Long Term Administration of Inhaled Mannitol in Cystic Fibrosis - A Safety and Efficacy Study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders congenital
Study type	Interventional

Summary

ID

NL-OMON32987

Source
ToetsingOnline

Brief title
DPM-CF-302

Condition

- Respiratory disorders congenital
- Congenital respiratory tract disorders

Synonym
mucoviscidosis

Research involving
Human

Sponsors and support

Primary sponsor: Pharmaxis Pharmaceuticals Limited
Source(s) of monetary or material Support: Pharmaxis

Intervention

Keyword: Mannitol, Mucoviscidosis

Outcome measures

Primary outcome

Change in absolute FEV1

Secondary outcome

Efficacy:

• Change in absolute FEV1(rhDNase group)

• Pulmonary exacerbations in those taking rhDNase as a sub-group and in the

total cohort

• Quality of life scores using Cystic Fibrosis Questionnaire-R

• Rescue antibiotic use (number of agents, course and days of use)

• Change in absolute FVC, FEF25-75 from baseline

• Days in hospital due to pulmonary exacerbations

Safety:

• Adverse events

• Laboratory safety tests: complete blood count, blood urea nitrogen,

electrolytes, liver function tests

• Qualitative sputum microbiology

• Quantitative sputum microbiology for S. aureus and P. aeruginosa

• Physical examination findings

Cost-Effectiveness:

• Total costs incurred in intervention and control groups

* Costs associated with inhaled mannitol

* Cost of antibiotic use and rescue medication

* Costs of hospitalizations and other secondary care services used

* Cost of primary and community care services used

• Indicators of effectiveness and quality of life for intervention and control groups

* As above

• Determination of cost-effectiveness ratios

• Sensitivity analysis

* To assess extent to which variation in parameter estimates affect cost effectiveness ratios

Study description

Background summary

Inhaled mannitol is being developed as a therapeutic agent for the treatment of cystic fibrosis and other diseases characterized by difficult to clear, thickened respiratory mucus. The mucoactive effects of inhaled mannitol have been examined in several acute and short term studies and now warrant further investigation. As part of the development plan, information on the efficacy and safety of inhaled mannitol over the long term is required. Running concurrently is a 6 -12 month sister study, being conducted in the United Kingdom, Ireland and Australia. Expected to complete in 2009, this study is will further provide

efficacy and safety evidence for use in cystic fibrosis.

Different trials demonstrate the efficacy of Mannitol (see protocol p. 11-13)
• Mannitol as a Bronchial Provocation Test
• Mucociliary Clearance Studies in Cystic Fibrosis, Bronchiectasis and Asthma
• Therapeutic Studies in Bronchiectasis
• Therapeutic Studies in Cystic Fibrosis

Study objective

The purpose of this study is to examine the efficacy and safety of 26 weeks treatment with inhaled mannitol in subjects with cystic fibrosis. Previous studies with inhaled mannitol have demonstrated improvements in lung function, mucociliary clearance, mucus rehydration and quality of life. The results of this study in combination with its European, Australian and New Zealand counterpart study seek to confirm these early findings and to extend the evidence to support its use as a mucoactive therapy for promoting bronchial hygiene in subjects with cystic fibrosis.
We hypothesize that inhaled mannitol will improve the overall health and hygiene of the lung through regular and effective clearing of the mucus load. On commencing treatment, we expect an acute clearance of the retained mucus and with twice daily use, ongoing mucus clearance to be associated with reduced mucus production. Acute clearance is cough assisted, however once the chest is cleared, patients should experience long cough free periods both during the day and following the evening treatment, at night. It is expected that this will be reflected as an improvement in health related quality of life.
In respect to the lung, we expect findings on auscultation to improve in line with respiratory function as a result of clearing blocked and impeded airways. As a consequence of the reduction in mucus load, exacerbations, and related antibiotic use should fall. Days in hospital and community health care costs are expected to change in line with improvements in respiratory health.
Finally, we plan to demonstrate that inhaled mannitol is safe and well tolerated over a 52 week period. We will test these hypotheses using 400 mg inhaled mannitol twice daily against control.

Study design

Randomized, controlled, parallel arm, double blind proceeding to open label

Intervention

After satisfying all inclusion & exclusion criteria, subjects will be given a mannitol tolerance test (MTT). Those with a negative MTT result will be randomized to receive for 26 weeks, 400mg BID inhaled mannitol or control, in a ratio of 3 subjects to mannitol to 2 subjects to control (see Diagram 1 on page 17 of the protocol). On completion of the blinded phase, subjects will

move into a 26 week open label phase.

Study burden and risks

See flow-chart on page 71 Appendix 3 of the protocol.
Regarding the risks, please see ICF

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Have given written informed consent to participate in this study in accordance with local regulations
2. Have a confirmed diagnosis of cystic fibrosis (positive sweat chloride value >= 60 mEq/L) and/or genotype with two identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype)
3. Be aged > 6 years old
4. Have FEV1 >40 % and < 90% predicted (using Wang <8 years and NHanes III >8years)
5. Be able to perform all the techniques necessary to measure lung function

Exclusion criteria

1. Be investigators, site personnel directly affiliated with this study, or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biologically or legally adopted.
2. Be considered *terminally ill* or eligible for lung transplantation
3. Have had a lung transplant
4. Be using nebulized hypertonic saline in the 4 weeks prior to visit 1
5. Have had a significant episode of hemoptysis (>60 mL) in the three months prior to enrolment
6. Have had a myocardial infarction in the three months prior to enrolment
7. Have had a cerebral vascular accident in the three months prior to enrolment
8. Have had major ocular surgery in the three months prior to enrolment
9. Have had major abdominal, chest or brain surgery in the three months prior to enrolment
10. Have a known cerebral, aortic or abdominal aneurysm
11. Be breast feeding or pregnant, or plan to become pregnant while in the study
12. Be using an unreliable form of contraception (female subjects at risk of pregnancy only)
13. Be participating in another investigative drug study, parallel to, or within 4 weeks of visit 0
14. Have a known allergy to mannitol
15. Be using beta blockers
16. Have uncontrolled hypertension -e.g. for adults: systolic BP > 190 and / or diastolic BP > 100
17. Have a condition or be in a situation which in the Investigator*s opinion may put the subject at significant risk, may confound results or may interfere significantly with the patient*s participation in the study
18. Be *MTT positive or incomplete*. (As evaluated in section 3.3.8.5)

Study design

Design

Study phase: 3

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2009
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mannitol droogpoeder voor inhalatie
Generic name:	Mannitol droogpoeder voor inhalatie

Ethics review

Approved WMO

Date:	06-04-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO

Date:	10-08-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2008-002740-42-NL
ClinicalTrials.gov	NCT00446680
CCMO	NL27486.003.09