Anti-IL-5 in asthma

Module 4

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Learning objectives

- Know why IL-5 is an appropriate treatment target in eosinophilic disorders
- Understand the potential that biologics have in revolutionising severe asthma treatment
- Understand the proof-of-concept studies for mepolizumab and subsequent large-scale clinical trials
- Review mepolizumab’s safety data
- Understand mepolizumab’s posology
- Know the factors that affect blood eosinophil counts as markers for treatment

IL-5, interleukin-5.

Severe asthma: Immune components
Eosinophils

- Eosinophils are a leukocyte subclass involved in defence against parasites:\textsuperscript{1}
  - Low proportion of total white blood count\textsuperscript{1}
  - Usually absent in healthy lungs\textsuperscript{2,3}
- Eosinophilic inflammation is a predictor of asthma exacerbations\textsuperscript{4}
- Eosinophils are key in asthma pathogenesis, including airway hyperresponsiveness, elevated mucus production, airway narrowing and airway remodelling\textsuperscript{1,5,6}

In a UK cluster analysis of 187 patients with refractory asthma, 36% (n=68) had eosinophilic inflammation\textsuperscript{7}

In a Brazilian cross-sectional study of 74 patients with severe asthma, 79% (n=53) had eosinophilic disease (sputum eosinophil levels ≥3%)\textsuperscript{8}


Pathways towards eosinophilic airway inflammation: Allergic

Allergic eosinophilic inflammation is triggered by classical allergens, such as pollen. It is characterised by high IgE production resulting from Th2 cell activation.

Inhaled allergens such as pollen interact with dendritic cells and mast cells within the lower airways. This triggers an altered adaptive immune response, especially in people with a genetic predisposition.

Mast cells and basophils degranulate in response to IgE surface receptor activation. This releases inflammatory mediators such as cytokines, prostaglandins, leukotrienes and histamine. These mediators directly cause oedema and smooth muscle contraction in the lower airways, which results in the clinical symptoms of asthma.

Both mast cell mediators and Th2 cell cytokines like IL-5 and eotaxins can recruit eosinophils into the lung tissue.

IgE, immunoglobulin E; IL-5, interleukin 5; Th2, T-helper cell type 2.

Pathways towards eosinophilic airway inflammation: Non-allergic

The processes involved in **non-allergic eosinophilic inflammation** are a focus of ongoing research. They are thought to involve the innate immune system responding to environmental triggers like air pollution and viral infection\(^1\-^3\).

Patients with non-allergic eosinophilic asthma have persistently high sputum eosinophil levels but little evidence of clinical allergy and are often steroid-refractory\(^4\).

**Exogenous irritants** such as viruses and tobacco smoke can activate airway epithelial cells and trigger an innate immune response.\(^1\)

**Macrophages** are a type of resident cell of the innate immune system. They respond to triggers in the airway by releasing mediators such as CCL3.\(^2\)

Evidence is emerging for ILC2s, which are a type of effector cell reactive to a range of innate immune signals such as IL-33 from macrophages and epithelial IL-25, IL-33 and TSLP.\(^1\-^3\)

Activated ILC2s secrete IL-5, which is a key cytokine in eosinophil recruitment.\(^1,^5\)

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CCL3, chemokine ligand 3; IL-5/25/33, interleukin-5/25/33; ILC2, innate lymphoid cell type 2; TSLP, thymic stromal lymphopoietin.


IL-13 is produced by Th2 cells and ILC2s. It regulates IgE production, recruits eosinophils and other inflammatory cells and stimulates mucus hypersecretion from goblet cells.1-3

IL-13 shares a subset of receptors with IL-4. Blockade of these receptors inhibits the effect of both IL-13 and IL-4 on epithelial cells, smooth muscle cells, fibroblasts, monocytes and activated B cells.4

IL-4 is key in Th2 inflammation. It binds to two types of receptors. Type 1 receptors, which are found on B and T lymphocytes, monocytes, eosinophils and fibroblasts, control differentiation of Th2 cells and are activated by IL-4 alone. Type 2 receptors, found on epithelial cells, smooth muscle cells, fibroblasts, monocytes and activated B cells, are activated by both IL-4 and IL-13.4

IL-4 also stimulates B cell differentiation, antibody production and mucus hypersecretion.1,8,9

IL-5 is critical for eosinophil development, survival and recruitment into lung tissue.10 It is released by effector cells such as Th2 cells and ILC2s during airway inflammation.2,9,11 Eosinophils also produce IL-5, as well as expressing the IL-5 receptor on their surface. IL-5 binding to its receptor activates eosinophils and results in eosinophilic inflammation.12

IgE is a key mediator of allergic asthma and Th2 response. It causes airway oedema, bronchoconstriction and eosinophil recruitment when it binds to the Fc receptor on mast cells.5-7

Blocking IgE interrupts the allergic inflammatory cascade.3
IL-5 is responsible for eosinophil production, survival and migration\(^1\)

IL-5 is a logical therapeutic target for eosinophilic disorders such as severe asthma with eosinophilic inflammation, due to its key role in mediating eosinophil maturation and release from bone marrow prior to migration into affected tissues\(^2\)
- Its specific effect on eosinophil development and recruitment is an attractive feature as it reduces the likelihood of off-topic or adverse immune effects\(^2\)

Mepolizumab is a humanised mAb (IgG1, κ) that targets human IL-5 with high affinity and specificity\(^3\)
- It binds to the IL-5 receptor, inhibits signalling and reduces eosinophil action\(^3,4\)

Therapeutic options in patients with severe asthma have been limited, but new biologic agents are set to revolutionise this field\(^4\)

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IgG1, immunoglobulin G1; IL-5, interleukin-5; κ, kappa-type human antibody light chain; mAb, monoclonal antibody.

Proof of concept studies: Mepolizumab
What is mepolizumab?

Mepolizumab is a human mAb that inhibits the bioactivity of IL-5

- It targets human IL-5 with high affinity and specificity
- It blocks IL-5 bioactivity by binding to the alpha chain of the IL-5 receptor complex on the eosinophil cell surface
- This inhibits IL-5 signalling and reduces eosinophil production and recruitment

Mepolizumab is indicated as add-on treatment for severe refractory eosinophilic asthma in adult patients, at a dose of 100 mg s.c.

IL-5, interleukin-5; mAb, monoclonal antibody; s.c., subcutaneous.
Mepolizumab’s *in vivo* activity was first demonstrated in mouse models
- The features of asthma were significantly improved when IL-5 signalling was defective or eosinophils were absent

Mepolizumab’s pharmacokinetic properties have been studied in both primates and humans

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monkeys</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>13.0 ± 2.2 days (i.v. dosing)</td>
<td>16.2-21.7 days, regardless of administration route</td>
</tr>
<tr>
<td>Time to C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>4 hours (i.v. dosing)</td>
<td>Dose-proportionate</td>
</tr>
<tr>
<td>AUC</td>
<td>Dose-proportionate (i.v. and s.c. dosing)</td>
<td></td>
</tr>
</tbody>
</table>


Mepolizumab was also tested in preclinical studies in cynomolgus monkeys
- i.v. or s.c. mepolizumab were both well tolerated
- The only animal model with cross-reactivity between mepolizumab and endogenous IL-5
- Mepolizumab suppressed eosinophils in bronchoalveolar lavage and peripheral eosinophils, with no impact on the acute bronchoconstrictor response

AUC, area under the curve; C<sub>max</sub>, maximum serum concentration; IL-5, interleukin-5; i.v., intravenous; s.c., subcutaneous.
The first pharmacodynamics studies in humans

- Mepolizumab was first studied in humans in 2000
  - Double-blind, randomised, placebo-controlled, single dose, parallel-group trial
  - Examined the effect of a single i.v. dose in 24 men with mild allergic asthma
  - Assessed for airway hyperresponsiveness and blood and sputum eosinophil counts
- Demonstrated long-lasting reduction in peripheral blood and sputum eosinophils, but no protection against allergen-induced airway hyperresponsiveness

Mepolizumab clinical development programme
• Three key mepolizumab clinical trials:
  1. **DREAM** (MEA112997): demonstrated significant reductions in exacerbation rate versus placebo\(^1\)
  2. **MENSA** (MEA115588): further confirmed the benefits seen in the DREAM study\(^2\)
  3. **SIRIUS** (MEA115575): investigated the corticosteroid-sparing effect of mepolizumab, resulting in a lower daily OCS dose\(^3\)

• All were randomised, double-blind, placebo-controlled, parallel-group clinical studies of between 24 and 52 weeks in duration\(^1-3\)

• A total of 915 patients with severe refractory eosinophilic asthma received treatment with mepolizumab:\(^4\)
  - 263 patients received the licensed dose of 100 mg s.c.\(^2,3\)
  - 344 patients received mepolizumab 75 mg i.v.*\(^1,2\)
  - 152 patients received mepolizumab 250 mg i.v.*\(^1\)
  - 156 patients received mepolizumab 750 mg i.v.*\(^1\)

\(*\)This is an unlicensed dose/route of administration.

i.v., intravenous; OCS, oral corticosteroid; s.c., subcutaneous.


Overview of the mepolizumab clinical development programme


The DREAM study

Dose Ranging Efficacy And safety with Mepolizumab in severe asthma

Exacerbation reduction study
Objective: to examine the effects of mepolizumab 75 mg,* 250 mg* and 750 mg* administered i.v. on the frequency of clinically significant asthma exacerbations

Primary endpoint: the rate of clinically significant asthma exacerbations, defined as validated episodes of acute asthma requiring treatment with OCS, admission or visit to an emergency department

Secondary and other endpoints: FEV\(_1\); ACQ and AQLQ scores; blood and sputum eosinophil counts; safety profile

Patient population: 616 asthma patients aged 12-74 years old, with at least two exacerbations requiring systemic corticosteroids in the previous year and evidence of eosinophilic inflammation at study entry or in the previous year

Other points of note:
- 12-month duration
- Multicentre
- Double blind
- Randomised
- Placebo controlled
- Phase IIb/III
- Dose-ranging study

*This is an unlicensed dose/route of administration.

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV\(_1\), forced expiratory volume in 1 second; i.v., intravenous; OCS, oral corticosteroid.


DREAM study design

*This is an unlicensed dose/route of administration.
i.v., intravenous.

DREAM: Mepolizumab reduced the number of exacerbations

These results were statistically and clinically significant.

This is an unlicensed dose/route of administration.

i.v., intravenous.


### DREAM: Effect of mepolizumab on prespecified efficacy outcomes

<table>
<thead>
<tr>
<th>Efficacy endpoints at Week 52</th>
<th>Placebo group (n=155)</th>
<th>Mepolizumab 75 mg i.v.* (n=153)</th>
<th>Mepolizumab 250 mg i.v.* (n=152)</th>
<th>Mepolizumab 750 mg i.v.* (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of clinically significant exacerbations per patient per year†</td>
<td>2.40 (0.11)</td>
<td>1.24 (0.12)</td>
<td>1.46 (0.11)</td>
<td>1.15 (0.12)</td>
</tr>
<tr>
<td>Ratio to placebo</td>
<td>-</td>
<td>0.52 (0.39 to 0.69)</td>
<td>0.61 (0.46 to 0.81)</td>
<td>0.48 (0.36 to 0.64)</td>
</tr>
<tr>
<td>Rate of exacerbations requiring admission or visit to emergency department per patient per year†</td>
<td>0.43 (0.24)</td>
<td>0.17 (0.30)</td>
<td>0.25 (0.26)</td>
<td>0.22 (0.26)</td>
</tr>
<tr>
<td>Ratio to placebo</td>
<td>-</td>
<td>0.40 (0.19 to 0.81)</td>
<td>0.58 (0.30 to 1.12)</td>
<td>0.52 (0.27 to 1.02)</td>
</tr>
<tr>
<td>Rate of exacerbations requiring admission†</td>
<td>0.18 (0.29)</td>
<td>0.11 (0.35)</td>
<td>0.12 (0.32)</td>
<td>0.07 (0.39)</td>
</tr>
<tr>
<td>Ratio to placebo</td>
<td>-</td>
<td>0.61 (0.28 to 1.33)</td>
<td>0.65 (0.31 to 1.39)</td>
<td>0.37 (0.16 to 0.88)</td>
</tr>
<tr>
<td>Change of prebronchodilator FEV₁ from baseline (mL)‡</td>
<td>60 (38)</td>
<td>121 (38)</td>
<td>140 (37)</td>
<td>115 (37)</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-</td>
<td>61 (-39 to 161)</td>
<td>81 (-19 to 180)</td>
<td>56 (-43 to 155)</td>
</tr>
<tr>
<td>Change in score on ACQ from baseline‡</td>
<td>-0.59 (0.09)</td>
<td>-0.75 (0.09)</td>
<td>-0.87 (0.09)</td>
<td>-0.80 (0.09)</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-</td>
<td>-0.16 (-0.39 to 0.07)</td>
<td>-0.27 (-0.51 to 0.04)</td>
<td>-0.20 (-0.43 to 0.03)</td>
</tr>
<tr>
<td>Change in score on AQLQ from baseline‡</td>
<td>0.71 (0.09)</td>
<td>0.80 (0.09)</td>
<td>0.77 (0.09)</td>
<td>0.93 (0.09)</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-</td>
<td>0.08 (-0.16 to 0.32)</td>
<td>0.05 (-0.19 to 0.29)</td>
<td>0.22 (-0.02 to 0.46)</td>
</tr>
<tr>
<td>Ratio of geometric mean FE(NO) to baseline†</td>
<td>1.01 (0.06)</td>
<td>0.99 (0.06)</td>
<td>0.91 (0.06)</td>
<td>0.97 (0.06)</td>
</tr>
<tr>
<td>Ratio to placebo</td>
<td>-</td>
<td>0.97 (0.82 to 1.15)</td>
<td>0.90 (0.76 to 1.06)</td>
<td>0.96 (0.81 to 1.13)</td>
</tr>
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</table>

Data in parentheses are 95% CI unless otherwise stated.

*This is an unlicensed dose/route of administration; † Data are mean (SE logs); ‡ Data are mean (SE).

ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; CI, confidence interval; FE(NO), fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; i.v., intravenous; SE, standard error.


Blood eosinophil counts were performed for all patients at all study visits. Sputum eosinophil counts were performed in a subset of 94 patients from sites with previous experience, and only at baseline or screening, and Weeks 4, 16 and 52. Error bars indicate standard errors.

*This is an unlicensed dose/route of administration.

i.v., intravenous.

Change in pre-bronchodilator FEV$_1$ from baseline

Error bars indicate standard error.

*This is an unlicensed dose/route of administration.

FEV$_1$, forced expiratory volume in 1 second; i.v., intravenous.

DREAM: Effect of mepolizumab on health-related quality of life


Error bars indicate SE.

*This is an unlicensed dose/route of administration.

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; i.v., intravenous; SE, standard error.

A post-hoc subanalysis of the DREAM population identified the patients most responsive to mepolizumab as having a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL in the previous year.

Sputum eosinophils did not predict treatment response with mepolizumab.

The annualised rate of exacerbations for patients treated with mepolizumab is compared with the rate of exacerbations on placebo. To determine the percent reduction in exacerbations due to treatment with mepolizumab, the rate ratio is subtracted from 1. For a rate ratio that is equal to 1, there is no reduction compared with placebo response. The mean rate of reduction in exacerbations is higher (72%) in those that have a screening eosinophil count of 150 cells/µL or greater compared with those who are under 150 cells/µL at screening (30%).

Figure adapted from Katz, et al. 2014

• The rate of adverse events was similar across treatment arms, with the exception of injection site reactions: Placebo (6%), mepolizumab 75 mg (5%), 250 mg (8%) and 750 mg (12%)¹
• The most frequently reported adverse event in the DREAM study was headache, which was reported by 17% (n=27) of patients in the placebo group and 21% (n=32) in each mepolizumab group
• The proportion of patients with any adverse event ranged from 78-82% across all four study groups. Serious adverse events occurred in 12-16% of patients across treatment groups
• Three patients died during the study. Two were in the mepolizumab 250 mg i.v. group and one in the mepolizumab 750 mg i.v. group. None of the deaths were deemed to be related to mepolizumab

Summary of adverse events and serious adverse events with mepolizumab

<table>
<thead>
<tr>
<th>Adverse events leading to withdrawal</th>
<th>Placebo (n=155)</th>
<th>Mepolizumab 75 mg i.v.* (n=153)</th>
<th>Mepolizumab 250 mg i.v.* (n=152)</th>
<th>Mepolizumab 750 mg i.v.* (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal adverse events</td>
<td>0</td>
<td>0</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Any on-treatment serious adverse events†</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>25 (16%)</td>
<td>20 (13%)</td>
<td>24 (16%)</td>
<td>19 (12%)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (3%)</td>
<td>7 (5%)</td>
<td>3 (2%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (2%)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2 (1%)</td>
<td>0</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>0</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

*This is an unlicensed dose/route of administration.
†Patients can have more than one event; events shown are those reported in four or more patients across all groups.
i.v., intravenous.
The DREAM study showed the effect of mepolizumab versus placebo and a post-hoc subanalysis identified blood eosinophil levels predictive of response

- Defined a specific population of patients with severe refractory eosinophilic asthma who responded to mepolizumab as an add-on therapy:
  - Clinically and statistically significant reduction in exacerbation rate over 1 year versus placebo
  - Reduced blood and sputum eosinophil counts and good tolerability over 12 months
  - A post-hoc subanalysis demonstrated that an eosinophil cut-off of ≥ 150 cells/µL appeared predictive of response

- The rate of adverse events was similar across treatment arms, with the exception of injection site reactions

Refer to the appendix for baseline characteristics and safety profile.

The MENSA study

MEpolizumab as adjuNctive therapy in patients with Severe Asthma

Exacerbation reduction study
**Objective:** to compare the effects of mepolizumab 75 mg i.v.* and 100 mg s.c. to placebo (+ maintenance therapy) on clinically significant asthma exacerbations. Also compared clinical efficacy and safety

**Primary endpoint:** the annualised frequency of clinically significant asthma exacerbations, such that the treating physician administered systemic corticosteroids for ≥3 days and/or the patient was hospitalised or visited an emergency department

**Secondary and other endpoints:** frequency of exacerbations requiring hospitalisation or emergency department visit; frequency of exacerbations requiring hospitalisation; spirometry; haematologic parameters; ACQ-5 and SGRQ scores; safety; anti-mepolizumab antibodies

**Patient population:** defined by the DREAM study - 576 patients 12-82 years old with blood eosinophils ≥150 cells/μL at initiation of treatment or ≥300 cells/μL in the past 12 months

**Other points of note:**
- 34-week duration
- Multicentre
- Double blind
- Randomised
- Placebo controlled
- Double dummy
- Only the licensed 100 mg s.c. dose is discussed here

*This is an unlicensed dose/route of administration.

ACQ-5; Asthma Control Questionnaire 5-item version; i.v., intravenous; s.c., subcutaneous; SGRQ, St George’s Respiratory Questionnaire.


The unlicensed dose/route of administration 75 mg intravenously every 4 weeks is not discussed here. 191 patients were randomized to this study group. *Patients who received placebo received placebo both intravenously and subcutaneously.

ICS, inhaled corticosteroid; OCS, oral corticosteroid; s.c., subcutaneous.


Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.

CI, confidence interval; s.c., subcutaneous.


The time to first exacerbation was extended in the mepolizumab 100 mg s.c. group versus placebo. The HR for mepolizumab 100 mg s.c. versus placebo was 0.44 (95% CI: 0.32-0.60; p<0.001).

Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.

CI, confidence interval; HR, hazard ratio; s.c., subcutaneous.

Mepolizumab 100 mg s.c. reduced the rate of exacerbations requiring hospitalisation by 69% versus placebo (mean rate: 0.03 events/patient/year with mepolizumab 100 mg s.c. and 0.10 events/patient/year with placebo; p=0.03)

Statistical significance cannot be inferred due to the hierarchical ‘gatekeeping’ approach used. The p values provided are unadjusted for multiple comparisons.

Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.

CI: confidence interval; s.c., subcutaneous.

Measuring quality of life changes with mepolizumab versus placebo using SGRQ scores

- Statistical significance cannot be inferred due to the hierarchical ‘gatekeeping’ approach used. The p values provided are unadjusted for multiple comparisons.

Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.
s.c., subcutaneous; SGRQ, St George’s Respiratory Questionnaire.
Mepolizumab 100 mg s.c. was associated with improvements in FEV₁ versus placebo at Week 32:
- Pre-bronchodilation FEV₁ change from baseline was 98 mL greater than placebo (p=0.03)
- Post-bronchodilation FEV₁ change from baseline was 138 mL greater than placebo (p=0.004)
- Statistical significance cannot be inferred due to the hierarchical ‘gatekeeping’ approach used. The p values provided are unadjusted for multiple comparisons

FEV₁, forced expiratory volume in 1 second; s.c., subcutaneous.
MENSA: Safety profile

- The most common treatment-related adverse events in the MENSA study were injection-site reactions, headache and fatigue
  - The rates of adverse events were similar across treatment arms, with the exception of injection site reactions
- Serious adverse events were experienced by more patients in the placebo group than in either mepolizumab group. The most common fatal serious adverse event was asthma exacerbation, which occurred in 7% of patients in the placebo group and 3% in the mepolizumab 100 mg s.c. group

Summary of adverse events and serious adverse events with mepolizumab

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=191); n (%)</th>
<th>Mepolizumab 100 mg s.c. (n=194); n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>158 (83)</td>
<td>152 (78)</td>
</tr>
<tr>
<td>Non-asthma event</td>
<td>157 (82)</td>
<td>152 (78)</td>
</tr>
<tr>
<td>Worsening of asthma</td>
<td>29 (15)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Drug-related event, per investigator assessment*</td>
<td>30 (16)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Leading to study withdrawal</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>27 (14)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Drug-related event, per investigator assessment*</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Most common adverse events</strong>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>46 (24)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (17)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27 (14)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>18 (9)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>18 (9)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>15 (8)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>6 (3)</td>
<td>17 (9)</td>
</tr>
</tbody>
</table>

Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.

*The status was assigned by investigators whilst still blinded; †The most common adverse events were those that were reported in ≥5% of patients in any study group.

s.c., subcutaneous.


The MENSA study further confirmed the benefit of mepolizumab for reducing exacerbations in patients with severe refractory eosinophilic asthma

- Confirmed a specific population of severe asthma patients with blood eosinophils \( \geq 150 \) cells/μL at initiation of treatment or \( \geq 300 \) cells/μL in the past 12 months who responded to mepolizumab
  - Mepolizumab reduced the risk of exacerbations by approximately 50% (0.83 events/patient/year) versus placebo (1.74 events/patient/year)

- The rate of adverse events was similar across treatment arms, with the exception of injection site reactions (8% for mepolizumab, 3% for placebo)

Refer to the appendix for baseline characteristics and safety profile.
The SIRIUS study

Steroid Reduction with mepolizumab Study

Oral corticosteroid-sparing study
Objective: to investigate the corticosteroid-sparing effect of s.c. mepolizumab 100 mg s.c. versus placebo in patients with severe asthma on maintenance OCS for a minimum of 6 months prior to the study

Primary endpoint: the degree of reduction in the glucocorticoid dose

Secondary and additional endpoints: proportion of patients achieving from baseline a daily OCS reduction of ≥50% daily dose, to ≤5.0 mg, total reduction and medium percentage reduction; annualised rates of asthma exacerbations; FEV$_1$; ACQ-5 and SGRQ scores; safety profile

Patient population: 135 patients between 16-74 years old with severe refractory eosinophilic asthma, maintained on OCS

Other points of note:
• 26-week duration
• Multicentre
• Double blind
• Randomised
• Parallel group
• Placebo controlled

ACQ-5, Asthma Control Questionnaire 5-item version; FEV$_1$, forced expiratory volume in 1 second; OCS, oral corticosteroid; s.c., subcutaneous; SGRQ, St. George’s Respiratory Questionnaire.


SIRIUS: Study design

ICS, inhaled corticosteroid; OCS, oral corticosteroid; s.c., subcutaneous.


### Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=66)</th>
<th>Mepolizumab 100 mg s.c. (n=69)</th>
<th>Odds ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in oral glucocorticoid dose at 20-24 weeks: primary outcome - n (%)†</td>
<td></td>
<td></td>
<td>2.39 (1.25-4.56)</td>
<td>0.008</td>
</tr>
<tr>
<td>90% to 100%</td>
<td>7 (11)</td>
<td>16 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% to &lt;90%</td>
<td>5 (8)</td>
<td>12 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% to &lt;75%</td>
<td>10 (15)</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0% to &lt;50%</td>
<td>7 (11)</td>
<td>7 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment</td>
<td>37 (56)</td>
<td>25 (36)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=66)</th>
<th>Mepolizumab 100 mg s.c. (n=69)</th>
<th>Odds ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with daily OCS dose reduction of ≥50%, n (%)‡</td>
<td>22 (33)</td>
<td>37 (54)</td>
<td>2.26 (1.10-4.65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Patients with daily OCS dose reduction to ≤5.0 mg, n (%)‡</td>
<td>21 (32)</td>
<td>37 (54)</td>
<td>2.45 (1.12-5.37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients with 100% OCS dose reduction, n (%)‡</td>
<td>5 (8)</td>
<td>10 (14)</td>
<td>1.67 (0.49-5.75)</td>
<td>0.41</td>
</tr>
<tr>
<td>Median daily OCS dose reduction from baseline, % (95% CI)§</td>
<td>0% (-20.0 to 33.3)</td>
<td>50% (20.0 to 75.0)</td>
<td></td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Odds ratios are for the mepolizumab group as compared with the placebo group. †Data for the primary outcome were analysed with the use of a proportional-odds model (ordered multinomial logistic regression), with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 years vs ≥5 years), and baseline oral glucocorticoid dose during the optimisation phase. ‡Data were analysed with the use of a binary logistic-regression model with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 years vs ≥5 years), and baseline oral glucocorticoid dose during the optimisation phase. §The median difference and associated CIs were calculated with the use of the Hodges-Lehman estimation. p values were calculated with the use of a Wilcoxon rank-sum test. For patients who withdrew from the study before the maintenance phase, a value equal to the minimum percent reduction in oral glucocorticoid use for all patients was imputed for the analysis.

CI, confidence interval; OCS, oral corticosteroid; s.c., subcutaneous.  

SIRIUS: Effect of mepolizumab on exacerbations

Cumulative rate of clinically significant asthma exacerbations over 24 weeks


Change in quality of life measures with mepolizumab

ACQ-5
-0.52 (p=0.004)

SGRQ
-5.8 (p=0.019)

ACQ-5, Asthma Control Questionnaire 5-item version; SGRQ, St George’s Respiratory Questionnaire.


At Week 24, there was a non-significant trend towards greater changes from baseline in the FEV\(_1\) before and after bronchodilation in the mepolizumab group than in the placebo group. There were between-group differences of 114 mL before bronchodilation (p=0.15). Values are adjusted for covariates.

FEV\(_1\), forced expiratory volume in 1 second; s.c., subcutaneous.

The most common drug-related adverse events reported in the SIRIUS study were nausea, headache and injection-site reaction.

- The rates of adverse events were similar across treatment arms, with the exception of injection site reactions.

Twelve patients (18%) in the placebo group and one patient (1%) in the mepolizumab group experienced non-fatal serious adverse events during the study period.

- The most common non-fatal severe adverse event was asthma exacerbation (occurring in seven patients [11%] in the placebo group) and pneumonia (occurring in three patients [5%] in the placebo group).
- Neither of these serious adverse events occurred in the mepolizumab group.

### Summary of adverse events and serious adverse events with mepolizumab

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=66); n (%)</th>
<th>Mepolizumab (n=69); n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>61 (92)</td>
<td>57 (83)</td>
</tr>
<tr>
<td>Non-asthma</td>
<td>60 (91)</td>
<td>57 (83)</td>
</tr>
<tr>
<td>Worsening of asthma</td>
<td>8 (12)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Related to study drug*</td>
<td>12 (18)</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug or withdrawal from the study</td>
<td>3 (5)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>12 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

*This determination was made by investigators who were unaware of study-group assignments.


The SIRIUS study builds on previous studies showing corticosteroid-sparing effects of mepolizumab

- Patients treated with mepolizumab had a significantly reduced maintenance OCS dose whilst maintaining asthma control versus placebo:
  - Median OCS dose reduction was 50% in the mepolizumab group, as compared with no reduction with placebo
  - This finding is of note as patients in this study had already had their OCS dose optimised to the lowest required for asthma management prior to study treatment initiation
- Mepolizumab-treated patients also experienced improvements in exacerbations, ACQ-5 score and quality of life versus placebo
- The rate of adverse events was similar across treatment arms, with the exception of injection site reactions (8% for mepolizumab, 3% for placebo)

Refer to the appendix for baseline characteristics and safety profile.

ACQ-5, Asthma Control Questionnaire 5-item version; OCS, oral corticosteroid.

Mepolizumab: Safety profile and immunogenicity
• Mepolizumab’s safety profile has been studied in a total of 915 patients with severe refractory eosinophilic asthma who received either a s.c. or an i.v. dose during clinical studies of 24 to 52 weeks in duration

• Most commonly reported adverse reactions were headache, injection-site reactions and back pain

• The rate of adverse events was similar across treatment arms with the exception of injection-site reactions, which occurred more frequently in the mepolizumab 100 mg s.c. group (8%) versus placebo (3%)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Lower respiratory tract infection</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions (systemic allergic)</td>
<td>Common</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Very common</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain upper</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and s.c. tissue disorders</td>
<td>Eczema</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>Administration-related reactions (systemic non-allergic)*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Local injection-site reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td></td>
</tr>
</tbody>
</table>

*The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg s.c.

s.c., subcutaneous; i.v., intravenous.

Mepolizumab: Immunogenicity

- Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment.
- In the placebo-controlled trials, 15 patients (6%) treated with mepolizumab 100 mg s.c. developed anti-mepolizumab antibodies after receiving at least one mepolizumab dose.
- Neutralising antibodies were detected in one patient.
- Anti-mepolizumab antibodies did not discernibly impact mepolizumab’s pharmacokinetics or pharmacodynamics in the majority of patients. There was no evidence of a correlation between antibody titres and change in blood eosinophil level.

s.c., subcutaneous.

Mepolizumab: Dose selection
**Mepolizumab dose selection**

The licensed mepolizumab dose and administration route is 100 mg s.c. every 4 weeks,\(^1\) which was determined in the clinical development programme.

**MEA114092\(^2\)**
- Evaluated the pharmacokinetic/pharmacodynamic response relationship of 4-weekly mepolizumab 12.5 mg s.c., 75 mg i.v., 125 mg s.c. and 250 mg s.c. in patients with asthma and blood eosinophil levels >300 cells/µL.*
- Determined that the 75 mg i.v. dose was equivalent to 100 mg s.c., due to absolute s.c. bioavailability of approximately 75%.

**DREAM\(^3\)**
- One objective was to help determine the optimum mepolizumab dose for further studies.
- Frequency of clinically significant asthma exacerbations was significantly reduced at every dose.
  - No apparent difference between doses.

Based on clinical data from DREAM and supported by MEA114092, the mepolizumab 75 mg i.v. dose was selected as optimal, given the large therapeutic index/safety margin of the 10-fold dose range between 75 mg and 750 mg i.v.\(^2,3\)

*These are unlicensed doses/routes of administration.

i.v., intravenous; s.c., subcutaneous.


Mepolizumab’s dosing schedule of 100 mg s.c. every 4 weeks is based on its terminal half-life of approximately 20 days\(^1\)

- Repeat dosing every 4 weeks provides approximately two-fold drug accumulation at steady state\(^1\)
  - There are prolonged effects on blood eosinophil counts seen in a single dose
- Following s.c. dosing in patients with asthma, mepolizumab exhibited approximate dose-proportional pharmacokinetics over a dose range of 12.5-250 mg\(^1\)
- The same dose every 4 weeks for 32 weeks reduced blood eosinophils to 40 cells/μL, from a geometric mean baseline count of 290 cells/μL (N=182)\(^1\)
  - This was a reduction of 84% versus baseline
  - This magnitude of reduction was observed within 4 weeks of treatment
- Mepolizumab absorption was found to be slow, with a median \(T_{\text{max}}\) ranging from 4-8 days following s.c. administration to healthy subjects or patients with asthma\(^1\)

s.c., subcutaneous; \(T_{\text{max}}\), time to maximal serum concentration.
Prescribing considerations
Special warnings and precautions for use of mepolizumab

- Hypersensitivity and administration-related reactions:
  Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment.

- Mepolizumab should not be used to treat acute asthma exacerbations.

- Asthma-related adverse events or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

- Abrupt discontinuation of corticosteroids after initiation of mepolizumab therapy is not recommended. Reduction in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

- Parasitic infections:
  Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

1. Mepolizumab. Summary of product characteristics, 2016;
Eosinophils as biomarkers for treatment

- High blood eosinophil count with severe asthma symptoms is indicative of severe refractory eosinophilic asthma - eligible for mepolizumab treatment
- Data from DREAM helped define blood eosinophil threshold to identify patients who would respond to mepolizumab
  - Confirmed in MENSA and SIRIUS

Screening eosinophils is predictive of the eosinophil count in the following year

DREAM patient population most responsive to mepolizumab:

at least two severe asthma exacerbations in the past 12 months despite high-dose ICS, with or without OCS, and blood eosinophils ≥150 cells/μL at treatment initiation or ≥300 cells/μL in the past 12 months

ICS, inhaled corticosteroid; OCS, oral corticosteroid.

Some medications affect blood eosinophil counts, including severe asthma medications:¹

- **OCS**: strong eosinophil suppressant - prevent the production of many inflammatory mediators that are vital to eosinophil survival¹
- **Montelukast**: a LTRA, has a suppressant effect on eosinophils²,³
- **Omalizumab**: for severe allergic asthma,⁴ with an association between the reduction of IgE and significant decreases in blood eosinophil counts in patients with moderate-to-severe persistent allergic asthma⁵
- **Anti-IL-5 agents**: a new class of biologic targeted against IL-5, a key cytokine responsible for eosinophil proliferation and maturation in the bone marrow¹
Various conditions can also affect blood eosinophil counts

In countries where parasitic diseases are prevalent, parasite infection should be a differential diagnosis

Other differential diagnoses:
- Allergy
- Cancer
- Churg-Strauss syndrome
- Hypereosinophilic syndrome
- Hypersensitivity reaction resulting from drug ingestion
- Older age

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Potential disease cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Invasive helminth infection</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Eosinophilic pneumonitis; asthma; allergic bronchopulmonary aspergillosis; chronic eosinophilic pneumonia; subset of COPD patients</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inflammatory bowel disease; eosinophilic gastroenteritis; allergic colitis</td>
</tr>
<tr>
<td>Allergic</td>
<td>Allergic rhinoconjunctivitis; asthma; eczema; atopic dermatitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Idiopathic hypereosinophilic syndrome; vasculitis; Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Drug reaction; cytokine infusions</td>
</tr>
<tr>
<td>Malignant</td>
<td>Lymphoma; colonic carcinoma; Langerhans cell histiocytosis; myeloid or stem cell neoplasms</td>
</tr>
</tbody>
</table>

Diseases associated with high blood eosinophil levels


COPD, chronic obstructive pulmonary disease.
Summary

- IL-5 is a logical therapeutic target for eosinophilic disorders such as severe refractory eosinophilic asthma\textsuperscript{1}

- DREAM, MENSA and SIRIUS were the key studies for demonstrating mepolizumab efficacy and safety\textsuperscript{2-4}

- The rates of adverse events were similar across treatment arms, with the exception of injection site reactions (mepolizumab 8%, placebo 3\%)\textsuperscript{3-5}

- Historically, blood eosinophil threshold that defines severe eosinophilic asthma has been debated
  - Data from DREAM have driven the eosinophil threshold for mepolizumab treatment eligibility - confirmed in MENSA and SIRIUS\textsuperscript{2-4}

- Blood eosinophil counts can be measured using a complete differential blood count
  - Medication- and non-medication-related factors can affect the count\textsuperscript{6-8}

IL-5, interleukin-5.

Full mepolizumab prescribing information:

- Denmark
- Finland
- Norway
- Sweden
DREAM additional data
### Select inclusion criteria

- Clinical diagnosis of asthma
- At least two exacerbations requiring systemic corticosteroid treatment in the previous year
- Using a high-dose ICS and a second controller ± maintenance OCS
- Evidence of eosinophilic inflammation at study entry or in the previous year, demonstrated by:
  - Sputum eosinophil count ≥3%, **or**
  - $\text{FE}_{NO} \geq 50$ ppb, **or**
  - Asthma-related peripheral blood eosinophil count ≥300 cells/µL, **or**
  - Prompt deterioration of asthma control after ≤25% reduction in regular maintenance ICS or OCS

### Select exclusion criteria

- Present smoking or >10 pack-year smoking history
- Parasitic infection in the previous 6 months
- Substantial uncontrolled morbidity
- Possibility of pregnancy
- History of poor treatment adherence
- Treatment in the previous 130 days with omalizumab or another biologic for inflammatory disease
- Previous participation in any mepolizumab study

---

$\text{FE}_{NO}$: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; OCS: oral corticosteroids; ppb: parts per billion.

# DREAM: Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=155)</th>
<th>Mepolizumab 75 mg i.v. (n=153)*</th>
<th>Mepolizumab 250 mg i.v. (n=152)*</th>
<th>Mepolizumab 750 mg i.v. (n=156)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97 (63%)</td>
<td>104 (68%)</td>
<td>93 (61%)</td>
<td>93 (60%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>46.4 (11.3)</td>
<td>50.2 (10.8)</td>
<td>49.4 (11.6)</td>
<td>48.6 (11.1)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>28.3 (6.1)</td>
<td>28.4 (6.0)</td>
<td>28.3 (5.9)</td>
<td>28.9 (5.8)</td>
</tr>
<tr>
<td><strong>Former smoker</strong></td>
<td>34 (22%)</td>
<td>31 (20%)</td>
<td>31 (20%)</td>
<td>37 (24%)</td>
</tr>
<tr>
<td><strong>White ethnic origin</strong></td>
<td>140 (90%)</td>
<td>139 (91%)</td>
<td>135 (89%)</td>
<td>140 (90%)</td>
</tr>
<tr>
<td><strong>Use of long-acting β-agonists</strong></td>
<td>150 (97%)</td>
<td>143 (93%)</td>
<td>145 (95%)</td>
<td>151 (97%)</td>
</tr>
<tr>
<td><strong>Ultra-low dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance use of oral corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose (mg)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasal polyps‡</strong></td>
<td>16 (10%)</td>
<td>11 (7%)</td>
<td>22 (14%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td><strong>Atopy§</strong></td>
<td>81 (52%)</td>
<td>78 (51%)</td>
<td>76 (50%)</td>
<td>76 (49%)</td>
</tr>
<tr>
<td><strong>Prebronchodilator FEV₁ (mL)</strong></td>
<td>1900 (653)</td>
<td>1810 (637)</td>
<td>1850 (672)</td>
<td>1950 (670)</td>
</tr>
<tr>
<td><strong>Post-bronchodilator FEV₁ (mL)</strong></td>
<td>2290 (773)</td>
<td>2150 (695)</td>
<td>2220 (732)</td>
<td>2260 (784)</td>
</tr>
<tr>
<td><strong>Percentage of predicted prebronchodilator FEV₁</strong></td>
<td>59% (15)</td>
<td>60% (16)</td>
<td>59% (17)</td>
<td>61% (16)</td>
</tr>
<tr>
<td><strong>Post-bronchodilator FEV₁/FVC</strong></td>
<td>67% (12)</td>
<td>68% (12)</td>
<td>66% (13)</td>
<td>68% (20)</td>
</tr>
<tr>
<td><strong>ACQ score</strong></td>
<td>2.5 (1.1)</td>
<td>2.2 (1.1)</td>
<td>2.4 (1.1)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td><strong>AQLQ score</strong></td>
<td>4.1 (1.2)</td>
<td>4.2 (1.2)</td>
<td>4.2 (1.2)</td>
<td>4.2 (1.2)</td>
</tr>
<tr>
<td><strong>Blood eosinophil count (x10⁹/L)</strong>¶ǁ</td>
<td>0.28 (1.01)</td>
<td>0.25 (0.95)</td>
<td>0.23 (1.20)</td>
<td>0.25 (0.93)</td>
</tr>
<tr>
<td><strong>Sputum eosinophil count (%)</strong>¶ǁ</td>
<td>6.8% (2.01); n=24</td>
<td>13.9% (1.47); n=18</td>
<td>8.1% (1.79); n=23</td>
<td>5.8% (2.15); n=21</td>
</tr>
<tr>
<td><strong>FE₅₀ (ppb)</strong>¶ǁ</td>
<td>33.7 (0.79)</td>
<td>29.2 (0.76)</td>
<td>31.4 (0.80)</td>
<td>31.6 (0.81)</td>
</tr>
<tr>
<td><strong>Severe exacerbations in the previous year</strong></td>
<td>3.7 (3.8)</td>
<td>3.7 (3.1)</td>
<td>3.4 (2.4)</td>
<td>3.5 (2.8)</td>
</tr>
<tr>
<td><strong>Exacerbations requiring administration in previous year</strong></td>
<td>40 (26%)</td>
<td>35 (23%)</td>
<td>36 (24%)</td>
<td>39 (25%)</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD) or median (IQR), unless otherwise stated. *This is an unlicensed dose/route of administration; †Prednisolone equivalent; ‡Self-reported; §Positive allergic status was defined as a positive radioallergosorbent test for any of four specified aeroallergens; ¶Values below lower limit of quantification were replaced by half the lower limit of quantification; ¶ǁGeometric mean on log scale. ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BMI, body mass index; FE₅₀ fraction of exhaled nitric oxid; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR interquartile range; i.v., intravenous; SD standard deviation.


• Six patients (1%) tested positive for mepolizumab anti-drug antibodies
  - This is comparable to the false-positive rate observed in the placebo group, with two patients (1%) testing positive
• Neutralising antibodies were not detected in any patients
MENSA additional data
MENSA: Patient eligibility

<table>
<thead>
<tr>
<th>Select inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical diagnosis of asthma</td>
</tr>
<tr>
<td>• At least two exacerbations requiring systemic corticosteroid treatment in the previous year</td>
</tr>
<tr>
<td>• Receiving high-dose ICS and additional controller(s)</td>
</tr>
<tr>
<td>• Peripheral blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL during the previous year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Select exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Present smoking or &gt;10 pack-year smoking history</td>
</tr>
<tr>
<td>• Concurrent respiratory disease, eosinophilic disease or other substantial uncontrolled morbidity</td>
</tr>
<tr>
<td>• Parasitic infection in the previous 6 months</td>
</tr>
<tr>
<td>• Possibility of pregnancy</td>
</tr>
<tr>
<td>• History of poor treatment adherence</td>
</tr>
<tr>
<td>• Recent treatment with omalizumab or another biologic for inflammatory disease</td>
</tr>
<tr>
<td>• Previous participation in any mepolizumab study</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid.


MENSA: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Placebo (n=191)</th>
<th>Mepolizumab 100 mg s.c. (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>49 (12-76)</td>
<td>51 (12-81)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>107 (56)</td>
<td>116 (60)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>28.0 ± 5.6</td>
<td>27.6 ± 6.2</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>57 (30)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Duration of asthma, years</td>
<td>19.5 ± 14.6</td>
<td>20.5 ± 12.9</td>
</tr>
<tr>
<td>Use of oral glucocorticoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance use, n (%)</td>
<td>44 (23)</td>
<td>52 (27)</td>
</tr>
<tr>
<td>Mean daily dose (range), mg†</td>
<td>15.1 (5-80)</td>
<td>12.6 (2-50)</td>
</tr>
<tr>
<td>Allergic rhinitis, n (%)</td>
<td>95 (50)</td>
<td>95 (49)</td>
</tr>
<tr>
<td>FEV(_1) Before bronchodilation, L§</td>
<td>1.86 ± 0.63</td>
<td>1.73 ± 0.66</td>
</tr>
<tr>
<td>Predicted value pre-bronchodilation, %¶</td>
<td>62.4 ± 18.1</td>
<td>59.3 ± 17.5</td>
</tr>
<tr>
<td>Reversibility, %</td>
<td>27.4 ± 20.8</td>
<td>27.9 ± 24.0</td>
</tr>
<tr>
<td>FEV(_1):FVC ratio, %</td>
<td>64 ± 13</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Morning peak expiratory flow, L/min</td>
<td>277 ± 106</td>
<td>255 ± 108</td>
</tr>
<tr>
<td>ACQ scoreǁ</td>
<td>2.28 ± 1.19</td>
<td>2.6 ± 1.27</td>
</tr>
<tr>
<td>SGRQ score#</td>
<td>46.9 ± 19.8</td>
<td>47.9 ± 19.4</td>
</tr>
<tr>
<td>Log(_e) geometric mean IgE, cells/µL**</td>
<td>150 ± 1.5</td>
<td>150 ± 1.5</td>
</tr>
<tr>
<td>Log(_e) geometric mean blood eosinophil count, cells/µL††</td>
<td>320 ± 938</td>
<td>290 ± 1050</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe episodes in previous year, n/patient</td>
<td>3.6 ± 2.8</td>
<td>3.8 ± 2.7</td>
</tr>
<tr>
<td>Necessitating hospitalisation in previous year, n (%)</td>
<td>35 (18)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>History of asthma-related intubation, n (%)</td>
<td>3 (2)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

Data for the mepolizumab 100 mg s.c. dose only are shown, as this is the dose that received regulatory approval.

*Plus-minus values are means (or geometric means) ± SD. There were no significant between group differences at baseline.

†BMI = weight in kg divided by square of height in m; The listed value is the prednisone equivalent.

‡Reversibility was measured at baseline; The percent of the predicted value pre-bronchodilation was assessed at the screening visit.

§The FEV\(_1\):FVC ratio was calculated by dividing FEV\(_1\) by FVC and multiplying by 100 to express as a percentage.

¶Scores on the ACQ range from 0-6, with higher scores indicating worse control. A change of 0.5 points in the minimal clinically important difference; **Scores on the SGRQ range from 0-100, with higher scores indicating worse function. A change of 4 points is considered to be clinically relevant; ††Values below the lower limit of quantification were replaced by a value that was 50% of the lower limit of quantification.

ACQ, Asthma Control Questionnaire; BMI, body mass index; FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; Log\(_e\), logarithm \(_e\); s.c., subcutaneous; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire.


19 patients (3.3%) across the three treatment groups had confirmed positive anti-mepolizumab antibody results for at least one visit after baseline.

The positive test results of five anti-drug antibody-positive patients were considered unrelated to mepolizumab treatment because they included patients in the placebo group, and two had pre-existing antibodies at baseline.

No patients tested positive for neutralising activity.

SIRIUS additional data
SIRIUS: Patient eligibility

Select inclusion criteria

- Documented requirement for regular treatment with:
  - Maintenance systemic corticosteroids (5-35 mg/day prednisone or equivalent) for ≥6 months, **AND**:  
- High-dose ICS and additional controller(s)
- Blood eosinophil level ≥300 cells/µL that was related to asthma within the 12 months prior to Visit 3, **or**:
- Eosinophil level ≥150 cells/µL between Visit 1 and Visit 3

Select exclusion criteria

- Present smoking or >10 pack-year smoking history
- Concurrent respiratory disease, eosinophilic disease or other substantial uncontrolled morbidity
- Parasitic infection in the previous 6 months
- Possibility of pregnancy
- History of poor treatment adherence
- Recent treatment with omalizumab or another biologic for inflammatory disease
- Previous participation in any mepolizumab study

ICS, inhaled corticosteroid.

# SIRIUS: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Placebo (n=66)</th>
<th>Mepolizumab 100 mg s.c. (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>50 (28-70)</td>
<td>50 (16-74)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>30 (45)</td>
<td>44 (64)</td>
</tr>
<tr>
<td>BMI*</td>
<td>29.5 ± 6.0</td>
<td>27.8 ± 5.9</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>25 (38)</td>
<td>28 (41)</td>
</tr>
<tr>
<td>Duration of asthma, years</td>
<td>20.1 ±14.4</td>
<td>17.4 ± 11.8</td>
</tr>
<tr>
<td>Median daily oral glucocorticoid dose, mg†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At screening</td>
<td>15.0</td>
<td>12.5</td>
</tr>
<tr>
<td>During optimisation phase</td>
<td>12.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Duration of oral glucocorticoid use ≥5 years, n (%)</td>
<td>31 (47)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>FEV₁ before bronchodilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, litres</td>
<td>2.00 ± 0.82</td>
<td>1.90 ± 0.66</td>
</tr>
<tr>
<td>Percent predicted value</td>
<td>57.8 ± 18.5</td>
<td>59.6 ± 17.0</td>
</tr>
<tr>
<td>FEV₁:FVC ratio before bronchodilation‡</td>
<td>61 ± 11.7</td>
<td>63 ± 12.4</td>
</tr>
<tr>
<td>Percent FEV₁ reversibility</td>
<td>24.8 ± 18.1</td>
<td>27.3 ± 17.4</td>
</tr>
<tr>
<td>ACQ-5 score§</td>
<td>2.0 ± 1.2</td>
<td>2.2 ± 1.3</td>
</tr>
<tr>
<td>SGRQ score¶</td>
<td>45 ± 18</td>
<td>50 ± 18</td>
</tr>
<tr>
<td>Geometric mean IgE on logₑ scale, U/mL</td>
<td>114 ± 1</td>
<td>117. ± 1</td>
</tr>
<tr>
<td>Geometric mean blood eosinophil count on logₑ scale, cells/µLǁ</td>
<td>230 ± 1001</td>
<td>250 ± 1245</td>
</tr>
<tr>
<td>Severe exacerbations in previous year, n/patient</td>
<td>2.9 ± 2.8</td>
<td>3.3 ± 3.4</td>
</tr>
<tr>
<td>Exacerbations in the previous year requiring hospitalisation, n (%)</td>
<td>9 (14)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>History of asthma-related intubation, n (%)</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Plus-minus values are means (or geometric means) ±SD unless otherwise stated. There were no significant between group differences at baseline with the exception of sex (p=0.04). Percentages may not total 100 because of rounding.

*The BMI is the weight in kgs divided by the square of the height in metres; †Doses are provided as prednisone equivalents; ‡The FEV₁:FVC ratio was calculated by dividing the FEV₁ by the FVC and then multiplying by 100 to express the value as a percentage; §Scores on the ACQ-5 range from 0 to 6, with higher scores indicating worse control of asthma; a change of 0.5 points is the minimal clinically important difference; ¶Scores on SGRQ range from 0 to 100, with higher scores indicating worse function; a change of 4 units is considered to be clinically relevant; ‖Values below the LLQ were replaced by 50% of the LLQ.

ACQ, Asthma Control Questionnaire; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; LLQ, lower limit of quantification; s.c., subcutaneous; SD standard deviation; SGRQ, St George’s Respiratory Questionnaire.


• A total of 135 patients were evaluated for the presence of mepolizumab antidrug antibodies
• Six patients in the mepolizumab group tested positive during at least one post-baseline visit. No positive test occurred in the placebo group.
• One patient tested positive for neutralising antibodies at Weeks 13 and 32

Antibodies are immunoglobulins that specifically interact with antigens

- They elicit responses from immune cells that neutralise or eliminate the antigen
  - They all share a common structure of two identical light chains and two identical heavy chains, bound by disulphide bonds
  - There are five classes of antibodies in humans, each of which has a unique function or purpose

### Features of the five antibody classes

<table>
<thead>
<tr>
<th>Structure</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody in plasma (%)</td>
<td>Monomer</td>
<td>Pentamer</td>
<td>Dimer</td>
<td>Monomer</td>
<td>Monomer</td>
</tr>
<tr>
<td>Foetal circulation in pregnant women</td>
<td>75-85</td>
<td>5-10</td>
<td>10-15</td>
<td>0.001</td>
<td>0.2</td>
</tr>
<tr>
<td>Presence in sites other than blood, connective tissue and lymphoid organs</td>
<td>Surface of B cells (as a monomer)</td>
<td>Secretions, e.g. saliva, tears, milk</td>
<td>Surface of B cells</td>
<td>Surface of mast cells and basophils</td>
<td></td>
</tr>
<tr>
<td>Known functions</td>
<td>Activates phagocytosis, neutralises antigens</td>
<td>First antibody produced in initial immune response; activates complement</td>
<td>Protects mucosae</td>
<td>Antigen receptor triggering initial B cell activation</td>
<td>Destroys parasitic worms and participates in allergic response</td>
</tr>
</tbody>
</table>

---

IgA, immunoglobulin A; IgD, immunoglobulin D; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M.

Biologics for severe asthma

- Biologic agents target specific aspects of a disease - allowing selective therapy\(^1,2\)
- Often well-tolerated and can be highly engineered to fine-tune their pharmacologic properties for maximum clinical benefit\(^1,2\)
- The inflammatory cascade in asthma is complex
  - Different pathways link to different disease subtypes\(^3,4\)
- A variety of mAbs against inflammatory cytokines, chemokines or their receptors have reached or are approaching the market\(^4,5\)

Typical antibody structure\(^1-3\)

mAbs have the potential to treat and further define specific severe asthma phenotypes, because they target a specific underlying mechanism of disease\(^4\)

---


IgG molecules can be engineered into therapeutic antibodies

Several elements of the molecule may be engineered to alter antibody function:

- **The variable domain** is a segment of the Fab that contains the antigen-binding site. Its amino acid sequence can vary widely among antibodies. Each antibody has two antigen-binding sites.
- **The Fab**, or fragment antigen binding region, is responsible for the antibody's antigen-binding activity.
- **The Fc**, or fragment crystallisable region, is the same in all IgG molecules. It has no antigen-binding activity, but binds to Fc receptors expressed on the surface of cells such as macrophages, basophils and mast cells, and promotes phagocytosis.
- **Altering the antibody's glycosylation status** can fine-tune its effector functions. For example, blocking Fc region glycosylation eliminates the antibody's effector functions.

**Chimeric antibodies**

- 70% human fused with murine variable regions responsible for antigen binding, with fully human Fc region
- Considerably less immunogenic than early therapeutic antibodies
- Fully human Fc region lets the antibody interact with human effector cells and the complement cascade

**Humanised antibodies**

- Only the CDRs are of murine origin, so are 85-90% human and even less immunogenic than chimeric antibodies
- Most of the recently approved therapeutic antibodies are fully humanised

CDR, complementarity determining region; Fc, fragment crystallisable [region].

Therapeutic antibodies have various MoAs

**In ligand blockade,** the antibody binds to a ligand as its antigen, which interferes with the antigen’s activity and interaction with its normal receptor.\(^1,2\)

**In receptor blockade,** the antibody can target a cell surface receptor rather than the ligand that binds to it.\(^1,2\)

MoA, mechanism of action.

Anti-drug antibodies

- Therapeutic proteins have the potential to trigger an immune response in the patient - anti-drug antibodies
  - Neutralising antibodies might bind to the active site of the mAb
  - Non-neutralising antibodies might bind to sites other than the active site

Immunogenicity

- Immunogenic responses to therapeutic mAbs can affect both safety and pharmacokinetic properties, potentially impacting the efficacy and utility of the drug
  - The factors that influence immunogenicity are varied and may be inherent to the patient, the product or the disease

Hypersensitivity reactions

- Most occur after multiple doses and are due to cross-reacting or drug-specific IgG or IgE antibody production
  - Clinical signs of hypersensitivity may occur during or immediately after dosing or within a few days of dosing

Anaphylaxis

- Anaphylaxis can occur in response to the formation of anti-drug antibodies

Infusion reactions

- They can be either allergic reactions to foreign proteins (and thus classed as Type 1 hypersensitivity reactions) or non-IgE mediated (i.e. anaphylactoid) reactions
  - May be headache, nausea, fever, chills, dizziness, flush, pruritus, chest or back pain

IgE, immunoglobulin-E; IgG, immunoglobulin G; mAb, monoclonal antibody.