

Alan Shields,¹ Monica Brova,¹ Megan McLafferty,¹ Daniella Olonilua,¹ Sara Green,² Elaine Böing,³ Negar Karimian,³ Roger Lamoureux¹

¹Adelphi Values, Boston, MA, USA; ²Blueprint Medicines, Cambridge, MA, USA; ³Ipsen, Cambridge, MA, USA
Presenting author: Monica Brova

Background

- Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic disorder that is characterized by progressive, cumulative, and irreversible heterotopic ossification (HO), the transformation of soft and connective tissues into bone.^{1,2}
- HO accumulation occurs chronically and episodically in FOP but is more marked around FOP flare-ups. HO accumulation leads to the loss of joint function, complete immobility, and respiratory and thoracic complications often resulting in death.^{3,4}
- Despite the emergence of new therapies (e.g., palovarotene),^{5,6} little research has focused on the patient experience of FOP leaving a gap in our understanding of what constitutes a positive therapeutic outcome from the patient perspective.

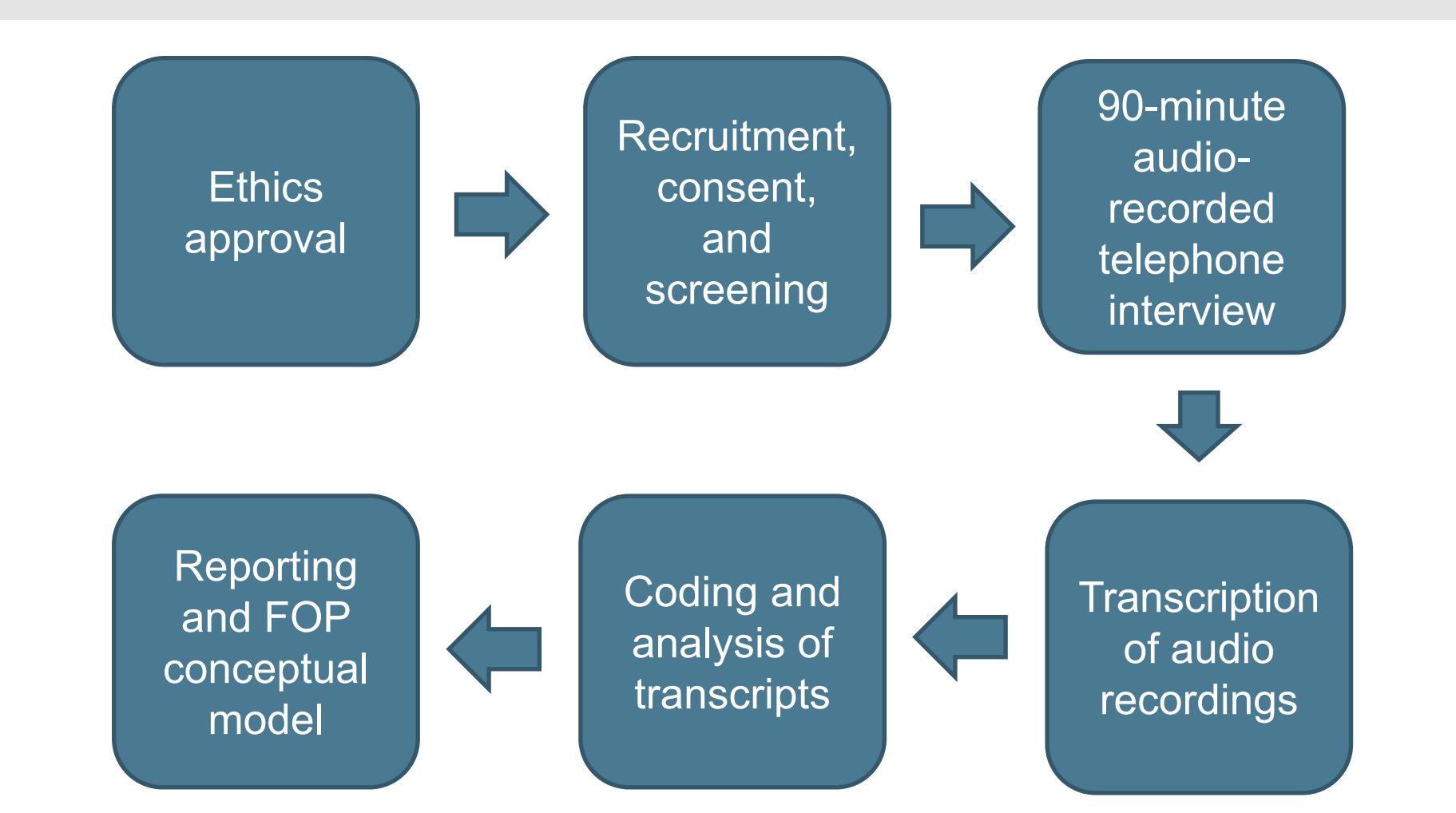
Objective

The purpose of the present study was to improve understanding of the experience of FOP and FOP flare-ups from the perspective of adolescents and adults with the condition, supporting the development of the FOP-FLare EXperience (FOP-FLEX) questionnaire, a novel assessment of FOP and FOP-flare-up signs, symptoms, and impacts.

Methods

- Participants were recruited through the International Fibrodysplasia Ossificans Progressiva Association (IFOPA).
- Eligible participants were ≥12 years of age, resided in the United States (US), were able to speak and comprehend English, and had a genetically confirmed diagnosis of FOP.
- During interviews, participants were asked about the signs and symptoms of FOP and FOP flare-ups, and their impacts on participants' lives.
- See (Figure 1) for an interview process schematic.

Figure 1. Interview process schematic



Results

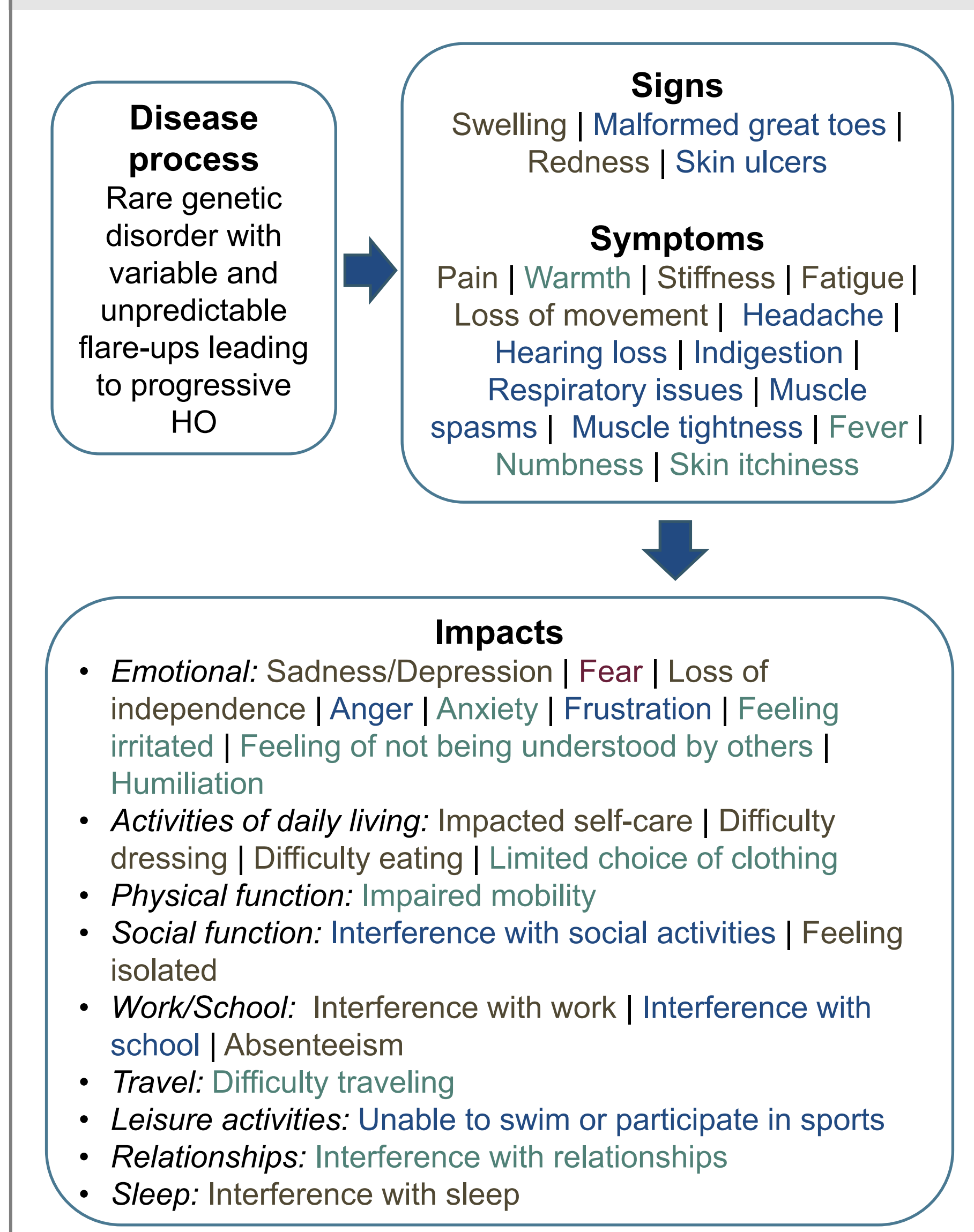
- Fifty-four individuals expressed interest in study participation. Of these, 38 did not meet screening criteria (e.g., resided outside of US, did not speak English, were unable to provide confirmation of diagnosis, were lost to follow-up).
- The remaining 12 individuals were enrolled into the interview study from 11 different US states, were mostly female (n=9, 75%) and white (n=11, 97.1%), and ranged from 12-61 years old (Mean=34.7, SD=14.7), including 1 adolescent (12 years old).
- Self-reported FOP was very mild (n=1, 8.3%), mild (n=2, 16.7%), moderate (n=3, 25.0%), severe (n=3, 25.0%), or very severe (n=3, 25.0%).
- Participants spontaneously reported experiencing 18 signs and symptoms of FOP and FOP flare-ups, with pain, swelling, redness, warmth, and stiffness being most common (Table 1). 9 aspects of their lives were impacted by FOP and FOP flare-ups (Table 2).
- Participants' reports were organized into a patient-centric conceptual model, summarizing the signs, symptoms, and impacts of FOP and FOP flare-ups (Figure 2 and Figure 3).
- Participants reported that FOP flare-ups:
 - Were variable and unpredictable
 - Ranged from days to weeks in duration
 - Could occur in more than one location at the same time
 - Usually occurred around major joints

Table 1. Signs and symptoms of FOP and flare-ups reported by participants

Sign or symptom	Frequency of report (N=12) n, %	Description based on participant reports
Pain*	12, 100.0	Dull, aching, cramping, shooting
Swelling*	11, 91.7	Tight skin hard to the touch
Malformed great toes	6, 50.0	Great toes turned inward
Redness*	6, 50.0	Localized, rash-like
Warmth*	6, 50.0	Skin warm to the touch
Stiffness*	5, 41.7	Tightness or rigidity limiting range of motion
Fatigue*	3, 25.0	Interfering with work and daily activities
Loss of movement	3, 25.0	Part of body stuck and unable to move
Respiratory issues	2, 16.7	Wheezy breathing
Fever	1, 8.3	No description provided
Headache	1, 8.3	Due to extra bone growth in neck
Hearing loss	1, 8.3	No description provided
Indigestion	1, 8.3	Due to needing to stand while eating
Skin itchiness	1, 8.3	Chronic itching at location of flare-up
Muscle spasms	1, 8.3	Due to transferring to and from wheelchair
Muscle tightness	1, 8.3	Muscles "tight as a rock"
Numbness	1, 8.3	Due to nerve compression
Skin ulcers	1, 8.3	Due to pressure between limbs due to joint immobility

*Symptoms measured by the FOP-FLEX questionnaire

Figure 2. Patient-centered FOP conceptual model



Reported as due to FOP but not experienced during an FOP flare-up(s)
Reported as occurring only during FOP flare-up(s)
Reported as occurring both during and/or outside of an FOP flare-up(s)

Results (Continued)

- Participants' reports suggested that pain, redness, stiffness, swelling, and skin warmth constituted the core signs and symptoms of FOP flare-ups and often presented in combination and with greater severity than outside of flare-ups.
- Participants reported that flare-up symptoms were generally noticeable based on severity and localized symptom experiences, however, the time taken to recognize flare-up symptoms varied from "right away" to "up to five days" after symptom onset.

Table 2. Impacts of FOP and flare-ups reported by participants

Type of impact	Frequency of report (N=12) n, %	Specific impacts described by participants
Emotional function*	11, 91.7	Sadness, fear, anger, anxiety, frustration, irritation, humiliation; loss of independence.
Activities of daily living*	11, 91.7	Difficulty with self-care, dressing, eating, and other daily activities.
Physical function	11, 91.7	Impaired mobility
Social function*	4, 25.0	Inability to see friends, isolation, missing holiday events, stares from other people
Work/School	4, 25.0	Interference with work or school; absenteeism
Travel	2, 16.7	Unable to drive; need assistance transferring in and out of car
Leisure activities*	1, 8.3	Unable to swim or participate in sports
Relationships	1, 8.3	Experienced when first confined to wheelchair
Sleep	1, 8.3	Interference with sleep due to pain from bone protrusions

*Impacts measured by the FOP-FLEX questionnaire

Figure 3. Participant quotations about FOP symptoms and impacts

My stamina is shot. I'm a pretty hardy and very strong person, but this disease has robbed me of my stamina which, needless to say, is very upsetting.
61-year-old female

I'm not able to see my friends as much because when I'm in pain I will usually be lying down with an ice pack or just try not to move as much, and I won't be able to go to school. And I won't be able to go outside and play.
12-year-old female

... I went from totally independent to... I couldn't even brush my own teeth... I mean, I can't shower myself. I can't get dressed, go to the bathroom, drive.
30-year-old female

CONCLUSIONS

- Interview results support previous findings that FOP is disabling, emotionally challenging, and severely impacts physical function, self-care, and daily and social activities.⁷ These results can help researchers identify outcomes for FOP treatment development programs.
- These interviews also served as the evidentiary basis for the creation of the FOP-FLEX questionnaire, which was subsequently modified into the FOP-FLEX-Revised (FOP-FLEX-R) questionnaire.
- One potential limitation of the present study is its small sample size. However, given the ultra-rarity of the disease, and the consistency of results with other research findings among patients with FOP,⁷ researchers can have confidence in the veracity of the results presented herein.

Abbreviations

FOP: Fibrodysplasia ossificans progressiva; FOP-FLEX: Fibrodysplasia Ossificans Progressiva - FLare EXperience; HO: heterotopic ossification; IFOPA: International Fibrodysplasia Ossificans Progressiva Association; US: United States.

References

- Pignolo RJ, et al. *PER*. 2013;10 Suppl 2:437-448.
- Pignolo RJ, et al. *J Bone Miner Res*. 2016;31(3):650-6.
- Pignolo RJ, Kaplan FS. *Bone*. 2018;109:111-114.
- Taslimi R, et al. *Clin Rheumatol*. 2015;34(2):379-384.
- Canada's Drug and Health Technology Agency. Palovarotene. Available at: <https://www.cdth.ca/palovarotene>. August 1, 2023. Last accessed September 20, 2023.
- United States Food and Drug Administration. Prescribing information for SOHONOS™ (palovarotene). Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/215559s000lbl.pdf. August 2023. Last accessed September 13, 2023.
- Markowitz JT et al. *Adv Ther*. 2022;39(6):2796-2805.

Author Contributions Substantial contributions to study conception/design or acquisition, analysis, or interpretation of data: AS, MB, MM, DO, SG. Drafting of the publication or revising it critically for important intellectual content: AS, MB, MM, DO, SG, EB, NK, RL. Final approval of the publication: AS, MB, MM, DO, SG, EB, NK, RL.

Disclosures AS, MB, DO, RL: employees of Adelphi Values, which was compensated by Blueprint Medicines for conducting the research reported here, and by Ipsen for the creation of this poster. EB: employee and shareholder of Ipsen; NK: employee of Ipsen. MM was employed by Adelphi Values at the time the research reported here was conducted. SG was employed by Blueprint Medicines at the time the research reported here was conducted.

Acknowledgements The authors thank all patients involved in the study. The authors also thank the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) for identifying potential participants for the study; Samantha Power, Masami Tabata-Kelly, and Iyar Mazar of Adelphi Values who assisted in conducting the original research.

Medical Writing Support The authors thank Nikita Murlil and Janette Santos of Adelphi Values for providing writing and editorial support, which was sponsored by Ipsen in accordance with Good Publication Practice Guidelines.



For further information, please send your question(s) to Monica Brova (monica.brova@adelphi-values.com)



To download the poster, please scan the Quick Response (QR) code



Copies of this poster obtained through QR Code are for personal use only and may not be reproduced without written permission from the authors.