A double-blind, placebo-controlled, multi-centre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled colistimethate sodium in the treatment of subjects with non-cystic fibrosis bronchiectasis chronically infected with Pseudomonas aeruginosa (P. aeruginosa)

Published: 18-07-2018
Last updated: 11-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48850

Source
ToetsingOnline

Brief title
PROMIS I

Condition

- Other condition
- Bacterial infectious disorders

Synonym
non-cystic fibrosis bronchiectasis chronically infected with Pseudomonas aeruginosa

Health condition

subjects with non-cystic fibrosis bronchiectasis chronically infected with Pseudomonas aeruginosa

Research involving
Human

Sponsors and support

Primary sponsor: Zambon SpA
Source(s) of monetary or material Support: Zambon SpA

Intervention

Keyword: double-blind, inhaled colistimethate sodium, non-cystic fibrosis bronchiectasis, placebo-controlled

Outcome measures

Primary outcome

Primary Efficacy Variable:

Mean annual pulmonary exacerbation rate.

Secondary outcome

Secondary Efficacy Variables:

* the time (in days) from the first dose of IMP until the first pulmonary

exacerbation;

* annualised number of pulmonary exacerbation-free days;

* number of severe pulmonary exacerbations, defined as those requiring

intravenous antibiotics and/or hospitalisation;

* the time (in days) from the first dose of IMP until the first severe

pulmonary exacerbation;

* quality of life (QoL) as measured by the total score of the Saint George*s Respiratory Questionnaire (SGRQ) and Quality of Life * Bronchiectasis (QOL B) questionnaire as well as changes in SGRQ and QOL-B from baseline to each post-baseline visit;

* number of days of work absence due to pulmonary exacerbations;

* P. aeruginosa density as determined by the mean change in log10 colony forming units (CFU)/g sputum from baseline (Visit 2) to Day 28 of treatment (Visit 3) as well as to Visits 5 and 7.

Study description

Background summary

Colistimethate sodium is an antibacterial cationic cyclic polypeptide belonging to the polymyxin group; it is currently approved in the US for i.v. administration and in Europe for both i.v. and inhaled administration.
The approved injectable forms of CMS in the US are indicated for the treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli and are particularly indicated when the infection is caused by sensitive strains of P. aeruginosa.
In Europe, CMS has been extensively used in clinical practice for over 30 years via the inhaled administration route, for the treatment of colonization and infections of the lung by susceptible P. aeruginosa in patients with Cystic Fibrosis (CF).

In conclusion, CMS is an established medicinal product which is widely approved in the EU and has been used for over 30 years to treat CF patients with P. aeruginosa infection. It is also used off-label extensively in NCFB patients in Europe in accordance with national and international society guidelines for the treatment of NCFB. Extensive real-life clinical use data show that long-term use of inhaled CMS is effective and has good safety and tolerability in children and adults.

(For more information see IB capture 2: Summary)

Study objective

The primary objectives of the trial are to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via the I-Neb for 12 months, compared to placebo in subjects with non*cystic fibrosis bronchiectasis (NCFB) chronically infected with P. aeruginosa on the frequency of pulmonary exacerbations.

Key secondary objectives are: time to first pulmonary exacerbation, number of exacerbation-free days, health-related patient reported outcomes, microbiology assessments, pharmaco-economic evaluations as well as safety and tolerability.

Study design

Randomised, multicentre, double-blind, placebo-controlled, parallel group trial. Subjects will be randomized to active or placebo in a 1:1 ratio.
The study will consist of a total of 7 clinic visits with a follow-up call two weeks after discontinuation of treatment. Additional clinic visits, where feasible, and weekly calls will be conducted following pulmonary exacerbations until resolution.

Intervention

Subjects will administer the investigational medicinal product (IMP) twice daily (morning and evening) via the I-neb Adaptive Aerosol Delivery (AAD) System.
The content of the vial is reconstituted with 1 mL of 0.45% sodium chloride (saline) solution and 1 mL of the medication placed in the I-neb device to fill the 0.3 mL nebulisation chamber to give a delivered dose of 10 mg colistin base activity (CBA).

Study burden and risks

In terms of safety profile, the use of Promixin in the previous trial (phase II) was not associated with the development of resistance to colistimethate sodium by P. aeruginosa and no overgrowth of other bacteria occurred. The safety profile of Promixin in patients with non-CF bronchiectasis was similar to the safety profile established for patients with CF bronchiectasis. There were no safety concerns, no significant changes in FEV1 and the incidence of adverse events was similar in both groups.
According to SmPC; approximately 10% of patients experience coughing and bronchospasm with the first administration by inhalation. So in the present study, a bronchodilator (salbutamol) is provided to prevent bronchospasm by administration about 15 minutes before inhalation of study drug. Spirometry tests are also performed 30 minutes after study drug administration to check any bronchoconstriction. In case a bronchospasm is observed even at the first administration at the study site or in the following visits, patients are to be withdrawn from the study.

Other common side effects include chest tightness and bronchoconstriction, sore throat and sore mouth,
which may be due to hypersensitivity or candidiasis, hypersensitivity reactions including skin rash,
neurotoxicity and nephrotoxicity.

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

Subjects can be included in the trial if they meet all the inclusion criteria listed below:, 1. are able and willing to give informed consent following a detailed explanation of participation in the protocol and signed consent obtained;
2. are aged 18 years or older of either gender;

3. diagnosed with NCFB by computerised tomography (CT) or high resolution CT (HRCT) as recorded in the subject*s notes;
4. had at least 2 NCFB pulmonary exacerbations requiring oral antibiotics or 1 NCFB pulmonary exacerbation requiring intravenous antibiotics in the 12 months preceding the Screening Visit (Visit 1) and had no NCFB pulmonary exacerbation with or without treatment during the period between Visit 1 and Visit 2;
5. have a documented history of P. aeruginosa infection;
6. are clinically stable and have not required a change in pulmonary treatment for at least 30 days before the Screening Visit (Visit 1);
7. have pre-bronchodilator FEV1 *30% of predicted;
8. had a positive sputum culture for P. aeruginosa from an adequate sample taken at the Screening Visit (Visit 1).

Exclusion criteria

Subjects are not eligible for the trial if they meet one or more of the exclusion criteria listed below:, 1. known bronchiectasis as a consequence of cystic fibrosis (CF);
2. known history of hypogammaglobulinaemia requiring treatment with immunoglobulin, unless fully replaced and considered immuno-competent by the Investigator;
3. myasthenia gravis, porphyria or myeloproliferative disease;
4. severe cardiovascular disease such as severe uncontrolled hypertension, ischaemic heart disease or cardiac arrhythmia and any other conditions that would confound the evaluation of safety, in the opinion of the Investigator;
5. had major surgery in the 3 months prior to the Screening Visit (Visit 1) or planned inpatient major surgery during the study period;
6. receiving treatment for allergic bronchopulmonary aspergillosis (ABPA);
7. had massive haemoptysis (greater than or equal to 300 mL or requiring blood transfusion) in the preceding 4 weeks before the Screening Visit (Visit 1) or between Visit 1 and Visit 2;
8. predominant lung condition being chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease in the opinion of the Investigator;
9. respiratory failure requiring long-term domiciliary oxygen therapy or non-invasive ventilation;
10. current active malignancy, except for basal cell carcinoma of the skin without metastases;
11. taking immunosuppressive medications (such as azathioprine, methotrexate, cyclosporine, tacrolimus, sirolimus, mycophenolate, rituximab), and/or anti-cytokine medications (such as anti-IL-6 and anti-tumour alpha necrosis factor products) in the preceding year before the Screening Visit (Visit 1);
12. known history of human immunodeficiency virus (HIV);
13. current diagnosis or current treatment for non-tuberculous mycobacterial (NTM) pulmonary disease or Mycobacterium tuberculosis infection;
14. known to be intolerant to inhaled beta-2 agonists (bronchodilators);

15. known or suspected to be allergic or unable to tolerate colistimethate sodium (intravenous or inhaled) or other polymixins, including previous evidence of bronchial hyperreactivity following inhaled colistimethate sodium;
16. treatment with long term (* 30 days) prednisone at a dose greater than 15 mg a day (or equivalent dose of any other corticosteroid) within 6 months of the Screening Visit 1 (Visit 1);
17. new maintenance treatment with oral macrolides (e.g. azithromycin/erythromycin/clarithromycin) started within 30 days of the Screening Visit (Visit 1) or started between Visit 1 and Visit 2;
18. use of any intravenous or intramuscular or oral or inhaled anti-pseudomonal antibiotic (except chronic oral macrolide treatment with a stable dose) within 30 days prior to the Screening Visit (Visit 1) and between Visit 1 and Visit 2;
19. pregnant or breast feeding or plan to become pregnant over the next year or of child-bearing potential and unwilling to use a reliable method of contraception for at least one month before randomisation and throughout their involvement in the trial;
20. significant abnormality in clinical evaluations and/or laboratory tests (physical examination, vital signs, haematology, clinical chemistry, clinically relevant impaired renal function, defined as serum creatinine levels *2.0x upper limit of normal, ECG) endangering the safe participation of the patient in the study at the Screening Visit (Visit 1) and during the study;
21. participated in another investigational, interventional trial within 30 days prior to the Screening Visit (Visit 1).
22. in the opinion of the Investigator not suitable for inclusion for whatever reason.

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:	Recruitment stopped
Start date (anticipated):	03-09-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Colistimethate sodium
Generic name:	Colistimethate sodium
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-12-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-07-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-002743-33-NL
CCMO	NL66006.042.18