Inhaled rhGM-CSF (molgramostim) in the first randomised, double-blind, placebo-controlled, international trial in patients with autoimmune pulmonary alveolar proteinosis (aPAP).

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https://clinicaltrials.gov/ct2/show/NCT02709180

INTRODUCTION

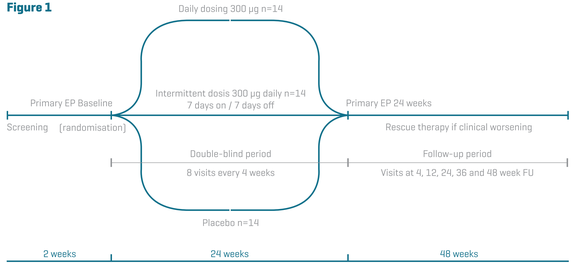
Granulocyte macrophage - colony stimulating factor (GM-CSF) is a cytokine and a hematopoietic growth factor produced by a variety of cells. In the lungs GM-CSF regulates surfactant homeostasis and lung host defense through innate immune functions. Alveolar macrophages from GM-CSF-/- mice have reduced capacity for surfactant catabolism, cell adhesion, phagocytosis and bacterial killing. (Hamilton et al. 2008)

PAP is a rare, debilitating disease with an estimated prevalence of 0.7 per 100,000. PAP is caused by accumulation of surfactant lipids and proteins in the alveoli, leading to progressive respiratory insufficiency. Spontaneous remissions are rare. 90% of PAP cases are autoimmune (aPAP) with autoantibodies against GM-CSF. Current therapy is whole lung lavage (WLL), and inhaled recombinant human (rh) GM-CSF has been reported as an effective, non-invasive medical therapy in a few uncontrolled studies. (Inoue et al. 2008)

STUDY DESIGN

This is the first randomised, placebo-controlled trial of inhaled rhGM-CSF in aPAP patients. The first patient was randomised in May 2016, total number of evaluable patients = 42.

Figure 1



PRIMARY ENDPOINT (EP)
Change in alveolar-arterial oxygen difference ($(A\text{-}a)DO_2$) after 24 weeks treatment

KEY SECONDARY ENDPOINTS
Requirement for, and time to, Whole Lung Lavage (WLL) during 24 weeks treatment

Change in Vital Capacity (VC) after 24 weeks treatment

METHODS

The trial adhered to the principles of the Declaration of Helsinki and Good Clinical Practice. The trial was approved by the Competent Authority and Independent Ethics Committee(s)/Institutional Review Board(s) in the participating country and center before trial initiation.

Sample size calculation

- Based on Tazawa et al 2010, AJRCCM: Mean $(A\text{-}a)DO_2$ = 31.3 (SD ± 7.4) mmHg before treatment and 12.9 (7.6) after treatment with inhaled rhGM-CSF. At least 42 subjects are required to show a mean difference of 10 mmHg on the $(A\text{-}a)DO_2$ between the two active arms (combined) and placebo using an unpaired t-test with a significance level of 0.01 and a power of 90%.

Inclusion criteria

- aPAP diagnosed by computer tomography (CT), or by biopsy, or by Broncho Alveolar Lavage (BAL), and by increased GM-CSF autoantibodies in serum.
- Stable or progressive aPAP (i.e. absolute VC not improved by more than 5% and/or diffusing capacity of the lungs for carbon monoxide (DLCO) not improved by more than 10% - assessed from medical records) during a minimum period of two months prior to the Baseline visit.
- PaO2 <75 mmHg/<10 kPa at rest, OR desaturation of >4 percentage points on the 6 Minute Walk Test (6MWT)
- An $(A\text{-}a)DO_2$ at Screening of minimum 25 mmHg/3.33 kPa
- Female or male ≥18 years of age
- + 4 standard inclusion criteria relating to pregnancy, contraception and informed consent

Exclusion criteria

- Diagnosis of hereditary or secondary PAP
- WLL within two months of Baseline
- Treatment with GM-CSF or plasmapheresis within three months of baseline, rituximab within 6 months of baseline or any investigational drug within 4 weeks of screening
- Concomitant use of sputum modifying drugs such as carbocystein or ambroxol
- History of allergic reactions to GM-CSF
- Connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring immunosuppressive treatment
- Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
- History of, or present, myeloproliferative disease or leukaemia
- Significant liver impairment (aspartate aminotransferase or alanine aminotransferase level >3 times the upper normal limit) or renal impairment (estimated Glomerular Filtration Rate <30 mL/min/1.73m^2) at Screening
- Known active infection (viral, bacterial, fungal or mycobacterial)
- Apparent pre-existing concurrent pulmonary fibrosis
- Any other serious medical condition

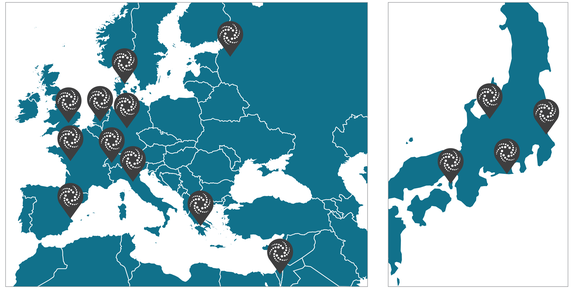
Assessments

Efficacy:

- Blood gas – PaO_2, $(A\text{-}a)DO_2$ (calculated)
- Lung function variables, VC, Forced VC, Forced Expiratory Volume in one second (FEV1) and DLCO – according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidance
- CT – A blinded independent assessor will examine the scans and grade the individual subjects score as: Improved / Worsened / No change / Data missing – impossible to evaluate.
- Quality of Life (QoL) score – St Georges Respiratory Questionnaire and EuroQol-5D
- Dyspnoea score – Borg CR10 Scale for dyspnoea
- Cough scores – Cough Questions
- 6MWT– according to ATS/ERS guidance
- Biomarkers: Surfactant Protein A (SP-A), SP-B, SP-C, SP-D, Krebs von den Lungen-6 (KL-6), Fragments of Cytokeratin-19 (Cyfra 21-1), Carcino-Embryonic Antigen (CEA), Lactate Dehydrogenase (LDH).
- GM-CSF and anti-GM-CSF in serum

Safety:
Number of adverse events (AEs), serious adverse events, adverse drug reactions, severe AEs and AEs leading to treatment discontinuation, including clinically significant changes in laboratory tests and echocardiographic (ECG) variables

Figure 2



Country	City	Institution	PI
Denmark	Århus	University Hospital Århus	Elisabeth Bendstrup
France	Rennes	CHU Rennes	Stephane Jouneau
Germany	Essen	Ruhrlandklinik	Francesco Bonella
Germany	Heidelberg	Thoraxklinik am Universitätsklinikum	Michael Kreuter
Germany	Homburg/Saar	Universitätsklinikum des Saarlandes	Robert Bals
Germany	Gauting	Asklepios-Fachkliniken München	Wolfgang Gesierich
Greece	Athens	Attikon University Hospital	Spyros Papiris
Italy	Pavia	Fondazione IRCCS Policlinico San Matteo	Kadija Zamir
Israel	Beilinson	Rabin Medical Center	Mordechai Kremer
Japan	Osaka	National Hospital Kinki-Chuo Chest Medical Center	Youshikazu Inoue
Japan	Niigata	Niigata University	Ryushi Tazawa
Japan	Nagakute	Aichi Medical Center	Etsuro Yamaguchi
Japan	Yokohama	Kanagawa Cardiovascular and Respiratory Center	Tomohisa Baba
Netherlands	Nieuwegein	St. Antonius Hospital	Marcel Veltkamp
Russia	St. Petersburg	City Hospital	Julia Ilkovich
Spain	Barcelona	Hospital de Bellvitge	Maria Molina Molina
Switzerland	Lausanne	Centre Hospitalier Universitaire Vaudois	Romain Lazor
United Kingdom	London	Royal Brompton	Cliff Morgan

ACTIVE COMPOUND, FORMULATION AND DELIVERY TO THE LUNGS

Molgramostim is an un-glycosylated rhGM-CSF produced in a strain of *Escherichia coli* bearing a genetically engineered plasmid which contains a human GM-CSF gene. A nebuliser solution containing molgramostim has been formulated and developed specifically for inhalation treatment of respiratory conditions.

Molgramostim nebuliser solution (Molgradex®) is a liquid formulation containing molgramostim 250 µg/mL and is delivered using eFlow® nebuliser system (PARI Pharma GmbH, Germany).

The eFlow® handset is a single patient use, reusable nebuliser, which has been optimised for nebulisation of molgramostim nebuliser solution.

Characteristics of eFlow nebuliser handset for molgramostim nebuliser solution

PARAMETER	RESULTS
Results from laser diffraction	
Particle size distribution	Mass Median Diameter: 3.5 µm (SD 0.37) Geometric Standard Deviation: 1.6 (SD 0.1) Respirable fraction < 5 µm: 76.9% (SD 8.03)
Results from breath simulation experiments	
Delivered dose Respirable dose < 5 µm	60.4% 46.3%

- Savara, Data on File, 2016

CONCLUSION

Autoimmune PAP is a medical condition with a high unmet medical need. Inhaled GM-CSF is a promising medical therapy for aPAP, but it is currently not licensed. This is the first global initiative and placebo-controlled randomized trial, with the overall aim of getting an inhaled medical therapy licensed for treatment of aPAP.

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