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ARTICLE

The natural history of fibrodysplasia ossificans progressiva: A prospective, global 36-month study

Robert J. Pignolo[1,*], Geneviève Baujat[2], Matthew A. Brown[3,4], Carmen De Cunto[5], Edward C. Hsiao[6], Richard Keen[7], Mona Al Mukaddam[8], Kim-Hanh Le Quan Sang[2], Amy Wilson[9], Rose Marino[9], Andrew Strahs[9], Frederick S. Kaplan[8,*]

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ABSTRACT

Purpose: We report the first prospective, international, natural history study of the ultra-rare genetic disorder fibrodysplasia ossificans progressiva (FOP). FOP is characterized by painful, recurrent flare-ups, and disabling, cumulative heterotopic ossification (HO) in soft tissues.
Methods: Individuals aged ≤65 years with classical FOP ($ACVR1^{R206H}$ variant) were assessed at baseline and over 36 months.
Results: In total, 114 individuals participated; 33 completed the study (mean follow up: 26.8 months). Median age was 15.0 (range: 4-56) years; 54.4% were male. During the study, 82 (71.9%) individuals reported 229 flare-ups (upper back: 17.9%, hip: 14.8%, shoulder: 10.9%). After 84 days, 14 of 52 (26.9%) imaged flare-ups had new HO at the flare-up site (mean new HO volume: 28.8×10^3 mm^3). Mean baseline low-dose whole-body computed tomography (excluding head) HO volume was 314.4×10^3 mm^3; lowest at 2 to <8 years (68.8×10^3 mm^3) and increasing by age (25-65 years: 575.2×10^3 mm^3). The mean annualized volume of new HO was 23.6×10^3 mm^3/year; highest at 8 to <15 and 15 to <25 years (21.9×10^3 and 41.5×10^3 mm^3/year, respectively) and lowest at 25 to 65 years (4.6×10^3 mm^3/year).
Conclusion: Results from individuals receiving standard care for up to 3 years in this natural history study show the debilitating effect and progressive nature of FOP cross-sectionally and longitudinally, with greatest progression during childhood and early adulthood.

Introduction

Comprehensive natural history studies (NHSs) are essential in understanding conditions with high unmet medical needs, especially rare conditions; they help describe the natural course of a disease, explore diagnoses or monitoring techniques, identify potential biomarkers, develop outcome measures, and connect centers of expertise.[1,2] The ultra-rare autosomal dominant genetic disorder fibrodysplasia ossificans progressiva (FOP; OMIM 135100)[3] has an estimated global prevalence of 0.61 to 1.43 per million individuals.[4-6] Although studies investigating the natural progression of

*Correspondence and requests for materials should be addressed to Robert J. Pignolo, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. *E-mail address:* pignolo.robert@mayo.edu OR Frederick S. Kaplan, Department of Orthopaedic Surgery, Perelman School of Medicine, The University of Pennsylvania, Penn Musculoskeletal Center – Suite 600, 3737 Market Street, Philadelphia, PA 19104. *E-mail address:* Frederick.Kaplan@pennmedicine.upenn.edu

Affiliations are at the end of the document.

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FOP have provided a general description of the disorder,[7-13] no study to date has provided a detailed, prospective, protocol-specified, longitudinal evaluation of FOP.

FOP is caused by a somatic de novo missense variant in the activin A receptor type 1 gene (*ACVR1*, also known as activin receptor-like kinase-2 [*ALK2*]), which encodes a receptor in the bone morphogenetic protein (BMP) signaling pathway.[14,15] The most common *ACVR1* variant observed in approximately 97% of patients with FOP is R206H (c.617G>A; $ACVR1^{R206H}$) in the glycine-serine activation domain of the gene.[16,17] This pathogenic variant increases BMP pathway signaling, which directs mesenchymal stem cells to chondrogenic and osteogenic fates, resulting in heterotopic ossification (HO) in muscles, tendons, ligaments, fascia, and aponeuroses.[14] HO is often associated with painful, recurrent episodes of soft tissue swelling, called flare-ups,[3,18,19] occurring more frequently in the neck, trunk, and upper limbs before age 8 years and more frequently in the lower limbs thereafter.[11] Until recently, there were no effective treatments to prevent HO in FOP. Therapeutic approaches focused on symptom management and flare-up prevention.[18]

Recurrent episodes of HO start in childhood resulting in ribbons, sheets, and plates of heterotopic bone throughout the body and across joints, progressively restricting movement and shortening the lifespan of individuals with FOP.[3,4,16] Although there is variability in the rate of disease progression,[11] once ossification occurs, it is permanent. Consequently, disability is cumulative. Most patients become immobilized and need to use a wheelchair by their 20s and require assistance to perform activities of daily living.[3,20] Early progressive developmental arthropathy of numerous diarthrodial joints is common.[21] Life-limiting complications of FOP include severe weight loss due to jaw ankylosis, thoracic insufficiency due to ankylosis of the costovertebral joints, ossification of the intercostal and paravertebral muscles, and progressive spinal deformity.[3] Thoracic insufficiency commonly causes complications such as pneumonia and right-sided heart failure, leading to markedly shortened life expectancy.[9,22] FOP also has features of accelerated aging.[23]

To further understand FOP, an NHS was designed to follow the progression of FOP over 3 years in a representative cohort of patients. Analysis of baseline data from this NHS identified new HO as a clinically meaningful end point, enabling clinicians to measure the progression of FOP over time;[24] in this article, we present the final 36-month data.

Materials and Methods

Study design and participating individuals

Males and females aged 2 to ≤65 years with clinically diagnosed FOP carrying $ACVR1^{R206H}$ were eligible. Individuals who had participated in an interventional clinical research study within 4 weeks before enrollment were excluded. All participants underwent baseline examination to confirm eligibility and disease status. Race was self-reported by study participants, and race categories were predefined by the investigators. Individuals with FOP learned about this study through physicians, patient support groups, clinicaltrials.gov, or other means. Written informed consent/assent was provided by all participants or by parents/legal guardians for those aged <18 years.

Individuals were enrolled in a prospective, longitudinal (36-month), global, non-interventional, NHS (NCT02322255) conducted at 8 international sites (Supplement 1A). All sites obtained approval from local institutional review boards and complied with all applicable national, ethics, and regulatory guidelines. The study was conducted according to the guidelines of Good Clinical Practice and the International Conference on Harmonization, and was in full compliance with the Declaration of Helsinki and its 2013 amendment.[25]

Individuals were enrolled between December 2014 and December 2016, and the final end-of-study (EOS) follow up was completed in April 2020. After enrollment, individuals were assessed at clinic visits on study Day 1 and Months 12, 24, and 36 (±3 weeks), with evaluation by telephone contact at weeks 1 to 3 and at Months 6, 18, and 30. In October 2017, the protocol was amended so that telephone contacts were every 3 months after study Day 1. Individuals reported flare-ups by calling the study site, followed by weekly telephone contact until flare-up resolution.

Assessments and end points

Flare-up incidence and progression of HO

Individuals experiencing a flare-up (presence of ≥2 of the 6 most common symptoms: pain, swelling, redness, warmth, stiffness, decreased range of motion [ROM])[11] underwent low-dose computed tomography and/or x-ray scans at the flare-up site on flare-up Days 1 (the day the individual presented to the site with a flare-up [or within 14 days of the flare-up/suspected flare-up]) and 84 to evaluate the extent of HO at the flare-up site. Individuals underwent a magnetic resonance imaging scan (or ultrasound if magnetic resonance imaging was not possible) to examine soft tissue swelling at the flare-up site.

HO in the body, excluding the head, was assessed by low-dose whole-body computed tomography (WBCT) scans at baseline and Months 12, 24, and 36/EOS. All WBCT images were obtained using standardized procedures established by a central imaging laboratory. Two independent musculoskeletal radiologists used these procedures to review all WBCT images and determine the presence/absence of HO across several body regions (upper-torso [including, neck, shoulders, back, chest], mid-torso, arm, hip, lower leg). HO was distinguished from skeletal bone and osteochondromas in the WBCT reads. HO volume was determined by segmenting each axial slice using

semiautomated seed-growing and shrink-wrap algorithms whenever possible. When not possible, manual contouring and nudging steps (Alice v9.0, PAREXEL Informatics) were used to optimize HO segmentations. HO volumes were calculated separately for each body region and summed for total body volume.

At baseline, after completing individual reads, the 2 readers reviewed the WBCT together and produced consensus results. Month 12, 24, and 36/EOS follow-up scans were compared with baseline, with qualitative assessment for new HO by region. In cases with no new HO, no re-measurement was performed, and baseline HO volume was used for the post-baseline timepoint. If new HO was determined, HO volume was remeasured and change from baseline was determined. An adjudicating reader made a third, separate assessment if there was disagreement on the presence/absence of new HO relative to the first timepoint or if the difference between the 2 new measurements was $>25.0 \times 10^3$ mm^3 ($>10.0 \times 10^3$ mm^3 if >20% of the total new HO volume). The adjudicator read was recorded in these instances.

Functional assessments and patient-reported outcomes

Functional assessments of each individual's ROM were evaluated using the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP.[26] Physical function was evaluated using the FOP Physical Function Questionnaire (FOP-PFQ).[27] Age-appropriate forms of the FOP-PFQ were completed by adults (aged ≥15 years), with the option for self-completion for individuals aged 8 to 14 years or completion by a parent acting in proxy for any individual aged ≤14 years. Because total scores vary across the age-appropriate FOP-PFQ instruments, analysis was performed on transformed scores expressed as a percentage of the worst possible score (higher percentages indicate worse functioning). Patient Reported Outcome Measure Information System (PROMIS) Global Physical and Mental Health Scales were used to assess the physical and mental health of patients aged ≥15 years;[28] the PROMIS Pediatric Global Health Scale was used for patients aged ≤14 years.[29] Scores were converted to T-scores such that a value of 50 represents the general population average in the United States and a score of ±10 indicates ±1 SD from the mean. Higher T-scores indicate better physical/mental health.

Pulmonary function tests (PFTs), including forced vital capacity (FVC) assessed by spirometry, were conducted during clinic visits. The use of aids, assistive devices, and adaptations (AADAs) was assessed using the International FOP Association's list of AADAs that may be used by patients with FOP.[30,31] Prior medications were defined as medications taken by participants upon, or within 30 days before, study entry. Concomitant medications initiated during the study period were recorded by telephone contact or clinic visits. Medications taken during flare-ups were recorded during telephone contact assessing flare-up progression or during clinic visits.

Medical conditions and adverse events

Each individual underwent a medical history assessment at baseline to identify existing conditions. Existing and new medical conditions were monitored during the study. Adverse events (AEs) and serious AEs were also recorded, assessed for severity, and followed up by the investigator until resolved or stabilized or until the end of the study. Suicidal ideation was assessed by the Columbia Suicide Severity Rating Scale. Any individual experiencing type 4 or 5 ideation or any suicidal behavior was referred for appropriate evaluation and treatment.

Statistical analysis

Sample size

A sample size of approximately 100 patients was based on realistic enrollment projections. Total study enrollment consisted of ≥10 individuals/age group in the following categories: 2 to <8, 8 to <15, 15 to <25, and 25 to ≤65 years.

Analyses

These data document progression of FOP over the planned 36 months, using descriptive statistics by timepoint and by age group when appropriate. Observed values as well as changes from baseline are presented. The full analysis set (FAS) included all individuals with baseline data. The FAS was used for incidence of all flare-ups, mean functional assessment scores, AADA and medication assessment, and medical events. The progression analysis set included individuals in the FAS who provided data for ≥1 post-baseline timepoint and was used for HO assessments at baseline and progression over time. The imaged flare-up analysis set, used to assess the incidence and volume of HO associated with flare-ups, included individuals in the FAS who had ≥1 imaged flare-up assessment. All statistical analyses were performed using SAS version 9.4 or later.

Results

Disposition

Overall, 114 individuals enrolled in the FAS at baseline, of whom 33 completed the 3-year study; 81 individuals discontinued for reasons including enrollment in an interventional study ($n = 66$), withdrawal of consent ($n = 9$), noncompliance ($n = 2$), loss to follow up ($n = 1$), death ($n = 1$), or other reasons ($n = 2$; Supplement 1B).

Demographics

Participant baseline demographics and flare-up characteristics are shown in Table 1. Median age was 15.0 years, and there were more males than females. Median time since the last flare-up before enrollment was 0.5 years. Two-thirds of

Table 1 Baseline demographics, medical history, and flare-up characteristics

Characteristic	Baseline (N = 114)
Age, y	
n	114
Mean (SD)	17.6 (9.7)
Median (range)	15 (4-56)
Sex, *n* (%)	
n	114
Male	62 (54.4)
Female	52 (45.6)
Race and ethnicity, *n* (%)	
n	114
White	84 (73.7)
American Indian or Alaska Native	1 (0.9)
Asian	8 (7.0)
Black or African American	0
Hispanic or Latino	23 (20.2)
Native Hawaiian or Other Pacific Islander	0
Multiple	2 (1.8)
Other	4 (3.5)
Not available[a]	15 (13.2)
Height, cm	
n	114
Mean (SD)	153.2 (20.3)
Median (range)	159 (103-189)
Median (range) *z*-score for age <18 years[b] (n = 66)	0.29 (–4.2 to 2.5)
Weight, kg	
n	114
Mean (SD)	50.0 (22.0)
Median (range)	48 (16-140)
Median (range) *z*-score for age <18 years[b] (n = 66)	0.23 (–5.4 to 3.8)
FOP medical history, *n* (%)	
n	114
Great toe malformations	114 (100.0)
Thumb malformations	60 (52.6)
Cervical spine malformations	55 (48.2)
Shortened femoral necks	16 (14.0)
Hearing loss	39 (34.2)
Received misdiagnosis, *n* (%)	
n	114
Yes[c]	64 (56.1)
Aggressive juvenile fibromatosis	13 (11.4)
Soft tissue sarcoma	12 (10.5)
Lymphedema	1 (0.9)
Other	42 (36.8)
Years since first flare-up	
n	109
Mean (SD)	12.7 (9.5)
Median (range)	10 (0-45)
Years since last flare-up before study enrollment	
n	110
Mean (SD)	1.5 (2.6)
Median (range)	0.5 (0-15)

Data are from the full analysis set.

FOP, fibrodysplasia ossificans progressiva.

[a]Race and ethnicity data were not recorded for 15 individuals owing to local regulations.

[b]*z*-Scores were calculated using data collected by the Centers for Disease Control and Prevention.

[c]Participants could have had more than 1 misdiagnosis.

participants (66.7%) reported having ≥1 flare-up in the 12 months before enrollment, with an overall mean of 2.5 flare-ups per individual. All participants had great toe malformations, and approximately half had thumb malformations (Table 1).

Flare-up incidence and progression of HO

During the study period, 82 (71.9%) individuals had a total of 229 flare-ups, with the highest proportion reporting ≥1 flare-up in the 2 to <8 years age group (Supplement 2A). Common flare-up locations included the upper back, hip, shoulder, and lower spine/abdomen (Table 2).

A total of 52 flare-ups in 40 (35.1%) individuals were imaged (Supplement 2A). The proportion of individuals with ≥1 imaged flare-up was highest in the 2 to <8 years age group (47.1%) and lowest in the 25 to 65 years age group (25.9%). HO was present at the flare-up site in 71.2% of imaged flare-ups at flare-up Day 1, and 26.9% had new HO at flare-up Day 84 (Figure 1A). Mean volumes of HO at the flare-up site at flare-up Day 1 and new HO at flare-up Day 84 are presented in Figure 1B. Of all imaged flare-ups, 55.8% had baseline edema, with a higher incidence of new HO observed in these flare-ups than those without edema (34.5% vs 15.4% at flare-up Day 84).

Among individuals who had flare-ups (n = 40 imaged; n = 82 telephone contact only), the most common symptoms were pain (86.5%; 78.3%, respectively) and soft tissue swelling (78.8%; 81.1%, respectively). The mean number of flare-up symptoms was 3.0 (SD = 1.6), and 55.5% of flare-ups were associated with ≥3 symptoms. Overall, 71.2% of flare-ups were treated with systemic corticosteroids.

At baseline, mean WBCT HO volume in the progression analysis set was 306.1×10^3 (SD = 364.1×10^3) mm^3 (Figure 2A). The mean baseline HO volume was lowest in individuals aged 2 to <8 years (Figure 2A). Mean annualized volume of new HO was 23.6×10^3 (SD = 48.5×10^3) mm^3/year overall; highest means were observed in age groups <25 years (Figure 2B).

Cumulative mean HO volumes by joint region and age category at baseline and each 12-month interval are presented in Supplement 2B. During the study, individuals aged 2 to <8 years had new HO predominantly in the upper- and mid-torso regions. Substantial new HO in these regions was also observed in individuals aged 8 to <15 years in addition to the hip region. New HO was observed predominantly in the hip and lower-leg regions in individuals aged 15 to <25 years. Individuals aged 25 to 65 years had relatively small volumes of new HO across all body regions during the study. At Month 36, the mean number of body regions with new HO was 2.6 (SD = 2.0) in the overall population, highest in those aged 2 to <8 years (3.9 [SD = 2.5]) and lowest in those aged 25 to 65 years (1.5 [SD = 1.1]).

Table 2 Flare-up body regions across age groups

Flare-Up Location	Age Category, y				Overall
	2-<8, M = 54, m (%)	8-<15, M = 76, m (%)	15-<25, M = 59, m (%)	25-65, M = 40, m (%)	M = 229, m (%)
Upper back	28 (59.1)	9 (11.8)	3 (5.1)	1 (2.5)	41 (17.9)
Hip	4 (7.4)	10 (13.2)	13 (22.0)	7 (17.5)	34 (14.8)
Shoulder	0	9 (11.8)	9 (15.3)	7 (17.5)	25 (10.9)
Lower spine/abdomen	9 (16.7)	12 (15.8)	0	2 (5.0)	23 (10.0)
Knee	1 (1.9)	8 (10.5)	8 (13.6)	3 (7.5)	20 (8.7)
Head/neck	5 (9.3)	5 (6.6)	4 (6.8)	2 (5.0)	16 (7.0)
Upper spine/chest	1 (1.9)	8 (10.5)	2 (3.4)	4 (10.0)	15 (6.6)
Jaw	3 (5.6)	3 (3.9)	5 (8.5)	3 (7.5)	14 (6.1)
Distal lower extremities	0	5 (6.6)	3 (5.1)	3 (7.5)	11 (4.8)
Distal upper extremities	3 (5.6)	0	2 (3.4)	6 (15.0)	11 (4.8)
Elbow	0	2 (2.6)	7 (11.9)	1 (2.5)	10 (4.4)
Cervical spine	0	4 (5.3)	3 (5.1)	1 (2.5)	8 (3.5)
Not reported	0	1 (1.3)	0	0	1 (0.4)

"M" is the number of flare-ups in the age group; "m" is the number of flare-ups in the corresponding flare-up location. Percentages were calculated as the proportion of the total number of flare-ups within the age category. Data are from the flare-up analysis set.

Of 48 individuals with ≥1 flare-up at Month 12, 34 (70.8%) had new HO. The mean volume of annualized new WBCT HO from baseline to Month 12 was markedly higher in these individuals (37.7×10^3 [SD = 80.9×10^3] mm^3) than in the 44 who did not have a flare-up (6.2×10^3 [SD = 22.1×10^3] mm^3).

WBCT inter-read variability

Evaluation of variability in WBCT reads (intraclass correlation coefficients) revealed substantial inter-reader agreement for the qualitative determination of new HO and quantitative measurements, providing evidence of general consistency between readers (data not shown).

Changes in functional measures

At baseline, mean CAJIS total score was 11.8 (SD = 7.0) points and mean FOP-PFQ percentage of the worst total score was 46.3% (SD = 28.1%); small increases were observed from baseline to Month 36 (1.6 points and 7.3%, respectively; Supplement 3A and B).

Analysis of HO volume by percentage of normal arc of motion showed that the higher the mean HO volumes were, the worse the arcs of motion were across all body regions (Supplement 3C). In addition, the higher the mean HO volumes were in specific body regions the worse the joint-specific CAJIS scores were within those regions (Supplement 3D). In those who had new HO, the mean change in FOP-PFQ was 6.5% (SD = 14.1%) vs 5.0% (SD = 10.6%) in those who did not. Similarly, flare-ups with new HO had a greater increase in mean FOP-PFQ from flare-up Day 1 to Day 84 than flare-ups without new HO (5.8% [SD = 12.2%] vs –0.1% [SD = 4.9%]). Every 100.0×10^3 mm^3 increase in WBCT HO volume was associated with a 1.1-point increase in CAJIS total score and a 4.0% increase in FOP-PFQ percentage of worst total score (both $P < .0001$).

PROMIS Global Health T-scores did not substantially decline for the adult or pediatric populations or between those with or without new HO over 36 months (Supplement 3E). Mean PROMIS adult Global Health T-scores did not change from imaged flare-up Day 1 to Day 84 overall or in those flare-ups with new HO or without new HO.

PFTs at baseline showed moderate restriction among individuals aged <15 years and more severe restriction in those aged >15 years. At baseline, the youngest individuals in the study had the highest mean percent predicted FVC (2-<8 years: 60.8% [SD = 20.9%]; 8-<15 years: 59.8% [SD = 14.5%]), declining to approximately half of normal FVC by the early 20s before plateauing (15-<25 years: 47.6% [SD = 16.7%]; 25-65 years: 48.0% [SD: 17.0%]; Supplement 4). Over 36 months, compared with baseline, mean percentage predicted FVC increased most in those aged 8 to <15 years (5.5% [SD = 13.3%]), and decreased in those aged 15 to <25 years (–4.1% [SD = 6.7%]).

Skeletal abnormalities

At baseline, 34.5% of individuals had femoral head abnormalities, including irregular femoral head or joint space narrowing (24.0%) and femoral head osteoarthritis with sclerosis of the acetabulum and/or marginal osteophytes (13.3%), and 14.0% had femoral neck shortening. The only physeal (growth) plate abnormality observed in this NHS was presence of dense metaphyseal bands (DMBs), which were reported in the knee in all cases. At baseline, 39.4% of pediatric individuals (<18 years at enrollment) had DMBs; this was similar at Month 36 (42.9%). Among pediatric individuals, mean increases in tibial length and femur length from baseline to Month 36 were 2.61 (SD = 2.56) cm and 3.34 (SD = 3.19) cm, respectively, with plateauing observed for older pediatric individuals (Supplement 4B). Linear height z-scores were generally within 2 SDs of the general pediatric

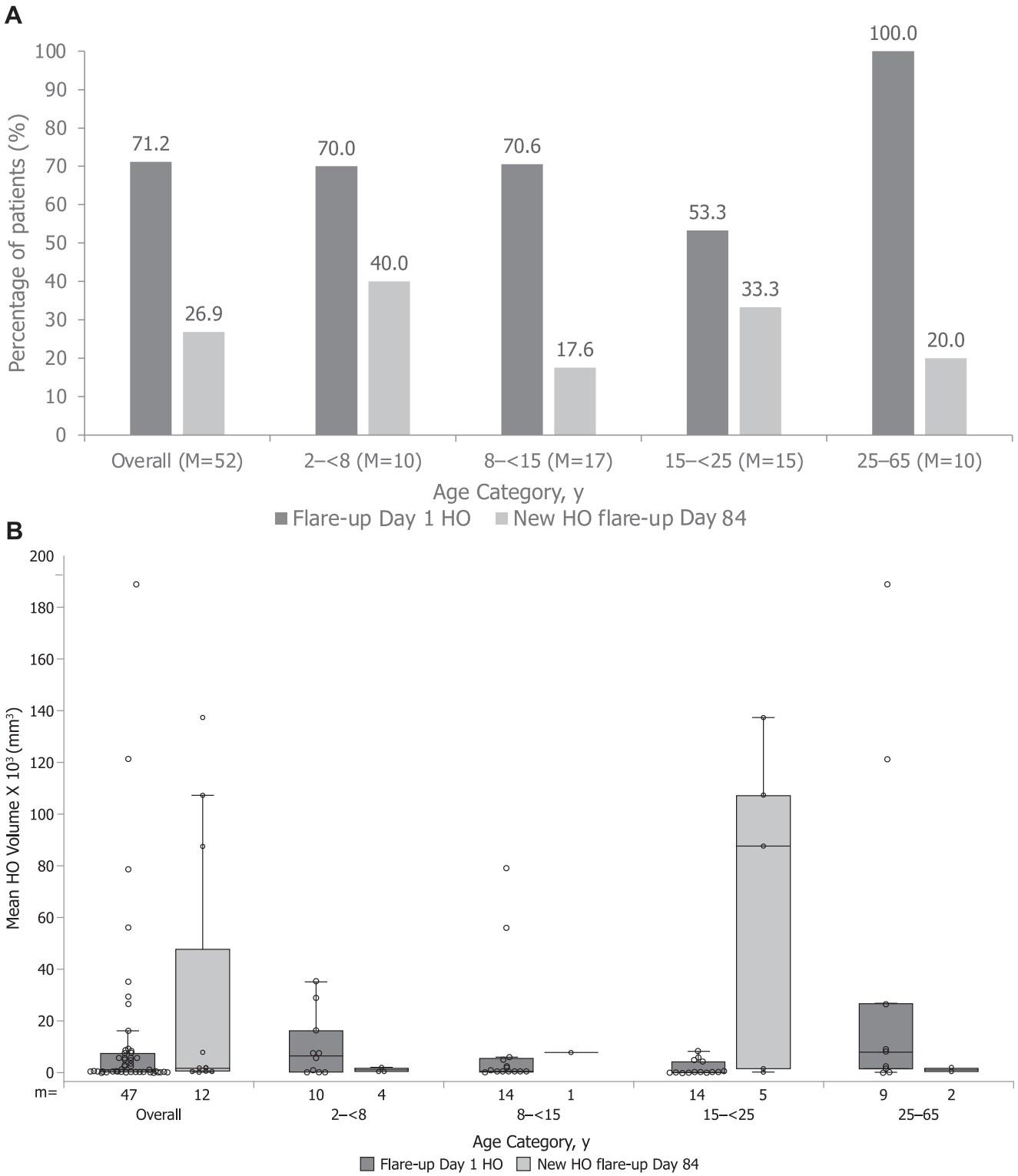

Figure 1 **Incidence and volume of HO at the flare-up site in individuals with imaged flare-ups.** A. Incidence of HO. B. Flare-up site HO volume at flare-up Days 1 and 84 for flare-ups that had new HO at flare-up Day 84. Flare-up Day 1 was defined as the day the individual presented to the site with a flare-up; this was within 14 days after the individual experiencing the flare-up or suspected flare-up. Incidence of new HO at flare-up Day 84 reflects any new HO since flare-up Day 1. Volumes are presented only for imaged flare-ups that had new HO at flare-up Day 84; not all flare-ups had new HO at flare-up Day 84. "M" refers to total number of evaluable imaged flare-ups; "m" refers to number of evaluable imaged flare-ups for each age group. Data are from the imaged flare-up analysis set. HO, heterotopic ossification.

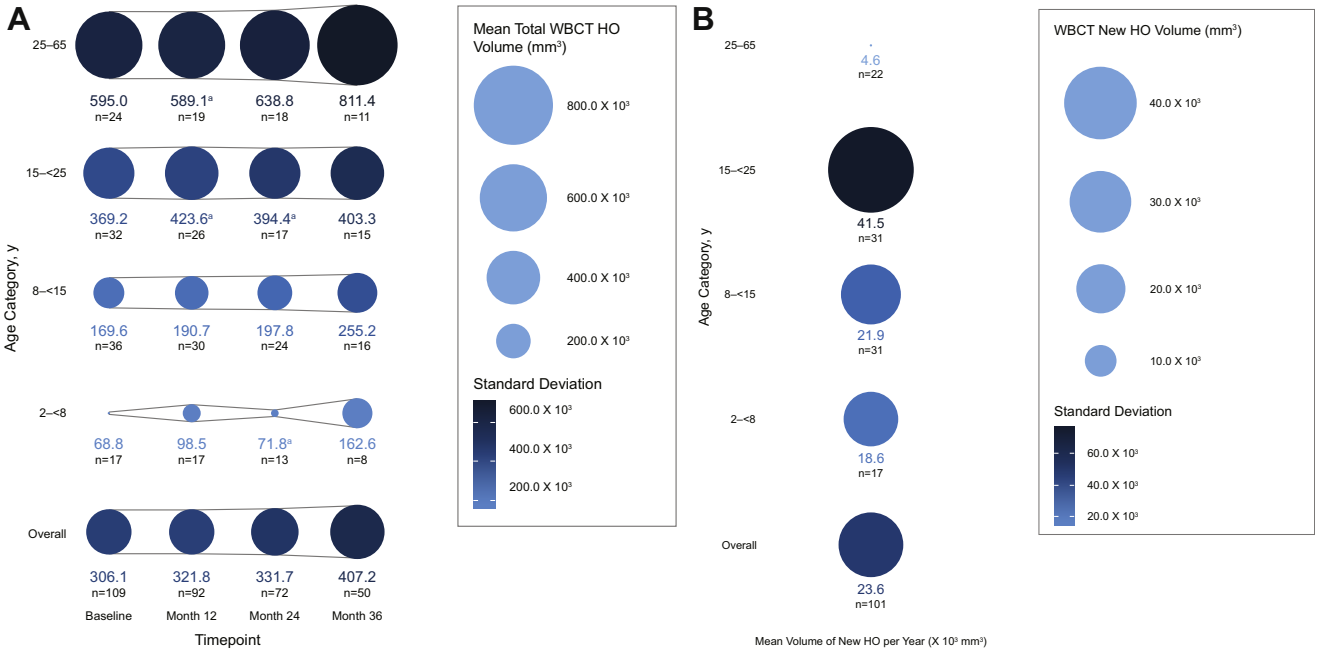

Figure 2 **Burden of HO.** A. Cumulative total WBCT HO volume across age groups over 36 months. B. Mean annualized volume of new WBCT HO across the full study in participants with WBCT HO assessment. Shading represents SD, with darker shading indicating a higher SD. [a]Apparent decreases in cumulative HO volumes were due to individuals with relatively high WBCT HO volumes dropping out of the study between the marked and previous timepoints. Month 36 can include unscheduled visits for WBCT. Data are from the progression analysis set. HO, heterotopic ossification; WBCT, whole-body computed tomography (excluding head).

population at baseline but were highly variable and decreased over 36 months (mean change from baseline: –0.40 [SD = 0.65]); *z*-scores tended to decrease in later adolescence (Supplement 4B).

AADAs

At baseline, 108 out of 114 study individuals used AADAs, most commonly requiring personal care tools/aids (71.3%) and care attendants (61.1%; Supplement 5A). At Month 36, 37 of 41 (90.2%) individuals began using a new AADA, most commonly requiring care attendants (48.6%), personal care tools (45.9%), and bathroom aids and devices (45.9%; Supplement 5B). Requirements for care attendants and personal care tools during the study were more common among older individuals than in the younger age groups.

Medications

At baseline, the most common ongoing prior medication classes were non-steroidal anti-inflammatory drugs, used by 28.9% of individuals; other common medications included glucocorticoids, leukotriene receptor antagonists, and anilides, including acetaminophen, proton pump inhibitors, and antihistamines (Supplement 5C). Throughout the 36-month study period, 79.8% of participants initiated a new medication. A higher percentage of individuals aged 2 to <8 and 8 to <15 years initiated new medications compared with older individuals (Supplement 5B). The most common newly initiated medications were non-steroidal anti-inflammatory drugs (initiated by 31.6% of participants), glucocorticoids (32.5%), corticosteroids for systemic use (17.5%), and anilides (24.6%). A disproportionately higher percentage of individuals aged 2 to <8 years initiated corticosteroids for systemic use than the other age groups (Supplement 5C).

Medical conditions and AEs

At study entry, medical conditions reported by participants included cardiopulmonary, musculoskeletal, gastrointestinal (including locked jaw), ear, genitourinary, renal, reproductive, psychiatric, neurologic, and endocrine/metabolic conditions (Supplement 5D). The 5 most common medical conditions present at baseline were restricted chest expansion, hearing loss (sensorineural and/or conductive), locked jaw, fractures, and reduced vital capacity. Over 36 months, new-onset medical conditions were reported across all categories (Supplement 5D; Table 3); the musculoskeletal and cardiopulmonary systems were most affected.

In total, 14 individuals had 26 study-related AEs (24 mild; 2 moderate), occurring during blood draws (n = 11), PFTs (n = 4), or traveling to the study site (n = 3). No study-related serious AEs occurred. One death occurred during the study: a 38-year-old female individual had fatal cardiac arrest not due to study procedures. At baseline, 15 of 94 (16.0%) individuals with Columbia Suicide Severity Rating Scale data

Table 3 Medical history and common new-onset medical conditions

Body System	Medical Condition	Interval	Age Category, y				Overall
			2-<8, *n* = 17, *n* (%)	8-<15, *n* = 36, *n* (%)	15-<25, *n* = 34, *n* (%)	25-65, *n* = 27, *n* (%)	*N* = 114, *n* (%)
Cardiopulmonary disorders	Restricted chest expansion	Present at BL	2 (11.8)	12 (33.3)	17 (50.0)	17 (63.0)	48 (42.1)
		New-onset between BL and Month 36	1 (5.9)	1 (2.8)	0	0	2 (1.8)
	Reduced vital capacity	Present at BL	2 (11.8)	7 (19.4)	18 (52.9)	10 (37.0)	37 (32.5)
		New-onset between BL and Month 36	2 (11.8)	3 (8.3)	1 (2.9)	1 (3.7)	7 (6.1)
	Thoracic insufficiency syndrome	Present at BL	0	2 (5.6)	4 (11.8)	0	6 (5.3)
		New-onset between BL and Month 36	0	0	0	1 (3.7)	1 (0.9)
Ear	Hearing loss	Present at BL	6 (35.3)	17 (47.2)	11 (32.4)	14 (51.9)	48 (42.1)
		New-onset between BL and Month 36	2 (11.8)	3 (8.3)	0	1 (3.7)	6 (5.3)
Gastrointestinal disorders	Recurrent vomiting	Present at BL	0	1 (2.8)	0	0	1 (0.9)
		New-onset between BL and Month 36	0	1 (2.8)	1 (2.9)	1 (3.7)	3 (2.6)
	Locked jaw	Present at BL	1 (5.9)	6 (16.7)	16 (47.1)	20 (74.1)	43 (37.7)
		New-onset between BL and Month 36	2 (11.8)	2 (5.6)	0	0	4 (3.5)
	Unintentional weight loss	Present at BL	2 (11.8)	4 (11.1)	4 (11.8)	3 (11.1)	13 (11.4)
		New-onset between BL and Month 36	0	0	0	2 (7.4)	2 (1.8)
Genitourinary and renal disorders	Kidney stones	Present at BL	0	0	3 (8.8)	4 (14.8)	7 (6.1)
		New-onset between BL and Month 36	0	0	2 (5.9)	2 (7.4)	4 (3.5)
	Recurrent urinary tract infections	Present at BL	0	1 (2.8)	2 (5.9)	4 (14.8)	7 (6.1)
		New-onset between BL and Month 36	0	0	1 (2.9)	1 (3.7)	2 (1.8)
Musculoskeletal disorders	Fractures	Present at BL	1 (5.9)	9 (25.0)	16 (47.1)	15 (55.6)	41 (36.0)
		New-onset between BL and Month 36	5 (29.4)	2 (5.6)	2 (5.9)	0	9 (7.9)
Psychiatric disorders	Depression	Present at BL	0	7 (19.4)	8 (23.5)	7 (25.9)	22 (19.3)
		New-onset between BL and Month 36	0	1 (2.8)	2 (5.9)	2 (7.4)	5 (4.4)

Only medical conditions of particular clinical interest are reported in this table; all medical conditions and new-onset medical events are presented in Supplement 5D. Patients underwent a medical history assessment against a checklist of predefined key medical history terms at the study center. Data are from the full analysis set.

BL, baseline.

expressed suicidal ideation ranging from milder passive ideation (type 1-2; 8.5%) to more severe active ideation (type 3-5; 7.4%). Participants also had non-suicidal self-injurious behavior and suicidal behavior ranging from preparatory acts, interrupted attempts, and actual attempts. Participants continued to express type 1 to 3 suicidal ideation over the 36 months.

Discussion

FOP is a severely debilitating genetic disorder associated with progressive disability, immobility, and reduced quality and length of life.[32] Previous NHSs in FOP have used retrospective[8-13] or patient-reported[7,33] data that provided insights to disease characteristics and changes in joint mobility over time. In this study, we evaluated the progression of HO, functional impairment, changes in joint function and association with HO, need for AADAs, and medical events in the largest, most comprehensive, prospective NHS of FOP to date. Given the size and representability of the data set relative to the known world-wide population of people with FOP (approximately 15% of all known individuals were included),[34] data obtained from this NHS will be instrumental in the design and execution of interventional trials of potential therapeutics in FOP.

Most individuals reported at least 1 flare-up during the study. Flare-up site imaging revealed HO involvement at the time of the flare-up, with many accumulating new HO in the following 12 weeks. Previous studies have reported that HO

usually proceeds from axial to appendicular, cranial to caudal, and proximal to distal.[7,8,24] This study confirmed that the progressive nature of FOP follows this pattern and showed that HO volume varied by age, with the greatest mean volume of new HO per year occurring in adolescents and young adults. Although individuals aged 25 to 65 years had the lowest new HO volume at annual visits, approximately 70% continued to accumulate new HO. With increasing age, smaller changes in HO volumes may be attributable to multiple factors, including reduced soft tissue availability for conversion to HO and a decrease in the initiation of new HO lesions.

HO can cause restricted ROM and severe pain.[35] In this study, although the estimated average increase in total body HO volume was 62.4×10^3 mm^3 over 36 months, only small increases in CAJIS and FOP-PFQ were reported. Cross-sectional analyses have shown that CAJIS generally increases by approximately 1 point every 2 years;[24] therefore, a longer study duration is required to detect substantial increases in CAJIS. By comparison, measurement of new HO is likely sufficiently sensitive to measure FOP disease progression over a 3-year period. This NHS also found that >9 in every 10 individuals started using at least 1 new AADA during the study, suggesting that use of AADAs could provide a real-world indicator of decreased mobility in FOP.

Cardiopulmonary disorders often develop in older patients with FOP, with thoracic insufficiency being a common cause of death.[3,9] Severe restrictive lung disease occurs in patients with FOP due to progressive spinal deformities, such as kyphoscoliosis, and restrictive chest wall disease due to ankylosis of the costovertebral joints, ribs, and ossification of the intercostal muscles.[18] These processes contribute to reduced vital capacity and restricted chest expansion, as observed in more than one-third of participants at baseline. More severe pulmonary restriction was observed among individuals aged >15 years than in younger individuals, and little difference was observed between those aged 15 to <25 and 25 to 65 years, whose predicted FVC was mostly lower than 50%. This finding is consistent with worsening restrictive lung disease in individuals with FOP during their early to late teenage years and early 20s, at which point most individuals have clinically significant, but stable, restrictive chest wall disease.

The most common physeal (growth) plate abnormality in individuals in this study was DMBs. DMBs are a common radiographic finding when growing bones are exposed to stressors or bone growth inhibitors that, when relieved, are followed by rapid deposition of new bone at the metaphysis, resulting radiographically in a dense radio-opaque horizontal band.[36] The high prevalence of DMBs in patients with FOP is likely a sequela of chronic disease, undernutrition (especially after jaw ankylosis), and medications (eg, steroids and bisphosphonates).[37] Furthermore, this abnormality may have been under-reported because WBCT may not be sufficiently sensitive to monitor DMBs. Another characteristic of FOP is hearing impairment.[8] Among individuals who entered this study, 42.1% had a sensorineural or conductive hearing impairment at baseline, similar to the prevalence reported in Morales-Piga et al[10] and Pignolo et al[31] but lower than the approximately 50% prevalence in a patient case series reported by Levy et al.[38] New or worsening hearing loss was reported in 5.3% of participants during the 36-month follow up.

Care should be taken in the interpretation of these results owing to the limitations of this NHS. First, only individuals with confirmed $ACVR1^{R206H}$ were enrolled. Because almost all patients with FOP have this variant, the limited number of individuals with other variants who could have been enrolled would not have been sufficient to determine any meaningful genotype–phenotype relationships. Second, assessment of total body HO was performed using only 1 imaging modality, WBCT. However, a comparison between whole-body dual-energy x-ray absorptiometry and WBCT determined that HO was better visualized and quantified using WBCT than using dual-energy x-ray absorptiometry, allowing more accurate determination of HO over time.[39] Finally, it may be possible that flare-ups were under-reported owing to intermittent assessments.

This NHS documents the burden and progressive nature of FOP in a group of representative individuals over 3 years. It is the first study to carefully assess flare-up characteristics and the association of new HO with functional end points. Across the population, total HO volume and use of AADAs increased substantially during the study. By comparison, there were only limited changes in functional and patient-reported outcomes (CAJIS and FOP-PFQ), although, differences were observed in individuals with new HO compared with those without. These results will facilitate the evaluation of meaningful end points in the development of new therapeutics, which are critically needed for individuals with FOP.

Data Availability

Qualified researchers may request access to patient-level study data that underlie the results reported in this publication. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan and dataset specifications may also be made available. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of study participants.

Where applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the US and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen's sharing criteria, eligible studies and process for sharing are available here (https://vivli.org/members/ourmembers/). Any requests should be submitted to www.vivli.org for assessment by an independent scientific review board.

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Author Information

Conceptualization and Methodology: A.W., A.S., E.C.H., F.S.K., M.A.B., R.J.P.; Data Curation: A.W., R.M.; Formal Analysis: A.W., A.S., R.M.; Investigation: R.J.P., G.B., M.A.B., C.D.C., E.C.H., R.K., M.A.M.; Data Interpretation: R.J.P., G.B., M.A.B., C.D.C., E.C.H., R.K., M.A.M., K.-H.L.Q.S., A.W., R.M., A.S., F.S.K.; Writing-original draft: A.W.; Writing-review and editing: R.J.P., G.B., M.A.B., C.D.C., E.C.H., R.K., M.A.M., K.-H.L.Q.S., A.W., R.M., A.S., F.S.K.

Ethics Declaration

All study sites obtained ethics approval from local institutional review boards and complied with all applicable national, ethics, and regulatory guidelines. The study was conducted according to the guidelines of Good Clinical Practice and the International Conference on Harmonization and is in full compliance with the Declaration of Helsinki and its 2013 amendment. Informed consent or assent was obtained from all participants as required by the institutional review boards.

Conflict of Interest

R.J.P. is a research investigator at Clementia Pharmaceuticals/Ipsen and Regeneron Pharmaceuticals, Inc and is part of the advisory board as President of the International Clinical Council on Fibrodysplasia Ossificans Progressiva. G.B. is part of the advisory boards of Clementia Pharmaceuticals/Ipsen, FOP European Consortium, and International Clinical Council on FOP and is a speaker at Clementia Pharmaceuticals/Ipsen. M.A.B. is part of the advisory boards of AbbVie, Janssen, Pfizer, UCB Pharma, and Novartis; receives grant support from AbbVie; is a research investigator at AbbVie, Clementia Pharmaceuticals/Ipsen, Janssen, Novartis, Pathios Therapeutics Ltd, and Regeneron Pharmaceuticals, Inc; and is a speaker at AbbVie, United States, Janssen, Novartis, Switzerland, Pfizer, United States, Regeneron Pharmaceuticals, Inc, United States, and UCB Pharma, United Kingdom. C.D.C. is a research investigator at Clementia Pharmaceuticals/Ipsen and is a speaker at Novartis. E.C.H. is part (all voluntary) of the Fibrous Dysplasia Foundation Advisory Board, International Fibrodysplasia Ossificans Progressiva Association (IFOPA), United States Registry Medical Advisory Board, and International Clinical Council on FOP Advisory Board; receives clinical research support from Clementia Pharmaceuticals/Ipsen, France, Neurocrine Biosciences Inc, United States, and Regeneron Pharmaceuticals, Inc; and is a research investigator at Clementia Pharmaceuticals/Ipsen. R.K. is a research investigator at Clementia Pharmaceuticals/Ipsen, Kyowa Kirin, and Regeneron Pharmaceuticals, Inc and is part of the IFOPA Fibrodysplasia Ossificans Progressiva Registry Medical Advisory Board and International Clinical Council on Fibrodysplasia Ossificans Progressiva Advisory Board. M.A.M. receives research support from Clementia Pharmaceuticals/Ipsen and Regeneron Pharmaceuticals, Inc; is a non-paid consultant for BioCryst Pharmaceuticals, Inc, United States, Blueprint Medicines, Daiichi Sankyo, Incyte, and Keros Therapeutics; is part (all voluntary) of the IFOPA Registry Medical Advisory Board, Incyte Advisory Board, and International Clinical Council on FOP Advisory Board; and receives non-restricted educational fund from Excel and Catalyst sponsored by Ipsen. K.-H.L.Q.S. is a coordinator of Ipsen FOP-program and multiple osteochondromas-trial. A.W., R.M., and A.S. are employees of Ipsen. F.S.K. is a research investigator at Clementia/Ipsen and Regeneron Pharmaceuticals, Inc, is part of the IFOPA Medical Advisory Board, is a Founder and immediate past President of the International Clinical Council on FOP, and is the Chair of the Publications Committee of the International Clinical Council. In April 2019, Ipsen acquired Clementia Pharmaceuticals.

Additional Information

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Affiliations

[1]Department of Medicine, Mayo Clinic, Rochester, MN; [2]Département de Génétique, Hôpital Universitaire Necker-Enfants Malades, Institut Imagine, Université Paris Cité, Paris, France; [3]Department of Medicine and Molecular Genetics, Faculty of Life Sciences and Medicine, School of Basic and Medical Biosciences, King's College London,

London, United Kingdom; [4]Genomics England, London, United Kingdom; [5]Pediatric Rheumatology Section, Department of Pediatrics, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [6]Division of Endocrinology and Metabolism, the UCSF Metabolic Bone Clinic, the Eli and Edyth Broad Institute for Regeneration Medicine, and the Institute of Human Genetics, Department of Medicine, and the UCSF Program in Craniofacial Biology, University of California San Francisco, San Francisco, CA; [7]Centre for Metabolic Bone Disease, Royal National Orthopaedic Hospital, Stanmore, United Kingdom; [8]Departments of Orthopaedic Surgery and Medicine, Center for Research in FOP and Related Disorders, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [9]Ipsen, Cambridge, MA

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