Molgramostim inhalation is a new drug to treat autoimmune pulmonary alveolar proteinosis (PAP). Autoimmune PAP is a rare lung disease that causes a build-up of protein material in the air sacs of the lungs, making it difficult to breathe. Molgramostim inhalation is breathed in and works by altering the body’s immune response, helping to prevent the build-up of protein in the lungs.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Autoimmune pulmonary alveolar proteinosis (PAP) — first-line.

TECHNOLOGY

DESCRIPTION

Molgramostim inhalation (Molgradex; rhGM-CSF inhalation - Savara; molgramostim nebuliser solution) is an inhaled formulation of molgramostim, a recombinant human granulocyte macrophage colony stimulating factor (GM-CSF). GM-CSF plays a key role in surfactant homeostasis by regulating the maturation and function of alveolar macrophages. Administration of exogenous GM-CSF may reduce the neutralising activity against GM-CSF in patients with autoantibodies to GM-CSF.

In a phase II/III clinical trial, molgramostim is administered at 300µg via inhalation once every day or once every day for 7 days followed by an inhaled placebo once a day for 7 days¹.

Molgramostim inhalation does not currently have Marketing Authorisation in the EU for any indication. It is in a phase II clinical trial for acute respiratory distress syndrome.

INNOVATION and/or ADVANTAGES

If licensed, molgramostim inhalation will offer an additional treatment option for patients with autoimmune PAP.

DEVELOPER

Savara Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Molgramostim inhalation is in phase II/III clinical trials.

PATIENT GROUP

BACKGROUND

PAP is a rare lung disease characterised by the accumulation of lipoproteinaceous material in the alveoli²,³. It is considered an autoimmune disease (also known as acquired or idiopathic) in which an individual’s antibodies target GM-CSF for neutralisation and/or destruction³, and is associated with high levels of GM-CSF autoantibodies in alveoli and blood⁴. Autoimmune PAP is the most common type; other forms of the condition include secondary and congenital types⁴. Adult patients are most commonly affected by autoimmune PAP and or PAP secondary to toxic inhalation or haematological disorders, which arise without anti-GM-CSF antibodies⁵. It has been suggested that in PAP, alveolar macrophages do not function properly, failing to break down material they ingest¹. Symptoms may include shortness of breath and cough and in severe cases, respiratory failure may occur³.
Autoimmune PAP is more common in males than females, and in those who are aged 20-50 years.

### CLINICAL NEED and BURDEN OF DISEASE

Autoimmune PAP accounts for about 90% of all cases. The prevalence of PAP in the EU is estimated at 1-9 per 1,000,000 population. Expert opinion estimates a lower occurrence at 1 per 1,000,000 population or less. The most common cause of death is respiratory failure followed by secondary pulmonary bacterial infections. Estimated 5-year mortality rates vary between 10-30%, with overall disease specific survival rates at 5 years exceeding 80%.

The population likely to be eligible to receive molgramostim inhalation could not easily be estimated from available routine published sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**
- No relevant guidance identified.

**NHS England Policies and Guidance**

**Other Guidance**
- No relevant guidance identified.

### CURRENT TREATMENT OPTIONS

Current treatment options for autoimmune PAP include:

1. **Whole lung lavage (WLL)** — this is the most common first-line treatment for symptomatic idiopathic PAP i.e. washing out the lungs under general anaesthesia. This provides temporary symptomatic relief. Expert opinion states that this therapy may be sufficient for many patients.
2. **GM-CSF therapy** (subcutaneous or inhaled).
3. **Plasmapheresis** — to reduce the number of anti-GM-CSF antibodies and restore surfactant catabolism in alveolar macrophages.
4. **Rituximab** — reducing autoantibody levels by depleting B lymphocytes.

In general, a stepwise treatment approach is advised, starting with WLL, continuing to inhaled GM-CSF, and then to rituximab if other treatments are unsuccessful. Due to the invasiveness of the WLL procedure, some physicians start with inhaled GM-CSF and conduct WLL only if this approach is insufficient. However, in GM-CSF therapy the optimal dose and duration of therapy is still uncertain, with the risk of recurrence after initial therapy,

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a Expert personal opinion.
b Company comment.
and long term safety is not yet established. Furthermore, the precise place of existing preparations of GM-CSF in the treatment pathway for autoimmune PAP (i.e. sole therapy or as an add-on to WLL) still needs to be confirmed\textsuperscript{11}. Expert opinion states that autoimmune PAP is very rare, debilitating and potentially fatal if poorly managed\textsuperscript{6}. In clinical practice, patients with severe autoimmune PAP that are treated with inhaled GM-CSF have shown a reduction in the number of WLL procedures required, reduced the interval time between WLL procedures\textsuperscript{6}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMPALA, NCT02702180, MOL-PAP-002, EudraCT2014-002479-28; molgramostim inhalation continuously or intermittently vs placebo; phase II/III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Savara Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{1} and manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), Russian Federation, Israel, and Japan.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>(n=51) (planned); aged 18-75 yrs; autoimmune PAP diagnosed by computed tomography (CT), biopsy or broncho alveolar lavage (BAL), with increased GM-CSF autoantibodies in serum; arterial oxygen concentration (&lt;75) mmHg at rest, or desaturation of (&gt;4)% on the 6 min walk test (6MWT); alveolar-arterial oxygen difference ((A-a) DO2) (\geq 25) mmHg; no hereditary or secondary PAP; no WLL within 2 mths, GM-CSF within 3 mths, rituximab within 6 mths, or plasmapheresis within 3 mths; no concomitant use of sputum modifying drugs such as carbocysteine or ambroxol.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to inhalation of molgramostim 300(\mu)g nebuliser solution once daily, or molgramostim 300 (\mu)g nebuliser solution once daily for 7 days followed by matching placebo nebuliser solution once daily for 7 days (repeated in 2 week cycles); or placebo nebuliser solution once daily.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 24 wks; 48 wks follow-up.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>((A-a) DO2) at 24 wks.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>WLL; vital capacity; pulmonary function; tolerance to exercise; dyspnœa; cough; quality of life measured by EQ-5D and St. George’s Respiratory Questionnaire; CT scoring; adverse events (AEs), serious AEs, and adverse drug reactions.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Q4 2017.</td>
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</tbody>
</table>

### ESTIMATED COST and IMPACT

#### COST

The cost of molgramostim inhaled is not yet known.

\textsuperscript{c} Expert personal opinion.
### IMPACT - SPECULATIVE

#### Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: improved quality of life for patients or carers. Expert opinion suggests that, molgramostim inhalation may improve lung function, exercise tolerance, and general well-being.
- No impact identified

#### Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services: the company claim that there is a potential for shorter length of stay and reduced referrals for more specialised care. Expert opinion states that molgramostim inhalation treatment reduces hospital admissions for WLL (typically 3-4 days with a full day spent in ICU after 3-6 hours in the operating theatre).
- 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: reduced need for WLL, including ICU admission.
- Other
- None identified

#### Other Issues
- Clinical uncertainty or other research question identified: expert opinion states that procurement, purchase, prescription and supply issues will need to be considered. In the UK, an unlicensed product is imported from the USA for patients for use off-label. Approximately 20-30 patients would benefit from inhaled molgramostim at any one time.
- None identified

### REFERENCES


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* Company comment.
* Expert personal opinion.
7 Khan A and Agarwal R. Pulmonary alveolar proteinosis. Respiratory Care 2011;56(7):1016-1028.