

A Narrative Review of Phase II and III Clinical Trials for the Pharmacological Treatment of Fibrodysplasia Ossificans Progressiva (FOP): Efficacy, Safety, and Challenges in Treatment Strategies

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Background: Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disorder marked by progressive heterotopic ossification (HO), causing severe disability and reduced life expectancy. Despite advancements in understanding its pathophysiology, effective treatments remain limited. Promising pharmacological approaches include retinoic acid receptor γ (RAR γ) agonists, such as palovarotene, and monoclonal antibodies targeting activin A, like garetosmab. However, the rarity of FOP complicates the generation of robust clinical evidence.

Methods: This narrative review analysed data from Phase II and III clinical trials on ClinicalTrials.gov, including completed and terminated interventional studies evaluating pharmacological treatments for FOP. Key trial details were systematically extracted and reviewed, including design, interventions, outcomes, and adverse events.

Results: Five trials met the inclusion criteria, focusing on palovarotene and garetosmab. Palovarotene significantly reduced HO progression, particularly during active disease phases or flare-ups. Garetosmab showed potential in preventing new HO lesions and reducing lesion activity. However, both treatments posed safety concerns, including premature epiphyseal fusion in younger patients (palovarotene) and systemic adverse events (garetosmab). Terminated trials revealed logistical and ethical challenges, such as recruitment difficulties, small sample sizes, and limitations of placebo-controlled designs.

Conclusion: Pharmacological advances, including palovarotene and garetosmab, show promise in managing FOP. Nevertheless, safety concerns and the complexities of clinical trial implementation highlight the need for innovative approaches to ensure effective and equitable treatments. Future research should prioritise long-term safety, efficacy, and patient-centred outcomes to improve FOP management.

Keywords: fibrodysplasia ossificans progressiva, heterotopic ossification, palovarotene, garetosmab, clinical trials, rare diseases

Introduction

Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare, debilitating genetic disorder marked by progressive heterotopic ossification (HO) of soft tissues, leading to severe disability and significantly reduced life expectancy.¹ This condition is caused by gain-of-function mutations in the ACVR1 gene, which encodes activin receptor-like kinase 2 (ALK2), a vital component of the bone morphogenetic protein (BMP) signalling pathway. These mutations lead to dysregulated BMP signalling and abnormal bone formation in muscles, tendons, and ligaments. FOP's hallmark features include congenital malformations of the great toes and episodic, painful flare-ups triggered by trauma, viral infections, or invasive procedures.^{2–4} As HO accumulates, it progressively immobilises joints, causes respiratory complications, and leads to substantial functional impairment, severely affecting the quality of life and psychosocial well-being.⁵ The extreme rarity of FOP is reflected in a global community of only 834 registered individuals, comprising 445 females (54%), 387 males (46%), and two unassigned cases, distributed across 67 countries on six continents.⁶ The prevalence of registered and confirmed cases varies significantly by region, with rates of approximately 0.65 per million in North America, 0.47 per million in Western Europe, 0.27 per million

in Latin America, 0.05 per million in Africa, and nearly 0.04 per million in the Asia-Pacific region.⁶ This scarcity poses substantial challenges for diagnosing and treating this ultra-rare condition. Many cases remain underdiagnosed or misdiagnosed, especially during the early stages, due to a lack of awareness among healthcare providers.⁷ Furthermore, the rarity of these conditions limits opportunities for clinical research, resulting in small patient cohorts, challenges in trial recruitment, and difficulties in establishing robust evidence for therapeutic interventions. These barriers contribute to the slow progress in understanding and managing this devastating disease.^{8,9} Despite these challenges, recent molecular and clinical research advancements have deepened understanding of FOP's pathophysiology, paving the way for innovative therapeutic approaches.¹⁰ Central to these advancements are targeted pharmacological strategies aimed at mitigating the underlying mechanisms of HO formation. Retinoic acid receptor γ (RAR γ) agonists, such as palovarotene, and monoclonal antibodies targeting activin A, such as garetosmab, represent two of the most promising therapeutic candidates.¹¹ Palovarotene inhibits endochondral ossification, the final mandatory process in the cascade of HO formation, while garetosmab disrupts activin A-mediated signalling pathways that drive ectopic bone development.¹¹ These therapies have demonstrated the potential to reduce HO progression, minimise flare-up frequency, and improve functional outcomes for FOP patients. In addition to these targeted therapies, other potential approaches under investigation for FOP management include the use of NSAIDs for symptomatic relief, immunomodulators such as tofacitinib, mTOR inhibitors like rapamycin, gene therapy strategies, and small-molecule inhibitors targeting key signalling pathways.^{12–14} However, their clinical development has not been without setbacks, with safety concerns such as premature epiphyseal fusion in children and systemic adverse events raising important questions about risk-benefit profiles.¹⁵ The heterogeneity of disease progression and patient responses to therapy further complicates the development of effective treatments for FOP. While some patients experience rapid and extensive HO development, others exhibit a slower disease trajectory, making it challenging to standardise treatment protocols.¹⁶ Moreover, the lack of validated biomarkers and reliable surrogate endpoints for measuring therapeutic efficacy adds complexity to the design of clinical trials and the interpretation of data. These limitations underscore the need for innovative trial methodologies, such as adaptive designs, to optimise the evaluation of emerging therapies in this rare disease context.¹⁷ Another significant consideration is the socio-economic burden of FOP on patients and their families. Beyond the physical and emotional toll, the high costs associated with disease management, including supportive care, rehabilitation, and potential pharmacological interventions, pose substantial financial challenges.¹⁸ As novel therapies progress through clinical trials, ensuring equitable access and affordability will be critical to translating scientific advancements into real-world benefits.¹⁹ Additionally, systemic strategies such as international funding collaborations, inclusion of rare disease therapies in national reimbursement schemes, and global advocacy initiatives are essential to improve equitable access to high-cost FOP treatments, especially in low-resource settings.²⁰ Current management strategies for FOP are largely supportive and aim to mitigate symptoms, prevent complications, and preserve mobility.²¹ Though promising, pharmacological interventions remain experimental and require rigorous evaluation to establish long-term efficacy and safety.²² Clinical trials, particularly those in Phases II and III, are essential for generating high-quality evidence to guide clinical decision-making. However, these trials face numerous obstacles, including limited patient populations, ethical considerations in placebo-controlled designs, and the logistical complexities of conducting multinational studies for a rare disease.²³ This narrative review synthesises data from Phase II and III clinical trials to evaluate the efficacy, safety, and challenges associated with pharmacological treatments for FOP. By analysing completed and terminated studies, this review aims to provide a comprehensive overview of the therapeutic landscape, identify critical gaps in knowledge, and highlight priorities for future research. The findings of this review will contribute to advancing the understanding of FOP treatment strategies and informing the development of optimised care protocols for this rare and challenging condition.

Methods

Data Source and Search Strategy

ClinicalTrials.gov was utilised as the primary data source for this review due to its comprehensive registry of clinical trials conducted across 221 countries. The registry provides detailed information on medical studies involving human participants, including interventional and observational trials. The search was conducted up to January 1, 2025, initially identifying 22 studies related to Fibrodysplasia Ossificans Progressiva (FOP). A systematic screening process was

applied to exclude trials that were incomplete or lacked available results. Trials that were terminated were included if they provided sufficient data for analysis. The inclusion criteria encompassed completed interventional studies across Phases II and III. Phase I and IV studies were omitted as no existing research satisfies the revised criteria. The review included studies involving children (0–17 years old), adults (18–64 years old), and older adults (65 years and above). Keywords such as “Fibrodysplasia Ossificans Progressiva”, “interventional studies”, and treatment-specific terms were employed to ensure comprehensive retrieval of relevant studies. The detailed review process is summarised in Figure 1.

Data Collection and Coding

Data collection involved systematically extracting key parameters from each eligible study, including the study title, status, brief summary, intervention (medication), primary outcome measures, age group, and study design. All data were manually coded to ensure precision and consistency in categorisation. This structured approach facilitated the identification and analysis of trends and outcomes across the included trials, allowing for a thorough evaluation of FOP management strategies.

Study Design Selection

To ensure methodological rigour, the review included only completed interventional studies with publicly available results on ClinicalTrials.gov. Trials that were terminated were included if they provided sufficient data for evaluation. To ensure a comprehensive evaluation of FOP treatment strategies, the inclusion criteria encompassed Phase II and III studies, covering a wide range of populations, including children, adults, and older adults. Observational and Phase I and IV studies were excluded due to the lack of eligible research meeting the specified criteria.

Screening and Inclusion Process

The initial search identified 22 studies. Nine studies were excluded because they were active but not recruiting, four because they were not interventional or observational, and four because they did not have available results. Ultimately, five studies met the inclusion criteria and were included in the analysis. The systematic screening process is illustrated in Figure 1.

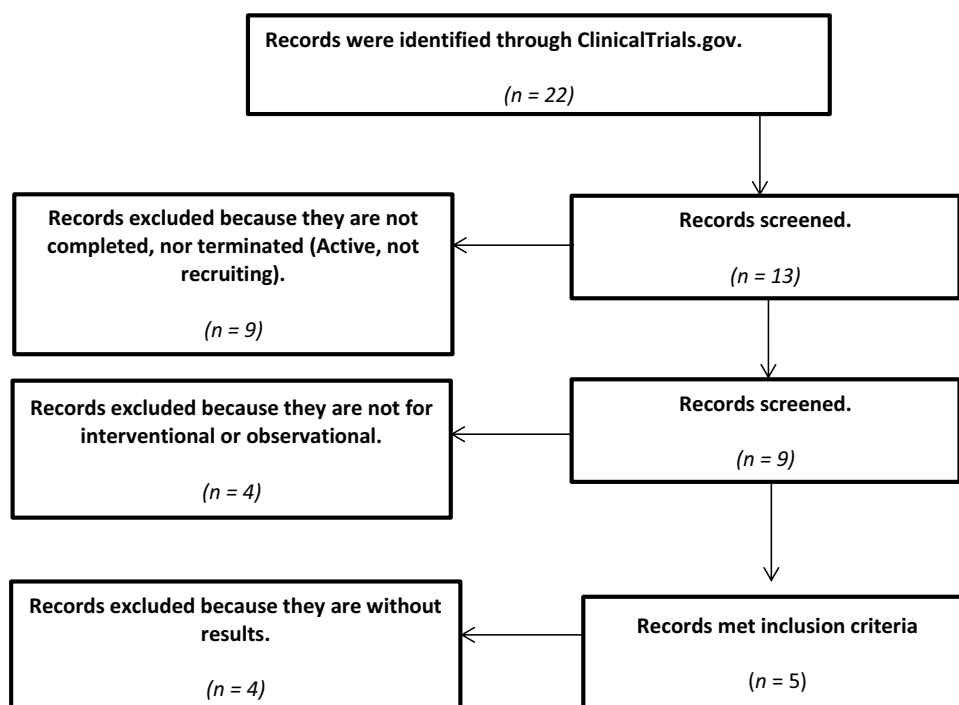


Figure 1 Summary of the review process. N.B.: Phases I and IV were omitted because no existing research satisfied the revised criteria.

Results

This review included five studies that satisfied the inclusion criteria after excluding others. These studies investigated pharmacological treatments for Fibrodysplasia Ossificans Progressiva (FOP) in Phase II and III clinical trials, addressing key challenges such as heterotopic ossification (HO) formation, flare-up management, and treatment safety. Collectively, the studies evaluated novel therapies, such as palovarotene and garetosmab, providing evidence of their potential to reduce HO progression and improve patient outcomes; however, adverse events remain a critical consideration. Terminated trials highlighted feasibility issues, emphasising the need for optimised trial designs and participant recruitment strategies. Including both completed and terminated trials provided a well-rounded understanding of the therapeutic landscape and the complexities of treating this rare disorder.

Table 1 shows that the included trials primarily focused on the safety, tolerability, and efficacy of treatments targeting HO and flare-ups. Garetosmab was evaluated through a placebo-controlled, parallel-group design, demonstrating a measurable reduction in HO lesion volume, particularly during the active phases of the disease. Palovarotene, a key investigational drug, was studied across multiple trials with various dosing regimens, showcasing its potential in both episodic and chronic treatment strategies for FOP patients. The studies incorporated diverse populations, spanning children, adults, and older adults, and were conducted across multiple countries, thereby enhancing the generalizability and applicability of their findings. Trial designs included randomised, open-label, and placebo-controlled methodologies, with outcomes centred on critical measures such as HO lesion activity, flare-up prevention, and adverse event profiles. These trials highlighted the critical role of precise dosing regimens and early intervention in optimising therapeutic outcomes.

Table 2 summarises the comparative results of the trials, revealing consistent trends in the efficacy of palovarotene and garetosmab in reducing new HO formation and managing symptomatic flare-ups. Palovarotene trials demonstrated significant reductions in HO volume during chronic and flare-up phases, with efficacy observed across various age groups. However,

Table 1 Overview of Clinical Trial Data on ClinicalTrials.gov as of 1 January 2025

	Study Title	Status	Brief Summary	Intervention	Primary Outcome	Age Group	Design	Locations
1	A Study to Examine the Safety, Tolerability and Effects on Abnormal Bone Formation of REGN2477 in Patients with FOP	Completed	Evaluated the safety, tolerability, and efficacy of garetosmab in FOP over placebo-controlled, open-label, and follow-up phases.	Garetosmab and placebo	TEAEs, lesion activity (PET), HO lesion volume (CT), new HO detection (CT)	Adult	Randomised, quadruple-masked, parallel-group	US, Canada, France, Italy, Netherlands, Poland, Spain, UK
2	In-Home Evaluation of Episodic Administration of Palovarotene in FOP Subjects	Terminated	Evaluated long-term safety and efficacy of palovarotene as RAR γ agonist in FOP patients post-PVO-1A-202 trial.	Palovarotene	TEAEs, including SAEs, post-treatment	Child, Adult, Older Adult	Single-group, open-label	US
3	An Open-Label Extension Study of Palovarotene Treatment in FOP	Completed	Assessed the effectiveness of palovarotene dosing regimens in preventing new HO formation in FOP.	Palovarotene	Percentage of flare-ups with minimal new HO; annualised HO volume change	Child, Adult, Older Adult	Non-randomised, single-group, open-label	US, Argentina, Australia, France, UK
4	An Efficacy and Safety Study of Palovarotene to Treat Preosseous Flare-ups in FOP Subjects	Completed	Evaluated palovarotene's ability to prevent HO during and post flare-ups in FOP.	Palovarotene and placebo	Percentage responders with minimal/no new HO	Child, Adult, Older Adult	Randomised, triple-masked, parallel-group	US, France, UK
5	An Efficacy and Safety Study of Palovarotene for the Treatment of FOP	Completed	Phase 3 study assessing efficacy and safety of palovarotene in reducing new HO in FOP over 24 months using low-dose CT; focused on annualised HO volume and related safety outcomes.	Palovarotene	Annualised new HO volume (CT), safety outcomes	Child, Adult, Older Adult	Single-group, open-label	US, Argentina, Australia, Brazil, Canada, France, Italy, Japan, Spain, Sweden, UK

Table 2 Comparative Results of Clinical Trials Investigating Pharmacological Therapies for FOP

	Study Title	Study Design	Treatment	Enrollment	Adverse Events	Key Findings
1	A Study to Examine the Safety, Tolerability, and Effects on Abnormal Bone Formation of REGN2477 in Patients with FOP (LUMINA-1)	Period 1: Double-blind, placebo-controlled; Period 2: Open-label; Period 3: Follow-up	Garetosmab 10 mg/kg infusion every 4 weeks	44 (24 placebo, 20 garetosmab)	100% AEs (nasopharyngitis, injection site abscesses); 20% severe AEs (infections requiring medical intervention)	Garetosmab reduced lesion activity and HO formation; however, infection risks warrant ongoing monitoring.
2	In-Home Evaluation of Episodic Administration of Palovarotene in FOP Subjects	Single-group, open-label	Palovarotene 10 mg daily (flare-ups), reduced to 5 mg	6	100% AEs (tinnitus, eczema); 25% severe AEs (myalgia)	Terminated early due to small sample size; highlighted frequent side effects but insufficient data.
3	An Open-Label Extension Study of Palovarotene Treatment in FOP (PVO-1A-202)	Open-label extension study, multiple parts	Palovarotene chronic 5 mg daily; 20/10 mg during flare-ups	58	Common AEs: dry skin (83%), alopecia; severe AEs: adrenal insufficiency (2%), pneumonia (9%)	Long-term palovarotene reduced HO volume during flare-ups; however, safety concerns necessitate ongoing monitoring.
4	An Efficacy and Safety Study of Palovarotene to Treat Preosseous Flare-ups in FOP Subjects	Randomised, double-blind, placebo-controlled	Palovarotene 10/5 mg or 5/2.5 mg during flare-ups	40	9–11% severe AEs; mild AEs: dry skin, headache, arthralgia	Palovarotene reduced flare-up duration and HO formation, particularly when used early.
5	An Efficacy and Safety Study of Palovarotene for the Treatment of FOP	Part A: Main study; Part B: 24-month extension; Part C: 2-Year follow-up (skeletally immature)	Palovarotene 5 mg daily or 20/10 mg during flare-ups	107 (49 completed, 58 dropped out)	98% AEs (dry skin, joint pain, premature epiphyseal fusion)	Palovarotene reduced HO and flare-ups, particularly in skeletally mature participants; the safety profile is acceptable, but caution is advised in younger patients.

safety concerns, such as dry skin, joint pain, premature epiphyseal fusion, and gastrointestinal symptoms, were frequently reported, emphasising the need for improved monitoring and supportive care during treatment. Garetosmab showed potential in reducing lesion activity and preventing new HO formations. However, serious adverse events, including increased infection rates and other systemic complications, highlighted areas requiring further research and safety refinement. Terminated trials provided valuable insights into the challenges of small sample sizes, adverse event management, and the complexities of recruiting patients for studies of rare diseases, which continue to hinder progress in this field.

Discussion

Main Findings

This narrative review highlights the progress and challenges in Phase II and III trials of pharmacological treatments for FOP. Palovarotene and garetosmab have shown promise in reducing heterotopic ossification and managing flare-ups; however, safety concerns, such as premature epiphyseal fusion and infection risks, remain significant. The inclusion of terminated trials highlights the challenges in recruitment and study design for rare diseases, underscoring the need for innovative approaches to advance the management of FOP.

Main Discussion

Fibrodysplasia Ossificans Progressiva (FOP) presents a profound challenge in rare disease management due to its severe clinical presentation and the lack of curative treatment options.²³ This review consolidates findings from Phase II and III trials to provide a comprehensive understanding of emerging pharmacological interventions. Palovarotene, a RAR γ agonist, has demonstrated the potential to significantly reduce heterotopic ossification (HO) by modulating the retinoic acid pathway, with its efficacy most evident when administered during active flare-ups.^{24,25} However, associated risks, including premature epiphyseal fusion and other dose-dependent adverse events in pediatric populations, underscore the need to balance therapeutic benefits with safety considerations. Similarly, garetosmab, a monoclonal antibody targeting

activin A, has shown promise in preventing new HO lesions and reducing lesion activity, aligning with disrupted signalling pathways observed in FOP.^{25,26} However, the increased risk of infections and systemic complications observed with garetosmab highlights the importance of cautious use and monitoring in clinical practice. Given the distinct safety profiles of these therapies, implementing tailored monitoring strategies is essential. Palovarotene requires periodic radiographic assessments and growth tracking in younger patients to detect early epiphyseal closure, whereas garetosmab necessitates routine clinical evaluations to identify and promptly manage infection risks.^{24,26} Emphasising flare-up prevention is critical in FOP management, with prophylactic anti-inflammatory approaches using agents such as anakinra, canakinumab, and tofacitinib being explored to reduce new lesion formation and improve long-term outcomes.²⁷ Terminated trials, despite their limitations, have provided valuable insights into the logistical and methodological challenges of conducting trials for rare diseases, including recruitment difficulties, small sample sizes, and ethical considerations associated with placebo-controlled designs. These challenges highlight the need for innovative trial designs, expanded international collaboration, and the use of patient registries to enhance feasibility and data quality. Variability in trial designs, dosing regimens, and patient demographics continues to pose challenges for direct comparisons of interventions. The diversity in primary and secondary endpoints, from HO volume reduction to flare-up prevention and adverse event profiles, reflects evolving management priorities in FOP. This underscores the necessity for standardised outcome measures and validated biomarkers to facilitate cross-study comparisons and improve data robustness. The global nature of FOP clinical trials enhances generalisability but introduces variability in healthcare infrastructure, patient access, and adherence, requiring coordinated efforts among stakeholders to ensure equitable treatment availability.²⁸ It is essential to note that while multiple trials have evaluated palovarotene, only one has examined garetosmab; therefore, the comparisons presented in Table 1 aim to illustrate emerging therapeutic trends rather than directly comparing the efficacy of these treatments. This context should be considered when interpreting relative efficacy and safety findings. Lastly, patient-centred outcomes, including quality of life, mobility, and psychosocial well-being, are critical for assessing the actual impact of therapies and should be integrated into future clinical trial designs to align treatment goals with patient needs.²⁹ Additionally, the high cost of novel FOP treatments highlights the need to develop cost-effective strategies, such as value-based pricing models and patient assistance programs, to ensure that advances in FOP management translate into accessible, real-world benefits.¹⁸

Strengths and Limitations

This review's systematic approach to identifying and analysing Phase II and III trials ensures a robust evaluation of current pharmacological strategies for FOP. The inclusion of diverse populations across multiple countries enhances the generalizability of findings. Moreover, the analysis of terminated trials adds depth to understanding feasibility challenges in rare disease research. However, the review is limited by its reliance on publicly available data from ClinicalTrials.gov, which may lack detailed information on unpublished studies or comprehensive adverse event profiles. Additionally, excluding Phase I and IV studies narrows the scope, potentially overlooking early-stage safety data and long-term outcomes. Excluding observational and Phase I/IV studies may limit insights into early-stage safety profiles and long-term outcomes; however, this approach ensures a focused evaluation of efficacy and safety within rigorously controlled Phase II and III trials, strengthening the reliability of the conclusions drawn in this review. Finally, the heterogeneity in study designs and outcome measures complicates direct comparisons of trials.

Conclusion

This review highlights the progress in developing treatments for FOP, while underscoring the significant challenges that remain. Palovarotene and garetosmab offer promising therapeutic options, but their safety concerns and feasibility issues necessitate further investigation. Addressing these challenges through innovative trial designs, enhanced safety monitoring, and international collaboration is essential for advancing FOP management and improving patient outcomes. Future research should prioritise long-term efficacy, patient-centred outcomes, and strategies to mitigate adverse events, paving the way for optimised therapeutic interventions.

Data Sharing Statement

The data is publicly available at clinicaltrials.gov.

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