A global natural history study (NHS) of fibrodysplasia ossificans progressiva (FOP): normal long bone growth and abnormalities in younger patients over 36 months

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Background

- FOP is an ultra-rare genetic disorder with an estimated prevalence of up to 1.4 per million individuals.[1]
- The median age at diagnosis is 5 years,[2] and individuals are supported by a range of medical specialties, including paediatric endocrinologists.
- FOP is characterised by progressive and irreversible heterotopic ossification (HO).[3]
- HO develops into ribbons, sheets and plates of extra bone throughout the body and across joints, restricting movement; most individuals are immobilised by the third decade of life.[2,4,5]
- Individuals with FOP often develop tibial osteochondromas, broad femoral necks and progressive spinal deformities.[6,7]

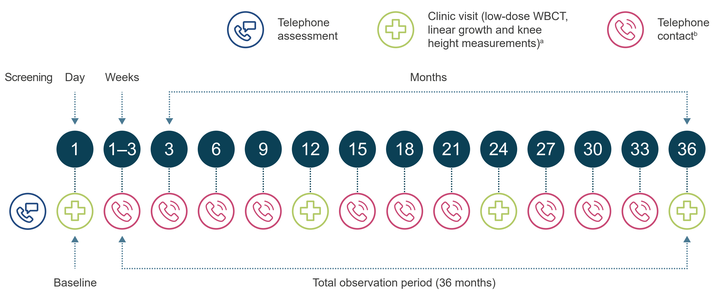
Objective

To describe normal long bone growth, linear growth changes and incidence of bone abnormalities at epiphyseal plates in individuals with FOP aged <18 years enrolled in a 3-year NHS.

Methods

- Individuals with FOP with a documented *ACVR1*^{R206H} mutation aged ≤65 years were eligible to participate in a 36-month, global, prospective, protocol-specified NHS (NCT02322255; Figure 1).
- The analysis presented here includes individuals aged <18 years at Baseline.
- Femur and tibia lengths, and abnormalities of hand/wrist and knee epiphyseal plates, were determined using low-dose whole-body computed tomography (WBCT).
- Knee height assessments were completed using a knee caliper.
- Linear growth assessments were completed using a stadiometer.

Figure 1. Natural history study design

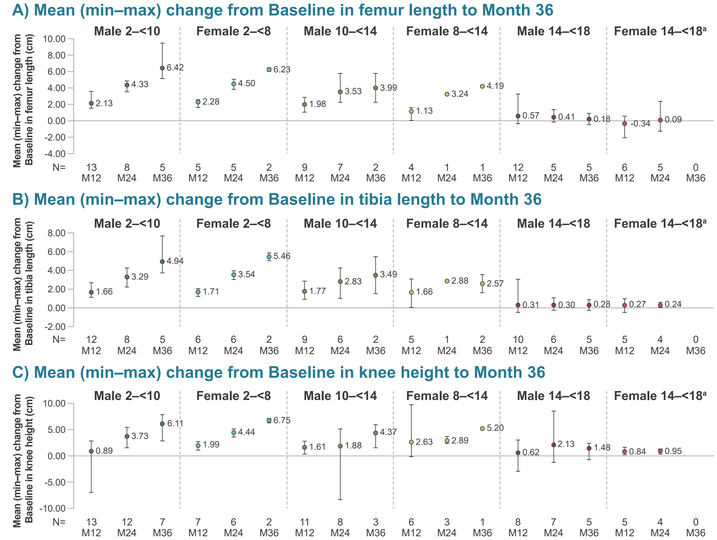


[a]Low-dose WBCT scan (excluding head) at all planned clinic visits (Baseline, study Months 12, 24, 36) or at early termination (within 2 months of termination); [b]Participants were asked to telephone the site with a suspected flare-up. In addition, telephone contact was to be performed every 3 months to determine whether new flare-ups occurred since the prior clinic visit or telephone contact.

TAKE-HOME MESSAGE

Individuals aged <18 years with FOP had high rates of knee abnormalities, and high variability in normal long bone growth and linear height over 36 months.

Figure 2. Change from Baseline in normal long bone growth and knee height over 36 months in individuals with FOP by age group



[a]Measurements for femur length, tibia length and knee height were only taken for participants aged <18 years; no female participants aged 14–<18 years at Baseline remaining in the study had these measurements recorded at Month 36.

CONCLUSIONS

- Younger participants aged <14 years at Baseline showed increases in femur and tibia length and knee height over 36 months, but these plateaued in older adolescent participants aged 14–<18 years at Baseline.
- Knee height losses were likely due to difficulties obtaining accurate measurements in participants who struggled to maintain a seated position.
- Decreasing linear height z-scores highlight the difficulties associated with obtaining accurate growth measurements in younger individuals with FOP due to worsening skeletal deformities such as scoliosis, kyphosis and ankylosis over time.
- The only growth plate abnormality identified was dense metaphyseal bands, the incidence of which appeared stable over 36 months.
- Comparatively low numbers of participants at Month 36 compared with Baseline limits comparison of the outcomes reported between age groups over 36 months.

Results

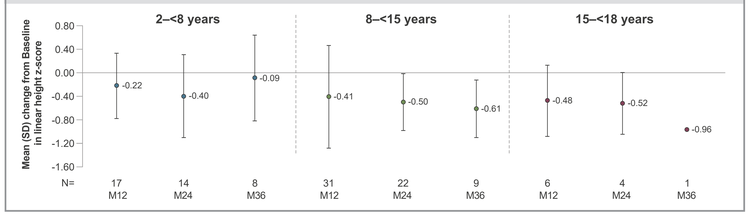
- 66 individuals aged <18 years at Baseline were included in this analysis
  - Baseline demographics and characteristics for participants aged <25 years are presented in Table 1.
- Change from Baseline in femur and tibia length was greatest in younger participants (Figure 2).
- Knee height generally increased over time; some knee height losses were reported (Figure 2).
- At Baseline, mean (SD) linear height z-scores were 0.70 (1.036), 0.08 (1.320) and 0.09 (1.414) for participants aged 2–<8, 8–<15 and 15–<18 years, respectively
  - Linear height z-scores were variable and generally decreased from Baseline to Month 36 (Figure 3).
- Comparatively low numbers of participants aged <18 years at Month 36 limits comparison between age groups (Figures 2 and 3).
- At Baseline, 39.4% had a bone abnormality at knee epiphyseal plates
  - At Month 36, 40.9% had a recorded abnormality; all knee abnormalities were dense metaphyseal bands and no hand/wrist abnormalities were recorded.

Table 1. Baseline demographics and characteristics for participants <25 years[a]

	2–<8 years (n=17)	8–<15 years (n=36)	15–<25 years (n=34)
Age, years, median (range)	6.0 (4–7)	11.0 (8–14)	18.5 (15–24)
Sex, male, n (%)	9 (52.9)	24 (66.7)	16 (47.1)
Years since FOP diagnosis, median (range)	3.8 (0.8–6.7)	6.9 (0.2–14.8)	13.7 (0.1–22.0)
Experienced one or more flare-ups within the 12 months prior to enrolment, yes, n (%)	13 (76.5)	25 (69.4)	21 (61.8)
Number of flare-ups within the 12 months prior to enrolment, median (range)	2 (0–10)	1 (0–40)	1 (0–8)

[a]Baseline demographics and characteristics are presented by protocol-specified age groups; 21 participants in the 15–<25 age group were over the age of 18 at Baseline and were not included in analyses presented in this poster.

Figure 3. Change from Baseline in linear height *z*-scores over 36 months in individuals with FOP



Abbreviations

ACVR1: activin A receptor type I; FOP: fibrodysplasia ossificans progressiva; M12/24/36: Month 12/24/36; NHS: natural history study; SD: standard deviation; WBCT: whole-body computed tomography.

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Disclosures RJP: Research investigator: Clementia/Ipsen, Regeneron; Advisory board: International Clinical Council on FOP (president); **GB**: Advisory board: Clementia/Ipsen, FOP European Consortium, International Clinical Council on FOP; Speaker: Clementia/Ipsen; **MAB**: Advisory board: AbbVie, Janssen, Pfizer, UCB Pharma, Novartis; Grant support: AbbVie; Research investigator: AbbVie, Clementia/Ipsen, Janssen, Novartis, Pathios, Regeneron; Speaker: AbbVie, Janssen, Novartis, Pfizer, Regeneron, UCB Pharma; **CDC**: Research investigator: Clementia/Ipsen; Speaker: Biogen; **ECH**: Advisory board (all voluntary): Fibrous Dysplasia Foundation, IFOPA Registry Medical Advisory Board, International Clinical Council on FOP; Research support: Clementia/Ipsen, Neurocrine Biosciences, Regeneron; Research investigator: Clementia/Ipsen; **RK**: Research investigator: Ipsen/Clementia, Kyowa Kirin, Regeneron; Advisory board: IFOPA FOP Registry Medical Advisory Board, International Clinical Council on FOP; **MAM**: Research support: Non-paid consultant: Biocryst, Blueprint, Daiichi Sankyo, Incyte, Keros; Advisory board (all voluntary): IFOPA Registry Medical Advisory Board, International Clinical Council on FOP; Non-restricted educational fund from Excel and Catalyst sponsored by Ipsen; **RM**, **AH**: Employees of Ipsen; **FSK**: Research investigator: Clementia/Ipsen, Regeneron; Advisory Board: IFOPA Medical Advisory Board; Founder and Immediate Past-President of the International clinical Council (ICC) on FOP; Chair of the Publications Committee of the ICC. In April 2019, Ipsen acquired Clementia Pharmaceuticals.

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