PRESS RELEASE

Ipsen's global Natural History Study of Fibrodysplasia Ossificans Progressiva shows debilitating impact of the disease over an individual's lifetime

First prospective study to assess the association of fibrodysplasia ossificans progressive (FOP) flare-ups and extra-skeletal bone growth (heterotopic ossification or HO) with functional impairment

PARIS, France, 28 September 2022 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced the publication of its Natural History Study (NHS) of FOP in *Genetics in Medicine,* the official journal of the American College of Medical Genetics and Genomics (ACMG*)*. This is the first time a global, prospective, longitudinal evaluation of FOP has been carried out, with data collected over a period of 36 months. Findings demonstrated the debilitating impact and progressive nature of the disease, with the greatest progression of new heterotopic ossification (HO; or bone growth that takes place outside of the normal skeletal system in joints and soft connective tissues), occurring during childhood and early adulthood.[1]

"Natural history studies are essential to understanding ultra-rare diseases with high unmet need like FOP, increasing our knowledge around the natural course of disease, diagnoses, monitoring techniques, potential biomarkers and new outcome measures," said Dr. Robert Pignolo, Professor of Geriatric Medicine, Mayo Clinic, USA. "This is the first study of its kind following the progression of FOP over three years. These results demonstrate the significant impact of the disease on people living with FOP. Furthermore, it will facilitate the evaluation of meaningful endpoints in the development of new therapies, which are critically needed for individuals with FOP."

Results from the NHS demonstrated at month 36, across the whole study population, a mean of 2.6 body regions with new HO; this was highest (3.9) in those aged between two and eight years and lowest (1.5) in those aged 25 – 65 years. However, although individuals aged 25 – 65 years had the lowest new HO volume at annual visits, approximately 70% continued to accumulate new HO across the duration of the study. These data confirmed the progressive nature of FOP with characteristic patterns of growth, starting in younger individuals initially across the upper and mid-torso, progressing into hip and lower-leg regions, and with accumulation of HO occurring over time and following disease flare-ups.[1]

The assessment of flare-ups showed, 82 (71.9%) individuals experienced a total of 229 flare-ups, most commonly in the upper back (17.9%), hip (14.8%) and shoulder (10.9%). Individuals between the ages of two and eight years, were most likely to report more than one flare-up throughout the study duration. For those who experienced flare-ups, the most common symptoms were pain and soft tissue swelling. Imaging at the site of the flare-up revealed HO occurring at the time of the flare-up, with many individuals going on to experience new HO in the following 12 weeks.[1]

In addition, the study assessed functional impairment, changes in joint function in association with HO, need for aids, assistive devices and adaptations (AADA), and medical events. Across the population studied, total HO volume and new AADAs increased during the study, with more than 9 in every 10 individuals using at least one new AADA during the study, suggesting the use of AADA could be a real-world indicator of decreased mobility in FOP. In comparison, there were only limited changes in functional and patient-reported outcomes, possibly due to the study duration being too short to detect substantial changes in joint function.[1] The WBCT data from the NHS confirmed new annualized HO volume as a clinically meaningful endpoint that can be used in interventional clinical trials.[1]

"As an ultra-rare disease there is still a lot we have to understand about the nature and progression of FOP, said Dr Howard Mayer, Head of Research and Development, Ipsen. "This first prospective study carried

out over a 3-year period, has helped to advance our knowledge of important characteristics of the disease, including when in a persons' lifetime new HO is most likely to form and how it progresses over time, in addition to better understanding the relationship between use of AADA and mobility. We are grateful to the significant number of individuals with FOP who participated in this important study."

FOP is an ultra-rare genetic disorder with an estimated prevalence of 1.36 per million individuals[2]. The median age at time of FOP diagnosis is five years old.[3] It is characterized by HO,[4] which can be preceded by painful soft-tissue swellings or 'flare-ups'.[3] Flare-up episodes are a substantial contributor to the formation of new HO, which once formed is irreversible.[4] Disability is therefore cumulative and most patients need to use a wheelchair by their 20's and require assistance to perform activities of daily living.[5,6] This loss of mobility, in addition to numerous life-limiting complications of FOP, leads to markedly shortened life expectancy.[7]

Previous Natural History Studies in FOP have used retrospective[3,7,8,9,10,11] or patient-reported[12,13] data to provide insights into disease characteristics and changes in joint mobility. In this prospective NHS, HO progression was evaluated using whole-body computed tomography (WBCT) scans at baseline and months 12, 24, and 36. Flare-ups were assessed using computed tomography (CT) scans or X-rays on the day the individual presented with the flare-up and at week 12, to evaluate the extent of HO at the flare-up site.[1]

It is estimated that 15% of all known individuals with FOP were included in the NHS at the time of the study.[2] Given the size of the dataset relative to the known world-wide population of people with FOP, this represents the largest, international, most comprehensive, prospective natural history study of FOP to date.[1]

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About the FOP Natural History Study

The study was conducted across eight international sites. Median age was 15 years and there were more males than females. Median time since the last flare-up prior to enrollment was 0.5 years. Two thirds of participants (66.7%) reported having ≥1 flare-up, with an overall mean of 2.5 flare-ups per individual, in the 12 months prior to enrollment. All participants had great toe malformations, and approximately half had thumb malformations. Overall, 114 individuals 4 to 56 years old participated in the study; of these, 33 individuals completed the study. All participants were genetically diagnosed with FOP carrying the activin receptor type-1 (*ACVR1)*^{R206H} pathogenic variant, the five most common clinical signs 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 history was reported across all categories; the musculoskeletal and cardiopulmonary systems were most affected.[1]
https://www.gimjournal.org/article/S1098-3600(22)00904-2/fulltext

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