2. SYNOPSIS

Name of Sponsor/Company: Pharmaxis	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)
Name of finished product: Bronchitol		
Name of active ingredient: Mannitol		

Tittle of study: A randomised, multicentre, double-blind, placebo-controlled, crossover trial determining the efficacy of dry powder mannitol in improving lung function in subjects with Cystic Fibrosis aged six to seventeen years (DPM-CF-204)

Global Principal Investigator: Prof. Dr. Anne Malfroot, MD, PhD

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Study centre(s): 39 Sites in 8 countries (Belgium 4; Canada 6; France 5; Germany 7; Italy 3; Switzerland 3; the Netherlands 2; United Kingdom 9)

Publication (reference): None

Study period: 13th June 2013 to 15th October 2015	**Phase of development:** 2

Primary Objective:	To determine the effect of eight weeks of twice-daily treatment with inhaled dry powder mannitol on lung function (FEV_1) in subjects with CF who are aged six to seventeen years
Secondary Objectives:	• To determine the effect of inhaled mannitol on FVC; • To determine the effect of inhaled mannitol on FEF_{25-75} (exploratory objective) and • To assess the safety of inhaled mannitol. • To evaluate the difference in treatment induced sputum weight in subjects treated with inhaled mannitol compared to those treated with placebo.
Methodology	Randomised, multicentre, double-blind, placebo-controlled, crossover study assessing the efficacy of 8-weeks treatment with inhaled mannitol 400 mg b.d. compared to an inactive placebo (non-respirable mannitol) in paediatric and adolescent subjects

	with CF who are aged six to seventeen years.
Number of subjects: **Planned:** 160 **Enrolled:** 117 **Randomised:** 95	
Diagnosis and main criteria for inclusion: Confirmed diagnosis of cystic fibrosis; aged ≥ 6 years and < 18 years; who have a screening percentage of predicted FEV_1 of ≥ 30% and ≤ 90% based upon Wang criteria (for children less than 8 years old) or NHanes III criteria.	
Test product, dose and mode of administration, batch number: Screening: inhaled Bronchitol 40 mg capsules to a maximum cumulative dose of 400 mg as mannitol tolerance test (MTT). Blinded phase: Inhaled mannitol, 400 mg b.d (10 x 40 mg capsules b.d) administered via a dry powder inhaler device (RS01 HR Model 7, Plastiape Italy). Batch numbers are listed in Appendix 16.1.6.	
Duration of treatment: Eight-week treatment period with either inhaled placebo b.d. or mannitol 400 mg b.d. followed by an eight-week wash out period. Subjects are then crossed over to the alternate treatment arm for a further eight-week treatment period with either inhaled mannitol b.d. or placebo b.d.	
Reference therapy: The placebo is mannitol with a large size particle which makes it non-respirable (10 x capsules b.d), 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.	
Criteria for evaluation: **Primary efficacy:** The absolute change from treatment period baseline to week 8 of each treatment period in percentage of predicted FEV_1 **Secondary efficacy:** • Change from treatment period baseline in percentage of predicted FVC • Change from treatment period baseline in percentage of predicted FEF_{25-75} (exploratory endpoint) • Treatment induced sputum weight **Safety endpoints:** • Adverse events (AEs) • Physical examination and vital signs	
Statistical methods: Analysis of the primary and secondary efficacy endpoints was on an intent to treat (ITT) basis, and was repeated in the per protocol (PP) Absolute and relative changes from baseline in percentage of predicted FEV_1 were	

calculated. The treatment effect on the primary endpoint was estimated based upon a modified Grizzle model for cross-over design (modified by the addition of period baseline). This model was analysed using a repeated analysis of covariance (ANCOVA) model including terms for patient, period, baseline within each period and treatment. As a sensitivity analysis the presence of a carryover effect of treatment from the first period to the second was explored.

The secondary endpoint, change from treatment period baseline in percentage of predicted FVC and change in FEF_{25-75}, was also analysed using the above model. Treatment induced sputum weight was analysed using the above model but without period baseline as a covariate in the model (sputum weight was measured only at the baseline visit for each period but is an on-treatment measurement as it was collected following the initial treatment in that period).

All safety parameters were analysed and presented as listings and summary tables based on the Safety Population if not otherwise specified. The number of subjects reporting an AE, the number of AEs, and percentages of subjects in each category were summarised. Adverse events by severity and relationship to trial were summarised in a similar way. Serious adverse events were summarised separately.

SUMMARY RESULTS

Demographics:

101 out of 117 subjects passed the MTT (86.3%). Of these, 95 (94.1%) subjects were randomised to the study, and 92 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 characteristics at screening. The mean (SD) age of study subjects was 12.0 (3.0) years, and study population was 59.8% female. The mean (SD) FEV_1 at screening was 72.2% (11.6) of the predicted value and 68.5% subjects were taking concomitant rhDNase.

EFFICACY

Primary:

There was a significant improvement in the primary endpoint of change in percentage of predicted FEV_1 in the mannitol group; treatment difference between the mannitol and placebo groups was 3.42% (p=0.004). The mean relative treatment difference in FEV_1 between groups was 4.97% (p=0.005). Improvements in % predicted FEV_1 on mannitol were seen irrespective of rhDNase use (rhDNase 3.29%, 95%CI 0.28, 6.30; no rhDNase 3.92%, 95%CI 0.42, 7.42).

Secondary:

The difference between groups for absolute change in FVC (% predicted) was 1.80% (-0.71, 4.32) p=0.158. For FEF_{25-75} the treatment difference in the relative change from baseline was 10.52% (1.82, 9.69; p=0.013). In the mannitol group, post-treatment sputum weight was significantly higher than in the placebo group (2.63g vs 1.30g; p=0.012).

SAFETY

- The number of treatment emergent adverse events was similar for the mannitol and

placebo groups (62.1% vs. 59.8%)

- There were fewer serious treatment emergent adverse events in the mannitol group than in the placebo group (8.0% vs. 11.5%)
- There was one death in the placebo group that occurred approximately nine months after the subject discontinued study treatment. The patient never received mannitol and the death was considered unrelated to study treatment.
- The rate of discontinuation from treatment due to treatment-emergent adverse events was 5.7% and 1.1% in the mannitol and placebo groups respectively. The rate of study withdrawal due to treatment-emergent adverse events (2.3% and 1.1% in the mannitol and placebo groups respectively) was similar in both groups.
- The most common treatment-emergent AEs were cough (16.1% vs. 16.1%) pulmonary exacerbation of CF (11.5% vs. 16.1%), headache (6.9% vs. 8.0%) and nasopharyngitis (6.9% vs. 6.9%) in the mannitol and placebo groups respectively.
- Haemoptysis rates were similar between groups (mannitol 3.4% vs. placebo 2.3%), with all events being classified as scant or mild.
- There was no apparent influence by age or rhDNase use on safety outcomes.
- Vital signs and physical examinations were similar in both treatment groups and unremarkable.

Conclusions:

In this double blind, randomized placebo-controlled phase 2 study of subjects with mild to moderately severe CF, mannitol (400 mg b.d) demonstrated clinically meaningful improvements in lung function (FEV_1) over baseline and compared to placebo. Outcomes favoured mannitol over placebo irrespective of rhDNase use, age group or baseline FEV_1. Improvements in FEV_1 are supported by other spirometry measures (FVC and FEF_{25-75}) and by post-treatment sputum weight.

Mannitol was well-tolerated in the majority of subjects and demonstrated an acceptable safety profile over the 8-week double blind treatment period. AEs reported in this study were generally consistent with the disease state and occurred with a frequency generally similar between treatment groups. No safety signals of concern were detected.

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