ABBREVIATED SYNOPSIS

NAME OF SPONSOR/COMPANY: Pharmaxis Ltd NAME OF FINISHED PRODUCT: Bronchitol NAME OF ACTIVE INGREDIENT(S): Mannitol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: DPM-CF-303

Title of Study: Long Term Administration of Inhaled Mannitol in Cystic Fibrosis – A Safety and Efficacy Trial in Adult Cystic Fibrosis Subjects

Coordinating Investigator: Moira Aitken, MD, Seattle, WA, United States of America

Study Centers: 101 sites in 21 countries (United States of America: 35; Canada: 4; South Africa: 3; Greece: 2; Belgium: 3; Spain: 3; Bulgaria: 3; Hungary: 4; Ukraine: 6; Italy: 4; Romania: 4; Slovakia: 3; Czech Republic: 1; Poland: 7; Mexico: 2; Argentina: 2; Australia: 1; New Zealand: 3; Russia: 5; Turkey: 3; Israel: 3).

Publication (Reference): Results of this trial have not been published at the time of clinical study report writing.

Study Period: 17 Sep 2014 – 21 Feb 2017 | **Phase of development:** 3

Objectives:

Primary objective:

The primary objective was to determine whether inhaled mannitol (400 mg twice daily [b.i.d.]) was superior to control (inhaled mannitol 50 mg b.i.d.) for improving lung function as measured by mean change from baseline forced expiratory volume in 1 second (FEV_1; L) over the 26-week treatment period in adult subjects with cystic fibrosis (CF).

Secondary objectives:

There were hierarchical and non-hierarchical secondary objectives (protocol-defined pulmonary exacerbations [PDPEs] were used in the main analysis of exacerbation endpoints). Formal analysis of hierarchical secondary objectives continued until a non-significant p-value (i.e., $p>0.05$) was returned.

Hierarchical secondary objectives were the following:

1. To determine whether inhaled mannitol (400 mg b.i.d.) was superior to control for improving lung function as measured by mean change from baseline forced vital capacity (FVC; L) over the 26-week treatment period in adult subjects with CF;
2. To determine whether inhaled mannitol (400 mg b.i.d.) was superior to control in increasing the time to first pulmonary exacerbation over the 26-week treatment period in adult subjects with CF;
3. To determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) was superior to control for reducing the number of days on antibiotics (oral, inhaled, or intravenous [IV]) due to pulmonary exacerbation;
4. To determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) was superior to control for decreasing the number of days in hospital due to pulmonary exacerbation;
5. To determine whether inhaled mannitol (400 mg b.i.d.) decreased the rate of pulmonary exacerbations over the 26-week treatment period compared to control in adult subjects with CF.

The non-hierarchical secondary objectives were to determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) was superior to control over the 26-week treatment period:

- For decreasing the incidence of exacerbations (i.e., the proportion of subjects with 1 or more exacerbation);
- For improving ease of expectoration as measured by a visual analogue scale (VAS);
- For improving subject-reported respiratory symptoms as measured by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain.

Methodology: This was a phase 3, double-blind, randomized, parallel group, controlled, multicenter, and interventional clinical trial. Subjects who satisfied all inclusion and exclusion criteria were given a mannitol tolerance test (MTT). Those subjects who passed the MTT were randomized to receive inhaled mannitol (400 mg b.i.d.) or control (mannitol 50 mg b.i.d.) for a period of 26 weeks, in a 1:1 ratio.

Randomization was stratified by recombinant human deoxyribonuclease (rhDNase) use and country.

The treatment phase consisted of 4 study visits over 26 weeks. Subjects who discontinued study drug were encouraged to remain in the trial and continue all pulmonary function tests, to minimize missing data.

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Number of Subjects (planned and analyzed):

Planned (treatment phase): at least 350 subjects (mannitol: 175 subjects; control: 175 subjects)

Enrolled in MTT: 486 subjects

Randomized (following sample size re-estimation): 423 subjects (mannitol: 209 subjects; control: 214 subjects)

Completed treatment with study drug: 339 subjects (mannitol: 170 subjects; control: 169 subjects)

Completed the trial: 373 subjects (mannitol: 183 subjects; control: 190 subjects)

Analyzed:

- Intent-to-Treat (ITT) analysis set: 423 subjects (mannitol: 209 subjects; control: 214 subjects);
- Safety (SAF) analysis set: 420 subjects (mannitol: 207 subjects; control: 213 subjects);
- Per-Protocol (PP) analysis set: 371 subjects (mannitol: 188 subjects; control: 183 subjects).

Diagnosis and Main Criteria for Inclusion:

- Cystic fibrosis;
- Age ≥18 years;
- FEV_1 >40% and <90% predicted;
- Negative (passed) MTT test;
- No concomitant maintenance hypertonic saline use;
- Permitted maintenance therapies (antibiotics and/or rhDNase) had to be maintained for the duration of the trial.

Test Product, Dose, Mode of Administration, and Batch No.:

MTT: mannitol 40 mg up to a cumulative dose of 400 mg. Batch numbers: 14039R154, 14039US, 14065BE, 14065CZ, 14065ES, 14065IL, 14065R193, 14065RO, 14065SK, 14065UA, 14115RU, 15071TR, 15122BG, 15122EL, 16027U.

Treatment phase: inhaled mannitol 400 mg b.i.d. Batch numbers: 14041, 14071, 14118, 15019, M15-041, M15-115.

Test product was administered as capsules for inhalation via Single-Dose Dry Powder RS01 Inhaler Model 7 (239700002AA), Plastiape (Italy).

Reference Product, Dose, Mode of Administration, and Batch No.:

Treatment phase: inhaled mannitol 50 mg b.i.d. Batch numbers: 14043, 14070, 14112, 15018, M15-043, M15-117.

Reference product was administered as capsules for inhalation via Single-Dose Dry Powder RS01 Inhaler Model 7 (239700002AA), Plastiape (Italy).

Duration of Treatment: 26-week treatment period

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the absolute change from baseline FEV_1 (L) over the 26-week treatment period (measured at Weeks 6, 14, and 26).

The hierarchical secondary efficacy endpoints were:

1. Absolute change from baseline FVC (L) over the 26-week treatment period;
2. The time to first PDPE;
3. The number of days on antibiotics over the 26-week treatment period due to PDPE;
4. The number of days in hospital due to PDPE over the 26-week treatment period;
5. The rate of PDPE over the 26-week treatment period.

The non-hierarchical secondary efficacy endpoints were:

- The incidence of PDPEs over the 26-week treatment period;
- Absolute change in ease of expectoration measured from baseline measured using VAS over the 26-week treatment period;
- Absolute change from baseline CFQ-R respiratory domain score over the 26-week treatment period.

In addition, the following endpoint was analyzed post-hoc:

- Absolute change in forced expiratory flow from 25% to 75% of vital capacity (FEF_{25-75}) over the 26-week treatment period.

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Safety:

Safety was assessed by adverse events (AEs), vital signs, and physical examination.

Statistical Methods:

The primary endpoint was analyzed for the ITT set (all randomized subjects), using a restricted maximum likelihood based mixed model repeated measures (MMRM) approach (primary analysis). Missing FEV_1 data because of withdrawal due to AE, death, physician decision, or lack of efficacy were imputed using a baseline observation carried forward single imputation strategy. A model-estimate for the overall treatment effect, i.e., the overall difference between mannitol and control with respect to the change from baseline over the 26-week treatment period, including a 95% confidence interval (CI) and a p-value were produced.

In order to assess the effect of the primary imputation strategy on the results, multiple (4 planned and 1 post-hoc) sensitivity analyses of the primary endpoint were performed, using different imputation strategies and also examining response rates according to different thresholds (0.05L, 0.075L, 0.1L). In addition, 8 supportive analyses of the primary endpoint were performed including use of a PP set.

For the primary endpoint, the following subgroups of subjects were analyzed to assess consistency of response: with and without rhDNase use, baseline percent predicted FEV_1 >70% and ≤70%, and with and without *Pseudomonas aeruginosa* infection at screening.

The main analyses of the absolute change in FVC, absolute change in FEF_{25-75} (post-hoc), the changes from baseline in ease of expectoration, and the CFQ-R respiratory domain score were analyzed according to the model for the primary analysis of the primary efficacy endpoint. The time to first PDPE was analyzed using the Cox's proportional hazards model. The number of days on antibiotics due to PDPEs, the number of days in hospital due to PDPE, and the rate of PDPE over the 26-week treatment period were analyzed using negative binomial models. Analysis of incidence of PDPEs over the 26-week treatment period was performed using logistic regression.

SUMMARY – CONCLUSIONS

DEMOGRAPHY AND DISEASE CHARACTERISTICS:

The study population included only adult CF patients (ages ranged from 18 to 78 years). Slightly more male (224 subjects [53.0%]) than female subjects (199 subjects [47.0%]) participated in the trial. Most subjects were Caucasian (411 subjects [97.2%]) and the mean age of subjects at screening was 27.7 years (median: 25.0 years); mean and median ages were similar for the 2 treatment groups.

The mean time since primary diagnosis of CF was 19.8 years and the mean age of subjects at diagnosis was 7.9 years. The mean percentage of predicted FEV_1 at baseline was 63.08%, and was similar for the two treatment groups. A total of 133 subjects (63.6%) in the mannitol group and 148 subjects (69.2%) in the control group had a percentage of predicted FEV_1 ≤70% at baseline. In both treatment groups, the majority of subjects had been treated with rhDNase prior to screening (75.1% in the mannitol group and 74.3% in the control group) and were using rhDNase at the time of screening (68.9% in the mannitol group and 66.4% in the control group).

Overall, more than half of subjects had not experienced a PE treated with IV antibiotics (54.1%) nor had been hospitalized for PE (60.5%) in the 12 months prior to screening. The percentage of subjects who experienced a PE treated with IV antibiotics in the 12 months prior to screening was slightly higher in the mannitol group than in the control group (47.8% vs. 43.9%), as was the percentage of subjects who had been hospitalized for PE (42.1% vs. 36.9%). The percentage of subjects with a history of hemoptysis was slightly higher in the mannitol group (68 subjects, 32.5%) than in the control group (60 subjects, 28.0%). There were no other clinically relevant imbalances between the randomized treatment groups.

EFFICACY RESULTS:

Primary efficacy endpoint:

The superiority of mannitol over control was demonstrated in terms of the change from baseline in FEV_1 over 26 weeks. The primary analysis of FEV_1 over the 26-week period showed that the difference between treatments was statistically significant in favor of mannitol, with an adjusted mean difference (95% CI) of 0.054 L (0.008; 0.100), p=0.020. For the mannitol group, there was a statistically significant increase from baseline in FEV_1 over the 26-week treatment period (0.063 L [0.025; 0.100]; p=0.001), but no change in the control group (0.008 L [-0.027; 0.044], p=0.644).

The sensitivity analyses confirmed the results of the primary analysis: For all thresholds (0.050 L, 0.075 L, 0.100 L), the percentage of subjects classified as FEV_1 responders was numerically greater in the mannitol group than in the control group, reaching a statistically significant difference between treatments with the 0.100 L threshold, p=0.022. The supportive analyses also confirmed the results of the primary analysis:

Subgroup analyses for the change from baseline in FEV_1 over the 26-week treatment period indicated that for the subgroups of subjects who did not use rhDNase, who did not have a *Pseudomonas aeruginosa* infection, and who had a disease severity with percent predicted FEV_1 at baseline of ≤70%, the difference between treatments was statistically significant in favor of mannitol. For the other subgroups, the results numerically favored mannitol over control.

Hierarchical secondary efficacy endpoints:

1. The analysis investigating the mean absolute change from baseline FVC (L) over the 26-week treatment period showed no statistically significant difference between the 2 treatment groups; adjusted mean difference (95% CI) was 0.040 L (-0.012; 0.092), p=0.128. Since the first hierarchical secondary efficacy endpoint did not achieve statistical significance (p-value<0.05), no further formal testing of the hierarchical secondary endpoints was performed. However, the significance of the analyses of the other endpoints is discussed below against a nominal 5% level;
2. The Cox's proportional hazards analysis investigating the time to first PDPE showed no difference between the 2 treatment groups in the time to first PDPE; estimate (95% CI) of 1.140 (0.671; 1.936), p=0.629;
3. The adjusted rate of number of days of antibiotic use per patient per year (including overlapping antibiotics) was slightly lower in the mannitol group (6.0) compared to the control group (7.9), with an adjusted rate ratio of 0.750 (95% CI: 0.198; 2.846), p=0.673;
4. The adjusted rate of number of days in hospital due to PDPE per patient per year was similar in the mannitol group (1.2) and the control group (0.9), with an adjusted rate ratio of 1.273 (95% CI: 0.315; 5.154), p=0.735;
5. The adjusted rate of PDPE over the 26-week treatment period (including imputation for early withdrawals) was numerically higher in the mannitol group (0.349) than in the control group (0.226), but analysis of the adjusted rate of PDPE over the 26-week treatment period showed no difference between the treatment groups (rate ratio: 1.545 [95% CI: 0.990; 2.411], p=0.055).

Non-hierarchical secondary efficacy endpoints:

- Incidence of PDPEs over the 26-week treatment period was similar between the treatment groups: 28 subjects (13.4%) in the mannitol group and 29 subjects (13.6%) in the control group. The logistic regression analysis showed no difference in the incidence of PDPEs between the 2 treatment groups (odds ratio 1.009 [95% CI: 0.555; 1.836], p=0.976);
- The analysis investigating the change from baseline in ease of expectoration using the VAS scale over the 26-week period was numerically in favor of mannitol (estimate: 0.259 [95% CI: -0.034; 0.551], nominal p=0.083). For both treatment groups, the ease of expectoration increased (p<0.0001 for both groups);
- The analysis of the change from baseline in CFQ-R respiratory domain score over the 26-week period was numerically in favor of mannitol (adjusted mean difference 0.870 [95% CI: -1.406; 3.145, p=0.453]). Over the 26-week period, there was a numerical increase in the mannitol group (0.308) and a numerical decrease in the control group (-0.562).

Post-hoc efficacy endpoint:

The analysis of mean absolute change from baseline FEF_{25-75} over the 26-week treatment showed a statistically significant difference between the 2 treatment groups in favor of mannitol, with an adjusted mean difference (95% CI) of 0.087 L/s (0.020; 0.155), p=0.012.

SAFETY RESULTS:

The percentage of subjects reported with treatment-emergent adverse events (TEAEs) was similar in the mannitol group (69.6%) and in the control group (65.7%). Those TEAEs reported in ≥5% of subjects in either treatment group were: condition aggravated, cough, hemoptysis, headache, upper respiratory tract infection, pyrexia and nasopharyngitis. Most TEAEs were not serious and were of mild or moderate severity.

The percentage of subjects reported with study drug-related TEAEs was also similar in the mannitol group (15.5%) and in the control group (12.2%). The most common related TEAEs in both groups were hemoptysis (mannitol: 3.4%, control: 5.6%) and cough (mannitol: 4.8%, control: 2.8%).

The percentage of subjects reported with serious TEAEs was also similar in the mannitol group (15.0%) and in the control group (13.6%). Condition aggravated and hemoptysis were the most frequently reported serious TEAEs, with 'condition aggravated' reported in 20 subjects (9.7%) and 15 subjects (7.0%) in the mannitol and control groups, respectively and 'hemoptysis' meeting the criteria for serious TEAE, reported in 1 subject (0.5%) and 3 subjects (1.4%) in the mannitol and control groups, respectively. Other serious TEAEs were reported for less than 3 subjects per treatment group.

One severe TEAE of condition aggravated led to the death of 1 subject (0.5%) in the control group. This fatal TEAE was considered as probably not related to study drug. No TEAEs leading to death were reported in the mannitol group.

The percentage of subjects reported with TEAEs leading to permanent discontinuation of study drug was similar in the mannitol group (9.2%) and the control group (8.5%). The percentage of subjects reported with TEAEs leading to withdrawal from the trial was also similar in the mannitol group (3.9%) and the control group (3.3%).

Evaluation of vital signs and physical examination did not reveal any safety concerns, nor were there any relevant differences over time or between treatment groups.

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CONCLUSION:

This randomized, double-blind, controlled Phase 3 study of inhaled mannitol in adults with mild to moderately severe CF demonstrated early and statistically significant improvements in FEV_1 across the 26-week study period over control. The study population was ≥18 years of age with well-managed CF as evidenced by the minimal FEV_1 deterioration across the study periods in the control group and high rates of the use of standard CF therapy. Inhaled mannitol demonstrated an acceptable safety profile over the 26-week treatment period. AEs reported in this study were generally consistent with the disease state and occurred with a similar frequency for both treatment groups. In conclusion, data from this double-blind, randomized, controlled Phase 3 study reaffirmed data previously published on the use of mannitol in subjects with CF aged ≥18 years.

Date of the report: 07 Nov 2017 (Full CSR), 13 September 2019 (Abbreviated Synopsis)