2 SYNOPSIS

Name of Sponsor/Company: Pharmaxis Ltd Name of Finished Product: Bronchitol Name of Active Ingredient: Mannitol	Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented Volume: CTD Module Number 5.3.5.1 Reference: Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	(For National Authority Use only)

Title of study: A Phase III Multicentre, Randomised, Parallel Group, Controlled, Double-Blind Study to Investigate the Safety and Efficacy of Inhaled Mannitol over 12 Months in the Treatment of Bronchiectasis

Global Principal Investigator: Dr Diana Bilton, Royal Brompton Hospital, London SW3 6NP, UK

Study centre(s): Total of 84 sites in USA, Europe, Australia, New Zealand and South America

Publication (reference): None

Study period: 19 October 2009 – 28 February 2013	**Phase of development:** III

Primary objective:

- To compare the rates of graded pulmonary exacerbations (GPEs) in subjects with bronchiectasis treated with either inhaled mannitol or control

Secondary objectives:

To compare the differences between bronchiectasis subjects treated with either inhaled mannitol or control, in the following parameters:

- Quality of Life as measured by the St. George's Respiratory Questionnaire (SGRQ)
- Antibiotic use prescribed for treated pulmonary exacerbations including number of discrete courses; days on antibiotics; and time to first antibiotic need
- Other graded exacerbation parameters (time to first exacerbation and duration of exacerbation)
- Sputum volume
- Daytime sleepiness scores
- Lung function (FEV_1, FVC, FEV_1/FVC, FEF_{25-75} values)
- Number of hospitalisations due to pulmonary exacerbations

Safety

- To monitor the safety profile of inhaled mannitol compared to control in subjects with bronchiectasis by investigating adverse events, airway reactivity, haematology, clinical chemistry, physical examination, sputum microbiology and vital signs

Costs, Health Status, Utilities and Cost-Effectiveness

- To compare health related costs of treating subjects with bronchiectasis with inhaled mannitol and control
- To compare health status and utility scores in subjects treated with inhaled mannitol compared with control
- To investigate health related quality of life (HRQL) and quality adjusted life years (QALYs) by treatment group using utility scores from the Health Utilities Index Questionnaire
- To investigate cost-effectiveness of treating subjects with bronchiectasis with inhaled mannitol

Methodology: Randomised, double-blind, controlled, parallel group study

Number of subjects:
Planned: 474 (237 mannitol; 237 control) **Actual:** 485 randomised

Diagnosis and main criteria for inclusion: Non-cystic fibrosis (CF) bronchiectasis; $FEV_1 \geq 40$ % and $\leq 85\%$ predicted and ≥ 1L; male or female aged 18-85 years; minimum two pulmonary exacerbations in previous 12 months and at least four exacerbations in previous two years; SGRQ score ≥ 30; 24 hour sputum ≥ 10 g; no significant haemoptysis in previous six months; no active *Mycobacterium tuberculosis*; not terminally ill or

listed for transplantation. Must not have previously used inhaled mannitol for more than one day.

Test product, dose and mode of administration, batch number:

Inhaled mannitol, 400 mg BID (10 x 40 mg capsules BID) administered via a dry powder inhaler device (RS01 HR Model 7, Plastiape Italy).

Batch numbers are listed in Appendix 16.1.6.1, 16.1.6.2 and 16.1.6.3.

Duration of treatment: 52 weeks treatment, with additional four weeks follow-up

Reference Therapy:

Mannitol 50 mg BID (thought to be a sub-therapeutic dose), (10 x 5 mg capsules BID), matched in appearance and packaging to the test product, administered via a dry powder inhaler device (RS01 HR Model 7, Plastiape Italy).

Batch numbers listed in Appendix 16.1.6.1, 16.1.6.2 and 16.1.6.3.

Criteria for evaluation:

Primary Efficacy:

- Graded Pulmonary Exacerbation (GPE) rates

Secondary Efficacy:

- St George's Respiratory Questionnaire (SGRQ) scores
- Courses of; days on; and time to need; for oral, IV or inhaled antibiotics prescribed for worsening respiratory signs and symptoms related to a treated pulmonary exacerbation
- Time to first graded exacerbation; duration of graded exacerbations
- 24 hour sputum weight
- Change in Epworth daytime sleepiness scores
- Change in FEV_1, FVC, FEV_1/FVC, FEF_{25-75} values
- (Exploratory) Number of hospitalisations due to pulmonary exacerbations

Safety endpoints:

- Airway reactivity following a mannitol tolerance test (MTT) (acute decrease in $FEV_1 \geq 20\%$)
- Adverse events (AEs)
- Laboratory tests: Complete blood count; electrolytes; creatinine and blood urea nitrogen; and liver function tests
- Qualitative sputum microbiology: disappearance or appearance of pathogens
- Vital signs and physical examination

Costs, Health Status, Utilities and Cost-Effectiveness

- Total costs incurred in intervention and control groups including: costs associated with inhaled mannitol; costs of antibiotic use and rescue medication; costs of hospitalisations and other secondary care services used; cost of primary and community care services used
- Results from Health Utilities Index Questionnaire in intervention and control groups to derive: Health status; Health related quality of life; Utility scores; Calculation of quality adjusted life years
- Determination of cost-effectiveness ratios for intervention and control groups, utilising: Sensitivity analysis to assess extent to which variation in parameter estimates affect cost-effectiveness ratios; Analysis on the extent to which variation in parameters affects results from the Health Utilities Index Questionnaire

Statistical methods: The primary endpoint of GPE rate was estimated using a negative binomial regression model, with treatment, region and baseline pulmonary exacerbation rate included as predictors. The GPE rate ratio and its 95% CI were reported. Sensitivity analyses were conducted for GPE to account for missing data. Secondary endpoints including number of antibiotic-treated PEs/GPEs, number of days on antibiotics for the treatment of PEs/GPEs, duration (days) of PEs/GPEs, and number of hospitalisations due to PEs/GPEs were also analysed by this method.

Change from baseline in SGRQ total and component scores were analysed using a mixed model of repeated measures (MMRM), with treatment, visit, treatment by visit interaction, region and baseline SGRQ score as predictors. The treatment effect and its 95% CI across the 52 weeks of treatment period were estimated from the model. Other secondary endpoints including 24-hour sputum weight, Daytime Sleepiness Scores, and lung

function variables were also analysed in a similar way.

The survival functions for time to first GPE and time to the first antibiotic use for the treatment of PE/GPE were estimated by the Kaplan-Meier method. Log-rank test stratified by region and baseline PE was used to compare survivor functions between the two treatment groups. A region and baseline PE stratified Cox's proportional hazards model was used to estimate the hazard ratio and its 95% CI between the two treatment groups.

SUMMARY RESULTS

Demographics:

486 out of 581 subjects passed the MTT (83.6%). Four hundred and eighty-five (485) subjects were randomised to the study, and 461 (Mannitol 233; Control 228) received at least one dose or part thereof of blinded study medication and were included in the Intent to Treat (ITT) population. Treatment groups were well balanced for baseline characteristics. The mean age of study subjects was 59.8 years, and study population was 62.7% female. Cause of bronchiectasis was unknown in approximately half (50.3%) of all subjects. 22.3% subjects were macrolide users at baseline. 21.9% of subjects grew pseudomonas in their baseline sputum sample.

EFFICACY

Primary: Fewer GPEs were reported in the Mannitol arm than in the Control arm (425 GPEs mannitol v 461 GPEs control) and fewer subjects in the Mannitol arm (160 subjects; 68.7%) than the Control arm (178 subjects: 78.1%) reported at least one GPE. The primary endpoint of GPE rate was lower in the Mannitol arm than the Control, however the difference was not significant, rate ratio = 0.92 (95% CI: 0.78 - 1.08); p=0.31.

Secondary: Time to first GPE was significantly longer in the Mannitol arm compared to Control (median 5.4 months v. 4.1 months), hazard ratio (Cox regression) = 0.78 (95% CI: 0.63 – 0.96); p= 0.0218. Duration of GPEs was slightly lower in the Mannitol arm (mean 31.49 days/year), than the Control arm (mean 35.74 days/year), but the difference was not significant (p=0.3602).

Subjects in the Mannitol arm had fewer days on antibiotics for the treatment of GPEs (mean = 19.88 days/year) than subjects in the Control arm (mean = 26.03 days/year), rate ratio = 0.76 (95% CI: 0.58 - 1.00), p=0.0496, and longer median time to first antibiotic use for treatment of a GPE (Mannitol 5.5 months v. Control 4.1 months), hazard ratio (Cox regression) = 0.77 (95% CI: 0.62-0.96); p = 0.0201.

SGRQ Total score improved for both treatment groups over the blinded treatment period, with absolute decrease in SGRQ Total score of 10.98 for Mannitol compared with 8.58 for Control. The difference between groups was statistically significant (difference = 2.40, 95% CI: 0.05 – 4.76; p = 0.0457). Each of the SGRQ subscores, namely Impact, Symptoms and Activity, showed numerically greater improvement in the Mannitol arm than the Control arm; only the difference in change from baseline in Activity score was significant (p=0.0339).

Mean 24-hour sputum weight remained higher in the Mannitol arm than the Control arm throughout the study. There was an average reduction in sputum weight for the on-treatment period of 6.66 g in the Mannitol arm, compared to 9.42g in the Control arm (p = 0.0355).

In the Mannitol arm there was an improvement in least squares mean Epworth Sleepiness Scale (ESS) total score of 0.95, compared to an improvement of 0.51 in the Control arm. The difference was not significant (p=0.1159).

There were some slight numerical improvements in FEV_1, relative change in FEV_1, percentage of predicted FEV_1, and FVC in the Mannitol arm compared to Control but none were statistically significant. A large but non-significant reduction in hospitalisation rate due to pulmonary exacerbation was noted in the Mannitol arm (0.14 hosp/year) compared to the Control arm (0.20 hosp/yr), rate ratio = 0.69 (95% CI: 0.40 - 1.19).

No subgroup showed statistically significant improvement in pulmonary exacerbation rate, however subjects who had SGRQ Total score greater than the median, subjects with FEV_1/FVC ratio less than 70%, subjects with FEV_1 less than 60% of predicted, and subjects who were smokers, all appeared to have a modest reduction in GPE rate compared to subjects in the Control arm.

SAFETY

MTT

The majority (83.6%) of subjects passed the test without bronchial hyperresponsiveness. The incidence of MTT-related AEs was low. Cough, and 'forced expiratory volume decreased', each experienced by 2.2% subjects, were the most frequent MTT-related adverse events. Oxygen saturation decreased (0.7%), bronchospasm (0.5%) and wheezing (0.5%) all occurred in less than one percent of subjects. One subject experienced the serious adverse event (SAE) bronchospasm shortly after the MTT; this fully resolved within two hours with nebulised salbutamol treatment. Overall, the MTT was safe and well tolerated.

Blinded Treatment Phase

Inhaled mannitol (400 mg BID) demonstrated an acceptable safety profile over 52-weeks of treatment in subjects with non-CF bronchiectasis. The incidence of subjects reporting AEs was similar in both groups, being 92.3% and 93.9% in the Mannitol and Control groups, respectively. The majority of adverse events were mild or moderate, with a slightly lower incidence of severe AEs being reported in the Mannitol arm (21.5%) than in the Control arm (28.1%). The most common AEs were respiratory in nature and were consistent with the disease state of bronchiectasis patients. 'Condition aggravated' (exacerbation of underlying bronchiectasis) was the most common event, and was reported less frequently in the Mannitol arm (63.9%) than the Control arm (69.7%). Common adverse events reported slightly more frequently in the Mannitol group than in the Control group included nasopharyngitis (15.5% v. 13.2% subjects), cough (12.9% v. 9.6% subjects), dyspnoea (8.6% v. 7.0% subjects), back pain (8.2% v. 5.7% subjects), sinusitis (7.3% v. 6.1% subjects), lower respiratory tract infection bacterial (5.2% v. 3.9% subjects) and wheezing (3.9% v. 1.3% subjects). Conversely, headache (11.6% v. 14.0% subjects), lower respiratory tract infection (6.9% v. 9.2% subjects), diarrhoea (6.4% v. 7.9% subjects), nausea (6.0% v. 7.9% subjects) and oropharyngeal pain (4.3% v.7.9% subjects) were all reported less frequently in the Mannitol arm than the Control arm. The incidence of haemoptysis (Mannitol: 10.3% subjects v. Control: 10.1% subjects) and bronchospasm (0.4% subjects in each arm) was similar in both groups. Fewer subjects in the Mannitol group (18.5%) than the Control group (22.4%) reported SAEs, the most common of which was 'condition aggravated' (Mannitol 9% subjects v. Control 11% subjects). Two deaths occurred during the study; both were in the Control arm and were unrelated to study treatment. No concerning changes in laboratory or microbiology markers were detected.

CONCLUSIONS

Although the study failed to meet its primary endpoint of an improvement in bronchiectasis exacerbation rate, time to first exacerbation was significantly longer on mannitol. In addition, several other secondary study endpoints were met, including improvement in quality of life and reduced antibiotic usage. Inhaled mannitol has a good safety profile, and no safety signals of concern were noted in bronchiectasis patients over 12 months of treatment. Overall, there was a favourable benefit-risk balance for inhaled mannitol in bronchiectasis.

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