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Benralizumab for chronic obstructive pulmonary disease (COPD)

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LAY SUMMARY

Chronic obstructive pulmonary disease (sometimes called chronic bronchitis or emphysema) is a lung disease that causes difficulties in breathing, mostly due to narrowing of the airways. The main cause of chronic obstructive pulmonary disease is smoking. Symptoms of this disease include increased difficulty breathing when active, persistent cough, and frequent chest infections. Patients with chronic obstructive pulmonary disease can have a sudden worsening of symptoms, known as an 'exacerbation' or 'flare-up', which can lead to being admitted to hospital.

Benralizumab is a new drug being developed for the treatment of chronic obstructive pulmonary disease. It is administered by injection under the skin and acts by targeting specific proteins that causes the airway to narrow. If benralizumab is licensed for use in the UK, it could be a new treatment option for patients with chronic obstructive pulmonary disease that may improve quality of life and reduce the number of exacerbations.

TARGET GROUP

Moderate to very severe chronic obstructive pulmonary disease (COPD); patients with exacerbation history.

TECHNOLOGY

DESCRIPTION

Benralizumab is a fully humanized anti-interleukin-5 receptor (IL-5R) alpha chain monoclonal antibody derived from mice. It binds to the alpha subunit of interleukin-5 receptor and inhibits its action. Interleukin-5 works together with other interleukin receptors and signalling proteins to induce eosinophil-mediated inflammatory responses. Benralizumab exhibits its action by targeting eosinophils and basophils whose functions are driven by Interleukin-5 receptor. It deletes these cells through apoptosis induction and checks the progression of the disease. It is based on POTELLIGENT technology platform, a new host cell line for the production of recombinant antibodies.

Benralizumab is a new molecular entity (NME). It is administered subcutaneously and is intended for the treatment of moderate to very severe COPD patients with exacerbation history.[1]

This product is not currently licenced for any indication in the EU or the US.

Benralizumab is in late stage clinical development in the EU and globally for the treatment of asthma, hypereosinophilic syndrome and granulomatosis with polyangiitis.[2]

INNOVATION and/or ADVANTAGES

If licensed, benralizumab will offer an additional treatment option for moderate to severe COPD for patients with exacerbation history who do not achieve adequate symptom control with existing agents.

DEVELOPER

AstraZeneca UK Ltd

AVAILABILITY, LAUNCH or MARKETING

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has adopted a positive opinion, recommending the marketing authorisation of benralizumab as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting b-agonists.[3]

PATIENT GROUP

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a treatable (but not curable) and largely preventable lungs disease with symptoms such as cough, sputum, and increasing breathlessness.[4] It is

characterized by airflow obstruction which is usually progressive, not fully reversible, and does not change markedly over several months.[5]

Airflow obstruction is due to a combination of airway disease (obstructive bronchiolitis) and parenchymal damage (emphysema), resulting from an enhanced inflammatory response to noxious particles or gases, usually from cigarette smoke, but also from environmental and occupational exposures.[4]

COPD is the preferred term for chronic bronchitis, emphysema, or chronic obstructive airways disease.[6]

Current NICE guidelines establish the following criteria for COPD diagnosis:[5]

- Airflow obstruction is defined as a reduced FEV1/FVC ratio (where FEV1 is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV1/FVC is less than 0.7.
- If FEV1 is ≥ 80% predicted normal a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.

COPD can be characterised by frequent (and sometimes preventable) exacerbations or 'flare-ups', where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations, which can lead to admission to hospital. According to current NICE guidelines, "an exacerbation is a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, and increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication".[5] Exacerbations of COPD occur at least annually in approximately 50-60% of patients with moderate/severe COPD.[7]

Over time, patients experience increasing breathlessness and more frequent exacerbations of respiratory symptoms, leading to increasing disability and reduced quality of life.[8] Patients with COPD often have significant co-morbidities such as heart failure, diabetes, lung cancer, osteoarthritis, and depression.[9] Type 2 respiratory failure is observed in a quarter of COPD patients admitted to hospital.

COPD produces symptoms, disability and impaired quality of life which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction.[10]

CLINICAL NEED and BURDEN OF DISEASE

An estimated 210 million people suffer from COPD worldwide, and it is predicted to be the third leading cause of death by 2020.[11] In the UK, an estimated 1.2 million people are living with diagnosed COPD.[12] In terms of diagnosed cases, this makes COPD the second most common lung disease in the UK, after asthma. Around 2% of the whole population – 4.5% of all people aged over 40 – live with diagnosed COPD.[12]

The prevalence of COPD increases with age (it is rare before 35 years of age), and is generally higher among smokers.[13] According to the British Lung Foundation, that prevalence is growing. From 2008 to 2012 there was a 9% increase. In the UK, 115,000 people are diagnosed with COPD each year.[12]

The UK is among the top 20 countries for COPD mortality worldwide. In Europe, only Denmark and Hungary have higher death rates for COPD. In the United States and New Zealand rates are higher

than in the UK.[12] For England, the COPD mortality rate was higher in the North East and North West of England, compared with the UK generally. In those regions, the relative increase was greater among females than males. Death rates from COPD were notably lower in the East of England and the South West than in other parts of the UK.[12]

In 2010 it was estimated that COPD cost the NHS more than £800 million each year, (equivalent to £1.3 million per 100,000 population). COPD was responsible for 24 million lost working days per annum estimated as costing £2.7 billion.[14]

The latest hospital Episodes statistics for 2016/17 revealed 1,283,972 admissions for other COPD (ICD-10 code J44) and 236,078 day cases.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Mepolizumab for treating chronic obstructive pulmonary disease (GID-TA10239). Expected date of issue to be confirmed.
- NICE technology appraisal. Roflumilast for treating chronic obstructive pulmonary disease (TA461). July 2017.
- NICE clinical guideline in development. Chronic obstructive pulmonary disease in over 16s: diagnosis and management (update) (GID-NG10026). Expected November 2018.
- NICE clinical guideline. Chronic obstructive pulmonary disease in over 16s: diagnosis and management (CG101). June 2010.
- NICE quality standard. Chronic obstructive pulmonary disease in adults (QS10). July 2011. Updated: February 2016.

NHS ENGLAND and POLICY GUIDANCE

None identified

OTHER GUIDANCE

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2016.
- Primary Care Respiratory Society UK. Diagnosis and management of COPD in primary care. 2015.
- Scottish Intercollegiate Guidelines Network. Chronic obstructive pulmonary disease services. 2010.

CURRENT TREATMENT OPTIONS

High value interventions in the management of COPD include smoking cessation advice, pulmonary rehabilitation and flu vaccination.[5,16]

Pharmacological treatments include:

• Beta-2 agonists:

  - Short-acting beta-2 agonists – salbutamol and terbutaline.
  - Long-acting beta-2 agonists – salmeterol, formoterol, indacaterol, olodaterol and vilanterol.

• Muscarinic antagonists:

- Short-acting muscarinic antagonists – ipratropium.
- Long-acting muscarinic antagonists – tiotropium, umeclidinium, aclidinium and glycopyrronium.

• Inhaled combination therapy:

- Formoterol plus budesonide.
- Salmeterol plus fluticasone propionate.
- Vilanterol flus fluticasone furoate.

• Oral therapy:

- Oral corticosteroid therapy – maintenance use of oral corticosteroid therapy in COPD is not normally recommended. However, some people with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn after an exacerbation.
- Mucolytics – carbocisteine.
- Methylxanthines – aminophylline and theophylline.

Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:[17]

- the disease is severe, defined as a forced expiratory volume in 1 second (FEV1) after a bronchodilator of less than 50% of predicted normal, and
- the person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.

Exacerbations are usually treated with an increase in usual medication combined with a course of steroids and/or antibiotics.[5] Non-invasive ventilation significantly reduces mortality in people with COPD who develop type 2 respiratory failure.[18] Pulmonary rehabilitation, a programme of exercise and education for people with long-term lung conditions, is also recommended.[19]

EFFICACY and SAFETY

Trial	TERRANOVA; NCT02155660; D3251C00004; Phase III
Sponsor	AstraZeneca
Status	Ongoing, not recruiting
Source of Information	Trial registry[20]
Location	Argentina, Australia, Brazil, Chile, Colombia, 8 EU countries (not UK); Israel, Mexico, New Zealand, Norway, Peru, Philippines, Serbia, Taiwan, Thailand, Turkey, Ukraine, United States, and Vietnam
Design	Randomised; placebo/controlled
Participants	n=2,255; aged 40-85 years; male and female; moderate to very severe COPD with Post Bronchodilator (BD) FEV1>20% and ≤65% -≥2 moderate or ≥1 severe COPD exacerbation(s) required treatment or hospitalization within 2-52 weeks prior to visit1

Schedule	Benralizumab subcutaneously on study week 0 until study week 48 inclusive
Follow-up	Active treatment for 48 weeks, follow up for primary outcome measure up to 56 weeks.
Primary Outcomes	Annual COPD (Chronic Obstructive Pulmonary Disease) exacerbation rate
Secondary Outcomes	• Effect of benralizumab on health status/health-related quality of life [Time Frame: up to 56 weeks] St. George's Respiratory Questionnaire (SGRQ), Chronic Obstructive Pulmonary Disease assessment tool (CAT) • Effect of benralizumab on pulmonary function [Time Frame: up to 56 weeks] Pre-dose/pre-bronchodilator Forced expiratory volume in one second (FEV1) at the study centre • Effect of benralizumab on respiratory symptoms [Time Frame: up to 56 weeks] Baseline/Transitional Dyspnea Index (BDI/TDI) • Effect of benralizumab on rescue medication use [Time Frame: up to 56 weeks] Total rescue medication use (average puffs/day), recorded by patient using electronic diary • Effect of benralizumab on nocturnal awakenings [Time Frame: up to 56 weeks] Number of nights with awakening due to COPD, recorded by patient using electronic diary • Effect of benralizumab on the severity, frequency and duration of exacerbations of COPD [Time Frame: up to 56 weeks] Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO) - Patient-reported Outcome questionnaire • Effect of benralizumab on healthcare resource utilization [Time Frame: up to 56 weeks] Annual rate of hospitalizations, combined hospitalizations and emergency department visits, unscheduled visits and healthcare encounters due to COPD • Benralizumab concentration in serum [Time Frame: up to 60 weeks] • Pharmacokinetics (PK) - steady-state serum pre-dose concentration • Safety and tolerability of benralizumab [Time Frame: From baseline visit up to 56 weeks] Adverse Events/ Serious Adverse Events (AE/SAE) - Laboratory variables - 12 lead Electrocardiogram (ECG) - Physical Examination - Vital Signs • Immunogenicity of benralizumab [Time Frame: up to 60 weeks] Determination of Anti-drug antibodies (ADA) development • Effect of benralizumab on general health status [Time Frame: up to 56 weeks] European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaire • Impact of benralizumab on blood eosinophil levels [Time Frame: up to 60 weeks] Blood eosinophils levels
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date April 2018 (Final data collection date for primary outcome measure)

Trial	GALATHEA; NCT02138916; D3251C00003; Phase III
Sponsor	AstraZeneca
Status	Ongoing, not recruiting

Source of Information	Trial registry[21]
Location	10 EU countries (incl. UK); Canada, Japan, Korea, Russian Federation, South Africa, Switzerland, and United States
Design	Randomised; placebo/controlled
Participants	N=1,656; age 40-85 years; male and female; moderate to very severe COPD with Post Bronchodilator (BD) FEV1>20% and ≤65%. 4.≥2 moderate or ≥1 severe COPD exacerbation(s) required treatment or hospitalization within 2-52 weeks prior to visit1.
Schedule	Benralizumab administered subcutaneously (regimen to specified)
Follow-up	Active treatment period N/R, overall follow-up period of 56 weeks
Primary Outcomes	Annual COPD (Chronic Obstructive Pulmonary Disease) exacerbation rate
Secondary Outcomes	• Evaluation of the effect of benralizumab on health status/health-related quality of life [Time Frame: up to 56 weeks] St. George's Respiratory Questionnaire (SGRQ), Chronic Obstructive Pulmonary Disease assessment tool (CAT) • Evaluation of the effect of benralizumab on pulmonary function [Time Frame: up to 56 weeks] Pre-dose/pre-bronchodilator Forced expiratory volume in one second (FEV1) at the study centre • Evaluation of the effect of benralizumab on respiratory symptoms [Time Frame: up to 56 weeks] Baseline/Transitional Dyspnea Index (BDI/TDI) • Evaluation of the effect of benralizumab on rescue medication use [Time Frame: up to 56 weeks] Total rescue medication use (average puffs/day), recorded by patient using electronic diary • Evaluation of the effect of benralizumab on nocturnal awakenings [Time Frame: Up to 56 weeks] Number of nights with awakening due to COPD, recorded by patient using electronic diary. • Evaluation of the effect of benralizumab on the severity, frequency and duration of Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO) - Patient-reported Outcome questionnaire defined events [Time Frame: Up to 56 weeks] Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO) - Patient-reported Outcome questionnaire • Evaluation of the effect of benralizumab on healthcare resource utilization due to COPD [Time Frame: up to 56 weeks] Annual rate of hospitalizations, combined hospitalizations and emergency department visits, unscheduled visits and healthcare encounters due to COPD • Evaluation of the pharmacokinetics parameters of benralizumab. [Time Frame: up to 60 weeks] Pharmacokinetics (PK) - steady-state serum pre-dose concentration • Assessment of the safety and tolerability of benralizumab [Time Frame: From baseline visit up to 56 weeks] Adverse Events/ Serious Adverse Events (AE/SAE) - Laboratory variables - 12 lead Electrocardiogram (ECG)- Physical Examination - Vital Signs • Evaluation of the immunogenicity of benralizumab [Time Frame: up to 60 weeks] Determination of Anti-drug antibodies (ADA)
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Estimated primary completion date April 2018 (final collection date for primary outcome measure)

ESTIMATED COST and IMPACT

COST

The cost of benralizumab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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