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Health Technology Briefing
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Mepolizumab add-on therapy for chronic obstructive pulmonary disease with eosinophil-associated exacerbations

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35867	NICE ID: Not available	UKPS ID: 641345

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Mepolizumab is in clinical development as an add-on therapy for chronic obstructive pulmonary disease (COPD) with eosinophilic disease. COPD is the name for a group of lung conditions that cause breathing difficulties. COPD is a long-term condition that is characterised by periods of acute exacerbations (worsening of respiratory symptoms) such as shortness of breath, cough and/or mucus production. COPD can be associated with a high level of eosinophils (a type of white blood cell) in the blood, which may contribute to inflammation, airway obstruction and mucus plugging. People with COPD are at increased risk of developing heart disease, lung cancer and a variety of other conditions, which significantly contributes to the morbidity and mortality of COPD. There is currently a high unmet need for appropriate treatment options for COPD.

Mepolizumab is a monoclonal antibody (a type of protein) which reduces the levels of eosinophils. Mepolizumab targets human interleukin-5 (IL-5 – a protein involved in immune response) which is responsible for the production and survival of eosinophils. By binding to IL-5, mepolizumab blocks its action and thereby reduces the numbers of eosinophils and inflammatory activation of further immune cells. This helps to reduce inflammation, potentially resulting in an improvement of symptoms. Mepolizumab is administered by subcutaneous injection. If licensed, mepolizumab would provide a new treatment option for patients with COPD with eosinophilic disease.

Proposed Indication

Mepolizumab is indicated as an add-on treatment for patients with chronic obstructive pulmonary disease COPD with eosinophilic disease with frequent exacerbations.[1]

Technology

Description

Mepolizumab (Nucala) is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.[2]

Mepolizumab is currently in clinical development as an add-on therapy for patients with moderate to severe COPD with frequent exacerbations and an eosinophilic phenotype. In the phase III clinical trial (MATINEE; NCT04133909), mepolizumab will be administered as a subcutaneous (SC) injection (100 mg/mL) delivered once every 4 weeks using a pre-filled safety syringe.[3]

Key Innovation

In the phase III clinical trials (METREX; NCT02105948) and (METREO; NCT02105961), mepolizumab was found to reduce the annual rate of moderate to severe exacerbations in patients with eosinophil-associated COPD.[1,4,5] In COPD patients who were already receiving maximal inhaled glucocorticoid–based triple inhaled maintenance therapy, mepolizumab resulted in lower rates of moderate or severe exacerbations than placebo and in longer times to a first exacerbation, and the extent of these effects was related to blood eosinophil count. With the use of mepolizumab as a targeted treatment to reduce blood eosinophil counts, these trials show the importance of blood eosinophils in COPD exacerbations.[4]
Further analysis of METREX and METREO studies showed that mepolizumab reduced the number of COPD flares that needed antibiotics or steroid tablets. The number of patients who went to hospital was also reduced by about one fifth, and quality of life was improved. Mepolizumab worked better in patients who had higher numbers of eosinophils in the blood before they were given mepolizumab. Mepolizumab also worked better for patients whose flares were treated with steroid tablets compared with antibiotics.[6]

If licensed, mepolizumab will offer an additional treatment option for patients with COPD with eosinophilic disease with frequent exacerbations.

Regulatory & Development Status

Mepolizumab currently has Marketing Authorisation in the UK as an add-on therapy for the following indications: [7]

- Severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older
- With intranasal corticosteroids in adult patients with severe chronic rhinosinusitis with nasal polyps for whom therapy with systemic corticosteroids and/or surgery do not provide adequate control
- Relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis in patients aged 6 years and older
- Inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause in adults

Patient Group

Disease Area and Clinical Need

Chronic obstructive pulmonary disease (COPD) refers to a group of lung conditions that cause breathing difficulties. It includes emphysema (damage to the air sacs in the lungs) and chronic bronchitis (long-term inflammation of the airways).[8] Exacerbations are acute episodes of worsening COPD symptoms (such as increased breathlessness, cough and sputum) which are beyond normal day-to-day variations of COPD.[9] Acute exacerbations of COPD can be triggered by a range of factors including respiratory tract infections (most commonly rhinovirus), smoking, and environmental pollutants.[10] Exacerbations accelerate rate of decline in lung function, reduce quality of life and increase risk of mortality. Exacerbations requiring hospital treatment are associated with poorer prognosis and increased risk of death.[11] Blood eosinophil is a biomarker to reflect underlying eosinophilic airway inflammation.[12] The main symptoms of COPD include: shortness of breath, persistent chest cough with phlegm, frequent chest infections and persistent wheezing. The major risk factors for COPD are smoking and long-term exposure to harmful fumes or dust.[8]

COPD is the second most common lung disease in the UK, after asthma. Around 2% of the population over 16 years old – 4.5% of all people aged over 40 – live with diagnosed COPD.[13,14] Reported mortality rates following hospitalisation for an acute exacerbation vary from 23–80% with a 5-year mortality rate of around 50%.[11] In England, 2022-23, there were 55,877 finished consultant episodes (FCE) and 30,340 admissions for COPD with acute exacerbation, unspecified (ICD-10 code J441) which resulted in 141,475 FCE bed days and 153 day cases.[15]

Recommended Treatment Options

NICE currently recommends roflumilast as an add-on to bronchodilator therapy, for treating severe COPD in adults with chronic bronchitis.[16]

Other pharmacological treatment options include:[17]

- Short-acting bronchodilator inhalers
  - beta-2 agonist inhalers – such as salbutamol and terbutaline
  - antimuscarinic inhalers – such as ipratropium
- Long-acting bronchodilator inhalers
  - beta-2 agonist inhalers – such as salmeterol, formoterol and indacaterol
  - antimuscarinic inhalers – such as tiotropium, glycopyrronium and aclidinium
- Steroid inhalers
- Theophylline tablets
- Mucolytics
- Steroid tablets
- Antibiotics

Clinical Trial Information

Trial	**MATINEE;** NCT04133909; A Multi-center, Randomised, Double-blind, Parallel-group, Placebo-controlled Study of Mepolizumab 100 mg SC as add-on Treatment in Participants With COPD Experiencing Frequent Exacerbations and Characterised by Eosinophil Levels **Phase III** – Active, not recruiting **Location(s):** 13 EU countries, UK, USA, Canada, and other countries

	Primary completion date: August 2024
Trial Design	Randomised, parallel assignment, double-blind, placebo-controlled
Population	N = 806 (actual); aged 40 years and older; participants with the following characteristics: a peripheral blood eosinophil count of >=300 cells per microliter (µL); a clinically documented history of COPD for at least 1 year; a history of two or more moderate COPD exacerbations that were treated with systemic corticosteroids with or without antibiotics or at least one severe COPD exacerbation requiring hospitalisation
Intervention(s)	Mepolizumab (SC) 100 mg/mL administered once every 4 weeks using a pre-filled safety syringe
Comparator(s)	Placebo (0.9% sodium chloride solution) (SC) administered once every 4 weeks using a pre-filled safety syringe
Outcome(s)	Annualised rate of moderate to severe exacerbations [Time Frame: Up to Week 104]
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**METREO; MEA117113;** NCT02105961**;** Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level **Phase III** – Completed **Location(s):** 6 EU countries, UK, USA, Canada, and other countries **Study completion date:** January 2017
Trial Design	Randomised, parallel assignment, triple masking
Population	N = 674 (actual); aged 40 years and older; participants with a clinically documented history of COPD for at least 1 year and a history of exacerbations
Intervention(s)	• Experimental: Arm 1 - 100 mg mepolizumab (SC) every 4 weeks (13 administrations during 52-week treatment period) along with their baseline standard of care COPD medication • Experimental: Arm 2 - 300 mg mepolizumab (SC) every 4 weeks (13 administrations during 52-week treatment period) along with their baseline standard of care COPD medication
Comparator(s)	Placebo (0.9% sodium chloride) (SC) every 4 weeks (13 administrations during 52-week treatment period) along with their baseline standard of care COPD medication
Outcome(s)	Rate of Moderate to Severe Exacerbations [Time Frame: From randomization to Week 52]
Results (efficacy)	The mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg mepolizumab

	group, and 1.49 per year in the placebo group. The rate ratios for exacerbations in the 100-mg and 300-mg mepolizumab groups versus the placebo group were 0.80 (95% CI, 0.65 to 0.98; adjusted P=0.07) and 0.86 (95% CI, 0.70 to 1.05; adjusted P=0.14), respectively. A greater effect of mepolizumab, as compared with placebo, on the annual rate of moderate or severe exacerbations was found among patients with higher blood eosinophil counts at screening.[4]
Results (safety)	The safety profile of mepolizumab was similar to that of placebo.[4] The frequency of adverse events was 81% in the placebo group, 83% in the mepolizumab 100mg group and 85% in the mepolizumab 300mg group; and the frequency of serious adverse events was 26% in the placebo group, 23% in the mepolizumab 100mg group and 24% in the mepolizumab 300mg group.[4]

Clinical Trial Information

Trial	**METREX; MEA117106;** NCT02105948; Mepolizumab vs. Placebo as add-on Treatment for Frequently Exacerbating COPD Patients **Phase III** – Completed **Location(s)**; 10 EU countries, USA, Canada and other countries **Study completion date:** January 2017
Trial Design	Randomised, parallel assignment, triple masking
Population	N = 837 (actual); aged 40 years and older; participants with a clinically documented history of COPD for at least 1 year and a history of exacerbations
Intervention(s)	Mepolizumab (SC) 100mg every 4 weeks (13 administrations during 52-week treatment period) along with optimized standard of care background therapy
Comparator(s)	Placebo (0.9% sodium chloride) (SC) every 4 weeks (13 administrations during 52-week treatment period) along with optimized standard of care background therapy
Outcome(s)	Rate of Moderate to Severe Exacerbations in Participants in the High Stratum [Time Frame: From randomization to Week 52]
Results (efficacy)	The mean annual rate of moderate to severe exacerbations in the modified intention-to-treat population with an eosinophilic phenotype (462 patients) was 1.40 per year in the mepolizumab group versus 1.71 per year in the placebo group (rate ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98; adjusted P=0.04); no significant between-group differences were found in the overall modified intention-to-treat population (836 patients) (rate ratio, 0.98; 95% CI, 0.85 to 1.12; adjusted P>0.99).[4]
Results (safety)	The safety profile of mepolizumab was similar to that of placebo.[4] The frequency of adverse events was 81% in the placebo group and 79% in the mepolizumab 100mg group; and the frequency of serious adverse events was 28% in the placebo group and 25% in the mepolizumab 100mg group.[18]

Estimated Cost

The cost of mepolizumab available to the NHS has been made confidential by GlaxoSmithKline UK Ltd

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Roflumilast for treating chronic obstructive pulmonary disease (TA461). July 2017.
- NICE clinical guideline. Chronic obstructive pulmonary disease in over 16s: diagnosis and management (NG115). December 2018. Last updated July 2019.
- NICE quality standard. Chronic obstructive pulmonary disease in adults (QS10). July 2011. Last updated September 2023.

NHS England (Policy/Commissioning) Guidance

No relevant guidance found.

Other Guidance

- BMJ Best Practice. Chronic obstructive pulmonary disease (COPD). 2023.[19]
- NHS RightCare. RightCare Pathway: COPD. 2017.[20]
- NHS Improvement. Lung: National Improvement Projects. Improving earlier diagnosis and the long-term management of COPD: Testing the case for change. 2011.[21]

Additional Information

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