A randomized, double-blind, placebo-controlled clinical trial of once-daily inhaled molgramostim nebulizer solution in adult subjects with autoimmune pulmonary alveolar proteinosis (aPAP).

Published: 08-10-2020
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The main objective of this trial is to investigate the efficacy of inhaled molgramostim compared to placebo.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON55020

Source
ToetsingOnline

Brief title
IMPALA-2

Condition

- Autoimmune disorders
- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
autoimmune PAP; pulmonary alveolar proteinosis

Research involving
Human

Sponsors and support

Primary sponsor: Parexel Nederland
Source(s) of monetary or material Support: Savara ApS

Intervention

Keyword: inhalation, molgramostim, pulmonary autoimmune proteinosis

Outcome measures

Primary outcome

The primary endpoint is the change in % predicted DLCO from baseline to Week 24. The aim of this endpoint is to demonstrate treatment effect on gas exchange, using a standardized lung function test that has been shown to predict need for rescue treatment.

Secondary outcome

- The secondary efficacy endpoints are Saint George*s Respiratory Questionnaire (SGRQ) Total, SGRQ Activity, exercise capacity (EC) and change in % predicted DLCO from baseline to Week 48. The aim of these endpoints is to serve as clinically meaningful endpoints that address health status and function.

Study description

Background summary

Savara ApS has developed a solution for inhalation of the known product molgramostim for the treatment of aPAP. Molgramostim contains the active substance recombinant human Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF).
GM-CSF is a protein that is naturally present in the human body as part of the immune system. Patients with aPAP have increased levels of antibodies towards the specific protein. These antibodies bind to the patient's GM-CSF and block its function. As a result, a protein-rich material builds up in the air sacs of the lungs, making it difficult to transfer oxygen to the blood. It is suggested

that inhaling molgramostim might enable the immune system in the lungs to clear this material to allow oxygen to enter the blood.

Study objective

The main objective of this trial is to investigate the efficacy of inhaled molgramostim compared to placebo.

Study design

This is an interventional, randomized, double-blind, 2-arm, parallel, placebo-controlled, multi-center, phase 3 trial in adult subjects who are diagnosed with aPAP.
The trial consists of a 6-week screening period, a 48-week randomized, double-blind treatment period, a 48-week open-label treatment period and a 4-week safety follow-up period.

Intervention

Eligible subjects will be centrally assigned through an Interactive Response Technology (IRT) system to 48-week double-blind once-daily treatment with either molgramostim 300 µg nebulizer solution or placebo.
Subjects who complete the double-blind 48-week treatment period and who have not permanently discontinued the investigational product due to unacceptable AE will continue into the open-label treatment period where they will receive once-daily open-label treatment with molgraqmotim nebulizer solution.

Study burden and risks

- Type I hypersensitivity reactions: This is considered a risk due to the inherent risk of
immunogenicity reactions to therapeutic proteins.
- Use in pregnancy: nonclinical studies have shown higher frequency of abortions and early deliveries in cynomolgus monkeys treated with molgramostim compared to control animals. Studies in humans to determine effects of molgramostim nebulizer solution on fertility have not been undertaken.
- Cough: In a previous clinical trial, there was a higher proportion of subjects reporting non-serious, mild to moderate Cough or Productive cough.
- Chest pains: In a previous clinical trial, there was a higher proportion of subjects reporting non-serious, mild *Chest pain*.
- Blood sampling: Blood sampling is invasive and there is always a slight risk of bruising, infections, pain etc.
- DLCO test: During the test, subjects will need to inspire minute amounts of carbon monoxide and tracer gases (e.g. 10% helium) and he/she needs to temporarily come off oxygen supply.
- Exercise treadmill test: In subjects with preexisting heart and respiratory

disease, e.g. angina, there may be a risk of exacerbation of these conditions during the test. The test must be performed without supplementary oxygen and this might induce a risk of desaturation. The assessment involves exercise on a treadmill which might cause a risk of fall.
- CT scans: slightly increase risk of developing cancer, although at the low doses used for CT, the risk is very small. The amount of X-ray radiation that you will be exposed to at each CT scan corresponds to approximately 3 years worth of background radiation.
- Use of placebo: 50% of the subjects will be treated with placebo during the 48-week double-blind period. This might result in deterioration of aPAP.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject must be >=18 years of age, at the time of signing the informed consent. Specific for Japan; Subject must be >=20 years of age, at the time of signing the informed consent.
2. A serum anti-GM-CSF autoantibody test result confirming autoimmune PAP.
3. History of PAP, based on examination of a lung biopsy, bronchoalveolar lavage (BAL) cytology, or a high-resolution computed tomogram (HRCT) of the chest.
4. DLCO 70% predicted or lower at the first Screening and Baseline visits.
5. Change in % predicted DLCO of <15% points during the screening period.
6. Willing and able to come off supplemental oxygen use prior to and during the treadmill exercise test, the DLCO assessment, and the arterial blood gas sampling.
7. Resting SpO2 >85% during 15 minutes without use of supplemental oxygen at the Screening visits.
8. Male or female
9. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
a. Male subjects: Males agreeing to use condoms during and until 30 days after last dose of trial treatment, or males having a female partner who is using adequate contraception as described below.
b. Female subjects: Females who have been post-menopausal* for >1 year, or females of childbearing potential** after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with <1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence***), during and until 30 days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at the screening visits, and a negative urine pregnancy test at Baseline visit (Visit 3) and must not be lactating.
* Post-menopausal is defined as no menses for at least 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
** A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
***Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence

needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures specified in the protocol as judged by the Investigator.

Exclusion criteria

1. Diagnosis of hereditary or secondary PAP, or a metabolic disorder of surfactant production.
2. WLL performed within 3 months prior to baseline.
3. Requirement for WLL at screening or baseline.
4. GM-CSF treatment within 6 months prior to baseline.
5. Treatment with rituximab within 6 months prior to baseline.
6. Treatment with plasmapheresis within 6 weeks months prior to baseline.
7. Treatment with any investigational medicinal product within 5 half-lives or 3 months (whichever is longer) prior to baseline.
8. Previously randomized in this trial.
9. History of allergic reactions to GM-CSF or any of the excipients in the nebulizer solution.
10. Inflammatory or autoimmune disease of a severity that necessitates significant (e.g. more than 10 mg/day systemic prednisolone) immunosuppression.
11. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.
12. History of, or present, myeloproliferative disease or leukemia.
13. Apparent pre-existing concurrent pulmonary fibrosis, or diagnosis of interstitial lung disease other than aPAP.
14. Acute or unstable cardiac or pulmonary disease that may be aggravated by exercise or confound assessment of the primary endpoint: including presence of pulmonary edema, or diagnosis of chronic obstructive pulmonary disease (COPD), pulmonary vasculitis, or pulmonary hypertension.
15. Known active infection (viral, bacterial, fungal, or mycobacterial) that may affect the efficacy evaluation in the trial.
16. Physical disability or other condition that precludes safe and adequate exercise testing.
17. Any other serious medical condition which in the opinion of the Investigator would make the subject unsuitable for the trial.
18. Pregnant, planning to become pregnant during the trial, or breastfeeding woman.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	molgramostim 300 microgram nebulizer solution
Generic name:	molgramostim

Ethics review

Approved WMO Date:	08-10-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-07-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2022
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-001263-85-NL
CCMO	NL74588.100.20