AT and/or AU were higher for female vs male individuals, adults vs children and adolescents, and in the Northeast vs other regions (*Mostaghimi et al 2023*).
- Risk factors for developing AA include a family history of AA or organ-specific autoimmune disease, and a personal history of autoimmune disease, thyroid disease, vitiligo, atopy, or atopic dermatitis. Potential triggers of the initial disease and episodic relapse(s) include environmental triggers, major traumatic life events, and acute stress (*Meah et al 2021*). The average age of onset is between 25 and 35 years; however, AA can affect people of all ages (*Ramírez-Marín and Tosti 2022*). Approximately 10% to 35% of patients with AA will eventually lose all the hair on the scalp or on the whole body.
- Pathophysiology of AA involves deregulation of JAK enzyme activity (*Ramírez-Marín and Tosti 2022*). JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate STATs which modulate intracellular activity including gene expression (*Olumiant Prescribing Information 2022*). Over 50 cytokines, including interferon and interleukin (IL)-15, are linked to the immunopathology of AA through the JAK/STAT pathway. Upregulation of IL-15 in hair follicles leads to recruitment and activation of natural killer T cells, resulting in production of interferon gamma and consequent collapse of hair follicle immune privilege (*Ramírez-Marín and Tosti 2022*). Thus, the hair shaft can no longer be anchored in the hair canal and is rapidly shed. However, the hair follicle stem cells are not destroyed, so the hair follicle retains its capacity to regenerate and continue cycling (*Gilhar et al 2012*).
- Variants of AA include patchy, AT, AU, diffuse, and ophiasis. The patchy variant appears as one or more round or oval, coin-sized patches on the scalp or other places on the body that grow hair. It commonly remains patchy but can convert into either AT or AU. AT causes hair loss across the entire scalp. AU results in hair loss on the entire body, including eyebrows and eyelashes. Diffuse AA appears as sudden and unexpected thinning of the hair all over the scalp. Ophiasis presents as hair loss occurring in a band along the sides and back of the head (*National Alopecia Areata Foundation 2023[a]*).
- AA exclusively affects the hair follicles, nails, and in some patients, retinal pigment epithelium. The most common presentation of AA is round patches of non-scarring hair loss on the scalp and beard. The diagnostic approach includes family history, physical examination of hair, skin, nails, and eyes, and laboratory tests (*Gilhar et al 2012*). If the diagnosis cannot be clearly made after a clinical evaluation, a skin biopsy may be done (*Gilhar et al 2012*, *Meah et al 2020*).
- AA can adversely affect quality of life and has been associated with anxiety and depression. In addition, patients with AA are at an increased risk of other autoimmune diseases, such as type 1 diabetes, vitiligo, RA, and autoimmune thyroid disease (*National Alopecia Areata Foundation 2023[b]*). Without treatment, 55% of patients with chronic AA will have persistent multifocal relapsing and remitting disease, 30% will develop AT, and 15% will develop AU. If active AA is untreated for lengthy periods, it may not respond to treatment (*Eisman and Sinclair 2021*).
- SALT is a standardized scoring system used to rate the extent of scalp hair loss and assess treatment outcomes in patients with AA. Scores range from 0 (no hair loss) to 100 (complete hair loss). The SALT score is calculated by taking the total of the percentage of hair loss in 4 defined areas of the scalp: vertex 40%, posterior 24%, right side 18%, and left side 18% (*Gupta et al 2023*).
- There are limited treatment options for the management of AA. Options such as corticosteroids (topical, oral, or intralesional), immunosuppressants (oral), calcineurin inhibitors (oral, topical), and minoxidil (topical) have been used off-label (*Meah et al 2020*). Treatment failure or disease relapse has occurred in up to 63% of patients treated with topical corticosteroids and up to 100% of patients treated with oral corticosteroids. Systemic treatment options such as cyclosporine and methotrexate have reduced utility for long-term use due to their broad mechanisms of action and unfavorable safety profiles. Intralesional corticosteroids, although effective for mild disease, are not a treatment option in moderate/severe AA (*Gupta et al 2023*).
- JAK enzymes have been implicated in the pathogenesis of AA and are a therapeutic target of interest. Numerous JAK inhibitors are approved for the treatment of autoimmune conditions, such as RA, psoriatic arthritis, and ulcerative colitis (*Ramírez-Marín and Tosti 2022*). The JAK family of enzymes (JAK1, JAK2, JAK3, and tyrosine kinase 2) are cytoplasmic tyrosine kinases that work in pairs to promote signaling from type I/II cytokine receptors (*Ramírez-Marín and Tosti 2022*).

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- Baricitinib, an orally administered JAK inhibitor, was initially FDA-approved in June 2018. In June 2022, baricitinib gained the indication for treatment of adult patients with severe AA, making it the first FDA-approved systemic treatment for this condition. Baricitinib has additional indications for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) blockers, and for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (*Olumiant Prescribing Information 2022).*
- Baricitinib was evaluated for the management of severe AA in two 36-week, Phase 3, randomized, DB, parallel-group (PG), PC trials, BRAVE-AA1 and BRAVE-AA2 (*King et al 2022*).
  - Both trials had identical eligibility criteria: Diagnosis of severe AA, SALT score of ≥ 50, and a current episode of AA lasting > 6 months to < 8 years, without spontaneous improvement (≤ 10-point reduction in the SALT score) during the previous 6 months. In both studies, patients were randomized to baricitinib 4 mg, baricitinib 2 mg, or placebo, and the primary endpoint was a SALT score of ≤ 20 at week 36.
  - In BRAVE-AA1 (N = 654), the primary endpoint was achieved by 38.8%, 22.8%, and 6.2% of patients in the 4 mg, 2 mg, and placebo groups, respectively.
    - The difference between baricitinib 4 mg and placebo was 32.6 percentage points (95% CI, 25.6 to 39.5), and the difference between baricitinib 2 mg and placebo was 16.6 percentage points (95% CI, 9.5 to 23.8) (p < 0.001 for each dose vs placebo).
  - In BRAVE-AA2 (N = 546), the primary endpoint was achieved by 35.9%, 19.4%, and 3.3% of patients in the 4 mg, 2 mg, and placebo groups, respectively.
    - The difference between baricitinib 4 mg and placebo was 32.6 percentage points (95% CI, 25.6 to 39.6), and the difference between baricitinib 2 mg and placebo was 16.1 percentage points (95% CI, 9.1 to 23.2) (p < 0.001 for each dose vs placebo).
- A pooled analysis of BRAVE-AA1 and BRAVE-AA2 aimed to determine the efficacy of uptitration to baricitinib 4 mg for 24 weeks in patients who had previously not responded to baricitinib 2 mg, defined as a SALT score of > 20 (*Ko et al 2023*).
  - At week 52, of the 340 patients initially treated with baricitinib 2 mg, 212 (62.4%) had a SALT score > 20 and were uptitrated to baricitinib 4 mg.
    - Of the 212 patients, 142 (67%) had a baseline SALT score of 95 to 100, indicating very severe AA.
    - At week 76, 55 of the 212 patients (25.9%) had achieved a SALT score of ≤ 20.
  - During the same period, response rates for clinician-reported outcome scores of 0 or 1 (full coverage or minimal gaps) increased from 19.3% to 37.9% for eyebrows and from 24.1% to 40.9% for eyelashes.
- Ritlecitinib is an orally administered, selective dual inhibitor of JAK3 and TEC. Ritlecitinib is indicated for the treatment of severe AA in adults and adolescents 12 years and older. Although it is the second FDA-approved systemic treatment for severe AA, it is the first one approved for patients who are 12 through 17 years of age (*FDA Multi-Discipline Review 2023, Litfulo Prescribing Information 2023*). The Appendix provides a comparison of ritlecitinib and baricitinib.

Indications

- Ritlecitinib is indicated for the treatment of severe AA in adults and adolescents 12 years and older.

Pharmacology

- Ritlecitinib is a kinase inhibitor. It irreversibly inhibits JAK3 and the TEC kinase family by blocking the ATP binding site.
  - In cellular settings, ritlecitinib inhibits cytokine induced STAT phosphorylation mediated by JAK3-dependent receptors. Ritlecitinib inhibits signaling of immune receptors dependent on TEC kinase family members. The relevance of inhibition of specific JAK or TEC family enzymes to therapeutic effectiveness is not currently known.

Clinical efficacy

Study design abbreviations: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

Search Strategy*: Studies supporting the FDA-approved indication were identified using search terms "ritlecitinib" and "alopecia areata" through August 18, 2023. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

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Study 1. Clinicaltrials.gov (ALLEGRO; NCT03732807); FDA Multi-Discipline Review 2023; King et al, *Lancet*. 2023;401(10387):1518-1529; Litfulo Prescribing Information 2023.

Study Objective: Evaluate efficacy and safety of ritlecitinib in adults and adolescents with AA.

Study Design, Follow-up	Treatment Groups
• DB, PC, MC, Phase 2b/3 RCT • Total duration: 48 weeks ○ PC period: weeks 0 to 24 ○ Extension period: weeks 24 to 48 • Clinical assessments were done at screening, baseline, and weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48 (or end of treatment)	• Treatment arms through week 24: ○ Ritlecitinib 200 mg daily x 4 weeks followed by 50 mg daily (n = 132) ○ Ritlecitinib 200 mg daily x 4 weeks followed by 30 mg daily (n = 130) ○ Ritlecitinib 50 mg daily (n = 130) ○ Ritlecitinib 30 mg daily (n = 132) ○ Ritlecitinib 10 mg daily (n = 63) ○ Placebo (n = 131) • At week 24, ritlecitinib groups continued their assigned doses and patients initially assigned to placebo switched to: ○ Ritlecitinib 200 mg daily x 4 weeks followed by 50 mg daily (n = 65) ○ Ritlecitinib 50 mg daily (n = 66) • The 10 mg group was included for pharmacokinetic, dose-response, and safety assessments only and was not included in statistical comparisons vs placebo.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 12 years • Clinical diagnosis of AA with no other etiology of hair loss • ≥ 50% hair loss of the scalp, including AT and AU, without evidence of terminal hair regrowth within 6 months at both screening and baseline visits • Current episode of hair loss ≤ 10 years	• Other types of alopecia, scalp disease, or active systemic disease that could impact AA assessment • Treatment with JAK inhibitors, B-cell-depleting agents, immunomodulatory biologics, or other systemic treatments that could affect AA within specific timeframes
Primary Endpoint	**Secondary Endpoints**
• Response based on SALT score ≤ 20 at week 24	• Response based on SALT score ≤ 10 at week 24 • Patient Global Impression of Change (PGI-C) score of moderately improved or greatly improved to week 48 • Response based on SALT score ≤ 20 and ≤ 10 to week 48 • Change from baseline in SALT scores to week 48 • Measures of eyebrow and eyelash regrowth • Exposure response based on SALT score ≤ 20 • Response based on 75% improvement in SALT score from baseline to week 48* • Change from baseline in Alopecia Areata Patient Priorities Outcome scales to week 48*

*These endpoints will be reported in detail with exploratory outcomes and post hoc analyses at a later date (*King et al 2023*).

- **Results**
  - In total, 718 patients were randomly assigned to receive ritlecitinib or placebo.
  - Of 715 patients treated, 104 patients discontinued treatment (34 withdrew, 19 AEs, 12 physician decision, 12 lack of efficacy, 13 lost to follow up, 5 rolled over to long-term study transfer, 4 pregnancies, 2 protocol deviations, one declined to attend follow-up due to COVID-19, one attended last visit very late due to COVID-19, and one non-compliance) and 614 completed the study.
  - Baseline demographic and disease characteristics were well balanced across treatment groups: 105 (15%) of 718 patients were adolescents and 613 (85%) were adults, 446 (62%) of patients were female and 272 (38%) were male, 488 (68%) were White, 186 (26%) were Asian, and 27 (4%) were Black or African American, and 330 (46%) had AT or AU.

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- Mean SALT score at baseline ranged from 88.3 to 93.0; mean SALT score for those without AT or AU ranged from 78.3 to 87.0.
- See Table 1 for summary of primary and key secondary efficacy results.

Table 1. Summary of primary and key secondary efficacy results from ALLEGRO study (*King et al 2023*)

Outcome	Placebo* (n = 131)	Ritlecitinib 10 mg (n = 63)	Ritlecitinib 30 mg (n = 132)	Ritlecitinib 50 mg† (n = 130)	Ritlecitinib 200 → 30 mg (n = 130)	Ritlecitinib 200 → 50 mg (n = 132)
SALT score ≤ 20 response at week 24‡						
n/N (%)	2/130 (2%)	1/59 (2%)	17/119 (14%)	**29/124 (23%)**	27/121 (22%)	38/124 (31%)
Difference from placebo (95% CI)		0.16 (-4.05 to 7.58)	12.75 (6.69 to 20.36)	**21.85 (14.65 to 30.23)**	20.78 (13.65 to 29.18)	29.11 (21.17 to 37.91)
P value			0.0002	**< 0.0001**	< 0.0001	< 0.0001
SALT score ≤ 10 response at week 24§						
n/N (%)	2/130 (2%)	1/59 (2%)	13/119 (11%)	**17/124 (14%)**	16/121 (13%)	27/124 (22%)
Difference from placebo (95% CI)		0.16 (-4.05 to 7.58)	9.39 (3.86 to 16.46)	**12.17 (6.27 to 19.53)**	11.68 (5.82 to 19.07)	20.24 (13.23 to 28.49)
P value			0.0019	**0.0002**	0.0003	< 0.0001
PGI-C¶ response at week 24#						
Estimated response (%)	9.23%	11.36%	41.95%	**49.17%**	45.40%	52.19%
Difference from placebo (95% CI)		2.15 (-6.91 to 11.22)	32.72 (21.95 to 43.50)	**39.96 (28.85 to 51.06)**	36.18 (25.22 to 47.14)	42.96 (31.68 to 54.25)
P value			< 0.0001	**< 0.0001**	< 0.0001	< 0.0001

*Both placebo groups were combined for week 24 analyses.
†The 50 mg treatment arm eventually became the FDA-approved dose.
‡Primary endpoint for overall clinical study (α = 0.05) and for the FDA (α = 0.00125).
§Key secondary endpoint for the overall clinical study (α = 0.05).
¶PGI-C response was defined as a PGI-C score of moderately improved or greatly improved.
#Key secondary endpoint for the European Medicines Agency (α = 0.01).

- **Other secondary endpoints**
  - Exposure response based on SALT score ≤ 20
    - Exposure response demonstrated an increased percentage of patients achieving a SALT score ≤ 20 with increasing doses of ritlecitinib.
  - Eyebrow regrowth
    - At week 24, 29% of patients in the ritlecitinib 50 mg group achieved eyebrow regrowth (defined as ≥ 2 grade improvement or normal eyebrow assessment score of 3 in patients without normal eyebrows at baseline) vs 4% to 6% of patients in the placebo groups.
  - Eyelash regrowth
    - At week 24, 29% of patients in the ritlecitinib 50 mg group achieved eyelash regrowth (defined as (≥ 2 grade improvement or normal eyelash assessment score of 3 in patients without normal eyelashes at baseline) vs 0% to 10% of patients in the placebo groups.
  - Secondary endpoints of PGI-C score of moderately improved or greatly improved to week 48, response based on SALT score ≤ 20 and ≤ 10 to week 48, and eyebrow and eyelash response scores to week 48 were reported graphically in the publication. In ritlecitinib-treated patients, responses further improved between week 24 and week 48 for these endpoints; however, there was no placebo group at week 48 for purposes of comparison.
- **Safety**
  - AEs of interest (including opportunistic infections; malignancy; and cardiovascular, neurological, and audiological events) were reviewed by adjudication committees by use of predefined criteria. Audiology testing was done and neurological events were reviewed on the basis of a finding of reversible axonal dystrophy in the nervous system of dogs in nonclinical chronic toxicology studies (*King et al 2023, FDA Multi-Discipline Review 2023*).

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- Most AEs were mild or moderate in severity. The most common AEs of any grade occurring in at least 10% of patients in any treatment group were upper respiratory tract infection, nasopharyngitis, and headache.
  - The incidence of nasopharyngitis during this period was higher with ritlecitinib than with placebo (10% to 14% of patients for ritlecitinib vs 6% for placebo).
  - The incidence of upper respiratory tract infection, urticaria, and urinary tract infection was highest with 200 mg + 50 mg and the incidence of folliculitis and dizziness was highest in the 200 mg + 50 mg and 200 mg + 30 mg groups.
  - Audiological events were identified from protocol-specified audiological testing; none were spontaneously reported. Six patients with adjudicated audiological AEs met the criteria as non-serious events of interest of sensorineural hearing loss. Of these, 2 patients experienced audiological AEs up to week 24 (one patient each receiving 50 mg and 30 mg). No events were consistent with central hearing disorder.

- **Authors' conclusion:**
  - Ritlecitinib doses of 50 mg and 30 mg once a day (with or without loading dose of 200 mg once a day) were efficacious and generally safe and well tolerated over 48 weeks in patients with AA.
- **Study Appraisal:**
  - Study sponsorship:
    - Pfizer
  - Study rating:
    - Fair
  - Study strengths:
    - Study design: DB, PC, MC, RCT
    - The baseline demographics and disease characteristics were generally balanced across the treatment groups, including representation of AT and AU
    - Adequate follow-up (> 80%)
    - Adequate sample size; standard endpoints
    - Adequate representation of patients with AT and AU, which are the most severe forms of the disease
  - Study limitations:
    - Underrepresentation of Black/African American patients
    - Investigators did not report some secondary endpoint data and adherence rates in treatment arms
    - Exclusion of patients with duration of current AA episode > 10 years
    - Missing data due to COVID-19-related reasons were excluded from this analysis, whereas patients with missing data due to other reasons were considered as non-responders.

- Based on a subgroup analysis of ALLEGRO, ritlecitinib treatment demonstrated clinician-reported efficacy, patient-reported improvement, and an acceptable safety profile through week 48 in adolescents with AA (*Hordinsky et al 2023*).
  - In total, 105 adolescents (14.6% of the overall study sample) were randomized. In adolescents in the 50 mg group, the primary endpoint of a SALT score ≤ 20 was achieved by 25% and 50% of patients at 24 weeks and 48 weeks, respectively, and the secondary endpoint of SALT score ≤ 10 was achieved by 13% and 33% of patients at these respective time points. The most common AEs in adolescents were headache, acne, and nasopharyngitis. No deaths, MACE, malignancies, pulmonary embolisms, opportunistic infections, or herpes zoster infections were reported.

- ALLEGRO-LT is an ongoing, Phase 3, single-arm, OL, MC, long-term study investigating the safety and efficacy of ritlecitinib in adults and adolescents 12 years and older with AA. A sub-study of approximately 60 adult patients will assess the immune response to tetanus and meningococcal vaccines in patients who have taken 50 mg ritlecitinib for at least 6 months. This study is estimated to be completed in early 2026 (*Clinicaltrials.gov [NCT04006457]*).

Clinical guidelines

The Alopecia Areata Consensus of Experts (*Meah et al 2020, Meah et al 2021*)
- Severity of disease is categorized by SALT score (0% to 30%, 31% to 50%, or > 50%) and chronicity (acute vs chronic).
- First-line treatment for AA depends on the patient age, disease severity, and chronicity (Table 2).

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Table 2. Expert consensus agreement for first-line treatment(s) in patient age groups for AA (*Meah et al 2020*)

	SALT 0% to 30%		SALT 31% to 50%		SALT > 50%	
Patient group (years)	**Acute**	**Chronic**	**Acute**	**Chronic**	**Acute**	**Chronic**
0 to 6	Topical corticosteroid		Topical corticosteroid		Topical corticosteroid	
7 to 12						
13 to 18	Topical corticosteroid or intralesional corticosteroid	Intralesional corticosteroid	Topical corticosteroid or oral corticosteroid		Topical corticosteroid, oral corticosteroid, or combined	Topical corticosteroid
Adults (> 18)	Intralesional corticosteroid		Intralesional corticosteroid, oral corticosteroid, or combined	Topical corticosteroid or intralesional corticosteroid	Topical corticosteroid, oral corticosteroid, or combined	Topical corticosteroid or oral corticosteroid

- Topical agents: There was some consensus on the effectiveness of topical corticosteroids, topical calcineurin inhibitors, topical prostaglandin analogues, and contact immunotherapy.
  - Corticosteroids
    - First-line treatment option alone or in combination for scalp, eyebrow, or beard AA
    - First-line treatment in children ≤ 12 years of age
  - Calcineurin inhibitors (eg tacrolimus, pimecrolimus)
    - Treatment option for scalp, eyebrow, or beard AA
    - Should not be considered first-line topical treatment, alone or in combination, for beard AA
  - Prostaglandin analogues (eg bimatoprost, latanoprost)
    - First-line treatment option, alone or in combination, for eyelash AA
  - Minoxidil
    - Can accelerate linear growth rate of hair regrowing within a patch of AA
    - Can be prescribed in conjunction with other topical/systemic agents
  - Contact immunotherapy (eg diphenylcyclopropenone, squaric acid dibutyl ester)
    - These are sensitizers and induce allergic contact dermatitis. Children with AT, AU, or ophiasis should be offered contact immunotherapy before systemic therapy is considered.
- Systemic agents considered by the expert panel included corticosteroids, cyclosporine, methotrexate, azathioprine, JAK inhibitors, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, IL-17A inhibitors, and apremilast.
  - Systemic corticosteroids
    - Prednisone or prednisolone is the preferred choice of systemic corticosteroid.
    - Systemic corticosteroids are appropriate for treatment of severe AA in adolescents aged 13 to 18 years. The initial dose of prednisolone may be 0.4 to 0.6 mg/kg/day with gradual taper over > 12 weeks to achieve durable remission.
    - To achieve durable remission in adults, prednisolone may require gradual taper over > 12 weeks.
    - Systemic corticosteroids reduce the risk of multifocal AA progressing to AT/AU.
  - Cyclosporine, methotrexate, and azathioprine
    - Cyclosporine
      - In adults with severe AA, the target dose of cyclosporine should be 3 to 5 mg/kg/day, and the maximum treatment duration should be 6 to 12 months.
      - In adults with AA, cyclosporine is an effective monotherapy agent.
    - Methotrexate
      - In adults, the target dose of methotrexate should be 15 to 20 mg weekly.
      - Methotrexate is appropriate for the treatment of severe AA in adolescents aged 13 to 18 years. When methotrexate is commenced in patients < 18 years with severe AA, the target dose should be 0.4 mg/kg/week.
    - Azathioprine
      - No consensus was reached on use of azathioprine as a treatment option.
    - JAK inhibitors
      - In adults with AA, JAK inhibitors are effective monotherapy agents and are the preferred systemic therapy.

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- JAK inhibitors reduce the risk of multifocal AA progressing to AT/AU and of disease relapse.
  - Efficacy of systemic agents in combination with systemic corticosteroids
    - In adults, the following agents are effective when used in combination with systemic corticosteroids: methotrexate, cyclosporine, or JAK inhibitors.
    - Dapsone, simvastatin/ezetimibe, sulfasalazine, or ustekinumab are not effective in combination with systemic steroids.
    - Where appropriate, in adolescents 13 to 18 years old, JAK inhibitors may be prescribed in combination with systemic corticosteroids.
- In patients < 18 years, ideally, the following agents should not be prescribed in combination with systemic corticosteroids: cyclosporine, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, IL-17A inhibitors, and apremilast.
- Indications for the discontinuation of systemic treatment, other than toxicity, include complete response, full coverage of alopecic scalp with terminal hair, cosmetically acceptable regrowth, or no response.
  - Systemic treatment is best discontinued once complete regrowth has been achieved and maintained for six months or when regrowth is sufficient to be managed topically.
  - If vellus regrowth fails to convert to terminal hair, systemic treatment should continue for 6 months, but not longer.

Safety

- **Contraindications**
  - Known hypersensitivity to ritlecitinib or any of its excipients
- **Warnings/precautions**
  - As a class, JAK inhibitors share a Boxed Warning for serious infections, mortality, malignancy, MACE and thrombosis.
    - A patient may be at increased risk of serious bacterial, fungal, viral and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Treatment should be interrupted if serious infection occurs until the infection is controlled. Ritlecitinib should not be given to patients with active TB. Latent TB should be tested for before and during therapy; latent TB should be treated prior to use. All patients should be monitored for active TB during treatment, even patients with initial negative, latent TB test.
    - There may be a higher rate of all-cause mortality, including sudden cardiovascular death with another JAK inhibitor vs TNF blockers in RA patients. Ritlecitinib is not approved for use in RA patients.
    - Malignancies have occurred in patients treated with ritlecitinib. A higher rate of lymphomas and lung cancers was observed with another JAK inhibitor vs TNF blockers in RA patients.
    - A higher rate of MACE was observed with another JAK inhibitor vs TNF blockers in RA patients.
    - Thrombosis has occurred in patients treated with ritlecitinib. An increased incidence of pulmonary embolism, venous and arterial thrombosis was observed with another JAK inhibitor vs TNF blockers.
  - Ritlecitinib has an additional warning for laboratory abnormalities in lymphocytes, platelets, liver enzymes, and CPK.
    - Ritlecitinib was associated with decreases in lymphocytes and platelets. Prior to ritlecitinib initiation, ALC and platelet count should be performed. After initiating treatment with ritlecitinib, treatment interruption or discontinuation are recommended based on ALC and platelet count abnormalities.
    - Treatment with ritlecitinib was associated with increased incidence of liver enzyme elevation compared to placebo. Liver enzymes should be evaluated at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed and drug-induced liver injury is suspected, ritlecitinib treatment should be interrupted until this diagnosis is excluded.
    - Treatment with ritlecitinib was associated with increased incidence of CPK elevation compared to placebo.
- **Adverse effects**
  - The most common AEs occurring at an incidence of ≥1% in the treated groups and at a higher rate than placebo are headache, diarrhea, acne, rash, urticaria, folliculitis, pyrexia, atopic dermatitis, dizziness, blood CPK increased, herpes zoster, red blood cell count decreased, and stomatitis (see Table 3 for AEs reported in ≥ 2% of patients).

Table 3. AEs reported in ≥ 2% of patients treated with ritlecitinib

	Ritlecitinib 50 mg (n = 130) n (%)	**Placebo** (n = 213) n (%)
Headache	14 (10.8)	18 (8.5)
Diarrhea	13 (10.0)	8 (3.8)

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Acne	8 (6.2)	10 (4.7)
Rash	7 (5.4)	2 (0.9)
Urticaria	6 (4.6)	3 (1.4)
Folliculitis	4 (3.1)	4 (1.9)
Pyrexia	4 (3.1)	0
Dermatitis atopic	3 (2.3)	1 (0.5)
Dizziness	3 (2.3)	3 (1.4)

- **Drug Interactions**
  - CYP3A substrates where small concentration changes may lead to serious adverse reactions
    - Ritlecitinib is a CYP3A inhibitor. Concomitant use of ritlecitinib increases area under the curve (AUC) and maximum serum concentration (C_{max}) of CYP3A substrates, which may increase the risk of adverse reactions of these substrates.
    - Consider additional monitoring and dosage adjustment in accordance with approved product labeling of CYP3A substrates where small concentration changes may lead to serious adverse reactions when used with ritlecitinib.
  - CYP1A2 substrates where small concentration changes may lead to serious adverse reactions
    - Ritlecitinib is a CYP1A2 inhibitor. Concomitant use of ritlecitinib increases AUC and C_{max} of CYP1A2 substrates, which may increase the risk of adverse reactions of these substrates.
    - Consider additional monitoring and dosage adjustment in accordance with the approved product labeling of CYP1A2 substrates where small concentration changes may lead to serious adverse reactions when used concomitantly with ritlecitinib.
  - CYP3A inducers
    - Concomitant use of strong CYP3A inducer(s) (eg, rifampin) may decrease AUC and C_{max} of ritlecitinib, which may result in loss of or reduced clinical response.
    - Coadministration with strong inducers of CYP3A is not recommended.

Dosage and administration

Recommended dosage

- The recommended dosage of ritlecitinib is 50 mg orally once daily with or without food.
  - Capsules should be swallowed whole and not crushed, split, or chewed.
  - If a dose is missed, administer the dose as soon as possible unless it is < 8 hours before the next dose, in which case, the dose should be skipped. Thereafter, the dose should be taken as scheduled.

Recommended evaluations and immunizations prior to treatment initiation

- The following evaluations are recommended prior to ritlecitinib initiation:
  - TB infection evaluation: Ritlecitinib initiation is not recommended in patients with active TB. For patients with latent TB or those with a negative latent TB test who are at high risk for TB, preventive therapy should be started for latent TB prior to initiation of ritlecitinib.
  - Viral hepatitis screening should be completed in accordance with clinical guidelines: Ritlecitinib initiation is not recommended in patients with hepatitis B or hepatitis C.
  - Treatment with ritlecitinib should not be initiated in patients with an ALC < 500/mm^3 or a platelet count < 100,000/mm^3.
  - Immunizations should be updated according to current immunization guidelines.

Specific populations

- **Geriatrics**
  - No dose adjustment is required for patients ≥ 65 years of age.
  - A total of 28 patients enrolled in AA trials were ≥ 65 years of age, and none were ≥ 75 years of age. Clinical trials of ritlecitinib did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger adult patients.
- **Pediatrics**
  - A total of 181 pediatric patients ages 12 to < 18 years were enrolled in AA clinical trials, with 105 pediatric patients ages 12 to < 18 years with AA randomized in a pivotal, DB, PC trial. Efficacy was consistent between the pediatric patients and adults. The AE profile in the pediatric patients was similar to adults.
  - The safety and efficacy of ritlecitinib have not been established in pediatric patients < 12 years of age.
- **Renal dysfunction**

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- Ritlecitinib has not been studied in patients with mild (estimated glomerular filtration rate [eGFR] 60 to < 90 mL/min) or moderate (eGFR 30 to < 60 mL/min) renal impairment, as a clinically relevant increase in ritlecitinib exposure is not expected in these patients.
- Ritlecitinib has not been studied in patients with end stage renal disease or in renal transplant recipients.

- **Hepatic dysfunction**
  - No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
  - Ritlecitinib is not recommended in patients with severe (Child-Pugh C) hepatic impairment.
- **Pregnancy and nursing**
  - There is a pregnancy registry for ritlecitinib; healthcare providers should report any pregnancies that occur in patients receiving ritlecitinib to the manufacturer.
  - Available data from clinical trials with ritlecitinib use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ritlecitinib to pregnant rats and rabbits during organogenesis caused fetotoxicity and fetal malformations at high doses.
  - There are no data on the presence of ritlecitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Ritlecitinib is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that it will be present in human milk.
  - Because of the serious AEs in adults, women should be advised not to breastfeed during treatment with ritlecitinib and for approximately 14 hours after the last dose.

APPENDIX

Appendix. Litfulo (ritlecitinib) and Olumiant (baricitinib) comparison

	Litfulo (ritlecitinib)	Olumiant (baricitinib)
Mechanism of Action	Primarily JAK3 and TEC inhibitor	Primarily JAK1 and JAK2 inhibitor
Indication	Treatment of severe AA in adults and adolescents 12 years and older	Treatment of: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF blockers • COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO • Adult patients with severe AA
Limitations of Use	Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants	AA: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants
Key Efficacy Results	ALLEGRO trial: SALT score ≤ 20 achieved by 23% of patients (vs 2% with placebo) at week 24	BRAVE-AA1 trial: SALT score ≤ 20 achieved by 39% (4 mg) and 23% (2 mg) of patients (vs 6% with placebo) at week 36 BRAVE-AA2 trial: SALT score ≤ 20 achieved by 36% (4 mg) and 19% (2 mg) of patients (vs 3% with placebo) at week 36
Class Boxed Warning	Serious infections, mortality, malignancy, MACE, and thrombosis	
Key Safety Information	• Decreased ALC and platelets • Avoid live vaccinations during treatment	• Gastrointestinal perforations • Abnormalities in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids • Avoid live vaccinations during treatment
Key Drug Interactions	• Ritlecitinib is a CYP3A inhibitor and CYP 1A2 inhibitor • Use with CYP3A and CYP1A2 substrates ↑ exposure to CYP3A/CYP1A2 substrate;	• Use with Organic Anion Transporter 3 (OAT3) inhibitors (eg, probenecid) ↑ exposure to baricitinib; dose reduction of Olumiant recommended

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	monitoring and dose adjustment of CYP3A/CYP1A2 substrates recommended • Use with strong CYP3A inducers ↓ exposure to ritlecitinib; coadministration not recommended	
Dosage Forms	• 50 mg capsules	• 1 mg, 2 mg, and 4 mg tablets
Dosing	• 50 mg once daily • No dose adjustments recommended	• Start with 2 mg once daily; increase to 4 mg once daily if the response to treatment is not adequate • Dose adjustment recommended in moderate and severe renal impairment

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New Drug Review
Sohonos (palovarotene)

Medication*	Marketer	Availability
Sohonos (palovarotene)	Ipsen Biopharmaceuticals, Inc.	**Brand:** 1, 1.5, 2.5, 5, 10 mg capsules
Therapeutic Class: Retinoic Acid Receptor Gamma Agonist		
Purpose of Review: To evaluate the safety and efficacy of Sohonos (palovarotene), a new molecular entity.		

* Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

Summary

Background

- Fibrodysplasia ossificans progressiva (FOP) is a rare, severely disabling condition and genetic disorder in which bone forms in muscles, tendons, ligaments, and other connective tissue; joints become locked and permanently immobile. This formation of extraskeletal bone (ie, heterotopic ossification [HO]) is cumulative and irreversible, causing deformities and decreased mobility (*Food and Drug Administration [FDA] Sohonos integrated review 2023, International Fibrodysplasia Ossificans Progressiva Association [IFOPA] Web site, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
- Classic clinical features include bilateral congenital malformations of the great toes, intermittent swelling and masses, and progressive HO (the abnormal accumulation of extraskeletal bone formation in muscles, tendons, and ligaments) in specific anatomic patterns that often form with “flares-ups” (sporadic, intermittent painful episodes of rapidly progressive connective/soft tissue swelling) (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
  - Typical features of FOP flare-ups include intense muscle edema, fibroproliferation, and angiogenesis characteristic of early pre-osseous FOP lesions and the rapid spread of the lesions along muscle planes into adjacent tissue. A lesion may appear within hours and can reach an alarming size literally overnight (*Kaplan et al 2022*).
    - Soft tissue swellings may resolve but more often transform skeletal muscles, tendons, ligaments, fascia, and aponeuroses into ribbons, sheets, or plates of abnormal heterotopic bone (*Kaplan et al 2022, Tis 2022*).
  - Flare-up occurrence, duration, and severity is unpredictable, with great individual variability in the rate of disease progression (*Kaplan et al 2022, Tis 2022*).
    - Flare-ups may be precipitated by soft tissue injury, intramuscular injections, surgical incisions, falls, muscular stretching, or viral illness (*IFOPA Web site, Kaplan et al 2022, Tis 2022*).
  - In addition to progressive immobility, accumulation of bone also results in weight loss, severe tooth decay, and malnutrition secondary to ankylosis of the jaw, as well as chest wall deformity (thoracic insufficiency syndrome) and localized skin breakdown. Patients become dependent upon diaphragmatic breathing (*FDA Sohonos integrated review 2023, Tis 2022*).
    - Flare-ups typically begin during the first decade of life; in a survey of 44 patients with FOP, the average onset of HO was at 5 years of age, 80% of patients had restrictive ossification by 7 years of age, and 95% had severely restricted motion in the upper extremity by 15 years of age (*Kaplan et al 2022, Tis 2022*).
    - Most patients with FOP are confined to a wheelchair or require mobility assistance by the third decade of life and require lifelong assistance in performing activities of daily living (ADLs) (*Kaplan et al 2022, Pignolo et al 2023*).
    - Survival is shortened (median, 56 years of age), and most patients die of respiratory depression or pneumonia due to cardiopulmonary complications of severe restrictive chest wall involvement (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
- The prevalence of FOP has been estimated at up to 1.4 per million individuals, with 289 unique patients reported in the U.S. as of 2021 and approximately 800 confirmed cases reported globally. All races are affected, with no ethnic, gender, or geographic predisposition (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2021, Pignolo et al 2023, Tis 2022*).
- Prior to the FDA approval of palovarotene, the standard of care for FOP has been mainly palliative and limited to symptom relief by decreasing pain and inflammation and prevention of flare-ups.

Indication

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- Sohonos (palovarotene) is an oral retinoid indicated for reduction in the volume of new HO in adults, females ≥ 8 years of age, and males ≥ 10 years of age with FOP.
- Palovarotene was approved by the FDA on August 16, 2023 and received Priority Review, Orphan Drug, Fast Track, and Breakthrough Therapy designations (*Drugs@FDA 2023, FDA Press Release 2023*).

Pharmacology

- In patients with FOP, abnormal bone formation, including HO, is driven by a gain-of-function mutation in the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I/activin-like kinase 2 (ACVR1/ALK2). This mutation renders ALK2 constitutively active to BMP ligands and drives ectopic chondrogenesis (cartilage development) and osteogenesis (bone formation), leading to the development of HO in connective tissue, joints, and muscle (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Tis 2022*).
  - Approximately 97% of patients with FOP have the same heterozygous mutation (c.617G>A; p.R206H) in the glycine-serine activation domain of the *ACVR1* gene ($ACVR1^{R206H}$) (*Kaplan et al 2022, Pignolo et al 2023*).
- Palovarotene is an orally bioavailable retinoic acid receptor (RAR) agonist, with particular selectivity at the gamma (γ) subtype of RAR (RARγ).
  - Through binding to RARγ, palovarotene decreases the BMP/ALK2 downstream signaling pathway by inhibiting the phosphorylation of suppressors of mothers against decapentaplegic homolog (SMAD)1/5/8, which reduces ALK2/SMAD-dependent chondrogenesis and osteocyte differentiation resulting in reduced endochondral bone formation.

Clinical Efficacy

- The FDA approval of palovarotene was based on interim and post hoc analyses of the 48-month Phase 3, open-label (OL), single-arm (SA), multi-center (MC) MOVE trial in 107 patients with FOP ≥ 4 years of age treated with palovarotene utilizing a 36-month Natural History Study (NHS) of 111 untreated patients (beyond standard of care) as an external control (*FDA Sohonos integrated review 2023, Pignolo et al 2023*).
  - Patients were treated with chronic/flare-up dosing of palovarotene as follows: chronic treatment with palovarotene 5 mg once daily and 12-week flare-up treatment ("20/10 mg") with palovarotene 20 mg orally once daily for 4 weeks (28 days) followed by palovarotene 10 mg once daily for 8 weeks (56 days). Flare-up treatment could be extended in 4-week increments for persistent symptoms.
    - Dosing was weight-adjusted in skeletally immature children (children who had not reached ≥ 90% skeletal maturity defined as a bone age ≥ 12 years 0 months in females and ≥ 14 years 0 months in males based on hand/wrist x-rays performed at screening).
    - Patients in both groups were treated with concomitant standard of care medications, including corticosteroids as needed. A total of 64.6% of patients in MOVE received corticosteroids vs 72.1% in the NHS.
    - Patients in the palovarotene group were a mean 15.1 years of age (range, 4 to 61; 75.8% < 18 years of age); NHS patients were a mean 17.8 years of age (range, 4 to 56; 59.5% < 18 years of age).
  - MOVE was initiated in November 2017. In December 2019, the FDA imposed a partial clinical hold for the dosing of patients < 14 years of age due to risk of premature epiphyseal closure (PPC) based on multiple reports of PPC among pediatric patients per scheduled radiographs. This partial clinical hold remains in effect; some affected patients resumed treatment after reaching 14 years of age (*FDA Sohonos integrated review 2023*).
    - Of note, the FDA approved palovarotene in children (females ≥ 8 years of age, and males ≥ 10 years of age) to allow most patients with ≥ 80% skeletal maturity (ie, bone age of 8 years in females and 10 years in males) to receive palovarotene for the prevention of HO despite the risk of PPC, given the severity of FOP (*FDA Sohonos integrated review 2023*).
  - On January 15, 2020, 12-month interim analyses, utilizing a Bayesian compound Poisson model (BcPM) with square-root transformation, met pre-specified futility criteria and dosing was paused for all patients in MOVE.
    - Post hoc analyses were initiated upon the pause and reviewed by an independent Data Monitoring Committee (DMC). Data were unblinded and raw, non-transformed mean annualized HO volumes were compared, including a BcPM omitting the square root transformation and a weighted linear mixed-effects (wLME) model.
    - Based on these post hoc analyses, the Bayesian analysis would have exceeded the pre-specified boundary for early efficacy at the 12-month interim analysis, meaning the futility criteria were not met.
    - The DMC recommended that palovarotene treatment continue in skeletally mature children ≥ 14 years of age (*FDA Sohonos integrated review 2023, Sohonos product dossier 2023*).
  - The primary endpoint was the annualized volume of new HO (cm^3/year) in the principal full analysis set (P-FAS) of palovarotene-treated (n = 97) vs NHS patients (n = 101), as assessed by low-dose whole-body computed tomography (WBCT; excluding head) at the 18-month interim analysis.

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- The P-FAS population included patients with the ACVR1^{R206H} pathogenic variant with no prior treatment with palovarotene who had a baseline HO volume measurement and ≥ 1 post-baseline HO volume measurement.
- The mean annualized new HO volume was 53.8% lower in palovarotene-treated vs NHS patients at 9.4 cm^3/year vs 20.3 cm^3/year, respectively, with an estimated treatment effect of 10.9 cm^3/year (95% CI, -21.2 to -0.6; p = 0.039), based on the wLME model.
- BcPM analyses without transformation showed 99.4% probability of any reduction in new HO with palovarotene vs NHS patients (with transformation, 65.4%).
- There was more variability in the annualized net change in HO volume among NHS vs palovarotene patients. A total of 5.0% of NHS vs 28.9% of palovarotene patients had a net negative annualized new HO, meaning that the measured volume of HO was reduced overall.

- For the key secondary endpoint, there was no significant difference observed between groups in the proportion of patients with any new HO or mean (standard deviation [SD]) number of body regions with new HO at Month 12 (treated patients: 64% and 1.3 [SD, 1.4], respectively, vs NHS: 62% and 1.5 [SD, 1.6], respectively).
- There were no significant differences between treated and untreated patients for the additional exploratory endpoints, including change from baseline in range of motion assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) at Month 24, change from baseline in physical function assessed by FOP physical function questionnaire (FOP-FPQ) at Month 24, and change from baseline in physical and mental health in patients ≥ 15 years of age as assessed by the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale at Month 24.
  - Post hoc computational analyses using WBCT showed decreased vertebral bone mineral density, content, and strength, and increased vertebral fracture risk in palovarotene-treated patients.
- For safety outcomes, all palovarotene-treated patients reported ≥ 1 adverse event (AE); 97.0% reported ≥ 1 retinoid-associated AE; 29.3% reported ≥ 1 serious AE, including PPC/epiphyseal disorder in 21/57 (36.8%) patients < 14 years of age.
  - Of note, a postmarketing observational registry study will be conducted to obtain further information on the incidence of flare-ups, premature epiphyseal closure, and fractures in pediatric and adult patients with FOP treated with palovarotene (*FDA Sohonos Integrated review 2023*).

- While clinical effectiveness was based on post hoc analyses, it was concluded that the various post hoc analyses demonstrated a consistency of results across the range of analyses and supported a conclusion of effectiveness.

Place in Therapy

- The International Clinical Council (ICC) on FOP states that the present management of FOP is focused on early diagnosis, diligent avoidance of trauma and injury, symptomatic amelioration of painful flare-ups, and optimization of residual function (*Kaplan et al 2022*).
  - There is presently no definitive medical treatment for FOP, and management is currently supportive. The ICC states that physicians treating patients who have FOP should keep in mind that no medications to date have been proven to alter the natural history of FOP.
    - Of note, palovarotene was not available at the time this statement was published and is listed as a Class III investigational drug.
- The ICC has classified various pharmacologic agents for FOP into 3 classes based on experimental or anecdotal experience with the drug as well as the drug's safety profile, with focus on the mechanism of action of the drug as it may relate to the proposed pathogenesis of FOP (*Kaplan et al 2022*).
  - Class I: Medications that have been widely used to control symptoms of acute flare-ups (swelling and pain), or chronic arthropathy with generally minimal AEs, and include short-term high-dose corticosteroids (eg, prednisone) and non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors (eg, ibuprofen, indomethacin, and celecoxib).
  - Class II: Medications that have theoretical application to various aspects of FOP, are approved for the treatment of other disorders, and have limited and well-described effects. Examples include leukotriene inhibitors (eg, montelukast), mast cell stabilizers (eg, cromolyn), aminobisphosphonates (eg, pamidronate and zoledronate) and specific tyrosine kinase inhibitors (TKIs; eg, imatinib). Class II Medications can be considered with caution at the physician's discretion.
  - Class III medications: Investigational new drugs under development and/or being tested in clinical trials not yet available for general use, including palovarotene.
  - Additional agents not classified include topical analgesics such as lidocaine (patch or gel) and capsaicin cream, and muscle relaxants such as cyclobenzaprine, metaxalone, or baclofen.

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Safety

- Palovarotene is contraindicated in patients during pregnancy.
- Palovarotene has a boxed warning for embryo-fetal toxicity and PPC in growing pediatric patients. Additional warnings and precautions include mucocutaneous AEs, metabolic bone disorder, psychiatric disorders, and night blindness.
- The most common AEs (incidence ≥ 10%) during treatment with chronic or flare-up dosing of palovarotene included dry skin (61% and 57%, respectively), lip dry (47% and 38%), arthralgia (36% and 31%), pruritus (34% and 48%), pain in extremity (29% and 28%), rash (28% and 30%), alopecia (24% and 30%), erythema (19% and 32%), headache, back pain, skin exfoliation, nausea, musculoskeletal pain, myalgia, dry eye, hypersensitivity, peripheral edema, and fatigue.
- Concomitant use of palovarotene with strong/moderate cytochrome P450 (CYP) 3A4 inhibitors, strong/moderate CYP3A4 inducers, and tetracyclines should be avoided. Concomitant administration of vitamin A in doses higher than the recommended daily allowance (RDA) and/or other oral retinoids must be avoided due to the risk of hypervitaminosis A.

Dosing

- The once-daily oral administration of palovarotene includes a chronic daily dose with dose increases for flare-up symptoms (ie, flare-up dose).
  - Adults and pediatric patients ≥ 14 years of age: The recommended dose is 5 mg once daily, with an increase in the event of FOP flare-up symptoms to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks.
  - Pediatric patients < 14 years of age: Dosing is weight-adjusted for both daily (range, 2.5 to 5 mg) and flare-up (range, 5 to 20 mg) dosing.
- Flare-up treatment should be initiated at the onset of the first symptom indicative of an FOP flare-up (eg, localized pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness) or a substantial high-risk traumatic event likely to lead to a flare-up (eg, surgery, intramuscular immunization, mandibular blocks for dental procedures, muscle fatigue, blunt muscle trauma from bumps, bruises or falls, or influenza-like viral illnesses).
- Palovarotene should be administered with food preferably at the same time each day.
- The dose of palovarotene should be reduced or modified for AEs or drug interactions, respectively, as appropriate.

Conclusion

- Sohonos (palovarotene) is a new molecular entity retinoid indicated for reduction in the volume of new HO in adults, female pediatric patients ≥ 8 years of age, and male pediatric patients ≥ 10 years of age with FOP.
- FOP is a rare, severely disabling condition and genetic disorder in which bone forms in muscles, tendons, ligaments, and other connective tissue; joints become locked and permanently immobile. The formation of HO (extraskeletal bone) is cumulative and irreversible, causing decreased mobility, deformities, severe disability, and shortened life expectancy.
- Safety and efficacy of palovarotene were based on interim and post hoc analyses of the 48-month Phase 3, OL, SA, MC MOVE trial in patients with FOP ≥ 4 years of age treated with palovarotene utilizing a 36-month NHS of untreated patients (beyond standard of care) as an external control.
  - The mean annualized new HO volume, as assessed by WBCT at the 18-month interim analysis, was 53.8% lower in palovarotene-treated (n = 97) vs NHS (n = 101) patients at 9.4 cm^3/year vs 20.3 cm^3/year, respectively, with an estimated treatment effect of 10.9 cm^3/year (95% CI, -21.2 to -0.6; p = 0.039), in patients with the $ACVR1^{R206H}$ pathogenic variant with no prior palovarotene treatment who had a baseline HO volume measurement and ≥ 1 post-baseline HO volume measurement.
- Prior to the FDA approval of palovarotene, the standard of care for FOP has been palliative and limited to symptom relief by decreasing pain and inflammation, prevention of flare-ups, and optimization of residual function.
  - Short-term high-dose corticosteroids (eg, prednisone), NSAIDs, and COX-2 inhibitors have been widely used to control symptoms of acute flare-ups (swelling and pain) and chronic arthropathy.
  - Additional medications have theoretical application to the various aspects of FOP, including leukotriene inhibitors (eg, montelukast), mast cell stabilizers (eg, cromolyn), aminobisphosphonates (eg, pamidronate and zoledronate) and specific TKIs (eg, imatinib).
- Palovarotene is contraindicated in patients during pregnancy and has a boxed warning for embryo-fetal toxicity and PPC in growing pediatric patients. Additional warnings and precautions include mucocutaneous AEs, metabolic bone disorder, psychiatric disorders, and night blindness.

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- Palovarotene capsules are orally administered once-daily as a chronic daily dose, with dose increases for flare-up symptoms (ie, flare-up dose). Dosing is weight-adjusted for both daily and flare-up doses in pediatric patients < 14 years of age.
- Palovarotene is the first pharmacologic therapy FDA-approved for the treatment of FOP. Palovarotene demonstrated an effect in decreasing the volume of new HO in patients with FOP, which is beneficial due to the irreversible, progressive, and severely debilitating nature of this condition. Use of palovarotene may slow the progression of FOP with the potential to preserve joint range of motion and movement for a longer period of time.

Background

- FOP is a rare, severely disabling condition and genetic disorder in which bone forms in muscles, tendons, ligaments, and other connective tissue; joints become locked and permanently immobile. This formation of extraskeletal bone (ie, HO) is cumulative and irreversible, causing decreased mobility, deformities, and severe disability (*FDA Sohonos integrated review 2023, IFOPA Web site, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
  - The abnormal bone function associated with FOP is caused by a gain-of-function mutation in the *ACVR1*/*ALK2* gene, which encodes for ACVR1/ALK2, a BMP type I receptor. This renders ALK2 constitutively active to BMP ligands and drives ectopic chondrogenesis (cartilage development) and osteogenesis (bone formation) leading to the development of HO in connective tissue, joints, and muscle. Most cases of FOP are sporadic, but autosomal dominant germline transmission has been reported in a small number of cases (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Tis 2022*).
    - Approximately 97% of patients with FOP have the same heterozygous mutation (c.617G>A; p.R206H) in the glycine-serine activation domain of the *ACVR1* gene ($ACVR1^{R206H}$) (*Kaplan et al 2022, Pignolo et al 2023*).
    - Approximately 3% of FOP patients have a novel non-R206H ACVR1 mutation; these patients have been identified with unusual clinical features for FOP, including a greater or lesser severity of the great toe malformations (*Kaplan et al 2022*).
    - The ACVR1-mediated BMP signaling is important in the regulation of joint and skeletal formation, with a direct link between the failure to restrict BMP signaling in the digit joint interzone and failure of joint cleavage at the presumptive interzone, due to the $ACVR1^{R206H}$ mutation (*Kaplan et al 2022*).
- Classic clinical features of FOP include bilateral congenital malformations of the great toes, intermittent swelling and masses, and progressive HO (accumulation of extraskeletal bone formation in muscles, tendons, and ligaments) in specific anatomic patterns that often form with “flares-ups” (sporadic, intermittent painful episodes of rapidly progressive connective/soft tissue swelling) (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
  - The most typical features of FOP flare-ups include intense muscle edema, fibroproliferation, and angiogenesis characteristic of early pre-osseous FOP lesions, and the rapid spread of the lesions along muscle planes into adjacent tissue. A lesion may appear within hours and can reach an alarming size literally overnight (*Kaplan et al 2022*).
    - FOP lesions go through predictable stages. Pain, erythema, tenderness, swelling, and warmth are present in the first few weeks. During the intermediate stage, induration increases but pain and erythema improve. During the late stage (after 12 weeks), the nodule hardens with radiographic ossification, but the swelling resolves (*Tis 2022*).
      - Soft tissue swellings may resolve but more often transform skeletal muscles, tendons, ligaments, fascia, and aponeuroses into ribbons, sheets, or plates of heterotopic bone. Flare-ups typically begin in the head, neck, and shoulders and progress from cranial to caudal, dorsal to ventral, axial to appendicular, and proximal to distal. The diaphragm, tongue, extraocular muscles, cardiac muscles, and smooth muscles are spared (*Kaplan et al 2022, Tis 2022*).
    - The sudden appearance and rapid spread of an FOP lesion has suggested the involvement of various inflammatory mediators along with an abnormal connective tissue wound response; inflammatory mast cells have been found at all stages of FOP lesional development including an intense aggregation of mononuclear inflammatory cells (eg, lymphocytes, macrophages, and mast cells) in the perivascular spaces of edematous muscle in pre-osseous FOP lesions. These inflammatory cells along with cellular hypoxia play a direct role in the generation of FOP lesions. Following the catabolic phase of muscle cell death, a highly anabolic fibroproliferative phase (often mistaken for aggressive juvenile fibromatosis) consists, in part, of Sca1+/PDGFR+/Tie2+/CD34- fibroadipogenic progenitor (FAP) cells that differentiate through an endochondral pathway into mature heterotopic bone (*Kaplan et al 2022*).

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- FOP flare-up occurrence, duration and severity is unpredictable, with great individual variability in the rate of disease progression (*Kaplan et al 2022, Tis 2022*).
  - Flare-ups may be precipitated by soft tissue injury, intramuscular injections, surgical incisions, falls, muscular stretching, or viral illness (*IFOPA Web site, Kaplan et al 2022, Tis 2022*).
- As FOP progresses, heterotopic bone extends across joints, resulting in progressive and irreversible immobility, weight loss, severe tooth decay, and malnutrition secondary to ankylosis of the jaw, chest wall deformity (thoracic insufficiency syndrome), and localized skin breakdown. Patients become dependent upon diaphragmatic breathing (*FDA Sohonos integrated review 2023, Tis 2022*).
  - Flare-ups typically begin during the first decade of life, and often occur as nodules on the head or back at a median 1.5 years of age, while 10% of patients present with nodules in the neonatal period (*Kaplan et al 2022, Tis 2022*).
  - In a survey of 44 patients with FOP, the average onset of HO was at 5 years of age, 80% of patients had restrictive ossification by 7 years of age, and 95% had severely restricted motion in the upper extremity by 15 years of age (*Tis 2022*).
  - Most patients with FOP are confined to a wheelchair or require mobility assistance due to HO around the hips by the third decade of life and require lifelong assistance in performing ADLs (*Kaplan et al 2022, Pignolo et al 2023*).
  - Survival in patients with FOP is shortened (median, 56 years of age). Most patients die of respiratory depression or pneumonia due to cardiopulmonary complications of severe restrictive chest wall involvement. Starvation, related to ankylosis of the jaw, used to be a common cause of death, but modern feeding tubes have minimized this (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
- The prevalence of FOP has been estimated at up to 1.4 per million individuals, with 289 unique patients reported in the U.S. as of 2021 and approximately 800 confirmed cases reported globally. All races are affected, with no ethnic, gender, or geographic predisposition (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2021, Pignolo et al 2023, Tis 2022*).
- The current standard of care for FOP has been mainly palliative and limited to symptom relief by decreasing pain and inflammation and preventing flare-ups. Prior to the FDA approval of palovarotene, no therapy has been shown to treat or slow progression of FOP, specifically the formation of HO and the resulting morbidity associated with chronic HO accumulation (*FDA Sohonos integrated review 2023, Kaplan et al 2022, Pignolo et al 2023, Tis 2022*).
  - Symptomatic treatment with short-term high dose steroids has been used to treat symptom flares (*FDA Sohonos integrated review 2023, Kaplan et al 2022*).
  - Mast cells, macrophages, lymphocytes, and their associated inflammatory-mediators associated with pre-osseous FOP lesions may be reduced with the use of mast cell stabilizers, long-acting non-sedating antihistamines, leukotriene inhibitors, NSAIDs, c-kit TKIs, and COX-2 inhibitors (*Kaplan et al 2022*).
- Palovarotene is an RARγ selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation. It was FDA-approved for the reduction in the volume of new HO in adults, female pediatric patients ≥ 8 years of age, and male pediatric patients ≥ 10 years of age with FOP. Approval was based on data from the Phase 3 MOVE trial and confirmatory evidence providing substantial evidence of effectiveness for the approved indication. Palovarotene is the first pharmacologic therapy FDA-approved for the treatment of FOP (*FDA Sohonos integrated review 2023*).
  - The confirmatory evidence of effectiveness came from post hoc analyses of 21 palovarotene-treated patients in the ongoing Phase 2 Study 202, Part C (202C), vs untreated patients from the NHS. Using the matched propensity score analysis, the mean annualized new HO volume was 16.1 cm^3/year in those receiving palovarotene vs 28.4 cm^3/year in untreated patients, for a treatment difference of 12.3 cm^3/year.
  - The FDA determined that treatment with palovarotene showed an effect in decreasing the volume of new HO in patients with FOP. This reduction in HO volume provides a clinically meaningful benefit to patients because of the irreversible, progressive nature of FOP; the progressive accumulation of HO over time is associated with worsening mobility. Therefore, treatment with palovarotene which leads to small changes in HO volume in short term trials, is expected to slow the progression of the disease with the potential to preserve joint range of motion and movement for longer periods of time (*FDA Sohonos integrated review 2023*).
- Prior to approval, the new drug application (NDA) for palovarotene received a Complete Response Letter (CRL) on December 23, 2022 due to various clinical deficiencies. 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 others. There were no interim analyses planned for the Phase 2 Study 202, and the original NDA included only limited descriptive summaries of the pre-pause 202B/C whole body HO data, which appeared to be inconsistent with findings from the Phase 3 MOVE trial. This raised concerns about consistency of the efficacy data, and the FDA

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requested additional analyses of the Study 202 vs NHS data (*FDA Sohonos integrated review 2023, FDA Sohonos other review 2023*).
  - The CRL response was reviewed by the multidisciplinary FDA Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on June 28, 2023.
  - The majority of the EMDAC agreed that the data demonstrated that palovarotene was effective in patients with FOP, acknowledging limitations of post hoc analyses and use of the NHS as an external control. Given the rarity and disease burden of FOP and the lack of treatment alternatives, most committee members considered that the benefits of palovarotene outweighed its risks for the treatment of patients with FOP.
  - The Advisory Committee recommended screening for PPC in pediatric patients, monitoring bone mineral density, and creation of a patient registry to better understand the patient population.
  - Post-marketing requirements (PMRs) for palovarotene include an observational safety study in pediatric and adult patients to assess the long term safety, risk of HO flares, and other risks associated with palovarotene, including PPC, bone fractures, and any pregnancy data available. The study will be conducted in ≥ 100 patients with FOP, with 50% pediatric patients and 2/3 treated with palovarotene.
- There are various investigational new drugs undergoing clinical trials, including selective ACVR1/ALK2 signal transduction inhibitors (STIs), monoclonal antibodies targeting Activin A or ACVR1/ALK2, and mammalian target of rapamycin (mTOR inhibitors) (*Kaplan et al 2022*).

Indications

- Palovarotene is a retinoid indicated for reduction in the volume of new HO in adults, female pediatric patients ≥ 8 years of age, and male pediatric patients ≥ 10 years of age with FOP.
- Palovarotene was approved by the FDA on August 16, 2023 (Type 1 - New Molecular Entity classification) and received Priority Review, Orphan Drug, Fast Track, and Breakthrough Therapy designations (*Drugs@FDA 2023, FDA Press Release 2023*).

Pharmacology

- In patients with FOP, abnormal bone formation, including HO, is driven by a gain-of-function mutation in the BMP type I receptor ALK2/ACVR1.
- Palovarotene is an orally bioavailable RAR receptor agonist, with particular selectivity at the γ subtype of RAR (ie, RARγ).
  - Through binding to RARγ, palovarotene decreases the BMP/ALK2 downstream signaling pathway by inhibiting the phosphorylation of SMAD1/5/8, which reduces ALK2/SMAD-dependent chondrogenesis and osteocyte differentiation resulting in reduced endochondral bone formation.

Clinical efficacy

Study design abbreviations: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indication were identified using search terms "palovarotene" and "fibrodysplasia ossificans progressiva" through October 24, 2023. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Study 1. Pignolo et al, *J Bone Miner Res*. 2023;38(3):381-394; FDA Sohonos integrated review 2023 (MOVE; NCT03312634)

Study Objective: Evaluate the safety and effectiveness of palovarotene in patients ≥ 4 years of age with FOP	
Study Design, Follow-up	**Treatment Groups**
• 48-month Phase 3, OL, SA, MC, external-controlled trial ○ The trial consists of a 24-month Part A (consisting of 3 interim analyses: IA1, IA2, and IA3) and a 24-month extension (Part B) ▪ IA2 included all patients who completed Month 12 assessments (n = 99)	• MOVE population: Chronic/flare-up palovarotene (n = 107) ○ Chronic treatment: Oral palovarotene 5 mg once daily ○ 12-week flare-up treatment ("20/10 mg"): Oral palovarotene 20 mg orally once daily for 4 weeks (28 days) followed by oral palovarotene 10 mg once daily for 8 weeks (56 days). Flare-up treatment could be

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▪ IA3 included patients who completed Month 18 assessments (n = 99) • IA3 principal enrolled population: All patients with the ACVR1^{R206H} pathogenic variant with no prior treatment with palovarotene (n = 99). • IA3 P-FAS: All patients from the IA3 principal enrolled population who had a baseline HO volume measurement and ≥ 1 post-baseline HO volume measurement (n = 97). ▪ A final analysis is planned for when all patients complete Month 24 of Part A. ▪ Part B: All patients could receive palovarotene for an additional 24 months until commercial availability, allowing longer-term safety and efficacy data to be obtained. ○ Both MOVE and the NHS study (*Pignolo et al 2022*) were completed at 16 international study sites in Argentina, Australia, Brazil, Canada, France, Italy, Japan, Spain, Sweden, the United Kingdom, and the United States (U.S.).	extended in 4-week increments for persistent symptoms (ie, until the Investigator determined flare-up resolved) ▪ Flare-up was defined as ≥ 1 symptom (eg, pain, swelling, redness) consistent with a previous flare-up or a substantial high-risk traumatic event likely to lead to a flare-up ○ Dosing was weight-adjusted in skeletally immature children (children who had not reached ≥ 90% skeletal maturity defined as a bone age ≥ 12 years 0 months in females and ≥ 14 years 0 months in males based on hand/wrist x-rays performed at screening). • NHS population: Untreated patients (beyond standard of care) from the 36-month FOP NHS were utilized as an external control (N = 111) ○ A total of 39 patients transferred from the NHS into the MOVE trial and contributed efficacy data to both studies. • Patients in both groups were treated with concomitant standard of care medications, including corticosteroids (eg, oral prednisone 2 mg/kg [maximum 100 mg daily] for 4 days as needed.
Inclusion Criteria	**Exclusion Criteria**
• Patients ≥ 4 years of age • Clinical diagnosis of FOP with the ACVR1^{R206H} pathogenic variant or other FOP variants reported to be associated with progressive HO • No flare-up symptoms within the past 4 weeks, including at the time of enrollment. • Abstinent or using 2 highly effective forms of birth control • No prior exposure to palovarotene (in the principal enrolled population)	• Weight < 10 kg • Concomitant medications that are strong inhibitors or inducers of CYP3A4 activity; or kinase inhibitors such as imatinib. • Concurrent tetracycline, tetracycline derivatives, vitamin A or beta carotene, or synthetic oral retinoids other than palovarotene within 4 weeks before screening • Amylase or lipase > 2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis. • Elevated aspartate aminotransferase or alanine aminotransferase > 2.5x ULN. • Fasting triglycerides > 400 mg/dL with or without therapy • Female patients who are breastfeeding • Patients with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease • Pregnancy
Primary Endpoint	**Secondary Endpoints**
• Annualized volume of new HO (cm^3/year) in the P-FAS palovarotene-treated population vs untreated NHS patients, as assessed by low-dose WBCT imaging (excluding head) at the 18-month interim analysis* ○ WBCT images were obtained at baseline and every 6 months in Part A of MOVE to document HO across different body regions and volume of total body HO; volume of new HO was quantified per region if new HO was judged to be present at post-baseline visits. ○ WBCT scans were obtained every 12 months in the NHS.	• Key: Proportion of patients with any new HO at Month 12 • Change from baseline to Month 12 in the number of body regions with new HO (ie, any body region in which the overall volume of HO increased), based on 9 anatomical regions†

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○ The 18-month interim analyses included 97 P-FAS palovarotene-treated patients and 101 NHS patients with post-baseline WBCT. ○ All WBCT images from patients in both MOVE and the NHS were read in a manner blinded to study origination.	

* The pre-specified primary endpoint was annualized change in new HO volume vs NHS patients (by low-dose WBCT), analyzed using a BcPM with square-root transformation. The 12-month interim analyses met futility criteria; dosing was paused. An independent DMC recommended trial continuation based on post hoc analysis. Post hoc 18-month interim analyses utilized BcPM with square-root transformation and HO data collapsed to equalize MOVE and NHS visit schedules, BcPM without transformation, and wLME models, alongside prespecified analysis.
† The 9 anatomical regions included the following: Right and left chest, neck, and shoulder through mid-humerus; mid torso (torso below shoulder regions and above iliac crests); right and left arms (mid-humerus through hand); right and left hips (iliac crest, hip through mid-femur); and right and left lower legs (mid-femur through foot).

- **Results:**
  - Breakdown of patient enrollment:
    - At baseline, 107 patients were enrolled in MOVE and received the palovarotene chronic/flare-up regimen.
    - The 18-month IA3 principal enrolled population consisted of 99 patients who had the ACVR1^{R206H} pathogenic variant; the 18-month IA3 P-FAS included 97 patients from the IA3 principal enrolled population who had a baseline HO volume measurement and ≥ 1 post-baseline HO volume measurement.
    - A total of 19 (17.8%) patients discontinued the study: 6 (5.6%) due to an AE, 2 (1.9%) due to a sponsor request, and 11 (10.3%) due to withdrawal by patient. A total of 88 patients are ongoing in the MOVE trial.
      - A total of 9 patients permanently discontinued palovarotene treatment due to treatment-emergent AEs, however, 3 had not yet completed the end of study visit at the time of the data cut-off.
  - Demographics and baseline data:
    - Patients in the palovarotene group were a mean 15.1 years of age (range, 4 to 61; 75/99 [75.8%] < 18 years of age); untreated patients in the NHS were a mean 17.8 years of age (range, 4 to 56; 66/111 [59.5%] < 18 years of age). There were more male than female patients in both populations (palovarotene, 53% male; NHS; 55% male).
    - In the palovarotene group, 70.7% were White, 9.1% Asian, and 18.2% multiple, other, or unknown; 39% of patients were enrolled in the U.S. In the NHS, 73.0% were White, 8.1% Asian, and 17.1% multiple, other, or unknown; 34% of patients were enrolled in the U.S.
    - During MOVE, 64/99 (64.6%) patients received corticosteroids for systemic use as a concomitant medication vs 80/111 (72.1%) in the NHS.
    - At baseline, 88/99 (88.9%) palovarotene-treated patients vs 97/111 (87.4%) patients in the NHS were walking, and 25/99 (25.3%) vs 34/111 (30.6%), respectively, were using a wheelchair based on CAJIS ROM assessment.
    - In the palovarotene vs NHS population, 64/99 (64.6%) vs 60/111 (54.1%), respectively, were able to carry out ADLs with some help, and 10/99 (10.1%) vs 13/111 (11.7%) required complete help with ADLs.
    - A total of 100% of patients in the palovarotene group and 97.3% of patients in the NHS group had a history of flare-ups at baseline.
  - Key milestones and interim analyses:
    - The NHS was initiated in 2014; MOVE was initiated in November 2017.
    - August 2019: 35 patients completed IA1 (Month 12 assessment)
    - December 2019: FDA imposed a partial clinical hold for the dosing of patients < 14 years of age due to risk of PPC based on multiple reports of PPC among pediatric patients per scheduled radiographs. This partial clinical hold remains in effect; some affected patients resumed treatment after reaching 14 years of age (*FDA Sohonos integrated review 2023*).
      - A protocol amendment was added with an extended 2-year safety follow-up for pediatric patients, including annual assessment of growth, hand/wrist radiograph, and WBCT.
    - January 15, 2020: All patients (n = 99) completed IA2 (Month 12 assessments). The 12-month interim analyses met pre-specified futility criteria. Futility was declared and dosing was paused in the remaining patients ≥ 14 years of age still receiving treatment.
      - The IA2 12-month interim prespecified analysis for the primary endpoint of annualized change in new HO volume (by low-dose WBCT) vs NHS patients was analyzed using a BcPM with square-root transformation.
        - The analysis included a square root transformation of each change in HO since the previous scan by region. This statistical model was chosen “to more appropriately accommodate the high degree of variability in the volume of new HO assessed by WBCT” (*FDA Sohonos integrated review 2023*).

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        - Futility criteria was defined as a < 5% posterior probability of a > 30% reduction in annualized new HO volume on a square root transformed scale (*Sohonos product dossier 2023*).
    - Post hoc analyses were initiated upon the pause and reviewed by an independent DMC with expertise in FOP, biostatistics, pediatric bone health, musculoskeletal radiology, hematology, and oncology.
        - The post hoc analyses unblinded the data and compared the raw, non-transformed mean annualized HO volumes. The post hoc analyses included a BcPM omitting the square root transformation and a wLME model.
        - Based on the post hoc analyses of raw, non-transformed HO volumes, the Bayesian analysis would have exceeded the pre-specified boundary for early efficacy at IA2, meaning the futility criteria were not met.
    - As the HO volume square root transformed and post hoc non-transformed results conflicted, treatment futility could not be confidently concluded and the DMC recommended that palovarotene treatment continue in skeletally mature children ≥ 14 years of age. Many patients resumed treatment following approximately 3 to 19 months' hiatus (*FDA Sohonos integrated review 2023, Sohonos product dossier 2023*).
- February 2020: Data cut-off for IA3 (Month 18 assessments)
    - To address prolonged treatment interruptions in patients < 14 years of age following the partial clinical hold due to PPC, and dosing interruptions for the remaining patients due to crossing the futility boundary, all efficacy analyses included assessments collected on or before these interruptions.
        - A total of 46/99 (46.5%) patients experienced ≥ 1 dose interruption with chronic dosing of palovarotene, while 8/99 (11.6%) and 10/99 (14.5%) experienced a dose interruption during high- and low-dose flare-up treatment, respectively.
    - Post hoc 18-month interim analyses utilized BcPM with square root transformation and HO data collapsed to equalize MOVE and NHS visit schedules, BcPM without transformation, and wLME models, alongside prespecified analysis.
- Primary endpoint: Annualized volume of new HO at the 18-month interim analysis
    - The wLME model estimated that the mean annualized new HO volume was 53.8% lower in palovarotene-treated vs NHS patients at 9.4 cm^3/year vs 20.3 cm^3/year, respectively, with an estimated treatment effect of 10.9 cm^3/year (95% CI, -21.2 to -0.6; p = 0.039).
        - wLME estimates were from a mixed model with the dependent variable being annualized new HO volume and independent variables including fixed effects of treatment, baseline total HO volume/baseline age, and a random patient effect, with observations weighted proportional to length of time between first and last WBCT.
        - There was a 60% reduction in the non-transformed raw mean annualized volume of new HO in palovarotene-treated patients vs the NHS when comparing annualized new HO as reported (including negative HO values), yielding a consistent result to the wLME model.
    - BcPM analyses without transformation showed 99.4% probability of any reduction in new HO with palovarotene vs NHS patients (with transformation, 65.4%).
    - There was more variability in the annualized net change in HO volume among NHS vs palovarotene patients. A total of 5.0% of NHS vs 28.9% of palovarotene patients had a net negative annualized new HO, meaning that the measured volume of HO was reduced overall.
- Key secondary endpoint: Proportion of patients with any new HO at Month 12
    - There was no significant difference observed between groups in the proportion of patients with any new HO or mean (SD) number of body regions with new HO at Month 12 (treated patients: 64% and 1.3 [SD, 1.4], respectively, vs NHS: 62% and 1.5 [SD, 1.6], respectively).
- Additional exploratory endpoints and post hoc computational analyses:
    - Exploratory endpoints included change from baseline in range of motion assessed by the CAJIS at Month 24, change from baseline in physical function assessed by FOP-FPQ at Month 24, and change from baseline in physical and mental health in patients ≥ 15 years of age as assessed by the PROMIS Global Health Scale at Month 24 (See Appendix). The results did not reveal any significant difference between treated and untreated patients.
    - Catastrophic HO was assessed in palovarotene-treated patients as an exploratory endpoint at Month 12 and at the last time point assessed. Catastrophic HO categories were defined post hoc as annualized new HO > 50 × 10^3 mm^3 and > 30 × 10^3 mm^3, based on 12-month observations. An additional cut-off of annualized new HO > 100 × 10^3 mm^3 was also explored.
        - While fewer patients treated with palovarotene experienced catastrophic new HO vs the NHS, the FDA noted that the list of patients with "catastrophic" large volumes of new HO (> 30 cm^3/flare-up event) at Week 12 demonstrated that the imaged flare-up full analysis set (IF-FAS) data were largely driven by a few patients with flare-ups mainly involving the hip, and to a lesser extent the shoulder and flare-ups of the knee appeared to be

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less consequential. The clinical impact of new HO is also dependent on factors other than HO volume, including the exact location of HO lesions around the adjacent joint.
    - Post hoc computational analyses using WBCT showed decreased vertebral bone mineral density, content, and strength, and increased vertebral fracture risk in palovarotene-treated patients.
  - Flare-ups were reported by 67% of palovarotene-treated patients vs 56% of NHS patients through Month 12, based on 1 relevant symptom, and at a higher frequency (0.15/patient-month vs 0.07/patient-month, respectively); data were similar for the subset of 39 patients who crossed over from the NHS to MOVE. Within MOVE, new flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events/month vs 0.12/month during chronic dosing). Most of the new flare-ups occurred at sites distant from the initial site. The FDA noted that flare-ups appear to have been under-reported in the NHS, so the validity of these findings remains unclear (*FDA Sohonos integrated review 2023*).
  - Safety:
    - All palovarotene-treated patients reported ≥ 1 AE; 97.0% reported ≥ 1 retinoid-associated AE; 29.3% reported ≥ 1 serious AE, including PPC/epiphyseal disorder in 21/57 (36.8%) patients < 14 years of age.

- **Author's conclusions:**
  - Post hoc analyses showed evidence for efficacy of palovarotene in reducing new HO in FOP, but high risk of PPC in skeletally immature patients (*Pignolo et al 2023*).
  - The FDA concluded that there was substantial evidence of the effectiveness of palovarotene chronic daily/flare-up dosing in reducing new volume HO in pediatric and adult patients with FOP (*FDA Sohonos integrated review 2023*).
    - Data demonstrated that patients who reported no flare-ups developed relatively small quantities of new whole body HO, either with or without chronic daily treatment. By comparison, patients who experienced flare-ups generally developed large quantities of new whole-body HO *without* chronic daily therapy and derived greater benefit from palovarotene (ie, reduced volume of new HO, both at and away from flare-up sites).
    - Treatment with palovarotene, which led to small changes in HO volume in short term trials, is expected to slow the progression of the disease with the potential to preserve joint range of motion and movement for longer periods of time.
    - The FDA stated that various post hoc analyses performed by the review team demonstrated a consistency of results across the analyses performed and supported a conclusion of effectiveness.
    - The FDA approved palovarotene in children (females ≥ 8 years of age, and males ≥ 10 years of age) to allow most patients with ≥ 80% skeletal maturity (ie, bone age of 8 years in females and 10 years in males) to receive palovarotene for the prevention of HO despite the risk of PPC, given the severity of FOP.

- **Study Appraisal:**
  - Study sponsorship:
    - Clementia Pharmaceuticals Inc.
  - Study rating:
    - Not applicable (non-randomized)
  - Study strengths:
    - The NHS and MOVE trials enrolled a relatively large proportion of the known global population of approximately 800 patients with FOP.
    - The NHS and MOVE trials were conducted at the same centers, with generally consistent standards of care and associated background treatment.
    - The relative objectivity and blinded assessment of the change in HO volume minimized the potential for bias.
    - The external control population was generally similar to that of the treatment group; concomitant treatments affecting the primary endpoint were not substantially different between groups.
    - The enrollment criteria for the NHS and MOVE were generally similar. NHS was restricted to patients with the classic R206H mutation (representing 97% of FOP patients) while the MOVE P-FAS population excluded a small number of patients with other mutations.
    - HO volume was objectively assessed by WBCT.
    - The FDA stated that the primary endpoint reduction in HO volume was clinically meaningful due to the irreversible, progressive nature of FOP; patients with FOP are known to have progressive accumulation of HO.
      - Progressive accumulation of HO over time is associated with worsening mobility.
      - Based on NHS data, there was a correlation between total body HO volume with increasing CAJIS score, indicating increasing restrictions on movement and joint range of motion.

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- While clinical effectiveness was based on post hoc analyses, the various post hoc analyses demonstrated a consistency of results across the range of analyses and supported a conclusion of effectiveness.
- Study limitations:
  - Current data supporting clinical efficacy is based on 18-month interim data and post hoc analyses.
  - MOVE was an OL, SA, external-controlled, non-randomized trial, with use of an external control group (NHS) as a comparator.
    - There is a lack of assurance of comparability between treated and untreated patients given the lack of randomization with an external control group.
  - There were some differences in baseline characteristics between patients in the NHS and MOVE; eg, patients in the NHS were relatively older and had worse disease severity.
  - For the primary endpoint of new HO volume, there can be a large variability in the amount of new HO due to differing anatomic sites of involvement as well as different rates of progression between patients. It can be difficult to determine what constitutes a clinically meaningful reduction in new HO volume over relatively short clinical trial timescales (*Pignolo et al 2023*).
  - There were prolonged interruptions (treatment pauses) and/or discontinuation of treatment in nearly all patients due to pediatric safety issues and futility criteria being met in the 12-month interim analysis (*FDA Sohonos integrated review 2023*).
  - Post hoc analyses
    - The prespecified primary analysis included a square root transformation of each change in HO since the previous scan by region and was based on a BcPM; it was chosen prior to various protocol amendments.
    - The trial crossed the futility boundary at the second interim analysis (IA2) and the study was paused for dosing.
    - Additional post hoc analyses, including the same Bayesian compound model but without square root transformation and a frequentist wLME model, found evidence of potentially clinically meaningful benefit of palovarotene, with lower annualized new HO of patients in MOVE vs the NHS. These analyses used regression adjustments to account for baseline differences between patients in the 2 studies.
    - The failure of the prespecified BcPM incorporating square root transformation was most likely due to the use of a square root transformation and the difference in WBCT assessment schedules between MOVE and the NHS (with WBCT scans every 6 and 12 months, respectively). It was determined that this prespecified analysis was not valid with inherent bias against palovarotene due to more frequent assessments vs the NHS, while the impact of the prespecified square root transformation was also unexpectedly large and appeared to have moved the statistical conclusion from significant therapeutic benefit to showing futility of the treatment.
      - Collapsing the new HO observed during the first 12 months in MOVE as if it were observed entirely at Month 12, to mimic the visit schedule of the NHS, yielded a 16% reduction in square root transformed new HO volume and increased the probability of any reduction in new HO to 90.7%.
      - The post hoc analyses indicated that the use of square root transformation in conjunction with the differential assessment schedule contributed to the failure of the prespecified primary analysis.
    - The DMC concluded that “the dilemma created by these highly disparate results precludes a confident conclusion about futility.” and it was recommended that “palovarotene be continued in skeletally mature children ≥ 14 years.”
    - Post hoc analyses are generally considered hypotheses generating only and not appropriate for providing substantial evidence of effectiveness. However, in this situation, the FDA acknowledged that the prespecified primary analysis for MOVE was inherently biased against palovarotene and that it was reasonable to use valid and more appropriate post hoc analyses to assess evidence of efficacy in this specific setting.

Clinical guidelines

ICC on FOP: The medical management of FOP (*Kaplan et al 2022*)

- The present management of FOP is focused on early diagnosis, diligent avoidance of trauma and injury, symptomatic amelioration of painful flare-ups, and optimization of residual function. There is presently no definitive medical treatment for FOP, and management is currently supportive.
  - Flare-ups often result from over-use and soft tissue injuries.
  - Prophylactic dental approaches are essential. Dental therapy should preclude mandibular blocks and stretching of the jaw.
  - Avoidance of intramuscular injections, muscle fatigue, and passive movement of joints is essential.
  - Prevention of falls, influenza, recurrent pulmonary infections, and complications of restrictive chest wall disease is important.

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- While physical therapy to maintain joint mobility may be harmful by provoking or exacerbating lesions, occupational therapy evaluations are often helpful.
- Other therapies have not been shown to be effective for FOP:
  - Removal of FOP HO is often followed by significant recurrence and expansion of HO.
  - Surgical release of joint contractures is unsuccessful, and risks new trauma-induced HO.
  - Spinal bracing is ineffective.
  - Surgical intervention is associated with numerous complications.

- The most typical features of FOP flare-ups include intense muscle edema, fibroproliferation, and angiogenesis characteristic of early pre-osseous FOP lesions, and the rapid spread of the lesions along muscle planes into adjacent tissue. A lesion may appear within hours and can reach an alarming size literally overnight. The sudden appearance and rapid spread of an FOP lesion suggests involvement of a repertoire of inflammatory mediators along with an abnormal connective tissue wound response, and points to a potential role for inflammatory mast cells and their mediators in the extension of the disease process.
  - This pathogenesis suggests a potential role for mast cells in the FOP process.
  - Little is known about the resident mast cells in skeletal muscle; however, a comprehensive analysis was undertaken of mast cell distribution in normal skeletal muscle, in uninvolved FOP muscle, in FOP lesions, in inflammatory and genetic muscle diseases, and in experimentally-induced animal models of HO. The mobilization and activation of inflammatory mast cells was found at all stages of FOP lesional development. These data documented an important role for mast cells in the pathology of FOP lesions.
  - Mast cells, macrophages, lymphocytes, and their associated inflammatory-mediators may be reduced with the use of mast cell stabilizers, long-acting non-sedating antihistamines, leukotriene inhibitors, NSAIDs, c-kit TKIs, and COX-2 inhibitors.
- The ICC has classified various pharmacologic agents for FOP into one of 3 categories (Class I, II, and III) based on experimental or anecdotal experience with the drug as well as the drug's safety profile, with focus on the mechanism of action of the drug as it may relate to the proposed pathogenesis of FOP. See Table 1 for a summary of the ICC classes of medications utilized in the current treatment of FOP.
  - High-dose glucocorticoids have limited use but are most effective in the management of the early inflammatory flare-ups affecting major joints of the appendicular skeleton and jaw, especially when used immediately after the onset of a flare-up.
  - Oral and topical NSAIDs, COX-2 inhibitors, mast cell stabilizers, leukotriene inhibitors, and occasional intravenous aminobisphosphonates are reported by patients to manage chronic pain, arthritic symptoms or ongoing disease progression.
  - Additional agents not classified include topical analgesics such as lidocaine (patch or gel) and capsaicin cream, and muscle relaxants such as cyclobenzaprine, metaxalone, or baclofen.
    - Topical lidocaine is most appropriate for patients with well localized neuropathic pain.
    - Use of capsaicin cream may have a theoretical advantage for pain control in FOP; however, clinical experience is very limited with concern over paradoxical effects.
    - The judicious short-term use of muscle relaxants may help to decrease muscle spasm and maintain more functional activity even in the setting of an evolving FOP lesion. This is especially true for painful flare-ups involving the limbs.
  - Physicians treating patients who have FOP should keep in mind that no medications to date have been proven to alter the natural history of FOP.

Table 1. Classes of medications utilized in the current treatment of FOP

Drug	Drug class	Proposed mechanism of action as it relates to FOP	Notes
Class I: Medications that have been widely used to control symptoms of acute flare-ups (swelling and pain) or chronic arthropathy with generally minimal AEs			

prednisone	corticosteroid	• Decreases lymphocyte and macrophage recruitment and tissue infiltration
		• Potent anti-inflammatory drug: Decreases inflammation, swelling and edema especially when involving jaw, throat, and major joints
		• Should not be used for flare-ups involving chest or back
			• Use of corticosteroids should be restricted to:
			  • Extremely early symptomatic treatment of flare-ups that affect major joints (eg, hip), the jaw, or the submandibular area
			  • Prevention of flare-ups following major soft tissue injury (severe trauma)
			  • Prophylactically as directed for dental or surgical procedures
			• For acute flare-ups involving the major joints of the major appendicular skeleton, typical treatment is immediate use

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			of daily prednisone 2 mg/kg/day (up to 100 mg) for ≤ 4 days. • The prednisone should be started within 24 hours of the onset of a flare-up, which corresponds to the earliest phase of acute and intense lymphocytic infiltration into skeletal muscle. • Patients may keep prednisone on-hand as a "pill-in-pocket" approach for emergencies. • Corticosteroids should not be used for the long-term chronic treatment of FOP. • When the prednisone is discontinued (or if a flare-up existing for more than 48 hours is being considered for treatment), symptomatic treatment may be considered with an NSAID or COX-2 inhibitor.
ibuprofen	NSAID (non-specific COX-1 and COX-2 inhibitor)	• Anti-inflammatory and anti-angiogenic: Symptomatic relief during a flare-up • Potential use in prevention by inhibiting production of inflammatory prostaglandins	• COX-2 inhibitors or oral/topical NSAIDS may be helpful for symptomatic management of flare-ups and chronic arthropathy when corticosteroids are not indicated. • COX-2 inhibitors should be used with caution in FOP patients with a history of cardiovascular disease or in older FOP patients who are severely immobilized or completely non-ambulatory.
indomethacin	NSAID (non-specific COX-1 and COX-2 inhibitor)		
celecoxib	COX-2 inhibitor		
Class II: Medications that have theoretical application to various aspects of FOP, are approved for the treatment of other disorders, and have limited and well-described effects. Class II Medications can be considered with caution at the physician's discretion.			
montelukast	Leukotriene receptor antagonist	• Blocks inflammatory mediators • Complementary action to COX inhibitors	
cromolyn	Mast cell stabilizer	• Reduces mast cell degranulation, but poorly absorbed from the gastrointestinal tract • May be more effective if used chronically	• Significantly decreases the total number of mast cells and specifically diminishes the number of degranulating and resting degranulated mast cells in pre-osseous FOP lesions
pamidronate	Amino-bisphosphonate	• Anti-angiogenic • Possibly anti-inflammatory • Potential inhibition of early angiogenic fibroproliferative lesion • Well-established effects on decreasing bone remodeling in normotopic skeleton and in protecting normotopic skeleton from profound osteopenic effects of chronic intermittent high dose glucocorticoids	• It remains unclear whether bisphosphonates have effects on flare-ups, though anecdotally they seem to decrease the flare symptoms in some patients.
zoledronate	Amino-bisphosphonate		
Imatinib	Selective tyrosine kinase inhibitor	• Off-target effects of blocking c-Kit, HIF1-α, PDGFRα, and multiple MAP kinases	• Presently, there is no definitive evidence that imatinib prevents or ameliorates flare-ups. However, early clinical observations support the implementation of clinical trials of imatinib in children with uncontrolled FOP flare-ups. • Imatinib has been successfully used to reduce airway hyper-responsiveness and mast cell number in severe asthma and to mitigate severe and unrelenting flare-ups.
Class III: Investigational new drugs; medications are under development and/or are being tested in clinical trials and are not yet available for general use.			
Palovarotene	RAR-γ agonist	• Inhibits ectopic chondrogenesis	• Palovarotene is being studied in FDA-approved clinical trials for FOP, including an ongoing Phase 3 trial* • Activation of the retinoid signaling pathway and RARγ agonists inhibit chondrogenesis and HO.
ACVR1/ALK2 STI	STI	• Blocks ACVR1/ALK2 signal transduction	• Ongoing clinical trials for all compounds
Monoclonal antibody against ACVR1/ALK2	ALK2 antibody	• Blocks ACVR1/ALK2 at cell surface	• Limited data available
mTOR inhibitor	mTOR inhibitor	• Inhibits ACVR1/ALK2 signal transduction	• Ongoing Phase 2 clinical trial
Monoclonal antibody against Activin A	Activin A antibody	• Blocks Activin A signaling through mutant ACVR1/ALK2	• Ongoing Phase 3 clinical trial

* Palovarotene was not FDA-approved at the time this ICC summary statement was published.

Safety

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- **Contraindications**
  - Pregnancy: Palovarotene can cause fetal harm.
  - Patients with a history of allergy or hypersensitivity to retinoids, or to any component of palovarotene
- **Warnings/precautions**
  - **Boxed warning:** Embryo-fetal toxicity and PPC in growing pediatric patients.
    - Embryo-fetal toxicity: Palovarotene can cause fetal harm; it is a member of the retinoid class of drugs which is associated with birth defects in humans. Due to the risk of teratogenicity and to minimize fetal exposure, palovarotene should be administered only if conditions for pregnancy prevention are met. For females of reproductive potential, it should be verified that the patient is not pregnant prior to initiating treatment, periodically during the course of therapy and 1 month after treatment discontinuation. Females of reproductive potential should be advised to use an effective method of contraception ≥ 1 month prior to treatment, during treatment with palovarotene and for 1 month after the last dose.
      - All patients should be informed not to donate blood during palovarotene therapy and for 1 week following discontinuation because the blood might be given to a pregnant patient whose fetus must not be exposed to palovarotene.
    - PPC: PPC has occurred with palovarotene. The patient's baseline skeletal maturity should be assessed before palovarotene therapy and linear growth should be closely monitored in growing pediatric patients.
  - Mucocutaneous AEs: Dry skin, lip dry, pruritus, rash, alopecia, erythema, skin exfoliation, and dry eye have occurred with palovarotene; these AEs should be prevented or treated with skin emollients, sunscreen, and artificial tears. Dosage reduction may be required in some patients.
  - Metabolic bone disorders: Decreased vertebral bone mineral content and bone density may occur. Patients should be assessed for spinal fracture periodically using radiologic method.
  - Psychiatric disorders: Depression, anxiety, mood alterations and suicidal thoughts and behaviors have occurred with palovarotene. A healthcare provider should be contacted if new or worsening symptoms develop in patients treated with palovarotene.
  - Night blindness: Night blindness may occur and make driving at night hazardous.
- **Adverse effects**
  - The most common AEs (incidence ≥ 10%) during treatment with chronic or flare-up dosing included dry skin (61% and 57%, respectively), lip dry (47% and 38%), arthralgia (36% and 31%), pruritus (34% and 48%), pain in extremity (29% and 28%), rash (28% and 30%), alopecia (24% and 30%), erythema (19% and 32%), headache (19% and 19%), back pain (17% and 11%), skin exfoliation (15% and 29%), nausea (15% and 13%), musculoskeletal pain (14% and 13%), myalgia (12% and 9%), dry eye (10% and 22%), hypersensitivity (10% and 20%), peripheral edema (9% and 19%), and fatigue (5% and 11%).
- **Drug Interactions**

Table 1. Significant drug interactions for palovarotene

Precipitant Drug	Object Drug		Description
CYP3A4 inhibitors	palovarotene	↑	• Co-administration may increase the risk of palovarotene AEs. • Concomitant use of strong CYP3A4 inhibitors, and grapefruit, pomelo or juices containing these fruits should be avoided. • Concomitant use of a moderate CYP3A4 inhibitor should be avoided, if possible. If co-administration occurs, the palovarotene dose should be reduced by half when co-administered with moderate CYP3A inhibitors
CYP3A4 inducers	palovarotene	↓	• Co-administration may reduce the effectiveness of palovarotene. • Concomitant use should be avoided.
Vitamin A	palovarotene	↑	• Palovarotene belongs to the same pharmacological class as vitamin A; therefore, the use of both agents at the same time may lead to additive effects. • Concomitant administration of vitamin A in doses higher than the RDA and/or other oral retinoids must be avoided due to the risk of hypervitaminosis A.
Tetracyclines	palovarotene	*	• Systemic retinoid use has been associated with cases of benign intracranial hypertension (also called pseudotumor cerebri), some of which have involved the concomitant use of tetracyclines.

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			• Coadministration of palovarotene with tetracycline derivatives should be avoided.

* Should be avoided due to risk of serious AE.
↑ = Object drug increased. ↓ = Object drug decreased.

Dosage and administration

- The once-daily oral administration of palovarotene includes a chronic dose with dose increases for flare-up symptoms (ie, flare-up dose).
  - Adults and pediatric patients ≥ 14 years of age: The recommended dose is 5 mg orally once daily, with an increase in the event of FOP flare-up symptoms 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).
  - Pediatric patients < 14 years of age: Dosing is weight-adjusted for both daily and flare-up dosing. Recommended daily dosing ranges from 2.5 to 5 mg. Refer to Table 3.
- Flare-up treatment:
  - Flare-up treatment should be initiated at the onset of the first symptom indicative of an FOP flare-up or substantial high-risk traumatic event likely to lead to a flare-up (eg, surgery, intramuscular immunization, mandibular blocks for dental procedures, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses).
  - Symptoms of an FOP flare-up typically include but are not limited to localized pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness.
  - If during the course of flare-up treatment, the patient experiences marked worsening of the original flare-up site or another flare-up at a new location, the 12-week flare-up dosing should be restarted at the initial flare-up dosage (20 mg daily).
  - For flare-up symptoms that have not resolved at the end of the 12-week period, the Week 5 to 12 flare-up dose (10 mg daily) may be extended in 4-week intervals and continued until the flare-up symptoms resolve.

Table 3. Palovarotene weight-based dosage for females ≥ 8 years of age and males ≥ 10 years of age

Weight (kg)	Once-daily dosing (mg)	Week 1 to 4 flare-up dosage (mg)	Week 5 to 12 flare-up dosage (mg)
10 to 19.9	2.5	10	5
20 to 39.9	3	12.5	6
40 to 59.9	4	15	7.5
≥ 60	5	20	10

- The lower, weight-based dosing regimen for pediatric patients and limitation of treatment to pediatric patients who have achieved ≥ 80% of their final adult height (ie, approximately > 8 years of age in females and > 10 years of age in males) was implemented to mitigate the risk of PPC associated with palovarotene use in growing children (*FDA Sohonos integrated review 2023*).
- Palovarotene should be administered with food preferably at the same time each day.
  - Palovarotene capsules may be opened and the contents emptied on a teaspoon of soft food and administered immediately. If not administered immediately, it can be taken after a maximum of 1 hour after the sprinkling, provided it was maintained at room temperature and not exposed to direct sunlight.
- The dose of palovarotene should be reduced or modified for AEs or drug interactions, respectively, as appropriate.

Specific populations

- **Geriatrics**
  - Clinical studies of palovarotene did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
- **Pediatrics**
  - The safety and effectiveness of palovarotene for the treatment of FOP have been established in female pediatric patients ≥ 8 years of age and male pediatric patients ≥ 10 years of age.
  - Palovarotene is not recommended for use in females < 8 years of age and males < 10 years of age due to the potential for PPC. Clinical studies have shown that growing patients with open epiphyses are at risk of developing PPC when treated with palovarotene.
  - Bone Safety: In clinical studies with palovarotene, assessments of growth and bone safety in growing children included linear and knee height, femur and tibia length measured by WBCT, and hand/wrist and knee radiographs. PPC has been identified as an irreversible serious risk associated with palovarotene treatment. PPC was observed

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as early as 6 months after initiating therapy with the majority occurring at or after 12 months. In palovarotene-treated patients there was a trend of declining height Z-scores in adolescents, potentially due to a loss of linear height and/or increasing spinal deformity. The long-term effects on final height in patients with FOP treated with palovarotene have not been established.
  - Prior to initiation of treatment with palovarotene, all growing children should undergo baseline clinical and radiological assessments including but not limited to an assessment of skeletal maturity via hand/wrist and knee x-rays, standard growth curves and pubertal staging. Continued monitoring is recommended every 6 to 12 months until patients reach skeletal maturity (eg, epiphyseal closure) or final adult height.
- **Hepatic dysfunction**
  - The effect of moderate or severe hepatic impairment on the pharmacokinetics of palovarotene has not been evaluated. Palovarotene undergoes extensive hepatic metabolism. No dose adjustment is recommended in patients with mild (Child-Pugh A) hepatic impairment, while use of palovarotene in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is not recommended.
- **Pregnancy and nursing**
  - Palovarotene is contraindicated during pregnancy. Based on the findings in animal studies and class effects of retinoids, palovarotene can cause fetal harm when administered during pregnancy.
  - There are no available human data on palovarotene use in pregnant women. If pregnancy occurs during treatment with palovarotene, treatment should be discontinued immediately and the patient referred to an obstetrician/gynecologist or other specialist experienced in reproductive toxicity for further evaluation and counseling.
- **Nursing**
  - There are no data available on the presence of palovarotene or its main metabolites in either animal or human milk, the effects on the breastfed infant, or on milk production. Because of the potential for serious AEs in breastfed infants exposed to palovarotene through breastmilk, females should be advised that breastfeeding is not recommended during treatment with palovarotene, and for ≥ 1 month after the final dose of palovarotene.
- **Males of reproductive potential**
  - Palovarotene is present in semen (0.7 ng/mL) in amounts 100-fold lower than the maternal plasma exposure at the no observed adverse effect level (NOAEL) for fetal toxicity observed in animal studies. Administration of palovarotene to a male patient is considered unlikely to affect development of an embryo or fetus carried by a pregnant female sexual partner exposed to palovarotene via the patient's semen.

APPENDIX

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Definitions of Exploratory measures in the MOVE trial (*Pignolo et al 2023*)

Measure	Description
Cumulative analogue joint involvement scale (CAJIS) for FOP	• Evaluates range of motion (ROM) • Assessed by trained investigators in the MOVE trial • CAJIS measures range of motion across 12 joints (shoulder, elbow, wrist, hip, knee, and ankle on both right and left sides) and 3 body regions (jaw, cervical spine [neck], and thoraco-lumbar spine). • Each joint or region is assigned a score (0: > 90% range of motion; 1: 10 to 90% range of motion; 2: < 10% range of motion), with a maximum total score of 30
FOP physical function questionnaire (FOP-PFQ)	• Evaluates the change from baseline in physical function using age-appropriate forms • Includes questions about the ADLs and physical functioning. • Age-appropriate forms were self-completed by adults (≥ 15 years of age), with the option for self-completion for patients 8 to 14 years of age or completion by a parent acting in proxy for patients ≤ 14 years of age. • Results were expressed as a percentage of the worst possible score (0 to 100%).
Patient reported outcomes measurement information system (PROMIS) Global Health Scale	• Evaluates the change from baseline in physical and mental health using age-appropriate forms • Physical and mental health (for patients ≥ 15 years of age) or global health (< 15 years of age) were assessed using the PROMIS Global Health Scale and PROMIS Pediatric Global Health Scale, respectively. • The scales measure what patients are able to do and how they feel. • Scores were converted to T-scores for adult and pediatric scales; a value of 50 (SD, 10) represents the average for the general population in the U.S.

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