NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
December 2022

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28656	NICE TSID: 10591	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Benralizumab is currently in clinical development for relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA). EGPA, formally known as Churg-Strauss Syndrome, is a rare disease characterised by blood vessel inflammation. This inflammation can restrict blood flow to organs and tissues, sometimes permanently damaging them. Relapsed refers to a disease that has come back, and refractory refer to a disease that stopped responding to a treatment. The symptoms of EGPA can include, but are not limited to, severe asthma, bowel trouble, blood loss and anaemia. There are limited, effective treatment options for patients with relapsing EGPA.

Benralizumab, is a type of protein designed to attach to the receptors (targets) called interleukin-5 receptors on the surface of a type of white blood cell called eosinophils. By attaching to its receptor, benralizumab activates the immune system (the body's natural defences) to kill the eosinophils in the blood and lungs, which helps to reduce inflammation. Benralizumab has been shown to be tolerable and effective in patients with EGPA. If licensed, benralizumab, which is administered under the skin, will offer an additional treatment option for patients with relapsing or refractory EGPA.

Proposed Indication

Treatment for patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) on corticosteroid therapy with or without stable immunosuppressive therapy.[1]

Technology

Description

Benralizumab (Fasenra) is an anti-eosinophil, humanised, afucosylated, monoclonal antibody (IgG1, kappa). It binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with high affinity and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells. This leads to apoptosis of eosinophils and basophils through enhanced antibody dependent cell-mediated cytotoxicity (ADCC) which reduces eosinophilic inflammation.[2]

Benralizumab is in clinical development for relapsing or refractory EGPA. In the phase III trial (NCT04157348) benralizumab was administered subcutaneously (SC) as a 30 mg/mL solution for injection in a single accessorised prefilled syringe.[1]

Key Innovation

Glucocorticoids are the mainstay of EGPA treatment. Notably, the cumulative dose of glucocorticoids has been identified as the main factor associated with adverse events, particularly infections. Patient outcomes are excellent with regard to 1-year and 5-year mortality rates (100% and 97%, respectively); however, relapses occur in more than one-third of the patients and glucocorticoids are still required for persistent symptoms, mainly asthma and ENT (ear, nose, throat) manifestations – these are poorly controlled by conventional therapy and represent a high disease burden. Thus, targeted treatments are recommended in order to achieve more effective disease control and reduce toxic effects compared with glucocorticoids.[3]

Benralizumab blocks the binding of interleukin 5 (IL-5) to its receptor and results in inhibition of eosinophil differentiation and maturation in bone marrow. In addition, this medicinal product is able to bind through its afucosylated Fc domain to the RIIIa region of the Fcy receptor on natural killer (NK) cells, macrophages, and neutrophils, thus strongly inducing antibody-dependent, cell-mediated cytotoxicity in both circulating and tissue-resident eosinophils. This double function of benralizumab induces almost complete fast and maintained depletion of eosinophils that is much greater than that induced by other monoclonal antibodies targeting the IL-5 pathway.[4] Furthermore, in a prospective, phase II clinical study (NCT03010436), benralizumab was well tolerated, facilitated oral corticosteroid reduction, and reduced exacerbations in EGPA.[5] If licensed, benralizumab will offer an additional treatment option for patients with relapsing or refractory EGPA.

Regulatory & Development Status

Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.[2]

Benralizumab is in phase III/II clinical development for a number of indications, some of which include:[6]

- Gastritis
- Bullous pemphigoid
- Chronic prurigo
- Eosinophilic gastritis

- Atopic dermatitis
- Asthma

Patient Group

Disease Area and Clinical Need

EGPA, formerly known as Churg-Strauss syndrome, is a disorder characterised by blood vessel inflammation. This inflammation can restrict blood flow to organs and tissues, sometimes permanently damaging them.[7] The symptoms of this condition include: asthma, autoimmunity, central nervous system degeneration, congestive heart failure, eosinophilia and more.[8] People who suffer with EGPA usually have severe asthma that may have developed as an adult. They often have other symptoms including sinus and nose symptoms. The cause of EGPA is not known. It is likely that a combination of factors leads to development of EGPA. Studies looking at genetics have shown some genes that are linked to EGPA, while some people have Anti Neutrophil Cytoplasmic Antibodies (ANCA) which may cause some types of auto-immune disease. Unusual levels of some types of hormone-like chemicals in the blood (cytokines) have also been found in people with EGPA, and this may contribute too.[9] EGPA can occur in people of all ages, from children to the elderly.[10] EGPA appears to affect men and women equally.[9,10]

EGPA is a rare disease. A systematic review and meta-analysis on burden of illness associated with EGPA estimated that incidence of EGPA is 1.07 (0.94, 1.35) cases per million person-years and prevalence is 12.13 (95% CI 6.98, 21.06) cases per million individuals in Europe and globally.[11] Around 11–13 people per million are diagnosed with EGPA. The average age of someone with a new diagnosis is 40 years old, and diagnosis is very rare in children or those over 65.[9] The population likely to be eligible to receive benralizumab could not be estimated from available published sources.

Recommended Treatment Options

Treatments for EGPA include:[9]

- Corticosteroids or steroids (e.g., prednisolone)
- Nasal and inhaled steroids
- Cyclophosphamide
- Azathioprine
- Methotrexate
- Rituximab

Clinical Trial Information

Trial	**MANDARA; NCT04157348; EudraCT 2019-001832-77;** A Randomized, Double-blind, Active-controlled 52-week Study With an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab Compared to Mepolizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis (EGPA) in Patients Receiving Standard of Care Therapy **Phase III –** Active, not recruiting **Location(s):** Four EU countries, UK, USA, Canada, Israel and Japan **Primary completion date:** July 2023
Trial Design	Randomised, parallel assignment, triple-blinded active-controlled

Population	N=140 (actual); adult subjects (18 years or older) who have EGPA diagnosis based on history or presence of asthma and eosinophilia
Intervention(s)	1x benralizumab SC 30 mg/mL injection + 3x placebo to mepolizumab SC injections
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: proportion of patients who are in remission at both weeks 36 and 48 [Time frame: 36 and 48 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Benralizumab is already marketed in the UK for treatment of eosinophilic asthma; a 30mg/1ml pre-filled disposable injection pen or syringe costs £1,955.00.[12]

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- American College of Rheumatology/Vasculitis Foundation. 2021 ACR/VF Guideline for ANCA-associated Vasculitis (GPA/MPA/EGPA). 2021.[13]

Additional Information

AstraZeneca UK Ltd 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.

References

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