2. SYNOPSIS

Name of Company: Pharmaxis Ltd	Volume:
Name of Finished Product: Bronchitol (mannitol)	Page:
Name of Active Ingredient: Inhaled mannitol	

Title of Trial: Determination of the pharmacokinetics of inhaled mannitol after single and multiple dosing in cystic fibrosis patients.

Principal Investigators:	**Trial Centre:**
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Publication (reference): Not Applicable.

Studied Period (months): Approx. 11 months Date of first patient, first visit: 22 January 2009 Date of last patient, last visit: 08 December 2009	**Phase of Development:** Phase 1

Objectives:

Primary objectives:

- Determine the pharmacokinetic (PK) parameters of inhaled mannitol in adult, adolescent and paediatric cystic fibrosis (CF) patients after a single dose.
- Determine the PK parameters of inhaled mannitol in adult, adolescent and paediatric CF patients after twice daily dosing for 5 days.
- Compare PK of inhaled mannitol in adult, adolescent and paediatric CF patients after single and multiple dosing.

Secondary objectives:

- Clinical safety of inhaled mannitol in adult, adolescent and paediatric CF patients after single and multiple dosing.

Name of Company: Pharmaxis Ltd	Volume:
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Methodology:
This study was a multiple-centre, open-label, single and multiple dose design, in which CF patients aged 6-32 years received inhaled mannitol using a dry powder inhaler.
Prospective patients were screened against inclusion criteria which included a test for bronchial hyperresponsiveness known as the Mannitol Tolerance Test (MTT). Patients who had a negative test result and satisfied all other eligibility criteria were entered into the study.
The treatment phase of the study was 7 days. A single dose of inhaled mannitol was administered on the morning of Day 1 and then twice daily (b.i.d.) from Day 2 to 6 with the final dose on the morning of Day 7. Salbutamol was administered as a bronchodilator at least 5 minutes prior to the MTT (at screening) and at least 5 minutes prior to inhalation of each study dose.
During the treatment period, patients attended the study centre for at least two visits. Patients were confined to the study centre for at least 12 hours on Days 1 and 7 for intensive blood sampling for the PK analysis. Patients were considered to have completed the study on Day 8, unless there was an adverse event requiring further follow up.

Number of Patients (Planned and Analyzed):
- Planned = 18 patients (6 adult, 6 adolescent and 6 paediatric)
- Dosed = 18 patients (7 adults, 4 adolescents and 7 paediatrics)
- Analysed = 18 patients included in safety analysis, 16 patients included in PK analysis.

Diagnosis and Criteria for Inclusion:
The trial population consisted of cystic fibrosis patients; adults (18+ years) and adolescents (12-17 years) and paediatrics (older 9-11 years, younger 6-8 years). Patients were required to have a negative MTT prior to enrollment.

Test product, dose and mode of administration:
Test Product: Mannitol powder for inhalation 10 x 40 mg capsule.
Mannitol was administered via the Single Dose Dry Powder RS01 Inhaler Model 7 (239700002AA) Plastiape (Italy).
Salbutamol was administered by inhaler (Ventolin® Inhaler Complete, CFC-free) at least 5 minutes prior to inhalation of mannitol dose.

Duration of Treatment:
The treatment phase of the study lasted for 7 days. Inhaled mannitol was administered once on the morning of Day 1, then twice a day for Days 2-6, with the final dose on the morning of Day 7.

Reference Therapy, Dose and Mode of Administration:
Not applicable.

Criteria for Evaluation:
Pharmacokinetics: Serum concentrations of mannitol. No efficacy parameters were assessed.
Safety: Safety monitoring included adverse events (AEs), clinical laboratory values (biochemistry and liver function tests), physical examinations and vital signs (heart rate, blood pressure, $Sp0_2$, respiratory rate and temperature).

Statistical Methods:
Pharmacokinetics:
The PK parameters (C_{max}, T_{max}, AUC_{0-12}, $AUC_{0-\infty}$, $t_{½}$, CL/F and V/F) were calculated using standard non-compartmental methods. No value for $AUC_{0\rightarrow\infty}$, $t_{½}$ was reported in the absence of a terminal log-linear phase of the concentration/time curve. Accumulation was assessed by calculation of the Day 7/Day 1 AUC_{0-12} ratio. Time to steady state serum levels was estimated by model fitting the PK data on Day 1 and simulating drug accumulation following b.i.d dosing for 7 days. All PK parameters were tabulated using arithmetic means, standard deviations and coefficient of variation.
Safety:
Adverse events were coded using the MedDRA coding system (version 11.0) and categorised according to body system, and summarised according to severity and relationship to study treatment. Safety and tolerability data were summarised by age group by appropriate descriptive statistics.

Name of Company: Pharmaxis Ltd	Volume:
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Results:

Pharmacokinetics:

Serum mannitol levels (mean tmax values) peaked approximately 0.75 to 2.54 hrs post dosing Between subject variability in mean Cmax values between adults, adolescents and paediatric (older and younger) subjects was moderate to high ranging from 15 to 51%. Between subject variability in mean $AUC_{0-\infty}$ values (Day 1) ranged from 22 to 47%.

Serum mannitol concentrations accumulated following multiple b.i.d. dosing over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, paediatric (older), and paediatric (younger) subjects respectively (Day 7/Day 1 AUC_{0-12} ratio).

There were no marked differences in the pharmacokinetics of mannitol (including C_{max}, AUC $_{0-\infty}$, $t_{1/2}$ and CL/F between adult, adolescent, paediatric (o) and paediatric (y) patients. The pharmacokinetic parameter estimates in patients were also similar to the pharmacokinetics of mannitol observed in study DMPK-101 when compared to the dose normalized (400 mg) PK parameter estimates in healthy subjects.

Time to steady state serum concentrations were predicted by model fitting the Day 1 pharmacokinetic data and simulating b.i.d. dosing over 7 days. Based on these analyses steady state levels are predicted to be achieved by the 2nd-3rd dose on day 2.

Results (continued):

Safety and Tolerability

Treatment-emergent adverse events (AE), from first dose to study exit, were reported for 3 of 18 subjects (17%). Treatment-emergent AE consisted of one event of each of headache, rotavirus and nausea, and cannula site pain. All AE were mild in intensity and deemed to be definitely not related to study medication.

No patient experienced a serious adverse event, and there were no deaths. One paediatric patient withdrew consent due to distress associated with pain at the cannula site for blood sample collection.

There were no trends in vital signs or physical examinations associated with study treatment. There were no trends by age group in any safety assessments.

Summary – Conclusions:

Serum mannitol concentrations accumulated following multiple b.i.d. dosing over 7 days by approximately 1.21 to 2.50 fold in patients. These levels of accumulation and exposure were well tolerated. There were no marked differences in the pharmacokinetics of mannitol (including C_{max}, AUC $_{0-\infty}$, $t_{1/2}$ and CL/F between adult, adolescent, paediatric (o) and paediatric (y) patients and were similar to the pharmacokinetics of mannitol observed in healthy subjects.

Inhaled mannitol was well tolerated, with no adverse events related to study treatment.