NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2023

Benralizumab for treating hypereosinophilic syndrome

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27119	NICE TSID: 11867	UKPS ID: N/A

Licensing and Market Availability Plans

Benralizumab is currently in phase 3 clinical development.

Summary

Benralizumab is currently in clinical development for the treatment of Hypereosinophilic Syndrome (HES). HES is a group of rare inflammatory disorders characterised by a high number of eosinophils in the blood (eosinophils are a type of white blood cell involved in the body's immune response). When eosinophils infiltrate (enter) tissues, they can cause inflammation and organ damage which, over time, can impact patients' day-to-day ability to function. Although any organ or organ system can be affected in HES, the most common are the heart, central nervous system, skin, and respiratory tract.

Benralizumab, administered subcutaneously (under the skin) (SC), is a monoclonal antibody (type of protein) designed to attach directly to eosinophils via the interleukin-5 receptor alpha (IL-5Rα). By attaching to IL-5Rα, benralizumab causes the death and rapid depletion of eosinophils. Benralizumab also inhibits eosinophil development. This double function quickly induces rapid, near complete and sustained depletion of eosinophils.. If licensed, benralizumab will offer a new treatment option for patients with HES who currently have few effective therapies available.

Proposed Indication

Treatment of hypereosinophilic Syndrome (HES) in patients 12 years and older.[1]

Technology

Description

Benralizumab (Fasenra)[2] is an anti-eosinophil, humanised afucosylated, monoclonal antibody (IgG1, kappa). It specifically binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα). 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.[3]

Benralizumab is currently in phase II and III clinical development (NCT02130882, NCT04191304) for HES in patients 12 years and older. Benralizumab (30mg) will be administered subcutaneously every 4 weeks.[1,4]

Key Innovation

The goal of HES treatment is to deplete eosinophils in the blood and tissues, prevent organ damage and slow disease progression.[2,5] Treatment options for patients are limited, have varying efficacy and are associated with adverse events.[2]

A Phase II trial (NCT02130882) has demonstrated that benralizumab can achieve near-complete depletion of eosinophils and improve clinical outcomes in HES. In the randomised phase of the 20-patient trial, the primary efficacy endpoint was the percentage of patients who reduced their absolute blood eosinophil counts by 50% or more at week 12. This was achieved by 90% of patients treated with Fasenra compared with 30% of patients treated with placebo, a statistically significant difference.[2]

If licensed, benralizumab will offer an additional treatment option to patients with HES.

Regulatory & Development Status

Benralizumab is currently licensed in the UK as an add on maintenance treatment for adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.[3]

Benralizumab is currently in phase II/III clinical development for the following indications:[6,7]

- Chronic Prurigo
- Bullous Pemphigoid
- Eosinophilic Gastritis
- Chronic spontaneous urticarla
- Asthma
- Non-cystic fibrosis bronchiectasis
- Nasal Polyps
- COPD

Benralizumab has been awarded a USA orphan drug designation in February 2019 for HES.[2]

Patient Group

[a] Information provided by AstraZeneca

Disease Area and Clinical Need
HES is traditionally defined as peripheral blood eosinophilia >1500/µL (>1.5 × 10^9/L) persisting ≥ 6 months.[8] An eosinophil is a type of white blood cell. Allergies, asthma, parasitic infections, and certain medicines may increase the number of eosinophils. Organs such as the skin, lungs, heart, or brain may be damaged if there are too many eosinophils. They may also harm the kidneys, intestines, liver, or spleen.[9] HES can happen at any age, although it is more common in adults. People with HES may suffer from a wide variety of symptoms, depending upon which parts of the body are affected. These symptoms include: skin rashes, dizziness, memory loss or confusion, cough, shortness of breath, fatigue, fever and mouth sores [8,10] HES has an estimated prevalence of 1.5 in every 100,000 people in the European Union.[11] In England, 2021–22, there were 468 finished consultant episodes (FCE) and 380 admissions for eosinophilia (ICD-10 code: D72.1; of which HES makes up a subset) which resulted in 631 FCE bed days and 261 day cases.[12]
Recommended Treatment Options
There are currently no approved pharmacological treatment options for HES in the UK.[13] Basic therapy in HES consists of administration of oral corticosteroids to control symptoms, eosinophilia and prevent organ damage.[14] This is not recommended by the National Institute for Health and Care Excellence (NICE).

Trial	**NATRON**, NCT04191304, EudraCT2019-002039-27, A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 24-week Phase 3 Study With an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients With Hypereosinophilic Syndrome (HES) **Phase 3:** Recruiting **Locations:** The US and 10 EU countries **Primary Completion Date:** November 2023
Trial Design	Randomised, quadruple masked, parallel assignment.
Population	N=120 (estimated), ≥12 years old. Documented diagnosis of HES.
Intervention(s)	Benralizumab (subcutaneous administration)
Comparator(s)	Matched placebo (subcutaneous administration)
Outcome(s)	Primary outcome measures: • Time to first HES worsening/flare [Time frame: up to 24 weeks] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**HESIL5R**, NCT02130882, A Phase 2a Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous

[a] Information provided by AstraZeneca

	Benralizumab (MEDI-563) in Reducing Eosinophilia in Subjects With Hypereosinophilic Syndrome (HES). **Phase II**: Complete[a] **Locations:** United States **Study Completion Date:** June 2020
Trial Design	Randomised, parallel assignment, triple masked
Population	N=20 (actual), adults aged18–75 years old with HES
Intervention(s)	Benralizumab (30mg, subcutaneous administration)
Comparator(s)	Matched Placebo (subcutaneous administration)
Outcome(s)	Primary Outcome Measures • Reduction of peripheral eosinophilia at 12 weeks [Time frame: 12 weeks] See trial record for full list of outcomes.
Results (efficacy)	In this small phase 2 trial, patients with *PDGFRA*-negative hypereosinophilic syndrome who received benralizumab for 12 weeks had lower absolute eosinophil counts than those who received placebo. During the open-label phase, clinical and hematologic responses were sustained for 48 weeks in 74% of the patients.[15]
Results (safety)	The most common drug-related adverse events, headache and an elevated lactate dehydrogenase level, occurred in 32% of the patients after the first dose of benralizumab and resolved within 48 hours in all patients. Other adverse events occurred with similar frequency in the two groups.[15]

Estimated Cost

Benralizumab is already marketed in the UK for the treatment severe eosinophilic asthma, a 30mg/1ml vial costs £1,955.[16]

Relevant Guidance

NICE Guidance

No relevant NICE guidance.

NHS England (Policy/Commissioning) Guidance

No relevant NHS guidance.

Other Guidance

- British Journal of Haematology. Guideline for the investigation and management of eosinophilia. 2017.[17]

Additional Information

[a] Information provided by AstraZeneca

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

1 Clinicaltrials.gov. *A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 24-week Phase 3 Study With an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients With Hypereosinophilic Syndrome (HES). Trial ID: NCT04191304*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04191304 [Accessed 01 February 2023].

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[a] Information provided by AstraZeneca

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[a] Information provided by AstraZeneca