NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Palovarotene for flare-ups in fibrodysplasia ossificans progressiva – first line

NIHRIO ID	27226	**NICE ID**	10251
Developer/Company	Ipsen Ltd	**UKPS ID**	652642

Licensing and market availability plans	Currently in phase II clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Palovarotene is in clinical development for episodic use in the prevention of heterotopic ossification (HO) in patients with fibrodysplasia ossificans progressiva (FOP). FOP is a disabling condition, caused by the formation of bony bars within the muscles of the body (HO). This bone formation is usually first noticed in early childhood as a series of hard lumps in the neck or along the spine. These lumps, which may be tender, gradually shrink in size as the affected muscles are replaced by bone. The appearance of bony lumps in muscles is usually spontaneous but can also be provoked by any injury to the muscles.

Palovarotene is an oral, once-daily medicine which attaches to a receptor in cells, called the retinoic acid receptor gamma, switching on processes that reduce bone formation. If licensed, palovarotene has the potential to prevent HO in patients with FOP, a condition for which the only available treatments are for symptomatic relief.

PROPOSED INDICATION

Prevention of heterotopic ossification for patients with fibrodysplasia ossificans progressiva episodic use (flare-up indication) – first line.[a]

TECHNOLOGY

DESCRIPTION

Palovarotene (IPN60120, RG-667) belongs to a class of medicines known as retinoids. It attaches to another receptor in cells, called the retinoic acid receptor gamma, switching on processes that reduce bone formation. Palovarotene is therefore expected to help prevent the abnormal bone formation seen in fibrodysplasia ossificans progressiva (FOP) and relieve the symptoms of the condition.[1]

Palovarotene is currently in clinical development for the prevention of heterotopic ossification for patients with FOP for episodic use. In the phase II clinical trials (NCT02190747 and NCT02279095 sections A, B and C),[2,3] varying doses were administered as reported in the Clinical Trial Information section, below.[a]

INNOVATION AND/OR ADVANTAGES

Bone morphogenetic proteins (BMPs) are part of the transforming growth factor β (TGF- β) known to regulate various cellular activities such as differentiation and proliferation and are particularly involved in fibrosis. Palovarotene exerts its action on bone formation through the regulation of the BMP pathway by binding of any of several extracellular BMP ligands such as BMP 2, 4, 7 and 9 to the BMP receptor which is membrane bound.[4] Palovarotene is expected to help prevent the abnormal bone formation seen in FOP, a condition for which no satisfactory methods of treatment have been authorised in the EU, with patients mainly managed by avoidance of injuries that could trigger a flare-up, and treatment of the symptoms including anti-inflammatory medicines for the pain and inflammation.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Palovarotene does not currently have a Marketing Authorisation in the EU/UK for any indication.

Palovarotene is in phase II clinical development for multiple osteochondromas.[5]

Palovarotene has the following regulatory designations/ awards:

- Orphan Drug status, awarded by the EMA in November 2014 for the treatment of FOP and multiple osteochondromas.[1]
- Breakthrough Therapy, awarded by the FDA in 2017 for the prevention of HO in patients with FOP.[6]

[a] Information provided by Ipsen Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Fibrodysplasia ossificans progressiva (FOP), also known as myositis ossificans progressiva, is a disorder in which muscle tissue and connective tissue such as tendons and ligaments are gradually replaced by bone (ossified), forming bone outside the skeleton (extra-skeletal or heterotopic bone) that constrains movement. This process generally becomes noticeable in early childhood, starting with the neck and shoulders and proceeding down the body and into the limbs. Extra-skeletal bone formation causes progressive loss of mobility as the joints become affected. Inability to fully open the mouth may cause difficulty in speaking and eating. Over time, people with this disorder may experience malnutrition due to their eating problems. They may also have breathing difficulties as a result of extra bone formation around the rib cage that restricts expansion of the lungs. People with FOP are generally born with malformed big toes. This abnormality of the big toes is a characteristic feature that helps to distinguish this disorder from other bone and muscle problems. Affected individuals may also have short thumbs and other skeletal abnormalities. Any trauma to the muscles of an individual with FOP, such as a fall or invasive medical procedures, may trigger episodes of muscle swelling and inflammation (myositis) followed by more rapid ossification in the injured area. Flare-ups begin early in life and may occur spontaneously or after soft tissue trauma, vaccinations, or influenza infections. Recurrent flare-ups progressively restrict movement by locking joints leading to cumulative loss of function and disability.[7]

FOP is caused by spontaneous mutations, predominantly in the ACVR1 gene. The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein type I receptors. The ACVR1 protein is found in many tissues of the body including skeletal muscle and cartilage. It helps to control the growth and development of the bones and muscles, including the gradual replacement of cartilage by bone (ossification) that occurs in normal skeletal maturation from birth to young adulthood. Researchers believe that a mutation in the ACVR1 gene may change the shape of the receptor under certain conditions and disrupt mechanisms that control the receptor's activity. As a result, the receptor may be constantly turned on (constitutive activation). Constitutive activation of the receptor causes overgrowth of bone and cartilage and fusion of joints, resulting in the signs and symptoms of FOP.[7] There is no ethnic, racial, gender, or geographic predilection to FOP. The median lifespan is approximately 40 years of age. Most patients are wheelchair-bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome.[8]

CLINICAL NEED AND BURDEN OF DISEASE

FOP is an extremely rare disease, which has a worldwide prevalence of 0.05/ 100,000.[9] The company (Ipsen Ltd) has estimated that there are circa 80 patients living with FOP in the UK.[b] The Hospital Episodes Statistics for England 2018/2019 recorded 60 finished consultant episodes (FCE), 57 hospital admissions, 42 FCE bed days and 42 day cases for myositis ossificans progressiva (ICD 10 code M61.1).[10]

[b] Information provided by Ipsen Ltd on UK PharmaScan

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no known effective treatments for FOP. Certain types of drugs have been used to relieve pain and swelling associated with FOP during acute flare-ups (most notably corticosteroids) and non-steroidal anti-inflammatory medication between flare-ups.[11]

Affected individuals may benefit from occupational therapy. Special shoes, braces, and other devices that assist in walking and weight-bearing have been used to help people with FOP. Affected individuals may have their physicians contact an occupational therapist who can help obtain special devices or tools to assist them in daily activities.[11]

Genetic counselling may be of benefit for families with the hereditary form of FOP. A team approach for infants with this disorder will also be of benefit and may include special social, educational, and medical services. Other treatment is symptomatic and supportive.[11]

CURRENT TREATMENT OPTIONS

When flare-ups begin, a brief 4-day course of high-dose corticosteroids such as prednisone can be used to relieve inflammation and tissue oedema, but corticosteroids can only be used to relieve inflammation in areas such as the mandibular joint. The frequent use of corticosteroids to treat swelling in the trunk and neck is not recommended due to the difficulty in assessing the onset of flare-ups.[12]

When corticosteroids are discontinued, mast cell inhibitors, amino bisphosphonates, non-steroidal anti-inflammatory drugs, and COX-2 inhibitors could be used to treat later flare-ups. A small dose of a muscle relaxant may help to relieve muscle spasms.[12]

Clinically, steroids, non-steroids, and anti-inflammatory drugs can mitigate inflammation and pain, but they cannot reduce the frequency of HO.[12]

PLACE OF TECHNOLOGY

If licensed, palovarotene has the potential to prevent HO in patients with FOP, a condition for which the only available treatments are for symptomatic relief.

CLINICAL TRIAL INFORMATION

Trial	**NCT02190747, Eudra CT 2014-001453-17; aged 6 years or older; palovarotene versus placebo; phase II**	**NCT02279095,Eudra CT 2014-002496-28; aged 6 years to 65 years; palovarotene dose level 1, 2, 3 and 4; phase II extension**
Sponsor	Clementia Pharmaceuticals Inc.	Clementia Pharmaceuticals Inc.
Status	Completed.	Ongoing.
Source of Information	Trial registries.[2,13]	Trial registries.[3,14]
Location	Two EU countries (incl UK), USA.	Two EU countries (incl UK), USA, Australia and Argentina
Design	Randomised, double-blind, placebo-controlled	Non-randomised, single group assignment, open label

Participants	N=40; aged 6 years and older; clinically diagnosed with FOP; symptomatic onset of a distinct flare-up within 7 days of study day 1 (start of study drug) and defined by the presence of at least two of six of the following symptoms: pain, soft tissue swelling, decreased range of motion, stiffness, redness, and warmth. Flare-up must be confirmed by the physician at the Screening visit.	N=58; aged 6 years to 65 years; completion of Study PVO-1A-202/part B; accessible for treatment with palovarotene and follow-up (able and willing to travel to a site for the initial and all follow-up clinic visits); able to undergo low-dose, WBCT scan, excluding head.
Schedule	Cohort 1: subjects will be randomly assigned 3:1 to either palovarotene or placebo daily for 42 days. Doses of palovarotene in dose level 1 are 10 mg once daily for 14 days, followed by 5 mg once daily for 28 days. Cohort 2: subjects will be randomly assigned 3:3:2 to two dose regimens of palovarotene (10 mg for 14 days and 5 mg for 28 days; 5 mg for 14 days and 2.5 mg for 28 days) or placebo daily for 42 days. Doses will be weight-adjusted and subjects randomised within three weight-range categories (20 to <40 kg, 40 to <60 kg, and ⩾60 kg).	Palovarotene dose level 1: subjects received weight-adjusted doses of palovarotene equivalent to 10 mg once daily for 14 days, followed by 5 mg once daily for 28 days for an eligible flare-up (part A). Palovarotene dose level 2: subjects with at least 90% skeletal maturity received 5 mg palovarotene once daily for up to 24 months; and 20 mg palovarotene for 28 days, followed by 10 mg for 56 days for eligible flare-ups (part B). Palovarotene dose level 3: subjects with less than 90% skeletal maturity received weight-adjusted doses of 20 mg palovarotene for 28 days, followed by 10 mg for 56 days for eligible flare-ups (part B). Palovarotene dose level 4: All subjects will receive 5 mg palovarotene once daily for up to 36 months; and 20 mg palovarotene for 28 days, followed by 10 mg for 56 days for eligible flare-ups (Part C). Doses are adjusted for weight in skeletally immature subjects.
Follow-up	Up to 84 days.	From baseline up to sixty months.
Primary Outcomes	Percentage of subject responders as assessed by plain radiographs. [Time frame: study day 42]	Change in new HO volume [Time frame: screening, every 12 months up to 60 months]
Secondary Outcomes	<u>Time frame: study days 42 and 84</u> •Numeric heterotopic ossification scores at the flare-up site as assessed by plain radiograph <u>Time frame: baseline, study days 42 and 84</u>	<u>Time Frame: baseline, every 12 months up to 60 months</u> •Subjects with new HO: the proportion of subjects with any new HO

	•Amount (area) of new heterotopic bone formed at the flare-up site assessed by plain radiographs •Amount of bone formation (volume) as assessed by low dose CT scan •Presence of soft tissue swelling and/or cartilage as assessed by MRI (or soft tissue swelling by ultrasound in subjects unable to undergo MRI) •Active range of motion measured by goniometer of the relevant joint •Subject and Investigator global assessment of movement •Use of assistive devices and adaptations for daily living by FOP subjects Time frame: study day 84 •Percentage of subject responders as assessed by plain radiographs Time Frame: Baseline, Study Days 14, 28, 42, and 84 •Plasma biomarker levels Time Frame: Baseline, Study Days 14, 28, 42, 63, and 84 •Pain and swelling at the flare-up site using a numeric rating scale for each symptom (or the Faces Pain Scale-Revised for subjects under 8 years of age) •Age-appropriate patient-reported assessment of physical function Time Frame: Symptom start date to symptom end date •Duration of active, symptomatic flare-up Time Frame: Study Days 1 (the first day of dosing), 14, 28, 42, 63, and 84 •Safety evaluation including adverse events, clinical safety laboratory parameters, and assessment of epiphyseal growth plate and linear growth in subjects under the age of 18 years	•Range of motion: change from baseline in range of motion as assessed by the Cumulative Analogue Joint Involvement Scale for FOP (CAJIS) •FOP-Physical Function Questionnaire: change from baseline in physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (PFQ) •PROMIS Global Health Scale: change from baseline in mental and/or physical health function for subjects using age-appropriate forms of the PROMIS Global Health Scale Time Frame: every month up to 60 months •Incidence of adverse events: monitor adverse events Time Frame: Pre-dose and 3, 6, 10, and 24 hours post-dose •Pharmacokinetics of palovarotene
Key Results	**Primary outcome:** Percentage of responders (subjects with no/minimal new flare-up heterotopic ossification versus baseline) for each treatment regime: Palovarotene 10/5 mg: 100% Palovarotene 5/2.5 mg: 88.9%	Not reported.

	Placebo: 88.9% p-value for trend = 0.16 **<u>Secondary outcomes:</u>** Percentage of Subjects With New HO at Day 84: Palovarotene 10/5 mg: 15% Palovarotene 5/2.5 mg: 44% Placebo: 40% p-value for trend = 0.08 Volume of New Heterotopic Ossification From CT Scan at Day 84: Palovarotene 10/5 mg: 16,396 mm^3 Placebo: 53,939 mm^3 p-value = 0.17	
Adverse effects (AEs)	Total subjects affected by serious adverse events/ number exposed to each treatment regime: Palovarotene 10/5 mg: 2 / 21 (9.52%) Palovarotene 5/2.5 mg: 1 / 9 (11.11%) Placebo: 1 / 10 (10.00%) Total subjects affected by non-serious adverse events/ number exposed to each treatment regime: Palovarotene 10/5 mg: 21 / 21 (100.00%) Palovarotene 5/2.5 mg: 9 / 9 (100.00%) Placebo: 10 / 10 (100.00%)	Not reported.
Expected reporting date	Estimated primary study completion date reported as May 2016. Estimated final study completion date reported as May 2016.	Estimated primary study completion date reported as March 2021. Estimated final study completion date reported as March 2021.

ESTIMATED COST

RELEVANT GUIDANCE

NICE GUIDANCE

None identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

None identified.

OTHER GUIDANCE

- Kaplan FS, Shore EM, Glaser DL, Emerson S. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc intl clin consort FOP. 2011.[15]

ADDITIONAL INFORMATION

REFERENCES

1 European Medicines Agency. *EU/3/14/1368*. 1995-2019. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141368 [Accessed 17 October 2019]

2 ClinicalTrials.gov. *An Efficacy and Safety Study of Palovarotene to Treat Preosseous Flare-ups in FOP Subjects*. 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT02190747 [Accessed 14 October 2019]

3 ClinicalTrials.gov. *An Open-Label Extension Study of Palovarotene Treatment in FOP*. 2019. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02279095 [Accessed 14 October 2019]

4 Clementia Pharmaceuticals INC. *SECURITIES AND EXCHANGE COMMISSION*. 2017. Available from: http://pdf.secdatabase.com/1232/0000930413-17-002527.pdf [Accessed 09 October 2019]

5 ClinicalTrials.gov. *An Efficacy and Safety Study of Palovarotene for the Treatment of MO (MO-Ped)*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03442985?cond=Palovarotene&phase=123&draw=1&rank=1 [Accessed 15 November 2019]

6 Specialty Pharma Journal. *FDA Grants Clementia's Palovarotene Rare Pediatric Disease Designation for Fibrodysplasia Ossificans Progressiva*. 2019. Available from: http://www.spjnews.com/2019/02/12/fda-grants-clementias-palovarotene-rare-pediatric-disease-designation-for-fibrodysplasia-ossificans-progressiva/ [Accessed 09 October 2019]

7 National Institutes of Health. *Fibrodysplasia ossificans progressiva*. 2019. Available from: https://ghr.nlm.nih.gov/condition/fibrodysplasia-ossificans-progressiva#genes [Accessed 09 October 2019]

8 Orphanet. *Fibrodysplasia ossificans progressiva*. 2019. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=337 [Accessed 14 October 2019]

9 Orphanet. *Prevalence and incidence of rare diseases: Bibliographic data*. 2019. Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed 17 October 2019]

10 Office for National Statistics. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis*. 2018-19. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 15 November 2019]

11 National Organization for Rare Disorders. *Fibrodysplasia Ossificans Progressiva*. 2019. Available from: https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva/ [Accessed 17 October 2019]

12 Qi Z, Luan J, Zhou X, Cui Y, Han J. Fibrodysplasia ossificans progressiva: Basic understanding and experimental models. *Intractable & rare diseases research*. 2017;6(4):242-8. Available from: https://doi.org/10.5582/irdr.2017.01055.

13 EU Clinical Trials Register. *Clinical Trial Results: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of a RARγ-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).* 1995-2019. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001453-17/results [Accessed 17 October 2019]

14 EU Clinical Trials Register. *Clinical trials* 1995-2019. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002541-29/SE [Accessed 14 October 2019]

15 Kaplan FS, Shore EM, Glaser DL, Emerson S. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc intl clin consort FOP; 2011. p. 1-100. Available from: http://fundacionfop.org.ar/wp-content/uploads/2019/05/GUIDELINES-May-2019.pdf

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.