

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Garetosmab for preventing abnormal bone formation in fibrodysplasia ossificans progressiva

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| NIHRIO ID | 21664 | NICE ID | 10069 |
| Developer/Company | Regeneron Pharmaceuticals | UKPS ID | Not Available |

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

Garetosmab is in clinical development for the prevention of abnormal bone formation, outside of the normal skeleton (heterotopic ossification), and soft-tissue flare-ups in patients with fibrodysplasia ossificans progressiva (FOP). FOP is a very rare disease caused by a mutation in the gene ACVR1. The mutation results in the formation of unwanted bone in muscles, tendons, and ligaments throughout the body. Abnormal, misplaced and mis-shapen (heterotopic) bone can bridge across joints causing immobility, scoliosis, and other deformities. Patients usually require a wheelchair by the time they reach their 20s. Death often results in the 40s from complications, such as pneumonia, heart failure and loss of mobility in the chest, neck and jaw.

Garetosmab is administered intravenously. It is designed to attach to activin A, which stops activin A from interacting with ACVR1. This is expected to stop or reduce unwanted bone formation. If licensed, garetosmab will offer a treatment option for preventing abnormal bone formation and soft-tissue flare-ups in patients with FOP.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Prevention of abnormal bone formation (heterotopic ossification) and soft-tissue flare-ups in patients with FOP.^a

TECHNOLOGY

DESCRIPTION

Garetosmab (REGN2477) is an investigational drug for FOP. Garetosmab is a fully-human monoclonal antibody to activin A, which plays a significant role in developing heterotopic ossification (HO) in FOP.¹ Garetosmab attaches to activin A, which stops activin A from interacting with ACVR1, a receptor involved in the formation of bone and cartilage.² This may slow or prevent the formation of new HO in patients with FOP.³

Garetosmab is currently in clinical development for the treatment of FOP. In the phase II clinical trial (NCT03188666) patients received garetosmab by intravenous infusion during treatments periods 1 (baseline to week 28 randomised, double-blind, placebo controlled), period 2 (6-months open label treatment with garetosmab), and period 3 (\geq 5 months follow-up open-label treatment period with garetosmab).⁴

INNOVATION AND/OR ADVANTAGES

Currently, there are no approved treatment for FOP. Garetosmab reduces the occurrence of heterotopic bone formation and flare-ups in FOP.⁵ In a phase II study, garetosmab decreased total lesion activity, both new and existing lesions as compared to placebo and 90% decrease in the number of new bone lesions. Patient-reported flare-ups were also reduced by 50%.¹

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Garetosmab was granted following designations:

- Orphan designation by EMA for treating FOP in November 2016.²

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.

^a Information provided by Regeneron Pharmaceuticals

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 a cumulative loss of function and disability.⁶

FOP is caused by spontaneous mutations, in the ACVR1 gene. The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein (BMP) type I receptors. The ACVR1 encoded protein (ALK2) 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 mis-perceives signalling by activin A. Under normal circumstances activin A is an inhibitor of ALK2 receptor; however, in FOP, mis-perception of activin A leads to stimulation of the receptor and heterotopic bone formation.⁷ Heterotopic bone formation leads to skeletal deformities which usually results in pain and a significant loss of movement.⁸

This contributes to profound disability, morbidity and mortality. Most patients are wheelchair-bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome.⁹ The median estimated lifespan of individuals with FOP is approximately 56 years. There is no ethnic, racial, gender, or geographic predilection to FOP.¹⁰

CLINICAL NEED AND BURDEN OF DISEASE

FOP is an extremely rare disorder, which has a worldwide prevalence of 0.05/ 100,000.^{11,12} 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).¹³

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no known effective treatments for preventing or reducing the development of HO in FOP. However, certain types of drugs (most commonly corticosteroids and non-steroidal anti-inflammatory medications) may provide a measure of utility in relieving pain and swelling associated with FOP during acute flare-ups.¹⁴

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.¹⁴

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.¹⁴

CURRENT TREATMENT OPTIONS

When flare-ups begin, a brief 4-day course of high-dose corticosteroids such as prednisone can be used as an attempt to relieve inflammation and tissue oedema. 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.¹⁵

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.¹⁵ However, there has been no demonstration these medications prevent or halt the progression of heterotopic bone.¹⁶ For patients with muscle spasm, a small dose of a muscle relaxant may help to relieve the symptoms.¹⁵

Clinically, steroids, non-steroids, and anti-inflammatory drugs can mitigate inflammation and pain, but they cannot reduce the frequency of HO and progression of FOP.¹⁵

PLACE OF TECHNOLOGY

If licensed, garetosmab will provide a treatment option for preventing abnormal heterotopic bone formation and soft tissue flare-ups in patients with FOP.

CLINICAL TRIAL INFORMATION

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| Trial | LUMINA-1, NCT03188666, R2477-FOP-1623 EudraCT 2016-005035-33 ; A randomized, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and effects on heterotopic bone formation of regn2477 in patients with fibrodysplasia ossificans progressiva Phase II Location(s): EU (including the UK), Canada, United States and other countries |
| Trial design | Randomised, parallel assignment, quadruple-blinded |
| Population | n= 44; aged 18-60 years; males and females; diagnosis of FOP; any ACVR1 mutation |
| Intervention(s) | Garetosmab ; powder for solution infusion; intravenous; administered |
| Comparator(s) | Matched placebo |
| Outcome(s) | <ul style="list-style-type: none"> • Incidence and severity of treatment-emergent adverse events (TEAEs) through the end of the period 1 [Time frame: Baseline to week 28] • Time-weighted average (standardised area under the curve [AUC]) of the percent change from baseline in total lesion activity by 18F-NaF positron emission tomography |

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| | <p>(PET) in patients with baseline-active HO [Time frame: Baseline to week 28]</p> <ul style="list-style-type: none"> Percent change from baseline in the total volume of HO lesions as assessed by computed tomography (CT) In patients with baseline-active HO [Time frame: Baseline to week 28] |
| Results (efficacy) | <p>Garetosmab, compared to placebo, was associated with:¹⁷</p> <ul style="list-style-type: none"> ~25% reduction in both time weighted average of percent-change from baseline in total lesion activity (TLA) as measured by ¹⁸F NaF PET over 28 weeks (p=0.07) and % Change from baseline in the total volume of HO lesions as assessed by CT at week 28 (p=0.37) 87% reduction in the rate of formation of new HO lesions measured by either PET or by CT (post-hoc; p< 0.01) 90% reduction in total volume of new HO lesions per patient by CT at week 28 (post-hoc; p = 0.02) 50% reduction in patient reported flare-up events assessed by patient e-diary (pre-specified; p=0.03) 76% reduction in investigator reported flare-up adverse events |
| Results (safety) | <p>During the 28-week treatment period treatment emergent adverse events (TEAEs) occurred in 100% of both treated and placebo groups; the majority were mild to moderate in severity. Notable imbalances in TEAEs included epistaxis (50.0% vs 16.7%) and skin events (madarosis [loss of eyebrows, 25.0% vs 0%], acne [30.0% vs 8.3%] and a composite of skin infections including abscess, carbuncle, folliculitis, furuncle). Two treated patients in the open-label portion of the trial developed serious abscesses requiring hospitalization for drainage but resolved while continuing garetosmab treatment. Nineteen out of 20 garetosmab patients and 24 out of 24 placebo-group patients completed the 28-week treatment period. One patient in the open-label portion of the trial died due to trauma unrelated to treatment.¹⁷</p> |

ESTIMATED COST

The cost of garetosmab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE health technology appraisal in development. Palovarotene for treating flare ups of heterotopic ossification associated with fibrodysplasia ossificans progressiva (GID-TA10593). Expected publication date: TBC

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a

OTHER GUIDANCE

- Kaplan FS, Shore EM, Glaser DL, Emerson S. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clinic Council FOP. 2011.¹⁸

ADDITIONAL INFORMATION

Regeneron Pharmaceuticals Inc, did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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