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Original Article

Inhaled dry powder mannitol in children with cystic fibrosis: A randomised efficacy and safety trial

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Abstract

Introduction: Inhaled mannitol has beneficial effects on lung function, mucociliary clearance, quality of life and sputum properties. This trial examined the efficacy of inhaled mannitol in children with cystic fibrosis (CF).
Methods: The efficacy of inhaled mannitol in children with CF aged 6–17 years was assessed in a phase 2, randomised, placebo-controlled crossover study. Subjects were randomly assigned to mannitol 400 mg every 12 h or matching placebo for 8 weeks, followed by an 8 week washout and an 8 week period with the alternate treatment. The primary endpoint was the absolute change from baseline in ppFEV1 (percent predicted FEV1).
Results: A total of 92 subjects were studied, with a mean age of 12 years and mean baseline ppFEV1 of 72.2%. During mannitol treatment ppFEV1 was 3.42% ($p = 0.004$) higher compared to placebo or a 4.97% ($p = 0.005$) relative difference; relative change from baseline FEF25-75 was 10.52% ($p = 0.013$). During mannitol treatment, acute post-treatment sputum weight was higher ($p = 0.012$). In pre-specified subgroups (rhDNase use, age, and disease severity), the treatment differences consistently favoured mannitol. The most common AEs were cough and pulmonary exacerbations. Pulmonary exacerbation AEs were approximately 30% lower in the mannitol group.
Conclusions: In children with CF, inhaled mannitol was associated with significant improvements in lung function and sputum weight, irrespective of rhDNase use, age or disease severity. Inhaled mannitol was well tolerated and was associated with a reduced incidence of pulmonary exacerbation AEs. (Clinical Trials.Gov: NCT 01883531)

Keywords: Cystic fibrosis; Mannitol; FEV1; Randomised; Paediatric

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1. Introduction

There has been remarkable progress in the treatment of patients with cystic fibrosis (CF) over the past 20 years. However, the limitations of current standard therapies and even newer compounds targeting correction of cystic fibrosis transmembrane conductance regulator (CFTR) protein highlight the continued need for better treatments of CF-related lung disease [1]. An important aim is to enhance mucociliary clearance (MCC) of airway secretions and consequently improve lung function and reduce respiratory exacerbations [2,3].

CF lung disease starts early in life and is relentlessly progressive so it is critical that therapies designed to attenuate the progressive course of respiratory damage in CF are evaluated in all age groups [4]. The longer term treatment of CF has a primary focus on the mitigation of downstream pathologies [5]. Globally, children and adolescents represent roughly half of all patients with CF so it is critical that therapies designed to attenuate the progressive course of respiratory damage in CF are available to all age groups affected by this disease [6,7].

Mannitol is a naturally occurring sugar alcohol, which when inhaled creates a change in the osmotic gradient, leading to movement of water into the CF airway hydrating the airway surface liquid and enhancing mucociliary clearance [8]. Mannitol is administered using a dry powder inhaler device. Two near identical, randomised, multicentre, double-blind, controlled, parallel-group phase 3 studies investigated the safety and efficacy of inhaled mannitol in subjects with CF aged at least 6 years over a period of 6 months [9,10]. These studies demonstrated clinically relevant benefits of inhaled mannitol even in study populations that were heavily treated with standard therapies. Inhaled mannitol has been approved for use in adults with CF in the European Union and in children and adults over 6 years of age in Australia.

The previous phase 3 studies of inhaled mannitol in subjects with CF showed significant improvements in FEV_1 within 6 weeks of treatment commencement [11,12]. The response at 6-weeks was highly correlated with the response over a 26-week period. While the effect of the 400 mg dose appeared consistent across age groups, an improvement in FEV_1 in the control arms in children and adolescents was also seen and this has subsequently led to some uncertainty of the actual effect size of inhaled mannitol in this age group. It has been postulated that the treatment effect was underestimated due to the use of inhaled mannitol (50 mg b.d.) as a control in these studies, albeit at a lower dose than in the treatment arm (400 mg b.d.). To clarify the treatment benefit of inhaled mannitol and to assess the efficacy and safety in children and adolescents, a trial comparing the standard dose of mannitol (400 mg b.d.) with a true placebo (non-respirable mannitol) was designed.

2. Methods

2.1. Study design

This double blind, randomised, placebo-controlled, cross-over, multicentre study of dry powder inhaled mannitol (Pharmaxis, Sydney, Australia) assessed the efficacy of mannitol in subjects with CF aged 6–17 years. Safety was evaluated as a secondary objective. Subjects were randomised across 39 sites in 8 countries (Belgium, Canada, France, Germany, Italy, Switzerland, The Netherlands and the United Kingdom). The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the institutional review board at each study centre. Exclusion criteria included failing a mannitol tolerance test (MTT) at screening. The MTT is used to identify and exclude subjects with bronchial hyperreactivity prior to initiating the use of inhaled mannitol (see additional information on the MTT and inclusion criteria in the on-line supplement).

Subjects were randomised in a 1:1 ratio and stratified according to age (6–11 years or 12–17 years) and rhDNase use (user/non-user) to receive treatment allocation as follows: mannitol 400 mg b.d. for 8 weeks followed by a 8-week washout followed by placebo b.d. for 8 weeks; or placebo b.d. for 8 weeks followed by a 8-week washout followed by mannitol 400 mg b.d. for 8 weeks.

The active product was inhaled mannitol (GMP, Pharmaxis Ltd., Australia; average particle diameter 3.0 μm; average fine particle dose 11.9 mg) 40 mg capsules ×10, by inhalation, twice daily. The placebo contained mannitol, physically different, but chemically identical: a nominal 10 mg of raw material mannitol i.e. non-spray dried and non-respirable (GMP, Pharmaxis Ltd., Australia; average fine particle dose ≤0.4 mg).

2.2. Study participants

Informed written consent was obtained from all participants (or their parent or guardian) prior to any study-related procedures. The MTT was performed on the day of screening and passing the test was a prerequisite for randomization. The MTT was utilised to identify subjects with airway hyperresponsiveness to a test dose of inhaled mannitol. Study inclusion criteria included: age ≥ 6–<18 years; a confirmed diagnosis of CF; percentage of predicted FEV_1 ($ppFEV_1$) 30%–90% [13,14]. Use of recombinant human deoxyribonuclease (rhDNase) and maintenance antibiotics was permitted if treatment was established at least 3 months prior to screening. Other standard CF therapies except nebulised hypertonic saline were permitted and continued during the study.

2.3. Study assessments

There were 5 trial visits and 7 telephone contacts over a 27 week period pre-specified in the study protocol. Eligible subjects who passed the MTT were randomised to one of the two treatment sequences. The spirometry measurements were performed with a dedicated spirometer across all visits and met the 2005 ATS/ERS criteria for number of trials, acceptability, and repeatability [15]. The difference in treatment induced wet sputum weight (of all sputum produced during and for 30 min post the initial dose) after inhaled mannitol compared to placebo was

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another secondary endpoint. Safety was assessed by tracking the number and percentage of adverse events (AEs).

2.4. Statistical analysis

All subjects who were randomised and received at least one dose of study medication were in included in the full analysis set (FAS). Analysis of the primary and secondary efficacy endpoints was on an intent-to-treat basis (randomised and treated).

The primary endpoint of this trial was the absolute change from treatment period baseline to week 8 of each treatment period in $ppFEV_1$ for mannitol compared to placebo. Missing values were imputed using baseline observation carried forward. Absolute and relative changes from baseline in percentage of predicted FEV_1 were calculated. The relative change in $ppFEV_1$ was also examined. Secondary respiratory endpoints included the absolute and relative change from baseline in the percentage of predicted FVC (ppFVC) and the percentage of predicted $FEF_{25–75}$ ($ppFEF_{25–75}$).

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) [16]. This model was analysed using a repeated analysis of covariance (ANCOVA) model including terms for patient, period, baseline within each

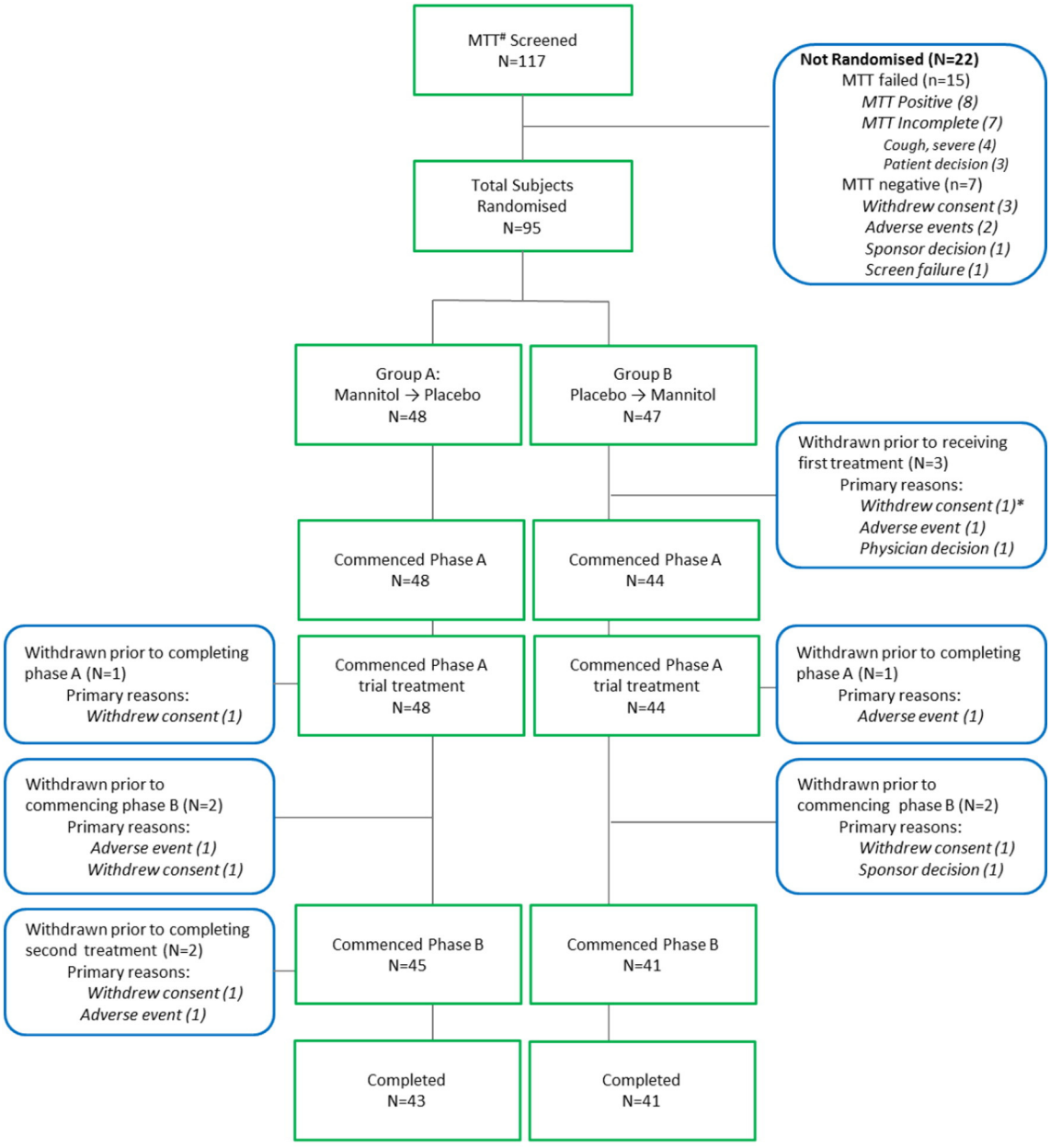

Fig. 1. Flow chart of the study.

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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 endpoints, change from treatment period baseline in percentage of predicted FVC and change in $FEF_{25–75}$, were also analysed using the above model. Treatment induced sputum weight was analysed using the above model but without period baseline as a covariate (sputum weight was measured only at the baseline visit for each period). Subgroup analyses were conducted on age groups (6–11 years, 12–17 years), rhDNase use (non-user vs user), screening $ppFEV_1$ (>70%, ≤70%) and annual decline in FEV_1 at screening (<2%, ≥2%). The methodology for calculating the annualised decline in FEV_1 which has not been separately validated as follows: (100-screening $ppFEV_1$)/pts age at screening.

The adverse events (AEs) reported here are those that either developed or worsened after the initial dose of study medication and up to 7 days after the last dose and are referred to as "treatment emergent AEs" (TEAEs).

The originally planned sample size was 160 subjects, which was calculated based on a 2-sided paired t-test to have 90% power of detecting a difference of 3% in absolute change in $ppFEV_1$ between treatments with a type I error of 5% and allowing for 20% dropouts. A between subject standard deviation (SD) of 11% and a correlation between measurements from the same subject of 0.55 were assumed, based on previous studies. It was planned to include at least 25% of subjects in each age and rhDNase use stratification category. Recruitment was halted early when 95 subjects had been randomised and study sites indicated that they had exhausted their potential candidate pool. The power was re-calculated prior to unblinding and there was still greater than 80% power to detect a treatment difference of 3.5% in $ppFEV_1$ change.

Table 1
Baseline characteristics and demography.

	Overall (N = 92)	M → P (N = 48)	P → M (N = 44)
Age (SD)			
Mean age	12.0 (3.0)	12.0 (2.8)	12.1 (3.2)
Age group – no. (%)			
6–11 years	39 (42.4)	21 (43.8)	18 (40.9)
12–17 years	53 (57.6)	27 (56.3)	26 (59.1)
Gender – no. (%)			
Female	55 (59.8)	28 (58.3)	27 (61.4)
CFTR mutation – no. (%)			
Both deltaF508	41 (44.6)	20 (41.7)	21 (47.7)
One deltaF508	36 (39.1)	20 (41.7)	16 (36.4)
At least one other known mutation	15 (16.3)	8 (16.7)	7 (15.9)
Screening $ppFEV_1$			
Mean (SD)	72.23 (11.6)	73.12 (10.4)	71.25 (12.8)
Min, max	38.3, 89.9	41.1, 89.9	38.3, 89.9
Annualised $ppFEV_1$ decline – no. (%)			
<1% per year	3 (3.3)	3 (6.3)	0 (0.0)
≥1% to <2% per year	36 (39.1)	14 (29.2)	22 (50.0)
≥2% per year	53 (57.6)	31 (64.6)	22 (50.0)
Categorised screening $ppFEV_1$ – no. (%)			
Mild >70%	59 (64.1)	33 (68.8)	26 (59.1)
Moderate >40% to ≤70%	32 (34.8)	15 (31.3)	17 (38.6)
Severe ≤40%	1 (1.1)	0 (0.0)	1 (2.3)
Use of antibiotics at screening – no. (%)			
Any antibiotics	65 (70.7)	32 (66.7)	33 (75.0)
IV	4 (4.3)	3 (6.3)	1 (2.3)
Inhaled/nebulised	40 (43.5)	18 (37.5)	22 (50.0)
Oral	51 (55.4)	25 (52.1)	26 (59.1)
RhDNase use at screening – no. (%)			
User	63 (68.5)	32 (66.7)	31 (70.5)
Non-user	29 (31.5)	16 (33.3)	13 (29.5)

Percentages are based on N.
M → P group: mannitol 400 mg b.d. for 8 weeks followed by a 8-week washout followed by placebo b.d. for 8 weeks.
P → M group: placebo b.d. for 8 weeks followed by a 8-week washout followed by mannitol 400 mg b.d. for 8 weeks.

3. Results

3.1. Study participants

The study was conducted between the June 2013 and October 2015. Of the 117 subjects who underwent the MTT for screening, 101 subjects tolerated inhaled mannitol in the MTT, 9 subjects did not and 7 subjects had an incomplete MTT (Fig. 1). One subject who failed the MTT was randomised in error. In total, 95 were randomised to the study with 48 randomised to the mannitol → placebo group and 47 randomised to the placebo → mannitol group. Of these, 92 subjects commenced at least one dose of blinded study medication and are therefore included in the pre-specified FAS.

Subject baseline characteristics are reported in Table 1. Treatment sequence groups were well balanced for the demographic variables assessed (Table 1). We highlight the mean age of 12.0 years and mean baseline $ppFEV_1$ of 72.2%) consistent with moderately severe CF lung disease. The majority of subjects were regular users of rhDNase (68%) and maintenance antibiotics (all) (71%).

3.2. Efficacy

All measures of lung function following 8 weeks of therapy favoured mannitol. In Table 2 the mean absolute and relative improvements from baseline in both treatment periods are given.

The primary study endpoint of improvement in $ppFEV_1$ was met: a 3.42% overall treatment benefit in the mannitol group (p = 0.0041) (Fig. 2a). Also meaningful and statistically significant overall treatment benefits were seen for other parameters: 4.97%, improvement in relative $ppFEV_1$ (p = 0.0052), 5.75% improvement in $ppFEF_{25–75}$ (p = 0.0047), 10.52% in relative change in $ppFEF_{25–75}$ (p = 0.0128).

In a post hoc responder analysis, almost twice as many subjects in the mannitol group as in the placebo group had a relative improvement in the $ppFEV_1$ of ≥5% (p = 0.003 Mainland-Gart test) and ≥10% (p = 0.114, Mainland-Gart test) (Fig. 2b).

At week 8, the mean absolute change in ppFVC in the FAS population was 2.20% and 0.40% for the mannitol and placebo treatment groups respectively. The overall treatment effect was 1.80% (p = 0.1578). The least squares mean change in $ppFEF_{25–75}$ in the mannitol group was 5.85% while in the

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Table 2
Efficacy results.

	Mannitol (N = 87)		Placebo (N = 87)
Change in $ppFEV_1$ (%)			
LS mean (95% CI)	3.59 (1.81, 5.37)		0.17 (−1.60, 1.95)
Difference (95% CI)		3.42 (1.12, 5.71)	
p-Value		0.0041	
Relative change in $ppFEV_1$ (%)			
LS mean (95% CI)	5.72 (2.87, 8.57)		0.75 (−2.09, 3.59)
Difference (95% CI)		4.97 (1.53, 8.42)	
p-Value		0.0052	
Change in ppFVC (%)			
LS mean (95% CI)	2.20 (0.32, 4.08)		0.40 (−1.48, 2.28)
Difference (95% CI)		1.80 (−0.71, 4.32)	
p-Value		0.158	
Relative change in ppFVC (%)			
LS mean (95% CI)	3.63 (0.99, 6.26)		1.08 (−1.54, 3.71)
Difference (95% CI)		2.54 (−0.72, 5.80)	
p-Value		0.1242	
Change in $ppFEF_{25-75}$ (%)			
LS mean (95% CI)	5.85 (2.70, 9.00)		0.10 (−3.04, 3.24)
Difference (95% CI)		5.75 (1.82, 9.69)	
p-Value		0.0047	
Relative change in $ppFEF_{25-75}$ (%)			
LS mean (95% CI)	13.51 (7.18, 19.83)		2.99 (−3.32, 9.30)
Difference (95% CI)		10.52 (2.30, 18.73)	
p-Value		0.0128	
Sputum weight (post- initial treatment) (g)			
LS mean (95% CI)	2.63 (1.72, 3.55)		1.30 (0.39, 2.21)
Difference (95% CI)		1.33 (0.30, 2.37)	
p-Value		0.0124	

CI = Confidence Interval; LS Mean = Least Squares Mean.
Difference, estimated from mixed model, is for mannitol vs placebo.
Model includes treatment, subject, and period.

placebo group it was 0.10%. The overall treatment effect was 5.75% (95% CI: 1.82–9.69, p = 0.0047). The relative changes in $ppFEF_{25-75}$ were consistent with the absolute changes. The test for carryover was not significant for any of the endpoints.

Following administration of mannitol, subjects produced a significantly greater sputum weight than subjects in the placebo group (mannitol 2.63 g; placebo 1.30 g (p = 0.0124) (Table 2).

Subgroups for age (6–11 yrs., 12–17 yrs), rhDNase use (user, non-user), annualised rate of decline in $ppFEV_1$ (<2% per year, ≥2% per year) and screening FEV_1 (>70%, ≤70%), were predefined in the SAP. Interactions between the treatment and each group variable were tested to assess whether the treatment effect was consistent across all the levels of the subgroups. None of these interactions were significant for the primary or secondary endpoints.

The treatment effect and its 95% confidence interval between the two treatment groups were also reported separately for each level of the subgroups. In the pre-specified subgroups the $ppFEV_1$ treatment differences consistently favoured mannitol with point estimates for all subgroups being consistent with the overall treatment difference; (age 6–11 years: 3.78%, 95% CI 0.13–7.43; age 12–17 years: 3.35%, 95% CI 0.14–6.55), (rhDNase user: 3.29%, 95% CI 0.28–6.30; rhDNase non-user: 3.92%, 95% CI 0.42–7.42), (annualised decline in $ppFEV_1$ at baseline (<2%) 2.91%, 95% CI −0.26–6.08; annualised decline in $ppFEV_1$ at baseline (≥2%) 3.23%, 95% CI 0.20–6.26), (screening $ppFEV_1$ > 70%: 3.43%, 95% CI 0.81–6.05; screening $ppFEV_1$ ≤ 70%: 2.87%, 95% CI −0.74–6.49). The point estimates for all subgroups are consistent with the overall treatment difference (see Forest Plot in on-line supplement). A similar pattern was also seen in the subgroup analyses for all secondary endpoints (data not shown).

3.3. Safety

The MTT is a test used as a safety measure to identify patients who may be hyperresponsive to mannitol prior to therapy being initiated. In this study the majority (86.3%) of subjects who underwent the MTT passed the test without evidence of bronchial hyperresponsiveness to inhaled mannitol. Subjects who were not randomised (including those who failed due to a positive test result or who did not complete the MTT) had a larger mean maximum percentage fall in FEV_1 (mean 18.22%, SD 10.59%) than those who were randomised (mean 8.89%, SD 8.06%).

Adverse events occurred within two days of the MTT in 23.1% subjects, with only 9.4% subjects experiencing adverse events considered to be causally related to the MTT. Cough, experienced by 6.0% subjects, was the most frequent MTT-related adverse event that occurred on the day of the MTT or the day after. Four (3.4%) subjects experienced SAEs following the MTT, none of whom experienced SAEs which were considered to be related to the MTT.

The proportion of subjects reporting at least one TEAE or an SAE during the study period was similar for the mannitol and placebo groups (62.1% versus 59.8% respectively for TEAE; 11.5% versus 14.9% respectively for SAEs). Cough was the most frequently reported treatment-emergent event, occurring in 16.1% of subjects in each treatment arm (Table 3, [3]). Pulmonary exacerbations occurred less frequently in the mannitol versus placebo arm (11.5% and 16.1% respectively). Common (≥5%) TEAEs all occurred with either equal or greater frequency in the placebo arm, including headache, nasopharyngitis and lung infections. Haemoptysis was uncommon, occurring in 3 mannitol subjects and 2 placebo subjects. All haemoptysis events were either scant or mild and all occurred in subjects ≥12 years of age.

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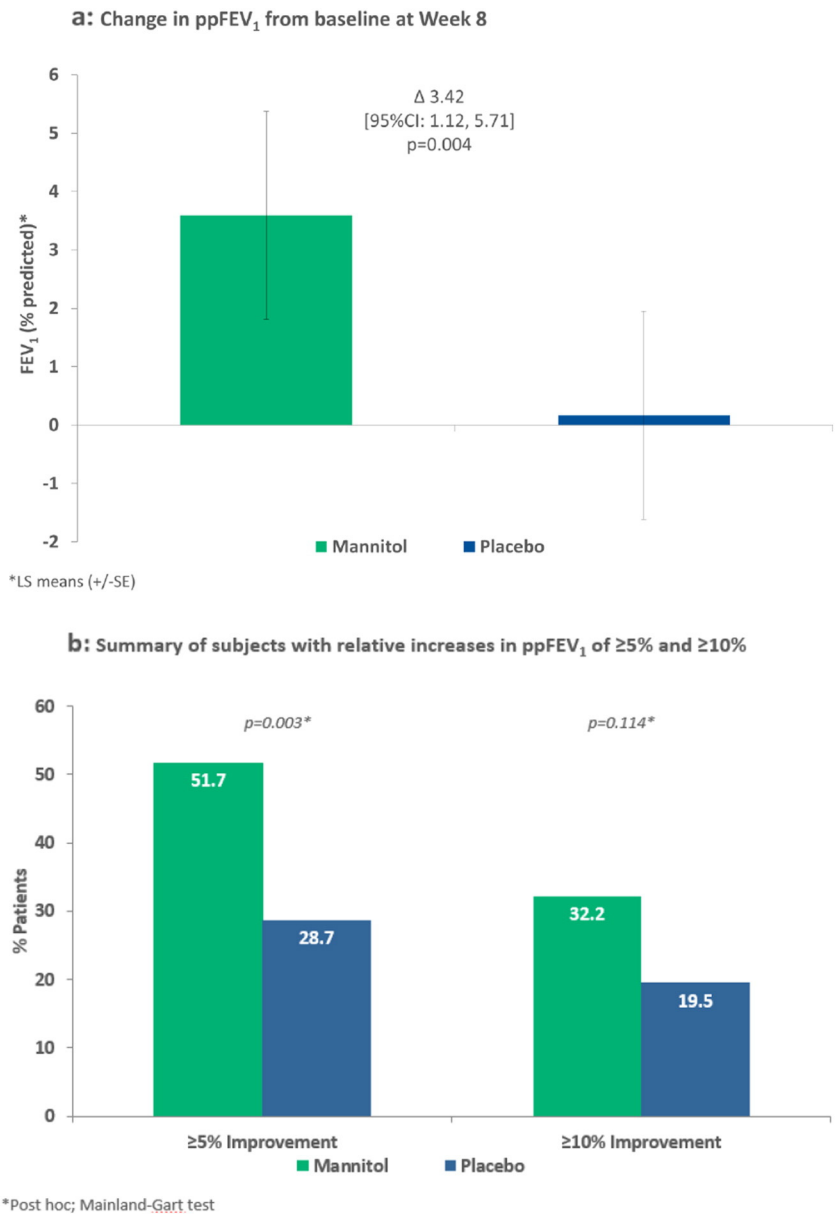

Fig. 2. a: Change in ppFEV$_1$ from baseline at week 8. b: Summary of subjects with relative increases in ppFEV$_1$ of ≥5% and ≥10%.

The majority of AEs were mild–moderate with only 4 (4.6%) subjects in the mannitol arm and 3 (3.4%) subjects in the placebo arm experiencing severe AEs. The severe events reported included abdominal pain, anal fistula, pyrexia, tonsillitis, gingivitis, headache, migraine, cough and respiratory distress. No instances of severe bronchospasm were reported.

Two subjects in the mannitol group and 1 subject in the placebo group discontinued the study due to AEs; of these, 2 subjects (both in the mannitol group) discontinued the study due to treatment-related AEs (events included cough, sore throat and dizziness) (Table 3). No deaths occurred during the study.

Inhaled mannitol demonstrated an acceptable safety profile and reported AEs were consistent with CF disease state and treatments. While the incidence of subjects reporting AEs overall was higher in the mannitol group (77.0% and 67.8% in the mannitol and placebo groups, respectively), the incidence of subjects reporting treatment-emergent AEs was similar between groups.

4. Discussion

One of the important factors predictive of survival in cystic fibrosis is FEV$_1$ [11,17,18]. Longitudinal spirometric measures of lung function including FEV$_1$ have been used as surrogate markers of disease severity and treatment response, in part due to the relative ease of reproducibility and accessibility and as such, have had a major impact on clinical decision making. Declines in FEV$_1$ have been found to be predictive of increased hospitalizations and death in patients with chronic obstructive pulmonary

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Table 3
Summary of treatment-emergent adverse events (TEAEs) and treatment-related AEs leading to withdrawal.

	Mannitol (N = 87) n (%)	Placebo (N = 87) n (%)
Subjects		
≥1 TEAE	54 (62.1)	52 (59.8)
≥1 treatment-related AE	16 (18.4)	11 (12.6)
≥1 SAE	10 (11.5)	13 (14.9)
≥1 treatment-related SAE	0 (0.0)	1 (1.1)
Total number of AEs	114	117
TEAEs by MeDRa preferred term [a]		
Cough	14 (16.1)	14 (16.1)
Infective pulmonary exacerbation of cystic fibrosis	10 (11.5)	14 (16.1)
Headache	6 (6.9)	7 (8.0)
Nasopharyngitis	6 (6.9)	6 (6.9)
Lung infection	2 (2.3)	5 (5.7)
AEs leading to withdrawal from study	2 (2.3)	1 (1.1)
Treatment-related AEs leading to withdrawal from study	2 (2.3)	0 (0.0)
Dizziness	1 (1.1)	0 (0.0)
Cough	2 (2.3)	0 (0.0)
Oropharyngeal pain	1 (1.1)	0 (0.0)

TEAE – Treatment Emergent Adverse Event (includes AEs commencing during the first 7 days of wash-out for Period A).
SAE – Serious Adverse Event.
Percentages are based on N.
Multiple occurrences of the same AE in one individual counted only once.
[a] Occurring in ≥5% subjects on either treatment.

disease [19]. In very recent times, treatments that aim to address the fundamental genetic defects in CF are emerging from the development pipeline and there is a guarded optimism that therapy specific to the varied mutant categories in CF can be realised and commercialised. While the first successful compounds in this area have been approved for sub-groups of CF patients, the efficiency of these compounds does not yet obviate the continued need for other effective, life-long therapies to maintain or improve lung function and reduce exacerbations in both paediatric and adult patients with CF [20].

Data from this study clarifies the findings previously published on the use of mannitol in subjects with CF aged 6–17 years [9,10,21]. In this current study, using a true placebo rather than low dose mannitol control, the mean relative improvement in $ppFEV_1$ over baseline for the 6–11 year age group was 7.6% and 5.0% for the 12–17 year age group with effect sizes in the placebo groups being only 2.3% and −0.2% respectively. In the pooled analyses from the CF-301 and CF-302 studies, the mean relative improvement in $ppFEV_1$ over baseline for the 6–11 year age group was 8.42% and 6.08% for the 12–17 year age group [22]. However only the 6–11 year age group reached significance against control potentially resulting from a treatment effect evident in the control groups (4.57%, 6–11 years; 4.96% 12–17 years).

Inhaled mannitol was associated with significant improvements in primary and secondary endpoints in subjects aged 6–17 years. The efficacy results were achieved when mannitol was added to existing standard of care (did not include hypertonic saline). There was a significant and clinically meaningful improvement in the primary endpoint of change in percentage of predicted FEV_1 in the mannitol group with a significant treatment difference between the mannitol and placebo groups. Secondary endpoints in this study included other measures of respiratory function and assessment of the difference in treatment-induced sputum weight between the treatment groups. All of the secondary spirometry measures also supported the efficacy of mannitol. Early in the course of CF disease, an interrelated pattern involving chronic obstruction, infection and inflammation develops with lifelong trajectory characterised by progressive structural lung damage and diminishing function, ultimately contributing to respiratory failure and death [2,23]. Lung function tests and CT scans in children with CF demonstrate that the small airways are involved early in this process [24,25]. This highlights the significance of the improvements seen in small airway patency in this current study with significant improvements in $FEF_{25–75}$ in the mannitol group after 8 weeks of therapy.

For all subgroups examined including age, rhDNase use and disease severity and background rate of decline in lung function, the benefits in respiratory function consistently favoured mannitol. In the mannitol group, post-treatment sputum weight was significantly higher than in the placebo which is consistent with the postulated mechanism of action of inhaled mannitol and enhanced mucociliary clearance following administration of the drug.

The study confirms that inhaled mannitol, when added to optimal care, provides rapid and significant incremental benefits in lung function and sputum weight in children and adolescents irrespective of rhDNase use, age or disease severity. The incidence of AEs was similar between groups and importantly, there appears to be a lower frequency of exacerbations. Importantly, these data show that inhaled mannitol significantly improves lung function and clearance and could provide significant benefits to patients aged 6–17 years with CF and moderate obstructive lung disease.

Authors' contributions

All authors helped to interpret data, write the manuscript and have seen and approved the final version.

Kris de Boeck and Anne Malfroot were the Protocol Steering Committee head and Global Principal Investigator for CF-204 respectively and had full access to all the data in the study and had final responsibility to submit for publication. Brett Charlton designed the CF-204 study and approved the statistical plan, and was the Sponsor's Responsible Medical Officer.

Conflict of interest statement

KdB, EH, JH, LCL, AM, JR, HT, SV and AM were all investigators during the studies and their institutions received standard clinical trial support from Pharmaxis. Investigators received travel support for the investigator meetings. No Investigator received any personal funding to participate in the study. BC is the Medical Director of and holds stock

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options in Pharmaxis Ltd. JL holds stock options in Pharmaxis Ltd.

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Role of the funding source

The study sponsor participated in the study design, data collection, data analysis, data interpretation and writing of the study report. Following completion of the trial, the data were held and analysed by the sponsor. The corresponding author had full access to all of the data, and had final responsibility for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2017.02.003.

References

[1] De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med 2016;4(8):662–74.
[2] Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. BMC Med 2012;10:88.
[3] Bhatt JM. Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev 2013;22(129):205–16.
[4] VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: a review of disease manifestation, progression, and response to early treatment. J Cyst Fibros 2016;15(2):147–57.
[5] Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care 2009;54(4):522–37.
[6] Flume PA. Smoothing the transition from pediatric to adult care: lessons learned. Curr Opin Pulm Med 2009;15(6):611–4.
[7] Ratjen F, Grasemann H. New therapies in cystic fibrosis. Curr Pharm Des 2012;18(5):614–27.
[8] Barry PJ, Jones AM. New and emerging treatments for cystic fibrosis. Drugs 2015;75(11):1165–75.
[9] Aitken ML, Bellon G, De Boeck K, Flume PA, Fox HG, Geller DE, et al. Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. Am J Respir Crit Care Med 2012;185(6):645–52.
[10] Bilton D, Robinson P, Cooper P, Gallagher CG, Kolbe J, Fox H, et al. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. Eur Respir J 2011;38(5):1071–80.
[11] Schluchter MD, Konstan MW, Davis PB. Jointly modelling the relationship between survival and pulmonary function in cystic fibrosis patients. Stat Med 2002;21(9):1271–87.
[12] Kulich M, Rosenfeld M, Campbell J, Kronmal R, Gibson RL, Goss CH, et al. Disease-specific reference equations for lung function in patients with cystic fibrosis. Am J Respir Crit Care Med 2005;172(7):885–91.
[13] Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15(2):75–88.
[14] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159(1):179–87.
[15] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319–38.
[16] Grizzle JE. The two-period change-over design an its use in clinical trials. Biometrics 1965;21:467–80.
[17] Liou TG, Adler FR, FitzSimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153(4):345–52.
[18] Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. J Pediatr 2007;151(2):134–9 [139 e1].
[19] Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr 1997;131(6):809–14.
[20] Tildy BE, Rogers DF. Therapeutic options for hydrating airway mucus in cystic fibrosis. Pharmacology 2015;95(3–4):117–32.
[21] Teper A, Jaques A, Charlton B. Inhaled mannitol in patients with cystic fibrosis: a randomised open-label dose response trial. J Cyst Fibros 2011;10(1):1–8.
[22] Bilton D, Bellon G, Charlton B, Cooper P, De Boeck K, Flume PA, et al. Pooled analysis of two large randomised phase III inhaled mannitol studies in cystic fibrosis. J Cyst Fibros 2013;12(4):367–76.
[23] Nixon GM, Armstrong D, Carzino R, Carlin J, Olinsky A, Robertson C, et al. Early airway infection, inflammation, and lung function in cystic fibrosis. Arch Dis Child 2002;87(4):306–11.
[24] Tiddens HA, Donaldson SH, Rosenfeld M, Paré PD. Cystic fibrosis lung disease starts in the small airways: can we treat it more effectively? Pediatr Pulmonol 2010;45(2):107–17.
[25] Linnane BM, Hall GL, Nolan G, Brennan S, Stick SM, Sly PD, et al. Lung function in infants with cystic fibrosis diagnosed by newborn screening. Am J Respir Crit Care Med 2008;178(12):1238–44.

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