Mepolizumab (Nucala) for chronic obstructive pulmonary disease with eosinophilic bronchitis – add on therapy

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’, which can lead to being admitted to hospital.

Mepolizumab is a new drug for the treatment of chronic obstructive pulmonary disease that is injected under the skin. If mepolizumab 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.

NIHR HSRIC ID: 9120
TARGET GROUP

• Chronic obstructive pulmonary disease (COPD): with eosinophilic bronchitis – add on therapy.

TECHNOLOGY

DESCRIPTION

Mepolizumab (Nucala; SB-240563) is an anti-interleukin-5 fully humanised IgG1 monoclonal antibody. Interleukin-5 stimulates the production, activation, and maturation of eosinophils. Mepolizumab binds to interleukin-5 with high specificity to inhibit its signalling. This causes a sustained reduction in the numbers of circulating eosinophils and is therefore intended to be used in conditions characterised by increased levels of eosinophils. Mepolizumab is administered by subcutaneous (SC) injection at 100mg every 4 weeks.

Mepolizumab (as Nucala) is licensed in the EU as an add-on treatment for severe refractory eosinophilic asthma in adult patients. Very common and common (≥1%) reported adverse events include headache, lower respiratory tract infection, urinary tract infection, pharyngitis, nasal congestion, abdominal pain, eczema, back pain, local injection site reactions, and pyrexia.

Mepolizumab is also currently in phase III development for the treatment of eosinophilic granulomatosis with polyangiitis, and in phase II development for asthma in children and nasal polyps in adults.

INNOVATION and/or ADVANTAGES

If licensed, mepolizumab will offer an additional subcutaneous treatment option for patients with COPD with eosinophilic bronchitis, who do not achieve adequate symptom control with existing agents.

DEVELOPER

GlaxoSmithKline UK.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

COPD is a lung disease characterised by airflow obstruction which is usually progressive, not fully reversible, and does not change markedly over several months. Symptoms include exertional breathlessness, chronic cough, regular sputum production, and frequent winter

* Company provided information.
bronchitis or wheeze\textsuperscript{2}. Possible extra-pulmonary effects include abnormal weight loss, ankle oedema, abnormal posture, drowsiness, fatigue, chest pain, and waking at night\textsuperscript{3,4}.

Airflow obstruction occurs 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\textsuperscript{5}. The progression of the disease can be slowed, but not halted, by stopping smoking\textsuperscript{6}.

The National Institute of Health and Care Excellence (NICE) guidance uses the following definition of COPD\textsuperscript{2}:

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

Severity of airflow obstruction is graded using categories of FEV\textsubscript{1} as a percentage of predicted normal values for a healthy reference population\textsuperscript{7}. Current categories of airflow limitation used in UK practice are:

- Mild disease: FEV\textsubscript{1} $\geq$80% of predicted value (in the presence of respiratory symptoms)
- Moderate disease: FEV\textsubscript{1} 50-79% of predicted value
- Severe disease: FEV\textsubscript{1} 30-49% of predicted value
- Very severe disease: FEV\textsubscript{1} <30% of predicted value

COPD can be characterised by frequent (and sometimes preventable) exacerbations, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations, which can lead to admission to hospital\textsuperscript{2,6}. Exacerbations of COPD occur at least annually in approximately 50-60% of patients with moderate/severe COPD\textsuperscript{7}. Over time, patients experience increasing breathlessness and more frequent exacerbations of respiratory symptoms, leading to increasing disability and reduced quality of life\textsuperscript{6,7}. Patients with COPD often have significant co-morbidities such as heart failure, diabetes, lung cancer, osteoarthritis, and depression\textsuperscript{2,4}. Type 2 respiratory failure is observed in a quarter of COPD patients admitted to hospital\textsuperscript{8}.

### CLINICAL NEED and BURDEN OF DISEASE

COPD affects 5-10% of people worldwide and is presently the fourth leading cause of death worldwide\textsuperscript{7,9}. The World Health Organization (WHO) predicts that it will become the third leading cause of death by 2030\textsuperscript{9}. In the UK, COPD is the second most common cause of emergency admissions, costing the NHS over £800 million per year\textsuperscript{10,11}. Around 1 million people in England have been diagnosed with COPD\textsuperscript{12}, and it is estimated that up to 1.3 million people may have COPD that has not yet been diagnosed\textsuperscript{13}. In 2014-15, the estimated prevalence of COPD in England was 1.82%. COPD is associated with eosinophilic bronchitis in 10-20% of patients\textsuperscript{14}.

Approximately 15% of patients with COPD have exacerbations each year that are severe enough to lead to hospital admission\textsuperscript{7}. In 2014-15, there were 130,124 hospital admissions for bronchitis, emphysema, or other chronic obstructive pulmonary disease (ICD-10 J40-44) in England, accounting for 229,704 finished consultant episodes and 754,634 bed days\textsuperscript{15}. Mortality rates are high with one in 12 patients dying during their hospital stay and one in 6\textsuperscript{b}.

\textsuperscript{b} Expert personal communication.
dying within 90 days. In 2014, 26,267 deaths due to COPD were registered in England and Wales.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal. Roflumilast for the management of severe chronic obstructive pulmonary disease (TA244). January 2012.
- NICE guidelines.

**NHS England Policies and Guidance**

- None identified.

**Other Guidance**

- Primary Care Respiratory Society UK. Diagnosis and management of COPD in primary care. 2015.

**CURRENT TREATMENT OPTIONS**

COPD is treatable, but not curable; early diagnosis and treatment can markedly slow decline in lung function and hence lengthen the period in which someone can enjoy an active life. However, expert opinion notes that enjoyment of an active life does not always correlate well with measured FEV1. There is great variation in the symptoms, functional limitations and degrees of psychological well-being of patients with COPD patients, as well as the speed of the progression of COPD towards more severe stages; this calls for a multi-faceted response. Encouraging patients with COPD to stop smoking is one of the most important components of their management.

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.

\(^c\) Expert personal communication.
Long-acting muscarinic antagonists – tiotropium, umeclidinium, aclidinium and glycopyrronium.

**Inhaled combination therapy:**
- Formoterol plus budesonide.
- Salmeterol plus fluticasone propionate.
- Vilanterol plus 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.

Exacerbations are usually treated with an increase in usual medication combined with a course of steroids and/or antibiotics². Non-invasive ventilation significantly reduces mortality in people with COPD who develop type 2 respiratory failure⁸. Pulmonary rehabilitation, a programme of exercise and education for people with long-term lung conditions, is also recommended²⁰.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02105948, 117106; mepolizumab vs placebo; phase III.</th>
<th>NCT02105961, 117113; mepolizumab vs placebo; phase III.</th>
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<tr>
<td>Sponsor</td>
<td>GlaxoSmithKline.</td>
<td>GlaxoSmithKline.</td>
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<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry&lt;sup&gt;2¹&lt;/sup&gt;.</td>
<td>Trial registry&lt;sup&gt;2²&lt;/sup&gt;.</td>
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<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=800 (planned); aged 40 yrs and older; COPD; pre- and post-salbutamol FEV1/FVC ratio &lt;0.7; post-salbutamol FEV1 &gt;20% and ≤80% of predicted normal values; at least two moderate COPD exacerbations in previous 12 mths; optimised standard of care background therapy that includes inhaled corticosteroids plus two additional COPD medications for 12 mths; no history of asthma; no pneumonia, exacerbation, or lower respiratory infection in previous 4 wks; no lung reduction surgery in previous 12 mths; no participants in the acute phase of a pulmonary rehabilitation programme; no oxygen therapy greater than 4L/min; no myocardial infarction, unstable angina, or unstable cardiac arrhythmia; no other hypereosinophilic syndromes, current malignancy, or immunodeficiency.</td>
<td>n=660 (planned); aged 40 yrs and older; COPD with eosinophilic inflammation (≥150 cells/µL) despite steroid therapy; FEV1/FVC ratio &lt;0.7; post-salbutamol FEV1 &gt;20% and ≤80% of predicted normal values; optimised standard of care background therapy that includes inhaled corticosteroids plus two additional COPD medications for 12 mths; no history of asthma; no pneumonia, exacerbation, or lower respiratory infection in previous 4 wks; no lung reduction surgery in previous 12 mths; no participants in the acute phase of a pulmonary rehabilitation programme; no oxygen therapy greater than 4L/min; no myocardial infarction, unstable angina, or unstable cardiac arrhythmia; no other hypereosinophilic syndromes, current malignancy, or immunodeficiency.</td>
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<td>Schedule</td>
<td>Randomised to mepolizumab 100mg SC every 4 wks; or placebo SC every 4 wks.</td>
<td>Randomised to mepolizumab 100mg SC every 4 wks; or mepolizumab 300mg SC every 4 wks; or placebo SC every 4 wks.</td>
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</table>
Follow-up  | Active treatment for 1 yr. | Active treatment for 1 yr.  
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Primary outcome  | Frequency of moderate/severe exacerbations. | Frequency of moderate/severe exacerbations.  
Secondary outcomes  | Frequency of COPD exacerbations requiring emergency department visits; change in St. George’s Respiratory Questionnaire-COPD score; change in CAT score; time to first moderate/severe exacerbation. | Time to first moderate/severe exacerbation; frequency of COPD exacerbations requiring emergency department visit; change in St. George’s Respiratory Questionnaire-COPD score; change in CAT score.  
Expected reporting date  | Study completion date reported as Jan 2017. | Study completion date reported as Jan 2017.  

**ESTIMATED COST and IMPACT**

**COST**

The cost of mepolizumab 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: if successful in reducing symptoms and risk of exacerbations requiring admission.
- 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: if successful in reducing symptoms and risk of exacerbations requiring admission.
- Other: uncertain unit cost compared to existing treatments.
- None identified

**Other Issues**
- Clinical uncertainty or other research question identified
- None identified
REFERENCES