16 February 2012
EMA/CHMP/121817/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Bronchitol

International non-proprietary name: mannitol

Procedure No. EMEA/H/C/001252

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

AE	Adverse event
AFFSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (NCA in France)
ANCOVA	Analysis of covariance
ASL	Airway surface liquid
AUC	Area under the concentration-time curve
BAL	Bronchoalveolar lavage
BAV	Bioavailability
BD	Twice a day
BMI	Body mass index
CF	Cystic Fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cl	Clearance
Cl_R	Renal clearance
Cmax	The peak plasma concentration
CNS	Central nervous system
CRP	C reactive protein
DNA	Deoxyribonucleic acid
DPI	Dry powder inhaler (device)
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FEF_{25-75}	Forced Expiratory Flow between 25% and 50% of FVC
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HS	Hypertonic saline
ITT	Intention to treat (population)
IV	Intravenous (administration route)
K_{el}	Elimination rate constant
LD_{50}	Median lethal dose
LS	Least squares
MMRM	Mixed model repeat measures
MTT	Mannitol tolerance test
NCA	National competent authority
NOAEL	No observed adverse effect level
NTP	National Toxicology Program (US)
PDCO	Paediatric Committee
PDPE	Protocol defined pulmonary exacerbation
PE	Pulmonary exacerbation
PEF	Peak expiratory flow
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP	Per protocol (population)
PT	Preferred term
QoL	Quality of life
rhDNase	Recombinant human DNase
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SOC	System organ class
SPC	Summary of product characteristics
$T_{1/2}$	Elimination half-life
TGA	Therapeutic Goods Administration (Australia)
TK	Thymidine kinase
Tmax	Time to reach C_{max}
V_D	Distribution volume

WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant, Pharmaxis Pharmaceuticals Ltd., submitted on 28 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bronchitol, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 September 2008.

Bronchitol was designated as an orphan medicinal product EU/3/05/325 on 7 November 2005. Bronchitol was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis.

The applicant applied for the following indication treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above as either an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting certain tests or studies.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on 27 April 2006 and follow-up Protocol Assistance on 18 October 2006. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Bronchitol has been given a Marketing Authorisation in Australia on 07 February 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Robert James Hemmings** Co-Rapporteur: **Philippe Lechat**

- Prior to the submission and in line with EMA guideline on accelerated assessment (EMEA/419127/05), an application for accelerated review was submitted to the EMEA on 2nd October 2009. On 29 October 2009, the CHMP agreed that an accelerated review should not be granted based on the claims and description of the available data provided by the applicant.
- The application was received by the EMA on 28 October 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 05 February 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2010.
- During the meeting on 15-18 March 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2010.
- The summary report of the inspection carried out at the following sites (United Kingdom between 2 and 5 March 2010 and Ireland between 24 and 26th February 2010) was issued on 31 May 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 03 September 2010.
- During the CHMP meeting on 20-23 September 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 12 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 02 December 2010.
- During the CHMP meeting on 19 January 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- On 20 January 2010, the CHMP adopted on a second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 14 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 28 April 2011.
- During the CHMP meeting on 18 May 2011, outstanding issues were addressed by the applicant during a second oral explanation before the CHMP.
- During the meeting on 23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Bronchitol.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **David Lyons** Co-Rapporteur: **Conception Prieto Yerro**

- The applicant submitted written notice to the EMA on 4 July 2011 to request a re-examination of Bronchitol CHMP opinion of 23 June 2011.
- During its meeting on 21 July 2011, the CHMP appointed David Lyons as Rapporteur and Conception Prieto Yerro as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 19 August 2011. The re-examination procedure started on 20 August 2011.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 26 September 2011. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 29 September 2011.
- During a meeting of the Bronchitol ad hoc expert group on 3 October 2011, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 14 October 2011.
- During the CHMP meeting on 17 October 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 18 October 2011, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.
- On 9 November 2011, the European Commission sent a letter to the CHMP Chairman requesting clarifications on some aspects of the CHMP Assessment Report adopted on 18 October 2011.
- During the meeting of December 2011, the CHMP provided the requested clarifications in the revised CHMP Assessment Report adopted on 15 December 2011.
- On 17 January 2012, the European Commission sent a letter to the CHMP Chairman requesting clarifications on some aspects of the CHMP Assessment Report adopted on 15 December 2011.
- During the meeting of February 2012, the CHMP provided the requested clarifications in the revised CHMP Assessment Report adopted on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease. The mean incidence is reported to be 1 in 2000-3000 live Caucasian births (WHO - 2004). It is the most common lethal genetic disorder affecting Caucasian populations. Cystic fibrosis has several manifestations, including gastrointestinal, though respiratory manifestations are the main and include bronchitis, bronchiolitis and bronchioectasis, which can lead to haemoptysis, pneumothorax and cor pulmonale. Lung disease is the most common (>90%) cause of death in cystic fibrosis patients. The life span of patients with cystic fibrosis has increased in Europe and the median life expectancy for cystic fibrosis patients has been estimated in 2000-2003 as 40 years. The increase in average age of death leads to increased proportion of adult CF patients, however, majority of patients are still in the paediatric population.

Cystic fibrosis is caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. The primary function of the CFTR protein is as an ion channel that regulates liquid volume on epithelial surfaces through chloride secretion and inhibition of sodium absorption.

One hypothesis for the pathogenesis of lung disease in patients with cystic fibrosis is that a lack of regulation of sodium absorption and chloride secretion reduces the water content of airway surface liquid, resulting in the accumulation of thick, tenacious mucus, and promotes the formation of adherent mucus plaques on airway surfaces. In cystic fibrosis patients, the ciliary system is unable to clear this mucus, leading to chronic inflammation and infection, airway damage, and ultimately respiratory failure.

Pulmonary exacerbations are significant clinical events for patients with cystic fibrosis and lead to lung function decline. Pulmonary exacerbations are usually associated with a change in the bacterial density of the bacterial flora residing in the airways. Lung infection and inflammation in cystic fibrosis are mainly treated with antibiotics. Other treatments include exercise and physical therapies, pancreatic enzymes replacement therapy, use of nutritional supplements, bronchodilators, mucolytics and anti-inflammatory medicines, local hydration with inhaled moisture, and in severe cases lung transplantation.

Recombinant human DNase is currently registered as the mucolytic agent in the treatment of cystic fibrosis. RhDNase cleaves the DNA present in sputum/mucus and degrades the large amount of free DNA that accumulates within CF mucus, thereby improving the viscoelastic properties of airway secretions and promoting airway clearance. RhDNase is recommended by current guidelines in CF patients 6 years and older as it has been shown to improve lung function with a low risk of adverse events.

Nebulised hypertonic saline (HS) has been proposed as an agent that increases hydration of airway surface liquid in cystic fibrosis by an osmotic gradient to improve mucociliary clearance (MCC). The quality of evidence for the use of HS in patients with CF is limited to published studies. A 2005 Cochrane review of hypertonic saline found that overall lung function improved compared with placebo, but the improvement was not as great as that seen with dornase alfa.

Even though currently available therapies have prolonged life expectancy for cystic fibrosis patients, it is still a progressive disease associated with increased mortality and significantly decreased average

age of death; therefore there exists an unmet medical need for new effective treatments for cystic fibrosis.

The product

Hyperosmolar agents such as inhaled mannitol are expected to facilitate clearance of mucus by ciliary and cough action by a number of different mechanisms. Inhaled mannitol is believed to create an osmotic gradient that increases the amount of water in the airway lumen encouraging hydration and subsequent restoration of the periciliary layer (airway surface liquid). This is expected to lead to changes in surface properties, to improve ciliary function and mucus transportability and to increase mucociliary clearance. The mucus load and subsequent inflammation and infection might therefore decrease, resulting in stabilisation of the cystic fibrosis patient's condition.

Mannitol (D-Mannitol) is a naturally occurring polyol (sugar alcohol). It is used intravenously as an osmotic agent for the treatment of cerebral oedema and renal failure and orally as a bowel preparation to alleviate constipation. Mannitol is also an excipient in pharmaceutical formulations, and a food additive. Inhaled mannitol has been approved for bronchial hyperresponsiveness testing.

Bronchitol has been developed for both adults and children with CF as an osmotic stimulus to lung clearance to be used either as an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to, rhDNase.

Bronchitol is an encapsulated powder for inhalation. The product consists of hard gelatine capsules containing 40 mg of respirable mannitol powder delivered to the patient via a dry powder inhaler, to be provided in the package of Bronchitol.

The original indication claimed by the applicant was:

- *"Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult population 6 years and above as either an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase."*

During the evaluation procedure the applicant has modified this indication to exclude those below 18 years of age.

The posology proposed by the applicant is 400 mg twice a day, which requires inhalation of the content of 10 capsules of 40 mg via the inhaler device twice a day. Before commencing treatment with Bronchitol, all patients during administration of their initiation dose are required to be assessed for bronchial hyperresponsiveness to inhaled mannitol, which is listed as a contraindication in the proposed SPC.

Initiation of Bronchitol treatment (at dose 400 mg) is proposed to be done under the supervision and monitoring of an experienced physician or another appropriately trained health professional, equipped to monitor oxygen saturation and able to perform spirometry and manage acute bronchospasm. A bronchodilator is proposed to be administered 5-15 minutes before Bronchitol is used.

Type of Application and aspects on development

This is a complete independent application. The legal basis of the application refers to Article 8.3 of Directive 2001/83/EC.

The applicant requested an accelerated assessment for the application. However, the CHMP did not accept this request as it could not be assumed that the product would be of major public health interest and in particular from the viewpoint of therapeutic innovation. It was noted that such claim

would require substantial data to assess the impact on reduced morbidity and prolonged life expectancy data, given the closeness of the therapeutic principle of inhaled mannitol to the one of available therapies. Based on the available evidence inhaled mannitol was considered not to address a major unmet need but instead to offer an alternative to adjunctive therapies used to support the therapeutic algorithm with the aim of dislodging sputum and encouraging its expectoration. The claimed innovator concept was thus not supported by the Committee. Furthermore, it was considered that a new mode and method of administration with a dry powder inhaler and small portable device that would improve compliance could not be recognised to fulfil such criterion.

Bronchitol, for the treatment of cystic fibrosis, has been designated as an orphan medicinal product.

For the development of products for cystic fibrosis a specific guideline has been developed by the CHMP (EMEA/CHMP/EWP/9147/2008) and is applicable also to the development programme of Bronchitol.

The applicant had obtained protocol assistance, during which it was advised that:

- A sub-therapeutic dose of mannitol would be acceptable as a control in the Phase 3 study.
- The trial design initially proposed by the applicant would not be adequate to evaluate efficacy of mannitol as both first line and add on therapy (to rhDNAse) in CF because rhDNAse treated and rhDNAse naïve patients are unlikely to be comparable in terms of severity of disease.
- From the data presented during scientific advice procedure, the indication for an add-on to existing therapy appears to be the most appropriate indication.
- Revisions to the protocol, as proposed by the applicant, are acceptable. However, it was noted that an add-on design (or alternatively a non-inferiority/superiority design against rhDNAse for a first line indication) is recommended for the clinical development. It was noted that the trial design might benefit from small-scale short-term trials first to determine if the chosen order of mannitol, postural drainage and bronchodilator is optimal for this drug.
- The FEV_1 would be a suitable primary efficacy endpoint in the pivotal Phase 3 studies.

In general the applicant has complied with the Protocol Assistance.

2.2. Quality aspects

2.2.1. Introduction

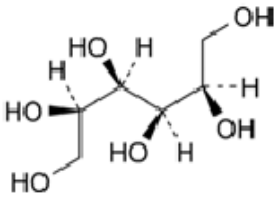
Bronchitol is an encapsulated powder for inhalation. The product consists of hard gelatine capsule containing 40 mg of respirable mannitol powder delivered to the patient via a dry powder inhaler. The dry powder device is provided in the package: type RS S01 Inhaler Model 7 HR, a high-resistance inhaler manufactured by Plastiape S.p.A.

Mannitol (D-Mannitol) is a naturally occurring polyol (sugar alcohol). It is used intravenously as an osmotic agent for the treatment of cerebral oedema and renal failure and orally as a bowel preparation to alleviate constipation. Mannitol is also an excipient in pharmaceutical formulations, and a food additive. Since 2006, inhaled mannitol (Aridol/OsmohaleTM in capsules of 5 mg, 10 mg, 20 mg, 40 mg) has been used as a bronchial provocation test to measure bronchial responsiveness.

The full list of ingredients is defined in section 6.1 of the SPC.

2.2.2. Active substance

Mannitol ($C_6H_{14}O_6$) is a well-characterised molecule for which a Ph.Eur. monograph exists. It is a white or almost white crystalline powder or free-flowing granules, with a relative molecular mass of 182.2 and the following structural formula:



Mannitol is freely soluble in water and very slightly soluble in alcohol, non-hygroscopic, with a melting point of 165 - 170 °C and shows polymorphism (α, β, δ-mannitol).

The quality of the active substance mannitol is supported by a Certificate of Suitability (CEP) of the monograph of the European Pharmacopoeia.

Manufacture

The manufacturing process of the active substance mannitol is supported by a Certificate of Suitability (CEP).

Specification

The specifications of mannitol are compliant with the Ph.Eur. monograph. The CEP contains no tests in addition to those in the Ph.Eur. monograph. Additional tests are performed to control the microbiological quality of the active substance.

Stability

A three-year re-test period for the active substance mannitol is supported by the CEP.

Comparability exercise for active substance

Not applicable

2.2.3. Finished medicinal product

Pharmaceutical development

Bronchitol consists of hard gelatine capsules of size 3 containing 40 mg mannitol. There are no excipients apart from the capsule gelatine, capsule colour agents and capsule printing ink. The capsules consist of gelatin of either bovine or porcine origin. The capsules are packaged in Al/Al blisters.

There are two proposed pack configurations: one initial dose Bronchitol package contains 10 capsules (1 blister) of 40 mg and 1 inhaler device; and the ongoing treatment pack contains 280 capsules (28 blisters) of 40 mg and two inhaler devices.

The development accounted for with respect to optimisation of the spray drying technique and particle size during scale-up. The finished product was developed in compliance with the specific development pharmaceutical studies requirements of this pharmaceutical form.

Adventitious agents

The active substance mannitol is absent of BSE/TSE risk.

A TSE Certificate of Suitability for each source of bovine-derived gelatine has been provided.

Manufacture of the product

A detailed description of the manufacture of the finished product is provided. The manufacturing process comprises dissolution of mannitol in purified water, filtration, and spray drying. Sub-batches are blended and sieved prior to encapsulation and packaging.

The critical steps in manufacture were identified and adequate in-process control and testing procedures were established. Process validation has been performed on a satisfactory number of batches. Process validation data indicate that the manufacturing process of Bronchitol 40 mg is capable of consistently producing inhalation powder in hard capsules of suitable quality which meet the release specification.

Product specification

The finished product specification includes tests for appearance, description, identification by two independent methods, water content, uniformity of delivered dose, aerodynamic particle size distribution, related substances, assay, and microbiological purity. The specification is considered generally justified for this dosage form.

All analytical procedures and test methods have been adequately described and validated. Batch analysis results are provided for a satisfactory number of batches. All batch results are acceptable; all data are well within the proposed specifications.

Stability of the product

Stability studies on the drug product were carried out on a satisfactory number of batches. The blistered capsules were stored at long-term, intermediate and accelerated storage conditions according to ICH guidelines. No significant tendencies in any of the parameters tested are observed. The proposed shelf-life of 2 years when stored at or below 25ºC is adequately justified.

Comparability exercise for finished medicinal drug product

Not applicable

GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general, satisfactory chemical and pharmaceutical documentation have been submitted for the marketing authorisation. There are no major deviations from EU and ICH requirements.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the medicinal product is acceptable. There were no quality outstanding issues on the quality of the active substance at the time of Opinion. However one non-major issue remains unresolved regarding the quality of the finished medicinal product: the characterisation of the preservative efficacy of mannitol against species such as Burkholdaria cepacia, Aspergillus fumigatus was not performed. These infective agents are commonly reported as pathogenic contaminants in cystic fibrosis and therefore this issue required investigation.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data consists of non-clinical studies sponsored by the applicant and published data. Since mannitol is a known active substance, mainly relevant published data have been submitted, supplemented with a bridging programme of studies conducted to support its use by the inhalation route. The additional studies comprised of single and repeated dose toxicity, including toxicokinetics, and local tolerance studies, which all were reported to be GLP compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Data from the literature indicate that the primary pharmacodynamic actions of inhaled mannitol relate to its osmotic effect on airway secretions. In the isolated ferret trachea[1], a solution of 15 g/dl mannitol increased mucin and lysozyme secretion. Mannitol appeared to induce mucin secretion to a greater extent than saline solution with similar osmolarity, although this was not statistically significant. Mannitol also caused a dose-dependent increase in respiratory tract fluid output in anaesthetised beagle dogs[2]. Overall, both models showed that mucus secretion is markedly stimulated in response to hyperosmolarity and support the hypothesis that Inhaled mannitol causes an osmotic gradient in the airway leading to an increase in secretion of water into the airway lumen, which rehydrates the mucus. This is expected to result in a change in mucus rheology, promoting mucociliary clearance.

Secondary pharmacodynamic studies

[1] Kishioka C, Okamoto K, Kim J-S, Rubin BK. Hyperosmolar solutions stimulate mucus secretion in the ferret trachea. Chest, July 2003;124:306-313

[2] Chen BT, Yeates DB. Ion transport and regulation of respiratory tract fluid output in dogs. J Appl Physio, 2001;90:821-831

Inhaled d-mannitol aerosol increases osmolarity, which leads to the release of inflammatory mediators such as histamine, leukotrienes and prostanoids from airway and inflammatory cells, which in turn results in bronchoconstriction and airway narrowing. This is the pharmacological activity of mannitol as the challenge agent. It is also relevant for patients receiving inhaled mannitol, therefore pertinent information has been included in the proposed SPC.

Taking into account the clinical experience with mannitol as a challenge agent, no further secondary pharmacodynamic studies are required.

Safety pharmacology programme

Safety pharmacology aspects have been investigated in repeat-dose toxicology studies. No evidence of respiratory or cardiovascular treatment-related effects was seen in the mannitol inhalation repeat-dose toxicology studies conducted. Cardiovascular and respiratory functions were monitored during the dog 2-week inhalation toxicity study and no changes in cardiovascular or respiratory functions were seen at doses up to 789 mg/kg/day. In the repeat-dose toxicology studies, inhalation of mannitol at up to 9 (rats) and 54 (in dogs) times the maximum recommended human dose did not cause any notable effects on the central nervous system. In addition, no reports of altered respiratory, cardiovascular or CNS functions were found despite widespread human and animal exposure to mannitol, except at systemic doses that are in excess of the recommended dose proposed in this application (800 mg/day). Therefore, further safety pharmacology studies are not considered required.

Pharmacodynamic drug interactions

Non clinical studies on pharmacodynamic interactions have not been performed, which can be accepted in the light of available clinical and literature data and the wide experience in administration of mannitol.

2.3.3. Pharmacokinetics

No specific pharmacokinetic studies by the inhalation route were conducted but toxicokinetic measurements were included for serum and bronchoalveolar lavage (BAL) fluid in the toxicity studies in the dog and for BAL fluid in two studies in the rat, which are discussed under Toxicology below. The absence of specific non clinical pharmacokinetic studies is acceptable. Additional data from the literature are presented in this section below.

Orally, mannitol is slowly and poorly absorbed, with a bioavailability of 17-20% and it exerts a laxative effect because of its osmotic effects. In addition, the literature provides some evidence that mannitol can be absorbed systemically from the lungs. Mannitol administered by inhalation or intratracheal administration in mice, rats and rabbits was absorbed relatively rapidly from the lung, in a manner suggesting first-order kinetics with a half-life of 26.5 minutes in the rat. Mannitol does not cross the blood-brain barrier.

A percentage of systemically absorbed mannitol undergoes hepatic metabolism to glycogen and carbon dioxide and the compound is primarily excreted unchanged in the urine or faeces. A minor proportion might be excreted as carbon dioxide in the expired air following complete metabolism by dehydrogenation to fructose and through the glycolytic pathway. No toxic metabolites are found and there is no evidence of accumulation.

Excretion following intravenous administration is mainly as unchanged mannitol via the urine; this would also apply to mannitol systemically absorbed following inhalation.

It is expected that a significant proportion of mannitol might be swallowed by patients using Inhaled mannitol and that it will be excreted unchanged in the faeces.

2.3.4. Toxicology

A single-dose study in rats and repeat-dose studies in rats and dogs were performed to examine the local respiratory tract tolerance and the systemic effects of inhaled mannitol. Ocular toxicity has been assessed in two studies; a rabbit eye irritation study and a bovine corneal opacity and permeability study.

Literature references were reviewed for repeat-dose toxicity, genotoxicity, carcinogenicity and reproduction toxicity data.

Single dose toxicity

One single dose toxicity study by inhalation administration was conducted in rats where male and female rats (5 per group) received 17.6, 80 or 98.1 mg/kg mannitol via inhalation. Slight reduction in body weight gain at 17.6 and 80 mg/kg dose and statistically significant at 98.1 mg/kg, as well as slight reduction in food consumption at 98.1 mg/kg dose was observed in male rats. In females body weight loss 1 day after dosing at 80 and 98.1 mg/kg was noted. Differences in body weight gain were explained by not balanced age of animals in the different groups. At post mortem, the weights of lungs and bronchi of the treated male animals were lower than those of the controls, achieving statistical significance in the 80 and 98.1 mg/kg groups. The findings were not consistent between genders. Some microscopic findings including arterial mural mineralization in lungs and bronchi, submucosal inflammatory cells in nasal turbinates and loss of cilia in trachea were noted primarily in high dosed animals. Study results do not raise any serious toxicological concerns. A No Adverse Effect Level (NOAEL) from this study was defined by the applicant as 98.1 mg/kg/day, which is 7 times higher than the anticipated dose in humans.

Information about single dose toxicity in mannitol via other administration routes is available in the literature.

A single-dose toxicity study [3] in 6-week old F344/N rats (50) and B6C3F1 mice (50) has been conducted. On day one, each group of 10 (5F, 5M) was offered, ad libitum in their water, either 6,000, 12,500, 25,000, 50,000, or 100,000 ppm of mannitol. They were observed twice daily for survival and other physical signs up to day 16. All animals survived, and no compound-related effects were observed.

According to published data [4] mannitol has low acute toxicity by the oral, intravenous (IV) or intraperitoneal (IP) routes:

- LD_{50} Rat oral: 13.5 g/kg
- LD_{50} Rat IV: 9.69 g/kg
- LD_{50} Mouse oral: 22 g/kg
- LD_{50} Mouse IP: 14 g/kg
- LD_{50} Mouse IV: 7.47 g/kg

[3] National Toxicology Programme Technical Report Series No. 236. U.S. Department of Health and Human Services. 1982
[4] Sax's Dangerous Properties of Industrial Materials. HSBD. 2001. Hazardous Substances Databank Number 714. Mannitol.

Repeat dose toxicity

2-week repeat dose inhalation toxicity studies in rats and dogs, 7-day and 13-week inhalation toxicity studies in rats and a 26-week inhalation toxicity study in beagle dogs have been conducted.

Two-week repeat-dose inhalation toxicity studies in rats and dogs were conducted and considered pivotal: 13-week inhalation toxicity studies in rats and a 26-week inhalation toxicity study in beagle dogs. The choice of the beagle dog for the pivotal 26-week study was justified on the basis of greater exposure achieved in the respiratory tract in this species. The dog also showed signs indicative of a more relevant pharmacodynamic effect, in the form of pulmonary oedema and frothing in the trachea.

The repeat-dose inhalation studies indicated no local toxicity to the respiratory tract, nor was any evidence of systemic toxicity noted. Mannitol by inhalation was generally well tolerated in rats for 13 weeks under a regimen of dosing at up to 210 mg/kg/day for 180 minutes daily and in dogs at doses up to 713 mg/kg/day for two 1-hour periods per day. Lymphocytosis was seen in the 2-week and 13-week rat studies and plasmacytosis was also seen in the 13-week rat study. In the 2-week rat study, some findings were also observed in tissues other than the respiratory tract in the high-dose animals, such as increased incidence of inflammatory cells in the myocardium and epididymides, and cortical renal tubular basophilia.

A minor increase in lung weight was evident at the end of the 2-week dog study and was thought to reflect the pharmacological response to the high mannitol load in the lungs and the time of death relative to the end of dosing. (Note: In contrast to all other studies reported, the dogs were killed immediately after exposure to assess the peak lung mannitol burden in this study). No similar treatment-related effects were seen in the 26-week dog study where the dogs were killed 20-24 hours after the last exposure when any pharmacological effects of mannitol had disappeared.

Also in the 13-week rat study, there was a significant increase in both the percentage and absolute number of natural killer cells in the 210 mg/kg group and the value remained increased at the end of the 4-week recovery period. There were no other notable effects on lymphocyte subpopulations, nor any evidence of immunotoxicity; the persisting slight increase in natural killer cells is not considered to indicate any risk for clinical use.

In dogs, BAL cell count investigations at 26 weeks revealed an increase in absolute white cell counts for mannitol-treated animals but this did not persist into the recovery period. This finding is consistent with the observations made following the use of mannitol as a diagnostic agent for hyper-reactivity of the lungs and is not considered to represent a significant toxic risk. Coughing and enlarged local lymph nodes were found but did not persist during the recovery period.

In rats a slight increase in NK cells was seen however the elevated levels were within historic control ranges for the laboratory. In addition there was no evidence of immunotoxicity in the dogs or humans. There were no treatment-related effects on organ weights and there were no necropsy or histology findings that could be attributed to administration of mannitol.

Published data on repeat-dose toxicity from mice, rats and monkeys did not show any toxicologically relevant signs of toxicity associated with the systemic administration of mannitol.

Genotoxicity

Scientific literature was reviewed for genotoxicity data. There was no evidence of genotoxicity on the part of mannitol in any of the available studies, which include reports on Bacterial Reverse Mutagenesis Test, Mouse Lymphoma TK assay, Sister Chromatid Exchange and Chromosome Aberration test, Mouse Micronucleus Bone Marrow and Peripheral Blood Study, Drosophila Sex-Linked Recessive Lethal Study,

In vivo Cytogenetics Chromosome Aberration study and others. On the basis of the published studies and the fact that mannitol is an approved pharmaceutical excipient, there are no concerns over genotoxicity.

Carcinogenicity

Long term studies

A long-term (104-107 weeks) toxicity and carcinogenicity study in the Wistar rat has been reported in the literature. Male and female rats were fed mannitol at doses of 4.4 and 5.2 g/kg respectively (10% in the diet). No toxicologically significant events or alteration in tumour incidence was seen[5].

In another study[6] F344/N rats and B6C3F1 mice were fed mannitol at doses of 25,000 and 50,000 ppm (5% limit dose) for 103 weeks. Mannitol was not carcinogenic in these studies. Mild nephrosis (focal vacuolisation of renal tubular epithelium) was noted in mice and a treatment related, but not dose related, increased incidence of dilatation of the gastric fundal gland was detected in the low- and high-dose female rats. Retinopathy and cataracts occurred at increased incidences.

Medium and short term studies

A carcinogenicity study in transgenic animals is reported in the literature. The study used p53-deficient mice that were fed mannitol at a dose of 5% in food for a period of 26 weeks. At the end of the study, mannitol was classified as non-carcinogenic[7]. However, it should be noted that also the positive control did not induce any tumours in this study.

Embryonic turkey and quail livers were examined after exposure to known non-carcinogens and carcinogens. The known carcinogen diethylnitrosamine induced preneoplastic liver lesions, whereas mannitol caused no histological changes in the embryonic livers[8]. The authors noted that these findings correlate with traditional long-term rodent bioassays.

There was no evidence of carcinogenicity of mannitol in the presented studies. On the basis of this and the fact that mannitol is an approved pharmaceutical excipient, there are no concerns over carcinogenicity. Furthermore, there were no proliferative lesions seen in the inhalation studies conducted on behalf of the applicant and there is no reason to assume that mannitol will be carcinogenic by the inhalation route.

Reproduction Toxicity

Literature data on the reproductive toxicity of mannitol have been adduced to demonstrate the absence of effects on fertility, embryo-foetal development and pre- and post-natal development. While the data were derived from different dosing routes and the study designs were not in accordance with current guidelines, nonetheless, the data indicate that there is no serious risk to reproduction associated with mannitol. In some investigations, mannitol even had been used as a negative control because of its lack of teratogenicity. It is also accepted as an excipient for use by the intravenous route. The available data do not preclude the use of inhaled mannitol during pregnancy.

[5] Lina BAR, Woutersen RA, Bruijntjes JP, van Benthem J, van der Berg JAH, Monbaliu J, Thoolen BJJM, Beems RB, van Kreijl CF. Evaluation of the Xpadeficient transgenic mouse model for short-term carcinogenicity testing: 9-month studies with haloperidol, reserpine, phenacetin, and D-mannitol. Toxicology Pathology, 2004;32:192-201.
[6] Carcinogenesis Bioassay of D-Mannitol (CAS No. 69-65-8) in F344/N Rate and B6C3F1 Mice (Feed Study); U.S. Dept of Health and Human Services; September 1982.
[7] Iatropoulos MJ, Jeffrey AM, Schluter G, Enzmann HG, Williams GM. Bioassay of mannitol and caprolactam and assessment of response to diethylnitrosamine in heterozygous p53-deficent (+/-) and wild type (+/+) mice. Archives of Toxicology, 2001;75: 52-58.
[8] Brunnemann KD, Enzmann HG, Perrone CE, Iatroulos MJ, Williams GM. In ovo carcinogenicity assay (IOCA): evaluation of mannitol, caprolactam and nitrosoproline. Archives of Toxicology, 2002;76:606-612.

Toxicokinetic data

Table 1. Studies providing toxicokinetic data

Test System	Study Duration	Group (Dose, mg/kg/day)	Samples collected	Study Number
Rat Crl:CD® (SD) IGS BR	7 day	Low (592-706)	BAL	Report No. 26482
		High (878-1347)		
Rat Crl:CD® (SD) IGS BR	13 weeks	Control	BAL	XIS 005/043185
		Low (124)		
		High (210)		
Beagle Dog	10 day		Serum, BAL	Report No. 25927
Beagle Dog	14 days	Control	Serum (Days 1 & 14), BAL (Day 14)	Report No. 26050
		Low (99)		
		Intermediate (251)		
		High (789)		
Beagle Dog	26 weeks	Control	Serum, BAL (Week 27)	Report No. 26966
		Low (171)		
		High (713)		

Analytical methods for the quantification of mannitol in dog serum and BAL fluid were developed and validated satisfactorily.

An issue of potential contamination of some pre-trial and control toxicokinetics samples in the 2-week dog study was identified. Even though no clear explanation for this finding was identified, based on consistency of results it is accepted that it is possible to draw valid conclusions from the study. It is also accepted that it is unlikely that an explanation can be provided for this finding.

BAL samples were obtained for the rat investigative study for 3 animals per sex per group. BAL analysis indicated that concentrations were in the range 12600-60100 ng mannitol/mL for the low-dose (592-706 mg/kg/day) group and 10400-58900 ng mannitol/mL for the high-dose (878-1347 mg/kg/day) group. There was large variability noted in mannitol levels between animals from both groups, but animals had clearly been exposed to mannitol.

In the 13-week repeat-dose study in rats, BAL was performed on satellite animals on day 1 and during weeks 7 and 13 and the resulting fluid assayed for mannitol content. The applicant reports that the data showed clear and dose-dependent levels of mannitol in the BAL fluid and thus provides "proof of exposure" for the study.

Toxicokinetic analysis was performed in the investigative study in dogs on 3 sampling occasions (days 1, 2 and 5). Serum concentration levels demonstrated a dose-related increase with maximum levels being reached within 0.5-1 hour post-dose. Pre-dose samples taken on days 2 and 5 of study indicated that there were very low residual levels of mannitol present.

Bioanalysis investigations on day 1 and during weeks 13 and 26 of 26-week repeat-dose study in dogs revealed that all low- and high-dose group animals had been exposed to mannitol as evinced by the presence of test item in serum. The serum concentrations showed a dose-related increase with maximum mean concentrations of approximately 280,000 ng/ml being reached within 1 hour post dose for each daily dose session. There were no substantive gender differences in serum mannitol concentrations and there was no evidence of accumulation. Lung lavage data demonstrated there was a very low level of mannitol in the lungs 20-24 hours after the final exposure indicating rapid clearance

from the lungs. Overall, the toxicokinetic serum data clearly demonstrated good exposure of low- and high-dose animals to mannitol.

In the rat investigative study, BAL analysis indicated that concentrations were in the range 12600-60100 ng mannitol/mL for the low-dose (592-706 mg/kg/day) group and 10400-58900 ng mannitol/mL for the high-dose (878-1347 mg/kg/day) group. For the 13-week repeat-dose study in rats, the applicant reports that the data showed clear and dose-dependent levels of mannitol in the BAL fluid and thus provides "proof of exposure" for the study.

In the 2- and 26-week repeat-dose toxicity studies in dogs, it was noted that all dosed animals had been exposed to test item as evidenced by the presence of mannitol in serum and BAL washes. The serum concentrations detected showed a dose-related increase with maximum mean concentrations being reached within 1 hour post-dose for each of the two daily dosing sessions. Lung lavage data demonstrated that there was a very low level of mannitol in the lungs 20-24 hours after the final exposure, indicating rapid clearance from the lungs. The increases in Cmax and AUC values (0-t and 0-inf) for the high-dosed animals compared to intermediate-dosed animals were greater than the corresponding increase in dose (165 to 750 mg/kg/day) indicating saturation of elimination mechanisms and non-linear kinetics at doses above 165 mg/kg/day.

Local Tolerance

Local tolerance was investigated in a bovine corneal opacity and permeability assay and an eye irritation study in the rabbit, to cover the possibility of accidental delivery of the powder to the eyes.

In a bovine corneal opacity and permeability assay corneal opacity and permeability were assessed and the scores combined to give an in vitro score that was assessed against a positive control (imidazole) and a saline negative control group. Mannitol, as a 20%w/w solution, was classified as negative in this assay and thus considered not a potential eye irritant.

In an eye irritation study performed three New Zealand White strain rabbits were given a single ocular dose of 78 mg (0.1 ml) of mannitol and then observed for reactions to instillation during a period of four days. Initial instillation induced a slight pain response and a minimal response (injection of the conjunctival blood vessels) in all animals one hour after dosing. This sign persisted overnight in two rabbits but all rabbits reverted to normal within 48 hours. Mannitol was assessed as "not irritating to the eyes".

There was no evidence of local irritation in either the respiratory tract in the repeat-dose studies or in the bovine corneal assay and the eye irritation study in the rabbit.

Other toxicity studies

The identified impurities are primarily sorbitol, maltitol and isomaltitol, which all are approved sweeteners. The levels specified for impurities have been adequately justified and additional toxicity studies are not considered necessary.

Assessment for the potential for immunotoxicity was undertaken by the applicant and was based on the following studies: 26-week inhalation toxicity study in dogs with a 4-week recovery period and also in the 13-week rat study. The results of the flow cytometry examinations do not suggest any effects of treatment, nor were there any effects on the bone marrow that would indicate immunotoxicity. It is concluded that there is no need for additional, specialised studies.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, mannitol is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The applicant's use of published data is deemed adequate in this case to support the pharmacodynamic action of the product, which is considered to be via hydration of the pulmonary secretions. The data cited support the conclusion that mannitol appears to induce mucin secretion to a greater extent than saline solution with similar osmolarity, although this difference was not statistically significant. Mucus secretion is markedly stimulated in response to hyperosmolarity.

Published data on repeat-dose toxicity from rats, mice and monkeys did not show any toxicologically-relevant signs of toxicity associated with the systemic administration of mannitol.

The bridging programme of toxicity studies conducted by the applicant to supplement the previously available data on other dosing routes is in line with the CHMP advice and is considered acceptable to support a marketing authorisation. The study programme is considered adequate.

Mannitol by inhalation was generally well tolerated in rats for 13 weeks under a regimen of dosing at doses up to 210 mg/kg/day for 180 minutes daily and in dogs at doses up to 713 mg/kg/day for two 1-hour periods per day, although these were not no-effect doses.

In dogs, BAL cell count investigations at 26 weeks revealed an increase in absolute white cell counts for mannitol-treated animals but this did not persist into the recovery period. This finding is consistent with the observations made following the use of mannitol as a diagnostic agent and is not considered to represent a significant toxic risk. Coughing and enlarged local lymph nodes were found but did not persist during the recovery period.

Most findings could be related to the inhalation of a large particulate load and were generally reversible. There was no specific target-organ or delayed toxicity in either species.

There was an issue with what was judged to be contamination of some pretrial and control toxicokinetics samples in the 2-week dog study. There is no clear explanation for this finding but it is accepted that it is possible to draw valid conclusions from the study. It is also accepted that it is unlikely that a clear explanation can be provided for this finding.

Literature data on the reproductive toxicity of mannitol have been adduced to demonstrate its absence of effects on fertility, embryo-fetal development and pre- and post-natal development. While the data were derived from different dosing routes and the study designs were not in accordance with current guidelines, nonetheless, the data indicate that there is no risk to reproduction with mannitol. In some instances, mannitol had been used as a negative control because of its lack of teratogenicity. It is also accepted as an excipient for use by the intravenous route.

There are no issues in respect of local tolerance, genotoxicity or carcinogenicity.

2.3.7. Conclusion on the non-clinical aspects

The applicant has conducted an acceptable non-clinical bridging programme in line with the advice given by the CHMP in order to supplement the published data.

Pharmacodynamic action of the product is considered to be via hydration of the pulmonary secretions. Inhaled mannitol was generally well tolerated; most findings could be related to the inhalation of a large particulate load and were generally reversible. There was no specific target-organ or delayed toxicity of any concern in either species.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme of inhaled mannitol consisted or several studies, which include 5 phase I studies, 3 phase II studies and 2 phase III studies. Two additional phase III studies in another indication provide supplementary information.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The CHMP requested a GCP inspection of the pivotal clinical study DPM-CF-301. The GCP inspection was carried out at one investigator site in the United Kingdom (dates of inspection: 2nd March - 5th March 2010) and at one investigator site in Ireland (dates of inspection: 24th February – 26th February 2010). Overall, compliance with ICH GCP and European and National legislation was considered satisfactory at both sites and the data presented in the application appear to be acceptable. None of the inspection findings and observations were thought to have critical consequences for the overall reliability of data.

- Tabular overview of clinical studies

Study ID	Design	Study and Control Drugs	Study Objective	No. of Subjects	Study Population	Primary Endpoints
DPM-PK-101	Open-label, randomized, three way crossover, single doses	Mannitol 635 mg inhalation 500 mg orally 500 mg IV Single doses	PK Safety	18/18	18M, healthy 27 yrs (19 – 48) Healthy subjects	PK parameters Relative and absolute bioavailability
DPM-OSM-403	Open, observational, non-interventional study in patients with CF	Inhaler containing empty capsule Single measurement	Inspiratory flow rates Safety	26/25	10M / 15F 16 yrs (6 – 37) CF patients FEV_1 57.6% predicted (30% - 89 %)	Inspiratory flow rates (PIF, MIF_{25}, MIF_{50}, MIF_{75}, FIF_{25-75}

Study ID	Design	Study and Control Drugs	Study Objective	No. of Subjects	Study Population	Primary Endpoints
DPM-OSM-401	Open, observational, non-interventional study	LR DPI containing empty capsule Single measurement	Inspiratory flow rates Safety	34/34	22M / 12F 21 yrs (7 – 65) Healthy subject and asthmatics FEV_1 87.9% predicted (67% - 123 %)	Inspiratory flow rates (PIF, MIF_{25}, MIF_{50}, MIF_{75}, FIF_{25-75}
DPM-OSM-402	Open, observational, non-interventional study	LR DPI containing empty capsule RS01 DPI containing empty capsule Single measurement	Inspiratory flow rates Safety	17/17	2M / 15F 60 yrs (22 – 72) Bronchiectasis FEV_1 78.1% predicted (52% - 114%)	Inspiratory flow rates (PIF, MIF_{25}, MIF_{50}, MIF_{75}, FIF_{25-75}
DPM-PK-102 Completed; Full	Open-label, single and multiple dose	mannitol: 400 mg single dose inhalation 400 mg b.i.d. for 7 days inhalation 7 days	PK Safety	9/9	5M / 4F 6 adults, 3M /3F 24 yrs (18 – 32) 3 adolescents, 2M / 1F 15 yrs (12 – 17) CF patients >6 yrs of age FEV_1 30% - 90% of predicted	Comparison of PK parameters after single and multiple dosing
DPM-CF-201 Completed; Full	Randomised, double-blind, placebo-controlled, cross-over.	DPI mannitol 420 mg, b.i.d. Crystalline mannitol 420 mg b.i.d. 2 weeks each treatment	Efficacy and Safety	39/36	16M / 23 F 19 (8 – 48) CF patients ≥8 yrs of age FEV_1 40% - 80% of predicted	Change in FEV_1 at 2 weeks for each treatment
DPM-CF-202 Completed; Full	Randomised, multicentre, open-label, cross-over dose response.	DPI mannitol 40, 120, 240 and 400 mg b.i.d. 2 weeks each treatment	Efficacy and Safety	48/48	26M / 22F 19 (7 – 68) CF patients ≥7 yrs of age FEV_1 40% - 90% of predicted	Change in FEV_1 and FVC at 2 weeks for each treatment Dose response
DPM-CF-203 Completed; Full	Open label, randomised, cross-over, comparative	DPI mannitol 400 mg b.i.d. rhDNase 2.5 mg daily DPI mannitol 400 mg b.i.d. + rhDNase 2.5 mg daily 12 weeks each treatment	Efficacy and Safety	48/26	9M / 17F 12.8 (9 – 17) CF patients 8-19 yrs of age FEV_1 <70% of predicted On rhDNase or eligible for rhDNase	Change in FEV_1 at 12 weeks for each treatment

Study ID	Design	Study and Control Drugs	Study Objective	No. of Subjects	Study Population	Primary Endpoints
DPM-CF-301 Completed; double-blind; Full	Double blind, randomised, controlled followed by open label (OLE)	DPI mannitol 400 mg b.i.d. DPI mannitol 50 mg b.i.d. 26 weeks double blind followed by 26 weeks open-label	Efficacy and Safety	324/295	132F / 163M 23 yrs (6 – 56) CF patients >6 years FEV_1 >30% and <90% predicted	Change in absolute FEV_1 over 26 weeks for each treatment
DPM-CF-302 Completed; double-blind; Full	Double blind, randomised, controlled followed by open label (OLE)	DPI mannitol 400 mg b.i.d. DPI mannitol 50 mg b.i.d. 26 weeks double blind followed by 26 weeks open-label	Efficacy and Safety	318/305	148F / 157M 17.5 yrs (6 – 53) CF patients >6 years FEV_1 >40% and <90% predicted	Change in absolute FEV_1 over 26 weeks for each treatment Effect of mannitol compared to control on FEV_1 in patients on existing RhDNase treatment Safety at 26 and 52 weeks
DPM-B-201 and 202 Completed; Full, combined	Randomised, double-blind, placebo-controlled, cross-over.	DPI mannitol 400 mg b.i.d. Crystalline mannitol 400 mg b.i.d. 2 weeks each treatment.	Efficacy and Safety	76/60	41F / 19M 55 (16 – 71) Bronchiectasis >15 years FEV_1 ≥50% predicted	Changes in SGRQ and lung function Safety
DPM-B-301 Completed; Full	Double blind, randomised, placebo controlled, parallel followed by open label extension (OLE)	DPI mannitol 320 mg b.i.d. DPI mannitol 80 mg b.i.d. 12 weeks double blind followed by 40-56 weeks open-label	Efficacy and Safety	442/345 OLE – 123/99	224F / 119M 61.5 (18 – 79) Non-CF bronchiectasis aged 15 to 80 years FEV_1 ≥50% predicted	Effect of treatment on QoL and mucus clearance

*Bronchiectasis clinical trials DPM-B-201, 202 and 301 provide only safety data relevant for this MAA.

2.4.2. Pharmacokinetics

Mannitol is a known substance, since it has been used for decades as a pharmaceutical excipient and therapeutic agent, both orally and intravenously. It has been approved also as a diagnostic pharmaceutical product for the inhalation route. This data are sufficient for not conducting full formal PK characterisation of the compound.

The applicant has submitted two studies which generated pharmacokinetic data regarding the use of inhaled mannitol relevant to its use in cystic fibrosis. These studies, DPM-PK-101 (in healthy volunteers) and DPM-PK-102 (in patients with cystic fibrosis) used inhaled mannitol in doses representative of those proposed for use in the clinical setting.

Study DPM-PK-101, a PK and bioavailability study of mannitol in healthy subjects, had an open-label, randomised, three-way crossover design, in which each subject received mannitol powder as inhalation, orally and intravenously. All subjects were screened by receiving 635 mg mannitol powder

for inhalation (maximum dose administered clinically during the course of a negative challenge test) as the mannitol challenge and subjects who had a negative test result and satisfied all other eligibility criteria were assigned to receive the three study treatments in random order. There was a minimum 7 day wash-out period between Screening and Visit 1, and between study drug administrations. Blood samples for the determination of mannitol in serum were started at 12 hours before treatment. Samples were collected at -12 and -0.5 hr pre-dose and at 5, 10, 20, 30 minutes and 1, 2, 3, 4, 8, 12 and 24 hours post-dose. The trial population consisted of healthy male volunteers, 18-65 years of age with no history of asthma or other chronic diseases which could compromise the airways or gut absorption. According to the protocol 18 subjects would enter the study to allow 15 subjects to complete treatment. No subjects withdrew from the trial during the treatment period. The data from all subjects were analysed for pharmacokinetics and safety.

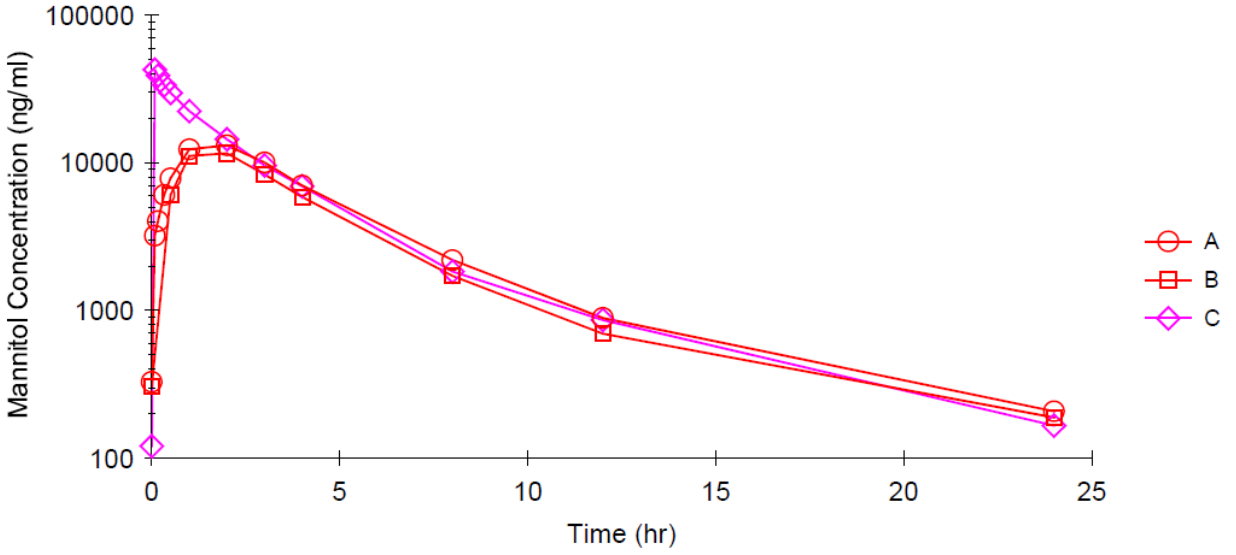
Study DPM-PK-101 results, presented below, showed only relatively minor differences in dose-normalised pharmacokinetic characteristics of a 635 mg inhaled, a 500 mg oral and 500 mg intravenous dose of mannitol.

Table 2. Summary of PK results, study DPM-PK-101

	Tmax (hr)	Cmax (ng/ml)	$t_{1/2}$ (hr)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng/hr.ml)	BAV	CL (ml/hr)	CL_R (ml/hr)	V_D (L)
Inhalation									
Mean	1.5	10792*	4.7	56265*	57599*	0.591			
S.D	0.5	2638	1.0	12586	12717	0.146			
Oral									
Mean	1.4	13094	5.2	59776	61414	0.625			
S.D	0.5	3085	1.1	13596	14059	0.142			
Intravenous									
Mean	0.11	44322	4.5	98719	100236	1.000	5099	4439	34.3
S.D	0.04	8775	1.1	21735	21561		989	1143	13.8

*values were dose-normalised to 500 mg dose

Table 3. Mean mannitol concentration (A – inhalation 635 mg, B – oral route 500 mg, C – intravenous 500 mg), study DPM-PK-101



Study DPM-PK-102, a PK study of inhaled mannitol after single and multiple dosing in CF patients, was a multiple-centre, open-label study, in which adult and paediatric cystic fibrosis patients received

mannitol powder for inhalation using a dry powder inhaler. Initially, as a part of the screening process, all patients were to receive 400 mg mannitol powder for inhalation as the Mannitol Tolerance Test (MTT). Patients who had a negative test result for airway hyperresponsiveness and satisfied all other eligibility criteria were entered into the study to receive the study treatment. The treatment phase of the study lasted for 7 days. A single dose of 400 mg of inhaled mannitol was administered on the morning of Day 1 and then twice daily from Day 2 to 6 and the last multiple dose on the morning of Day 7. 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, while additional PK samples were taken on the mornings of Days 2 and 8 (24 hours post-dose). The trial population consisted of adult (18+ years) and adolescent (12-17 years) cystic fibrosis patients. 18 patients (6 adult, 6 adolescent and 6 paediatric) were planned, while 9 (6 adults, 3 adolescents) were actually dosed and analysed.

Study DPM-PK-102 results, presented below, showed that pharmacokinetic characteristics of a single dose of inhaled mannitol in cystic fibrosis patients did not show significant differences from healthy volunteers, although the applied dose was lower (635 mg in healthy volunteers and 400 mg in cystic fibrosis patients). The pharmacokinetic properties in adults and adolescents were comparable.

Table 4. Mean (SD) serum PK parameters, study DPM-PK-102

Age group/Dose Day		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-12h} (hr*ng/mL)	Kel (1/hr)	$AUC_{0-infinity}$ (hr*ng/mL)	$t_{½}$ (hr)
Adult (n=6)	Day 1	7670 (1175)	2.42 (1.07)	41844 (4935)	0.116 (0.02)	50445 (9498)	6.10 (1.15)
	Day 7	9260 (2718)	1.37 (0.30)	50248 (13597)	0.129 (0.013)	59687 (11315)	5.42 (0.59)
Adolescents (n=3)	Day 1	8017 (2967)	1.84 (1.05)	38417 (6694)	0.098 (0.020)	48305 (5758)	7.29 (1.65)
	Day 7	7667 (2021)	1.83 (0.29)	45896 (8681)	0.106 (0.003)	57205 (9778)	6.52 (0.18)

Absorption

The systemic exposure to mannitol with the inhaled powder was investigated in healthy volunteers as well as in patients with cystic fibrosis. The absorbed fraction after inhalation (approximately 50-60 %) in healthy volunteers is comparable to that observed with the oral route.

Based on the available data, no unexpected accumulation has been observed in cystic fibrosis patients.

Distribution

Since the low level of accumulation noted in the DPM-PK-102 is not significant, and there is no other evidence of accumulation in the body, distribution of inhaled mannitol was not specifically investigated in human PK studies. From literature data, oral mannitol distributes almost entirely in the extracellular fluid.

Elimination

Since the low level of accumulation noted in the DPM-PK-102 is not significant, and there is no other evidence of accumulation in the body, the metabolic pathway of inhaled mannitol was not specifically

investigated in human PK studies. From literature data, oral mannitol is mainly eliminated unchanged in the urine.

Dose proportionality and time dependencies

Different doses of mannitol have been investigated by the applicant in a Phase 2 trial (see Dose response study below).

Special populations

Very limited data are available in paediatric patients (3 adolescent subjects) and no investigation was carried out in younger children. Based on this data no sound conclusions can be drawn on the pharmacokinetics in the paediatric population.

Pharmacokinetic interaction studies

PK interaction studies have not been performed by the applicant, justified by the nature and endogenous presence of mannitol.

Pharmacokinetics using human biomaterials

Studies using human biomaterials have not been performed since they are deemed not relevant to the formulation.

2.4.3. Pharmacodynamics

Pharmacodynamic properties have been addressed with references to published literature.

Mechanism of action

Inhaled mannitol has two mechanisms of action that are particularly relevant to this application – as a hyperosmolar agent creating a osmotic gradient in the airways and as an agent which can induce bronchospasm.

Mannitol's intended mechanism of action is related to its potential as a hyperosmolar agent to create an osmotic gradient in airways that facilitates an efflux of water into the airway lumen. This efflux of water is thought to increase the water content in the ASL, and thus decrease viscosity of sputum to promote the clearance of the mucus by cilia.

Induction of bronchospasm is the opposite pharmacodynamic effect to that intended for patients with CF (an increase in FEV_1). Published data indicate that inhaled mannitol increases the osmolarity in the airways which results in a release of different bronchoconstriction mediators from inflammatory cells within the airways.

Inhaled mannitol is licensed in the EU to identify bronchial responsiveness in subjects with a baseline FEV_1 of >70% predicted. Ascending doses are given from 5 mg up to a maximum cumulative dose of 635 mg. To circumvent the difficulty of bronchospasm induction, patients with asthma are excluded from the requested indication and patients are required to undergo an initial challenge with inhaled mannitol with close supervision of airway function. Before treating with mannitol, patients are also pre-medicated with an inhaled beta agonist. Despite excluding patients with a history of asthma and pre-

medicating with an inhaled beta agonist, one published trial in CF found that 6 of 49 subjects still had a fall in FEV_1 of >15% (mean 17%) with a mean provocative dose of mannitol of 270 mg[9].

Primary and secondary pharmacology

Results of a published study[10] showed that neither mannitol nor hypertonic saline (HS), combined with coughing, improved bronchial mucus clearance during intervention period, but after 90 minutes the total clearance was significantly higher for both mannitol and HS compared to control treatments. The mean clearance at the end of the study (i.e. 120 minutes) was 28% and 19% for the mannitol and empty capsule plus coughing, respectively ($p < 0.01$). The mean clearance was 31% and 21% for HS and physiological saline plus coughing, respectively ($p < 0.01$). The authors concluded that dry powder mannitol is a potential mucoactive agent in CF patients.

2.4.4. Discussion on clinical pharmacology

The two studies presented in this submission show that inhaled mannitol presents very similar pharmacokinetic properties to those seen with a similar oral dose and intravenous delivery systems. No significant differences were seen in healthy volunteers. Of importance the second study establishes that at the proposed dose of circa 400 mg cystic fibrosis patients present similar PK characteristics seen with healthy volunteers.

Published data indicate that inhaled mannitol increases the osmolarity in the airways which results in a release of different bronchoconstriction mediators from inflammatory cells within the airways. Therefore, a mannitol tolerance test (MTT) is required to exclude patients with bronchial hyperreactivity from the treatment with inhaled mannitol. This requirement is stated as a prerequisite measure in the SPC proposed by the applicant. A positive test to mannitol is stated as a contraindication of the product. The MTT criteria proposed in the SPC of Inhaled mannitol are in accordance with the MTT criteria adopted for currently approved inhaled mannitol for diagnostic use i.e. threshold of fall in FEV_1 i.e. $\geq$ 20% from baseline for considering the MTT as positive. This corresponds to the criteria applied in Phase 3 studies. Of note, a fall of 20% in FEV_1 is considerably greater than the mean benefit in FEV_1 as demonstrated in the Phase 3 trials.

Hyper-responsiveness was not controlled further during the course of the clinical studies that were submitted and several patients withdrew with symptoms that might have been induced by mannitol. It is not clear if the timing of the pre-medication with an inhaled beta agonist adequately reversed the bronchoconstrictor effect of mannitol over the whole treatment course. Thus mannitol induced bronchoconstriction may have been more marked than at the time of spirometry. Whether long term treatment with mannitol would have any impact on bronchial reactivity in cystic fibrosis patients is not documented. Such a survey should be part of the safety assessment for the chronic use of inhaled mannitol.

In the clinical studies submitted by the applicant, the rate of positive mannitol tolerance test at screening varied from 8 % to 30 % of the recruited patients. Patients with severe illness were excluded and were not tested. It is foreseen that in clinical practice mannitol treatment would be contraindicated in a significant proportion of patients. Patients who showed less than a 20% fall in FEV_1 on screening may show a greater fall in FEV_1 during an exacerbation and this possibility has not been investigated. Adverse events during the trial and during 12 month's open label use suggest that symptoms

[9] Jaques, A., E. Daviskas, et al. (2008). "Inhaled mannitol improves lung function in cystic fibrosis." Chest 133(6): 1388-96.
[10] Robinson, M., E. Daviskas, et al. (1999). "The effect of inhaled mannitol on bronchial mucus clearance in cystic fibrosis patients: a pilot study." Eur Respir J 14(3): 678-685.

attributable to pharyngeal and bronchial irritation may be common. It is possible that the thorough pre-treatment bronchoprovocation screening and pre-medication with a bronchodilator might not be carried out as thoroughly in clinical practice as they were in the clinical trial.

The applicant has claimed a sustained effect compared to hypertonic saline, but this claim is not supported with adequate data.

2.4.5. Conclusions on clinical pharmacology

PK characteristics of inhaled mannitol in CF patients are in line with PK characteristics in healthy volunteers and other routes of administration (oral and intravenous).

References to published literature justify the absence of pharmacodynamic studies with inhaled mannitol.

The impact of long term treatment with mannitol on bronchial hyperresponsiveness is not documented in the dossier and therefore remains unclear. This is especially important for clinical practice, where pre-treatment bronchoprovocation screening and pre-medication with a bronchodilator might not be carried out as thoroughly as in clinical trials.

2.5. Clinical efficacy

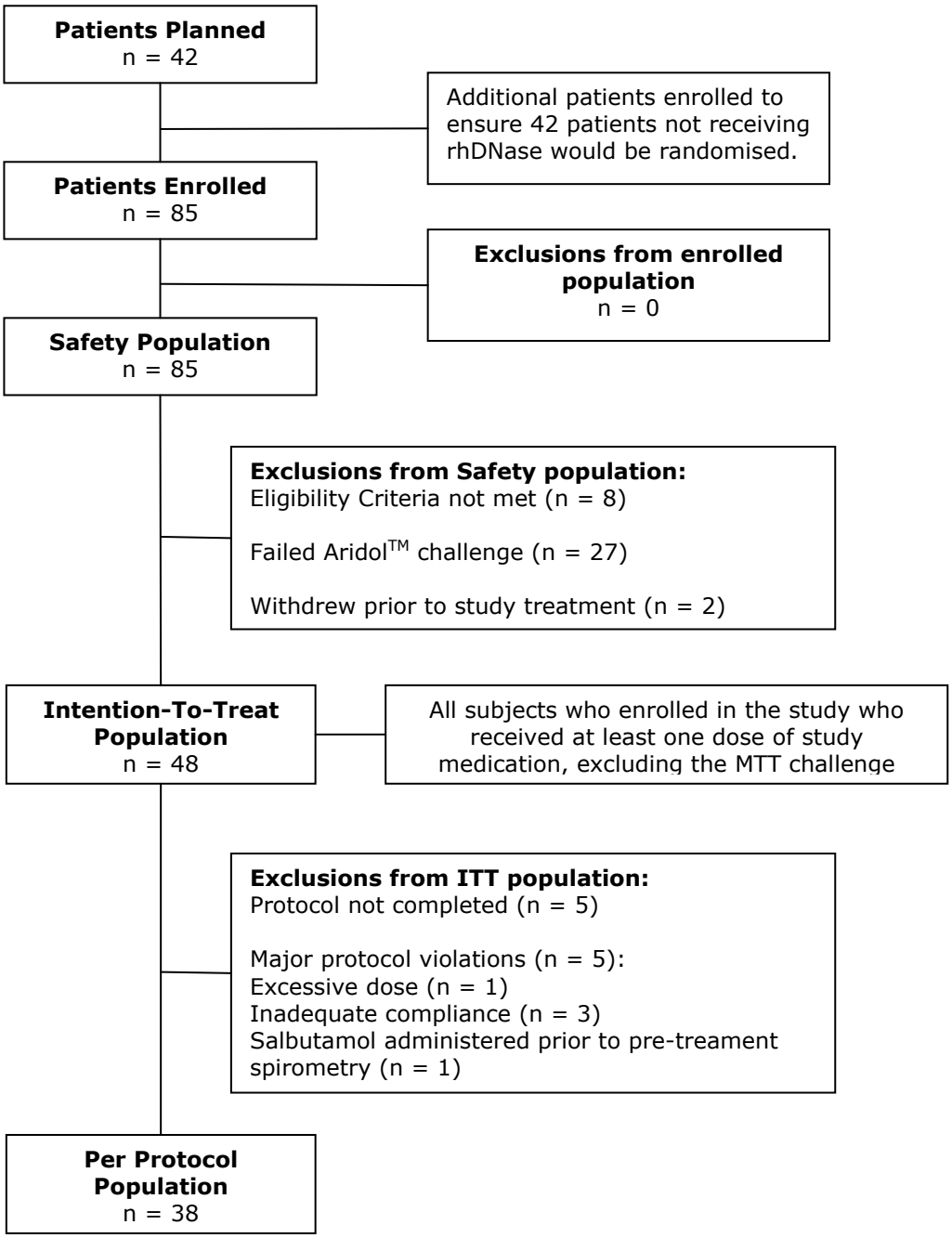
The main studies for clinical efficacy evaluation are a dose response phase II study DPM-CF-202, a phase II study in children DPM-CF-203, a phase II study DPM-CF-201 and the pivotal phase III studies DPM-CF-301 and DPM-CF-302.

2.5.1. Dose response study

Study DPM-CF-202: A Phase IIa Randomised, Open Label, Dose Response Study to Determine the Optimum Dose of Dry Powder Mannitol Required to Generate Clinical Improvement in Patients with Cystic Fibrosis

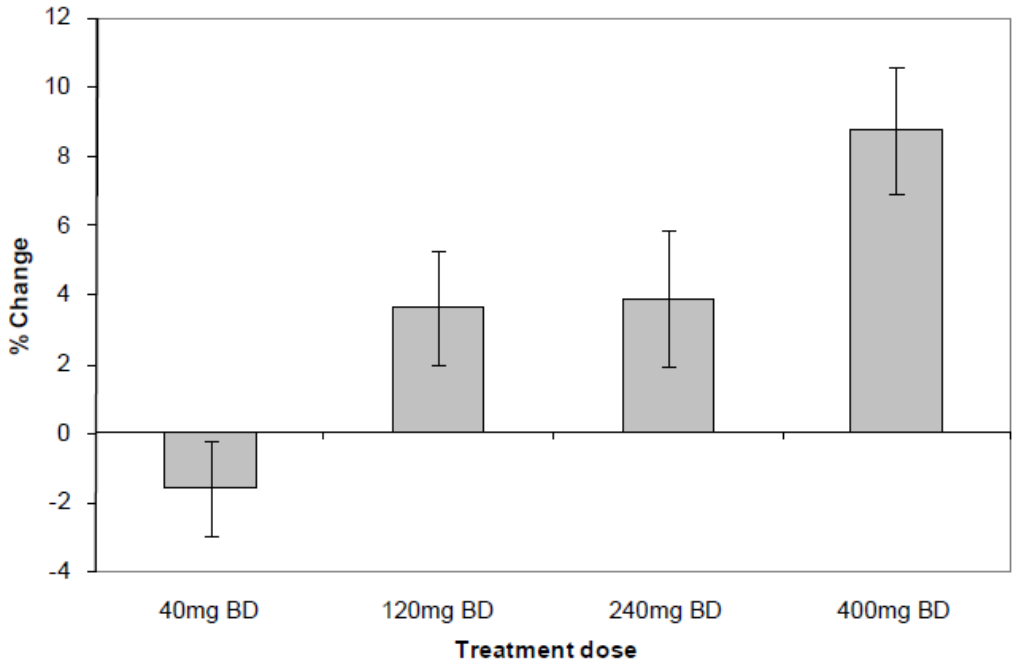
This was a phase IIa, randomised open label, dose response, cross-over, multicenter study in which 48 cystic fibrosis patients (ITT population) received 4 doses of inhaled mannitol: 40 mg (1 x 40 mg capsule), 120 mg (3 x 40 mg capsules), 240 mg (6 x 40 mg capsules) and 400 mg (10 x 40 mg capsules) twice daily via a dry powder inhaler device for 2 weeks in a random order. Patients in the ITT population were aged from 6 to 68 years including 19 adults (older than 18 years) and 29 children/adolescents (6 to 11 years: n = 18; 12 to 17 years: n = 11). The study objective was to determine the dose of dry powder Mannitol required to generate clinical improvement in FEV_1 in subjects with cystic fibrosis. Duration of the study was 13 weeks, including four treatment periods of two weeks with one week washout.

Figure 1. Subject disposition in study DPM-CF-202



Results from the study are presented below.

Figure 2. Percent change in FEV_1 by dose arm, study DPM-CF-202, ITT population



A clear dose effect between 40 mg to 400 mg was observed in this study as well as a dose dependent improvement in lung function as measured by absolute FEV_1 value and FVC. The 400 mg dose was the most efficacious whereas the 40 mg dose did not demonstrate any efficacy. The 120 mg and 240 mg doses showed some efficacy, however, the effect was smaller than that of 400 mg. It cannot be established whether the 400 mg dose reached the plateau effect as no higher doses were tested. There were few differences between the doses in other spirometric measurements evaluated (FEF 25-75 and PEF).

2.5.2. Main studies

Study DPM-CF-301: Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study

Methods

This was a multicenter, 26 week double blind, randomised, 2 parallel groups, controlled, trial to compare inhaled mannitol 400 mg twice daily to a control group receiving inhaled mannitol in a "subtherapeutic" dose of 50 mg twice daily.

Study Participants

This study included patients from 6 years of age with mild to moderate cystic fibrosis but excluded severe conditions and advanced stage of the disease. Subjects needed to have FEV_1 >30 and <90% predicted and to pass the mannitol tolerance test to enter the study. Pregnant, breast-feeding and intolerant to mannitol or beta-agonists subjects and subjects with concomitant use of beta blockers or hypertonic saline were excluded.

Treatments

Patients in the active group received 400 mg (10 x 40 mg capsule) of mannitol twice daily, and in the control group 50 mg (10 x 5 mg capsules) of mannitol twice daily. Patients received the therapy for 26 weeks via CE marked DPI Type RS01 Model 7 HR.

RhDNase use was permitted and the randomisation was stratified on rhDNase status at baseline (rhDNase user or rhDNase non users). If rhDNase use was initiated or ceased during the course of the study, the stratum was not adjusted.

Objectives

The study was aimed at investigating the efficacy and safety of inhaled mannitol for treatment of CF.

Outcomes/endpoints

The primary endpoint was the change in absolute FEV_1 over 26 weeks of therapy.

Secondary Efficacy endpoints were:

- Change from baseline in absolute FEV_1 by rhDNase treatment over 26 weeks
- Responders at week 26 on the basis of a 100 ml or >5% change in FEV_1 or total cohort and by rhDNase use
- Pulmonary exacerbations – protocol defined and all exacerbations for total cohort and by rhDNase use
- Hospital admissions – protocol defined and all pulmonary exacerbations
- Quality of Life Scores using Cystic Fibrosis Questionnaire- R for total cohort and by rhDNase use
- Responders at week 26 on the basis of a change in QoL which is ≥ 5 points for total cohort and by rhDNase use; Rescue antibiotics use (number of agents, course and days of use)
- Change from baseline in FVC, FEF25-75 over 26 weeks overall and by rhDNase use
- Days in hospital due to pulmonary exacerbations – protocol defined and all exacerbations

A protocol defined pulmonary exacerbation (PDPE) was any exacerbation treated with IV antibiotics and associated with at least four of the following signs and symptoms: change in sputum production (volume, colour, consistency), dyspnoea, new or increased haemoptysis, malaise fatigue or lethargy, fever >38 degrees Celsius, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, FVC or FEV_1 decreased by >10% from previous recorded value, radiographic signs indicative of pulmonary infection, increased cough, changes in physical examination of the chest.

A pulmonary exacerbation (PE) did not have to meet the aforementioned additional criteria.

Sample size

340 subjects were intended to be randomised to treatment. Approximately two thirds of these subjects were expected to be using rhDNase and approximately 20% of subjects were forecasted to withdraw prior to week 26. Therefore, approximately 163 evaluable subjects were estimated to complete the mannitol treatment and 109 evaluable subjects in the control treatment. It was estimated that of these evaluable subjects, approximately 109 subjects in the mannitol group and 73

subjects in the control group would be taking concurrent rhDNase. The study was powered to detect a FEV_1 change of 70 mL from baseline in the ITT population at week 26.

Randomisation

Randomisation was to be applied to subjects who passed the mannitol tolerance test in a ratio of 3:2 (mannitol 400mg BD: control). The randomisation was stratified by rhDNase use and region (Europe vs. Australia) but not by sites, age or severity of the disease. 250 randomisation numbers (150 mannitol and 100 control) were generated for each stratum, in blocks of 5. The randomisation number was assigned sequentially within each stratum.

Blinding (masking)

The investigators, site staff, pharmacists, subjects, monitors, project managers and data managers were blinded throughout the study. Both active and control treatments consisted of ten identical capsules. The use of opaque capsules was aimed at masking the difference in the capsule fill volume.

Statistical methods

For change in FEV_1 an analysis of this endpoint at Visit 2/Week 6, Visit 3/Week 14 and Visit 4/Week 26 was conducted using a mixed model repeated measures (MMRM) approach. The following main effect terms were specified in the applied model: treatment group, visit week, gender, rhDNase user status at screening, region of participation, baseline FEV_1, baseline percent predicted FEV_1, and age.

An AR(1) covariance structure was used. For each study visit, the difference between treatments was determined as the difference in least squares means for mannitol – control and was presented with 95% confidence limits. Overall, the statistical significance of the difference was estimated using the P-value for the term for treatment in the model.

A further model was fitted with a term for treatment-by-time interaction to obtain least square means (with 95% confidence limits) for each treatment group for each timepoint. The analyses described above were repeated by rhDNase use (using a three way interaction model for time-by-treatment-by-rhDNase use). Data summaries are also provided for the paediatric/adolescent population but no analyses were undertaken.

No imputation for missing data was planned. Analysis of the primary efficacy variable was conducted using a mixed model (within SAS PROC Mixed) where all available data are used. The applicant states that missing values are not problematic, provided the data are missing at random. The only missing data for FEV_1 was due to premature withdrawal of subjects. A Kaplan Meier plot was produced to explore the pattern of withdrawal.

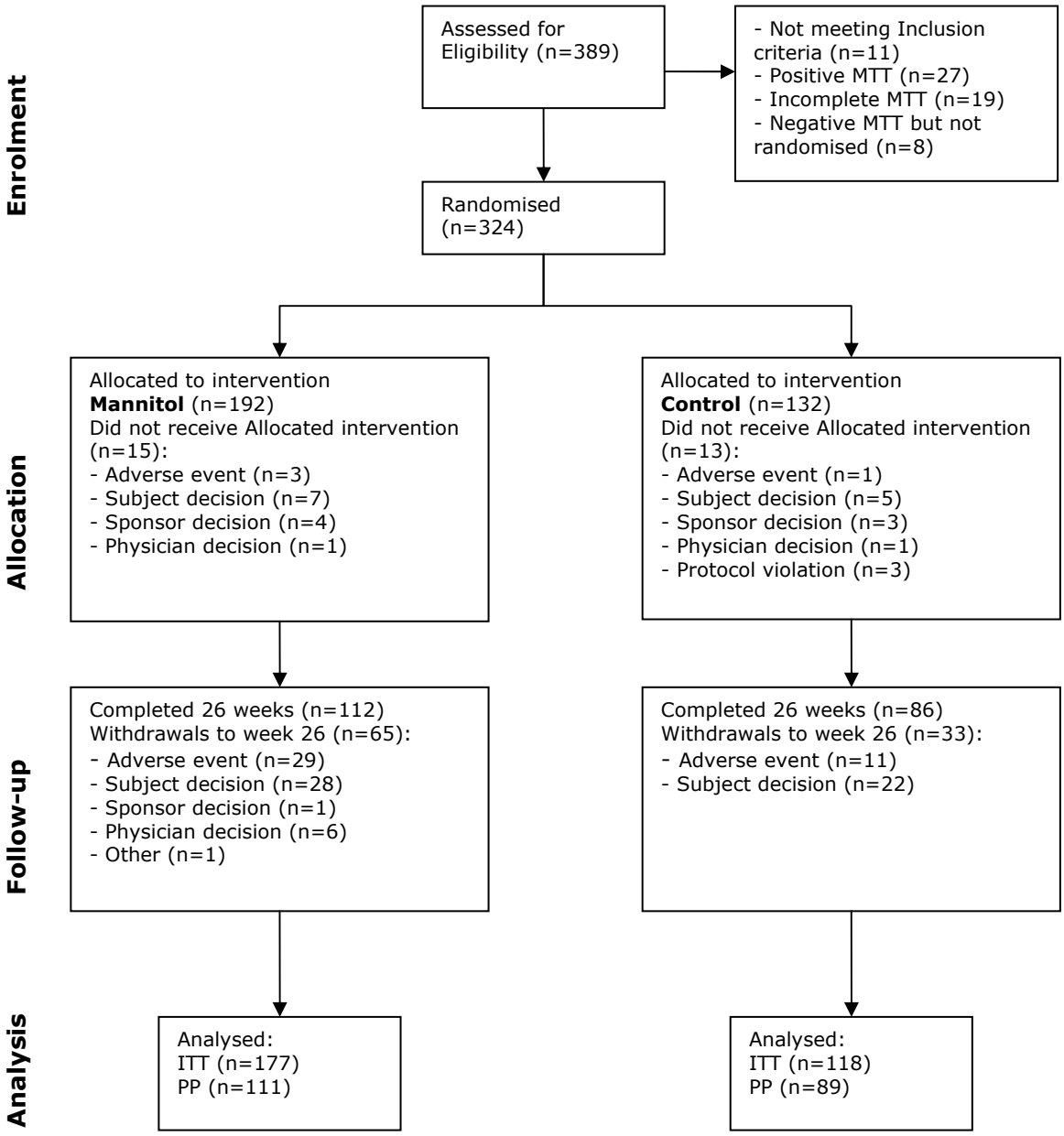
For the key secondary endpoints apart from FEV_1, namely pulmonary exacerbations and antibiotic use, the time in the study was incorporated in the analysis through the use of a negative binomial model with exposure time as an offset variable. Hence no imputation for missing data was considered to be required.

ITT population was defined as those subjects randomised who had completed study visit 1 at week 0, i.e. received at least one dose of study medication.

Results

Participant flow

Figure 3. Disposition of subjects in study DPM-CF-301



Recruitment

324 patients were randomised in ratio 3:2. 192 were allocated to mannitol 400 mg BD and 132 were allocated to control mannitol 50 mg BD.

Conduct of the study

The study was conducted from 5 April 2007 to 24 April 2009 in 40 study sites in UK, Australia, Ireland and New Zealand.

2 amendments to study protocol were made prior to study initiation and included administrative changes and changes recommended during scientific advice/protocol assistance (adding MTT test, removing 200 mg group, introducing stratification by rhDNase use, defining PDPE criteria and removing CRP analysis and chest X-ray). There have been 2 amendments to Study Protocol during the study, increasing number of participants, introducing interim safety evaluation, administrative changes and open-label extension phase.

Baseline data

The baseline data of subjects in ITT population is presented below.

Table 5. Demographic Characteristics of ITT Population, study DPM-CF-301

Intent-To-Treat Population Characteristic	Mannitol (N=177)	Control (N=118)	Total (N=295)
Age (Years)			
mean (SD)	23.1 (11.66)	22.8 (10.75)	23.0 (11.29)
median (min , max)	21.0 (6,56)	22.0 (6,48)	21.0 (6,56)
Age group			
6-11	31 (17.5%)	17 (14.4%)	48 (16.3%)
12-17	32 (18.1%)	25 (21.2%)	57 (19.3%)
6-17	63 (35.6%)	42 (35.6%)	105 (35.6%)
>=18	114 (64.4%)	76 (64.4%)	190 (64.4%)
Age at CF diagnosis (years)			
mean (SD)	3.4 (8.90)	2.4 (6.67)	3.0 (8.09)
Female	71 (40.1%)	61 (51.7%)	132 (44.7%)
Race			
Caucasian	169 (95.5%)	115 (97.5%)	284 (96.3%)
East/South East Asian	0 (0.0%)	1 (0.8%)	1 (0.3%)
West Asian	3 (1.7%)	1 (0.8%)	4 (1.4%)
Indigenous	1 (0.6%)	0 (0.0%)	1 (0.3%)
Other	4 (2.3%)	1 (0.8%)	5 (1.7%)
Body mass index (BMI) (kg/m^2)			
mean (SD)	21.07 (3.990)	20.38 (3.591)	20.80 (3.844)
median (min , max)	20.90 (13.3,37.3)	20.00 (13.6,30.7)	20.40 (13.3,37.3)
FEV_1 (L)[1]	N=176	N=118	N=295
mean (SD)	2.067 (0.8176)	1.952 (0.6911)	2.021 (0.7702)
median (min , max)	1.955 (0.71,4.92)	1.820 (0.78,3.75)	1.885 (0.71,4.92)
FEV_1 (%) predicted[1]	N=176	N=118	N=295
mean (SD)	62.4 (16.45)	61.4 (16.13)	62.0 (16.30)
median (min , max)	62.6 (26, 93)	63.1 (30, 94)	62.7 (26, 94)

Percentages are based on the number of subjects in the ITT population.
[1] *FEV_1 is the best value taken at week 0 (visit 1) pre-bronchodilator spirometry. FEV_1 % predicted is estimated from this value*

Numbers analysed

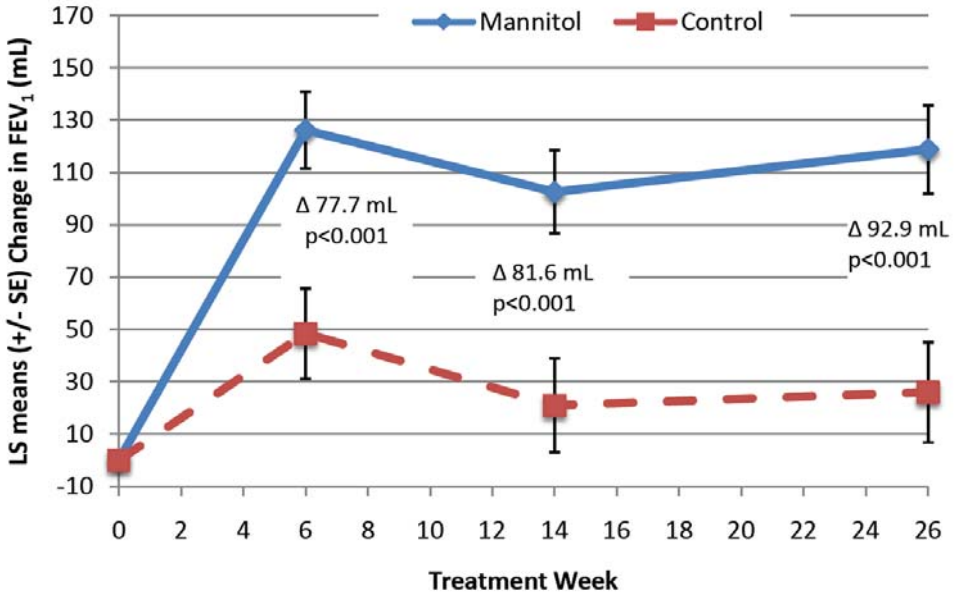
389 subjects were enrolled in the study and 324 of those were randomised. The ITT population consisted of 295 subjects (177 mannitol, 118 control) and the PP population – of 200 subjects (111 mannitol, 89 control).

Approximately a quarter of the patients on mannitol treatment (45 of 177, 25.4%) were excluded from the PP population because of failure to record both a baseline (Visit 1) lung function measurement or at least one measurement at a timepoint (Visits 2, 3 or 4) during treatment. For the control arm the percentage was considerably lower (15 of 118, 12.7%), although still relatively high.

Outcomes and estimation

The analysis submitted by the applicant showed a significant treatment effect at week 26 as change from baseline in absolute FEV_1: + 92.9 ml as compared to the control group (p<0.001).

Figure 4. Absolute Change in FEV_1 (mL) by Timepoint



The overall treatment effect over 26 weeks (defined primary efficacy endpoint) was 54.17 ml (95% CI: 24.73, 83.60) and was statistically significant (p<0.001).

When the analysis was performed in stratified subgroups defined by the rhDNase status at screening, the between groups difference in FEV_1 at week 26 was statistically significant in the so called rhDNase users strata (108 ml) but not in the so called rhDNase non users strata (69 ml). However, it appears that the mean change in absolute FEV_1 was higher in the strata of rhDNase non users as compared to the strata of rhDNase users.

Figure 5. rhDNase Users Change in FEV_1 by Timepoint

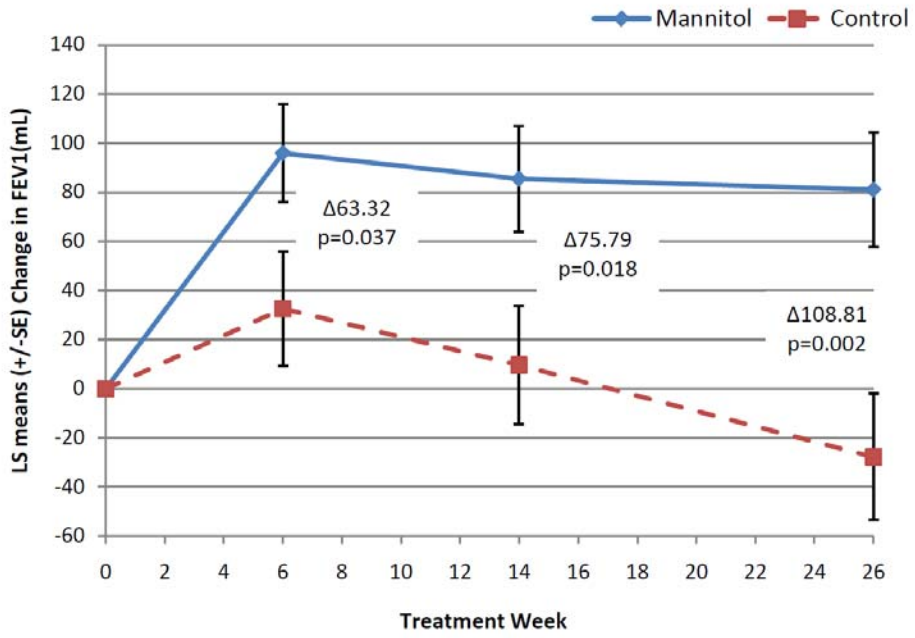
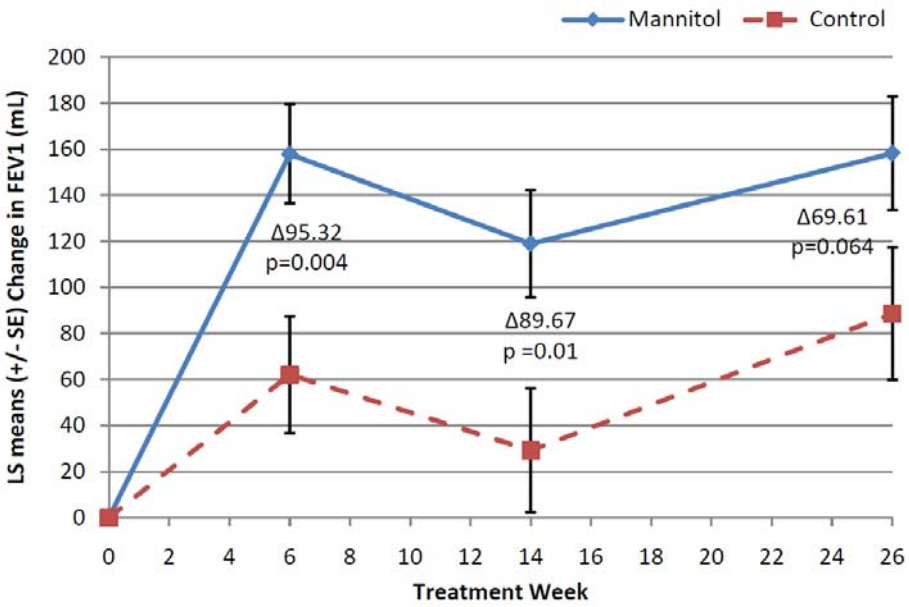


Figure 6. rhDNase Non-Users Change in FEV_1 by Timepoint



Similar patterns were seen in other spirometric parameters but the absolute change from baseline in FEF25-75 and PEF were not found to be significantly different between the 2 groups.

The secondary parameters associated with pulmonary exacerbation rate, hospitalisations, Quality of Life and use of systemic antibiotics did not show any significant differences between patients using rhDnase with mannitol or mannitol alone. However, trends were noted in favour of the patients receiving rhDNase and mannitol together as compared with mannitol alone.

Table 6. Summary Statistics for PDPE and PE, study CF-301

	Mannitol			Control		
	rhDNase used [N=96] n (%)	rhDNase not used [N=81] n (%)	Total [N=177] n (%)	rhDNase used [N=67] n (%)	rhDNase not used [N=51] n (%)	Total [N=118] n (%)
Incidence						
PE event	39 (40.6)	26 (32.1)	65 (36.7)	37(55.2)	23 (45.1)	60 (50.8)
PDPE event	22 (22.9)	10 (12.3)	32 (18.1)	21(31.3)	12 (23.5)	33 (28.0)
PE event rate *(per subject per year)*						
n	96	81	177	67	51	118
Mean (SD)	1.82(2.803)	1.37(2.792)	1.61(2.799)	2.18(2.746)	1.51(2.161)	1.89(2.522)
median	0.00	0.00	0.00	1.96	0.00	1.89
min, max	0.0, 10.7	0.0, 17.4	0.0, 17.4	0.0, 11.1	0.0, 9.6	0.0, 11.1
PDPE event rate *(per subject per year)*						
n	96	81	177	67	51	118
Mean (SD)	1.05(2.288)	0.47(1.479)	0.78(1.976)	1.19(2.303)	0.86(1.932)	1.05(2.148)
median	0.00	0.00	0.00	0.00	0.00	0.00
min, max	0.0, 10.4	0.0, 8.5	0.0, 10.4	0.0, 11.1	0.0, 9.6	0.0, 11.1

Table 7. Mean days of Hospitalisation for PDPE and PE, study CF-301

	Mannitol			Control		
	rhDNase used [N=96] n (%)	rhDNase not used [N=81] n (%)	Total [N=177] n (%)	rhDNase used [N=67] n (%)	rhDNase not used [N=51] n (%)	Total [N=118] n (%)
Days of hospitalisation due to PDPE (days per subject 26 weeks)[1]						
n	96	81	177	67	51	118
mean	6.58	1.01	4.03	3.83	3.19	3.55
SD	15.22	4.64	11.94	11.5	8.69	10.34
median	0.00	0.00	0.00	0.00	0.00	0.00
min, max	0.0, 64.1	0.0, 32.1	0.0, 64.1	0.0, 76.9	0.0, 38.4	0.0, 76.9
Days of hospitalisation due to PE (days per subject 26 weeks)[1]						
n	96	81	177	67	51	118
mean	8.59	1.94	5.55	6.38	4.92	5.75
SD	16.01	6.31	12.94	17.20	11.85	15.08
median	0.00	0.00	0.00	0.00	0.00	0.00
min, max	0.0, 64.1	0.0, 32.1	0.0, 64.1	0.0, 102.5	0.0, 54.6	0.0, 102.5

Percentages are based on the number of subjects in the ITT population
[1]. For each subject, the rate of hospitalisation is estimated as:
365.25 x (the number of days in hospital due to PE / the number of days of drug exposure).

Table 8. Quality of Life Domains, all Ages, Change from Week 0 to Week 26 by Treatment Group by rhDNase User Group and Overall, study CF-301

	Mannitol			Control		
QoL Domain	**rhDNase user mean (SD) [n]**	**rhDNase non-user mean (SD) [n]**	**Total mean (SD) [n]**	**rhDNase user mean (SD) [n]**	**rhDNase non-user mean (SD) [n]**	**Total mean (SD) [n]**
Physical	0.7 (14.49) [n=60]	-1.9 (18.03) [n=53]	-0.5 (16.22) [n=113]	-6.2 (17.96) [n=49]	-2.8 (17.08) [n=38]	-4.7 (17.56) [n=87]
Vitality	5.1 (13.68) [n=41]	-1.1 (17.54) [n=39]	2.1 (15.88) [n=80]	-3.3 (15.02) [n=35]	-7.4 (21.60) [n=27]	-5.1 (18.13) [n=62]
Emotion	-1.7 (9.72) [n=60]	1.3 (13.49) [n=54]	-0.3 (11.70) [n=114]	0.8 (12.10) [n=49]	0.0 (15.61) [n=38]	0.5 (13.66) [n=87]
Eating	4.1 (14.60) [n=60]	0.4 (16.29) [n=54]	2.3 (15.47) [n=114]	3.6 (13.11) [n=49]	-0.3 (14.72) [n=38]	1.9 (13.89) [n=87]
Burden	1.3 (18.23) [n=59]	-4.5 (13.74) [n=54]	-1.5 (16.43) [n=113]	1.4 (15.82) [n=49]	-1.5 (21.79) [n=38]	0.1 (18.60) [n=87]
Health	1.9 (15.28) [n=40]	0.9 (19.64) [n=39]	1.4 (17.47) [n=79]	0.6 (19.79) [n=35]	1.6 (16.51) [n=27]	1.1 (18.30) [n=62]
Social	-1.6 (10.66) [n=59]	2.3 (16.34) [n=54]	0.3 (13.75) [n=113]	0.7 (14.73) [n=49]	-2.5 (12.32) [n=38]	-0.7 (13.74) [n=87]
Body	-0.4 (14.73) [n=59]	3.8 (17.72) [n=52]	1.6 (16.26) [n=111]	-1.1 (15.09) [n=49]	5.7 (14.49) [n=37]	1.8 (15.14) [n=86]
Role	-0.2 (16.51) [n=41]	-0.6 (17.03) [n=39]	-0.4 (16.66) [n=80]	-0.7 (15.70) [n=35]	-2.8 (14.62) [n=27]	-1.6 (15.15) [n=62]
Weight	3.3 (23.34) [n=41]	4.3 (24.40) [n=39]	3.7 (23.72) [n=80]	8.6 (29.53) [n=35]	3.7 (35.00) [n=27]	6.5 (31.85) [n=62]
Respiratory	0.4 (15.77) [n=60]	2.2 (16.25) [n=54]	1.3 (15.95) [n=114]	-2.5 (16.91) [n=49]	-2.5 (18.58) [n=38]	-2.5 (17.55) [n=87]
Digestion	-0.4 (23.23) [n=60]	-1.0 (14.36) [n=54]	-0.7 (19.46) [n=114]	-0.9 (17.69) [n=49]	1.2 (26.06) [n=38]	0.0 (21.63) [n=87]

Ancillary analyses

A post hoc analysis of the rate of responders was performed in the population of patients completing the 26 weeks study with both baseline and visit 4 values for FEV_1 (responders were defined as mean improvement from baseline in FEV_1 of >100 ml or >5% (relative to baseline), or >5% relative change in % predicted were considered as responders. Among the completers receiving mannitol 400 mg BD only 41.4 % (n=48 patients/116 completers) had more than 5% increase in FEV_1 % predicted. This represents 48/177 = 27 % of the ITT population initially randomised to mannitol 400 mg BD. The rate of responders to mannitol 400 mg BD, as determined in a post hoc analysis, appears to be rather low.

Upon request from the CHMP the applicant performed analysis of change in FEV_1 efficacy outcomes in % predicted, which are presented below.

Figure 7. Change in FEV_1 % Predicted (absolute % points) All Subjects – MMRM

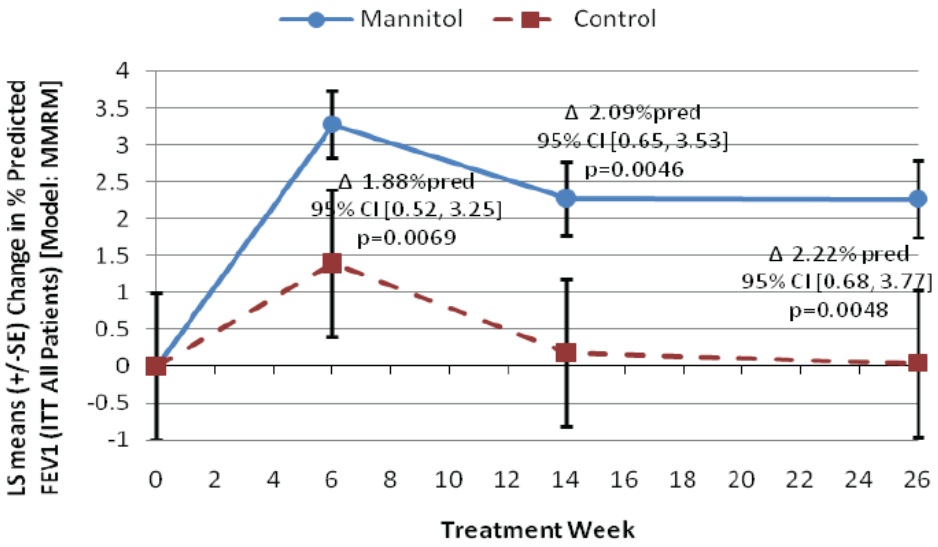


Figure 8. Change in FEV_1 % Predicted (absolute % points) All rhDNase Users – MMRM

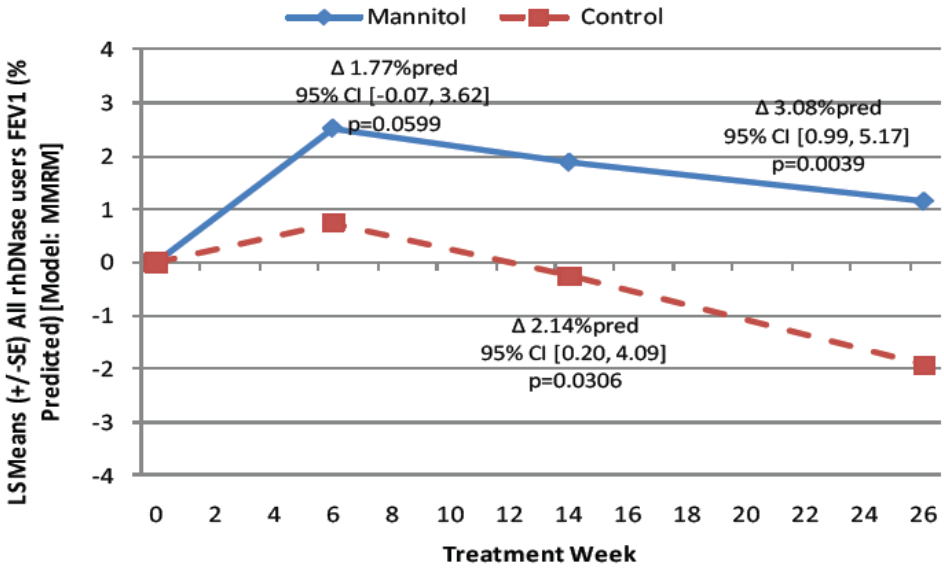
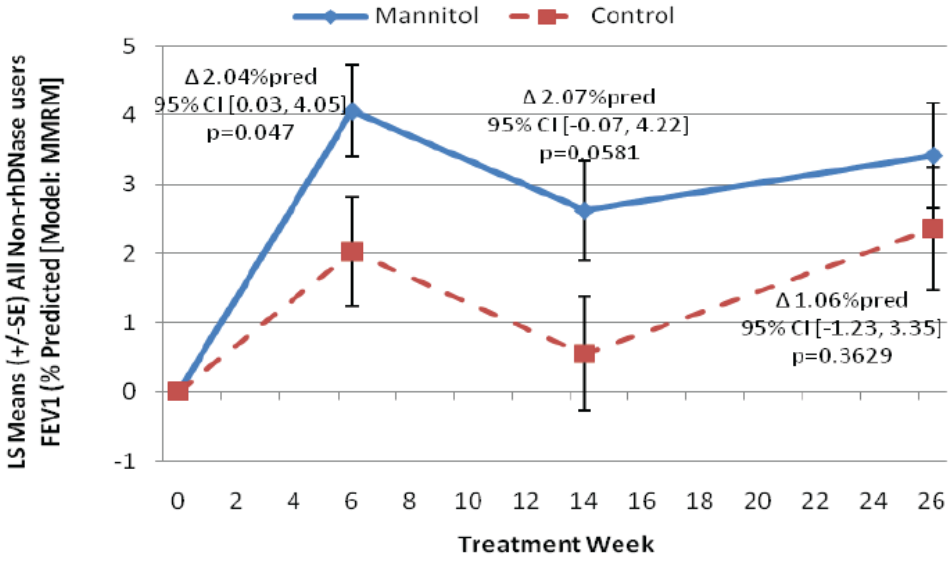
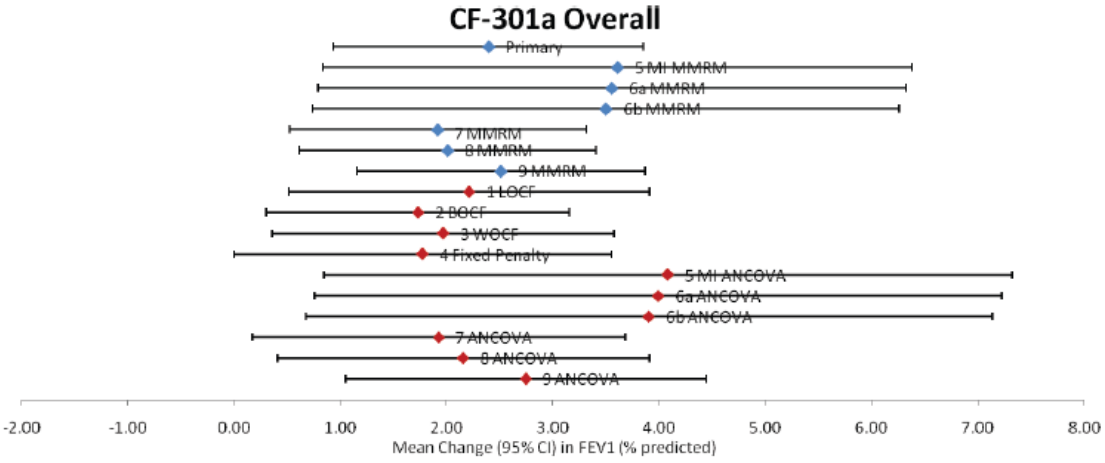


Figure 9. Change in FEV_1 % Predicted (absolute % points) All Non-rhDNase Users – MMRM



Since approximately 30% of the patients discontinued from the study, in some cases without providing any post baseline value of FEV_1, a sensitivity analysis was performed in order to handle missing data.

Figure 10. Sensitivity analysis for primary endpoint in study CF-301



The applicant has provided an ancillary analysis in the **adolescent/paediatric** population. The ITT (safety) population included 105 patients consisting of 48 paediatrics from 6 to 11 years (mannitol 400 mg : 31) and 57 adolescents from 12 to 17 years (mannitol 400 mg: 32). There was also a high rate of premature withdrawals more in adolescent (31.5%) than in paediatrics (25%), and the 2 groups were unbalanced (no stratification was planned by age). Few conclusions can be drawn from this analysis. Basically, no significant difference was shown on FEV_1 between the treatment groups. For the FEF 25-75 mean changes from baseline were even lesser in the mannitol 400 mg group as compared to the control group.

Figure 11. Absolute Change in Mean FEV_1 (mL) in the Paediatric/Adolescent Population, study CF-301

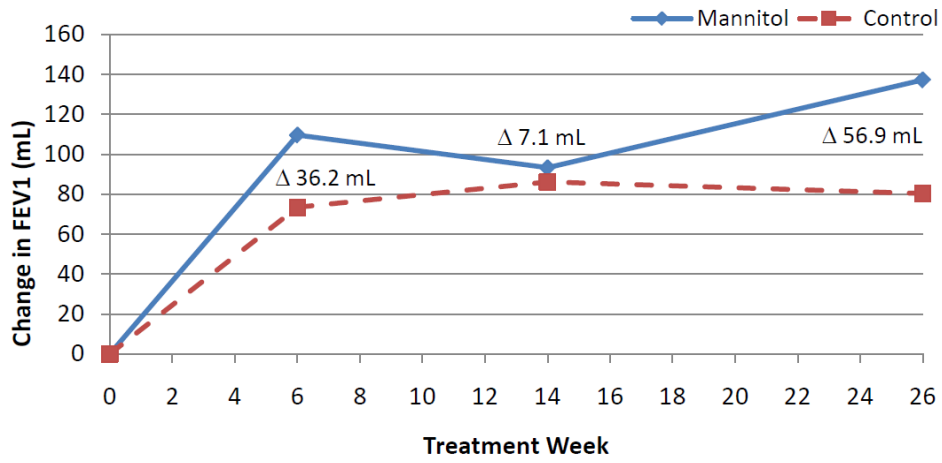
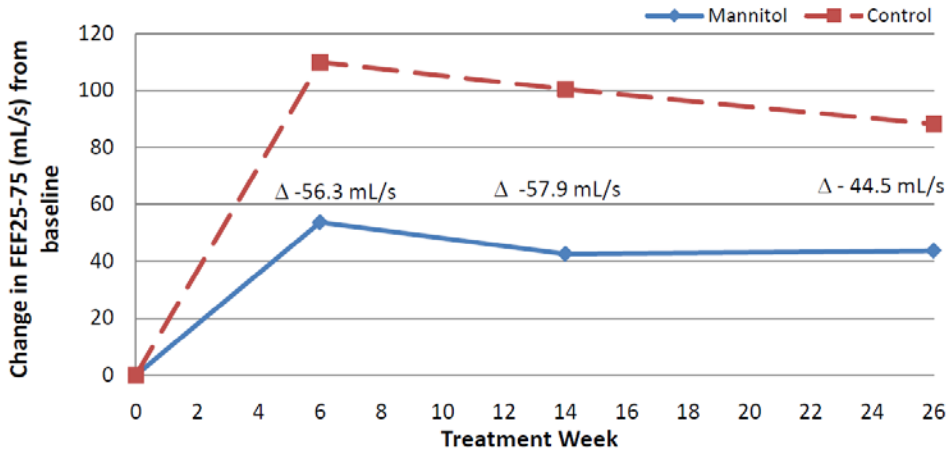


Figure 12. Absolute change in FEF25-75 in the Paediatric/Adolescent population, study CF-301



Study DPM-CF-302: Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study

Methods

This was a multicenter, 26 week double blind, randomised, 2 parallel groups, controlled, trial to compare inhaled mannitol 400 mg twice daily to a control group receiving inhaled mannitol in "subtherapeutic" dose of 50 mg twice daily.

Study Participants

This study included patients above 6 years of age with mild to moderate cystic fibrosis but excluded severe conditions and advanced stage of the disease. Subjects needed to have FEV_1 >40 and <90% predicted and to pass mannitol tolerance test to enter the study. Pregnant, breast-feeding and intolerant to mannitol or beta-agonists subjects and subjects with concomitant use of beta blockers or hypertonic saline were excluded, as well as subjects who have had a significant episode of haemoptysis (> 60 ml) in the previous three months or had selected serious health conditions.

Treatments

Patients in active group received 400 mg (10 x 40 mg capsule) of mannitol twice daily, and in the control group 50 mg (10 x 5 mg capsules) of mannitol twice daily. Patients received the therapy for 26 weeks via CE marked DPI Type RS01 Model 7 HR.

RhDNase use was permitted and the randomisation was stratified on rhDNase status at baseline (rhDNase user or rhDNase non users). If rhDNase use was initiated or ceased during the course of the study, the stratum was not adjusted.

Objectives

The study was aimed at investigating the efficacy and safety of inhaled mannitol for treatment of CF.

Outcomes/endpoints

Primary endpoint was change in absolute FEV_1 over 26 weeks of therapy.

Secondary Efficacy endpoints were:

- FEV_1 change from baseline (ml) in the rhDNase group
- Pulmonary exacerbations in those taking rhDNase as a sub-group and in the total cohort
- Quality of life scores using Cystic Fibrosis Questionnaire-R
- Rescue antibiotic use (number of agents, course and days of use)
- Change in absolute FVC, FEF_{25-75} from baseline
- Number of days in hospital due to pulmonary exacerbations
- Qualitative sputum microbiology
- Quantitative sputum microbiology for *S. aureus* and *P. aeruginosa*

Sample size

300 subjects were intended to be randomised to treatment. Approximately two thirds of these subjects were expected to be using rhDNase and approximately 30% of subjects were forecasted to withdraw prior to week 26. Therefore, approximately 126 evaluable subjects were estimated to complete the mannitol treatment and 84 evaluable subjects in the control treatment. It was estimated that of these evaluable subjects, approximately 84 subjects in the mannitol group would be taking concurrent rhDNase.

The study was planned to have 98% powered to detect a FEV_1 change of 120 mL in the ITT population at week 26 and 80% power in the rhDNase users.

Randomisation

Randomisation was to be applied to subjects who passed mannitol tolerance test in a ratio of 3:2 (mannitol 400mg BD: control). The randomisation was stratified by rhDNase use and country but not by sites, age or severity of the disease. 300 randomisation numbers (180 mannitol and 120 control) were generated for each stratum, in blocks of 5 which were paired for rhDNase users and non-users.

Blinding (masking)

The investigators, site staff, pharmacists, subjects, monitors, project managers and data managers were blinded throughout the study. Both active and control treatments consisted of ten identical capsules. The use of opaque capsules was aimed at masking the difference in the capsule fill volume.

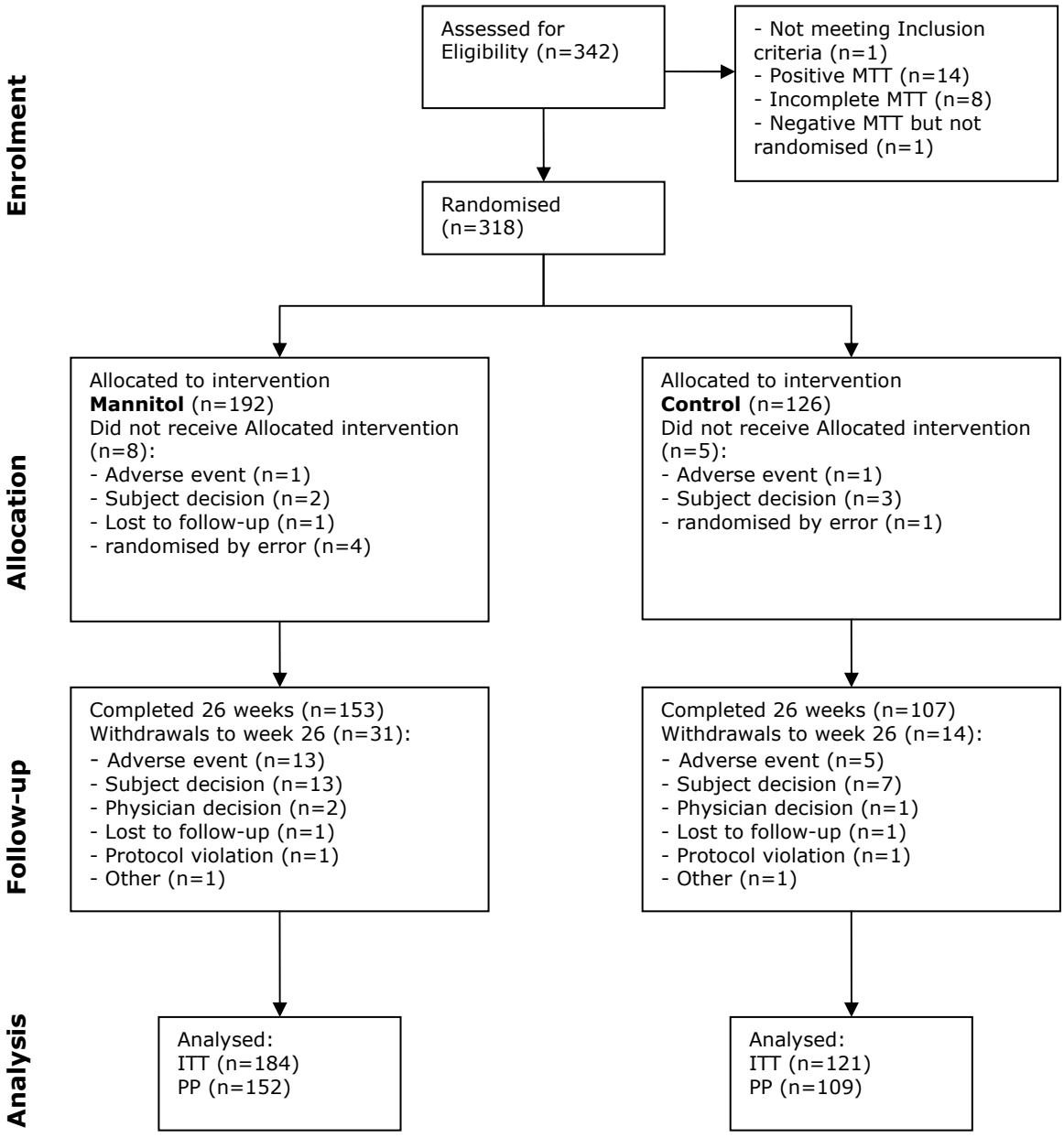
Statistical methods

The statistical methods were similar to the methods applied in study CF-301. In addition, for primary endpoint analysis a treatment group by visit week interaction was also included in the MMRM model. The analysis also did not include week 0 in assessment of the treatment effect, which was included in the pre-defined analysis for study CF-301.

Results

Participant flow

Figure 13. Disposition of subjects in study DPM-CF-302



Recruitment

318 patients were randomised in ratio 3:2. 192 were allocated to mannitol 400 mg BD and 126 were allocated to control mannitol 50 mg BD.

Conduct of the study

The study was conducted from 3 September 2008 to 12 April 2010 in 53 study sites in USA, Canada, Argentina, Germany, Belgium, France and the Netherlands.

There have been 2 amendments to Study Protocol, increasing number of participants, introducing minor changes in MTT, randomisation and unblinding procedures as well as administrative changes.

Baseline data

The overview of baseline data of subjects has been provided by the applicant for the safety population which is identical to defined (modified) ITT population (all subjects who received at least one dose of study medication).

Table 9. Demographic Characteristics of Safety Population, study DPM-CF-302

Safety Population Characteristic	Mannitol (N=184)	Control (N=121)
Age		
Children (6-11 years)	35 (19.0%)	24 (19.8%)
Adolescents (12-17 years)	56 (30.4%)	39 (32.2%)
Adults (18 years and older)	93 (50.5%)	58 (47.9%)
Mean (SD)	19.6 (9.29)	20.4 (10.23)
Median (Min, Max)	18.0 (6.0,48.0)	17.0 (6.0,53.0)
Gender		
Female	90 (48.9%)	58 (47.9%)
Race		
Caucasian	182 (98.9%)	119 (98.3%)
RhDNase		
User	137 (74.5%)	92 (76.0%)
Cystic fibrosis mutation		
ΔF508 / ΔF508	77 (41.8%)	45 (37.2%)
ΔF508 / other mutation	57 (31.0%)	52 (43.0%)
unknown /unknown	35 (19.0%)	19 (15.7%)
Pulmonary exacerbations in the year preceding study participation[§]		
Mean (SD)	0.7 (1.15)	0.6 (0.94)
Median (Min, Max)	0 (0, 9)	0 (0, 5)
Hospitalizations in the year preceding study participation[+]		
Mean (SD)	0.6 (1.11)	0.6 (0.93)
Median (Min, Max)	0 (0, 9)	0 (0, 5)
FEV_1 at screening (L)		
Mean (SD)	2.06 (0.71)	2.02 (0.72)
Median	1.97	1.93
Min, Max	0.69, 3.85	0.80, 3.85
Percent predicted FEV_1 (%)		
Mean (SD)	65.24 (13.90)	64.35 (15.29)
Median	65.96	64.42
Min, Max	33.89, 96.08	35.57, 95.06
BMI (kg/m^2)		
Mean (SD)	20.0 (4.12)	19.8 (3.70)
Median	19.8	19.1
Min, Max	12.8, 44.6	11.7, 33.4

[§] *Number of pulmonary exacerbations treated with IV antibiotics in the 12 months prior to the screening visit*
[+] *Number of times the subject was hospitalized for a pulmonary exacerbation in the 12 months prior to the screening visit*

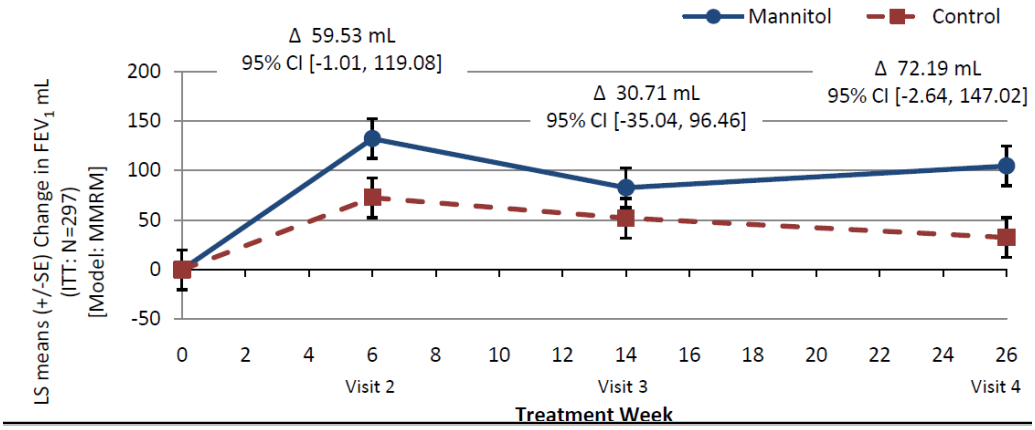
Numbers analysed

342 subjects were enrolled in the study and 318 of those were randomised. ITT population consisted of 305 subjects (184 mannitol, 121 control) and PP population – of 261 subjects (152 mannitol, 109 control).

Outcomes and estimation

Change in absolute FEV_1 across the study duration is presented below. At week 26 the difference between treatments was 72.19 ml.

Figure 14. Absolute Change in FEV_1 (ml) by timepoint, study CF-302



The analysis of primary endpoint showed overall treatment effect over 26 weeks in change in absolute FEV_1 of 54.14 ml as compared to the control group, which was not statistically significant (p=0.059). The applicant performed a post hoc corrected baseline analysis (based on average of screening and baseline FEV_1) using the MMRM model.

Table 10. Overall Treatment Effect FEV1 (mL), study CF-302

Endpoint	Planned	Model	LS Mean	95% CI	P-value
Baseline Model					
Absolute change from baseline in FEV_1 (mL)* (Analysed=297)	Yes	MMRM			
Mannitol			106.53	62.43, 150.62	<.001
Control			52.38	2.09, 102.68	0.041
Treatment difference over 26 weeks			54.14	-1.97, 110.26	0.059
Baseline Corrected Model					
Absolute change from the mean baseline and screening FEV_1 (mL) ^ (Analysed=297)	No	MMRM			
Mannitol			108.66	67.79, 149.54	<.0001
Control			37.56	-9.06, 84.17	0.114
Treatment difference over 26 weeks			71.10	19.11, 123.09	0.008

**Model with treatment by visit week interaction 14.2.2.1*
^ All main effects and treatment by visit interaction. Baseline FEV_1 replaced by mean of screening and baseline FEV_1
Source Section 14 Table 14.2.2.12 See Section 11.4.2 for explanation

The applicant has presented results also as FEV_1 in % predicted, which showed treatment difference of 2.42 % predicted at 26 weeks (p=0.024).

Table 11. Overall Treatment Effect on FEV_1 (% predicted), study CF-302

Endpoint	Planned	Model	LS Mean	95% CI	P-value
Absolute change in % Predicted FEV_1 # (Analysed=305)	Yes	ANCOVA			
Mannitol			3.14	1.49, 4.78	<0.001
Control			0.72	-1.18, 2.62	0.458
Treatment difference at 26 weeks			2.42	0.33, 4.51	0.024
Absolute change in % Predicted FEV_1§ (Analysed=297)	No	MMRM			
Mannitol			3.13	1.65, 4.61	<.0001
Control			1.27	-0.43, 2.96	0.14
Treatment difference over 26 weeks			1.87	-0.02, 3.75	0.052

 # If height or % pred missing at V4, baseline value carried forward. Based on generalized linear model Section 14 Table 14.2.6.6

§Heights imputed based on WHO popn tables for subjects<18 years. All main effects and treatment by visit interaction Section 14 Table 14.2.6.8

When the analysis was performed in stratified subgroups defined by the rhDNase status at screening, the between groups difference in FEV_1 at week 26 was not statistically significant in either of strata, while the trend was favourable for mannitol (overall treatment effect in rhDNase users 43.49 ml, p = 0.177, and in non-users 86.5 ml, p=0.124). As in study CF-301, also in this study it appears that effect on absolute FEV_1 was higher in the strata of rhDNase non users as compared to the strata of rhDNase users.

Figure 15. rhDNase Users Change in FEV_1 (ml), study CF-302

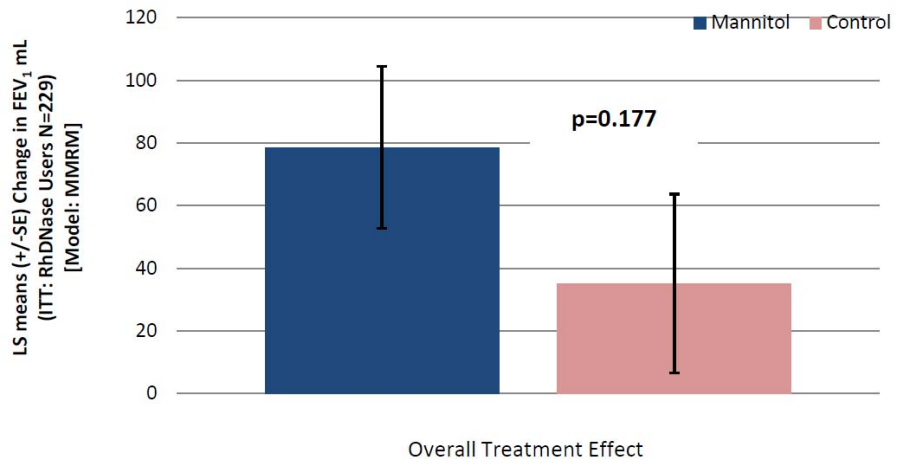


Figure 16. rhDNase Non-Users Change in FEV_1 (ml), study CF-302

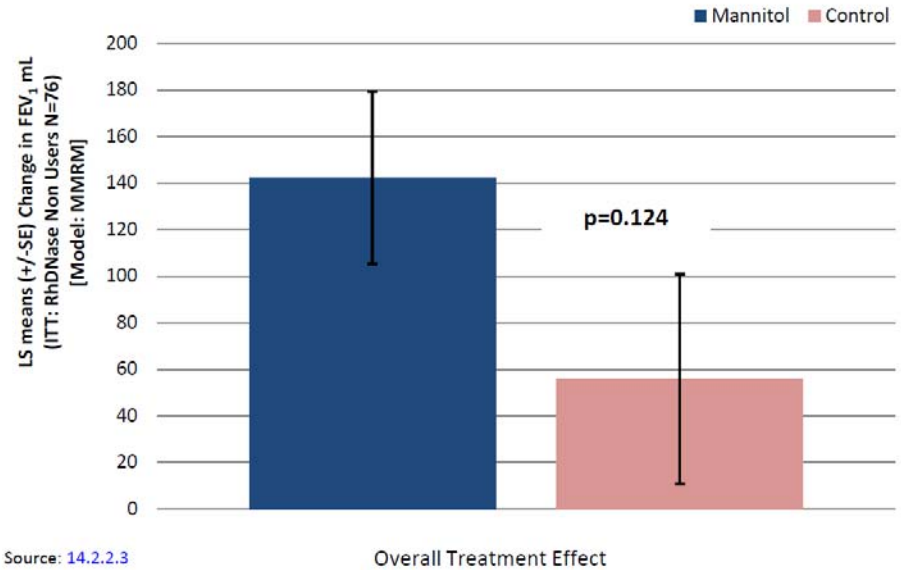


Table 12. Incidence of subjects with PDPE from Baseline through Week 26, study CF-302

PDPE	Mannitol N=184 n (%)	Control N=121 n (%)
Total subjects with ≥1 PDPE	28 (15.2)	23 (19.0)
Number of subjects with 1 PDPE	21 (11.4)	18 (14.9)
Number of subjects with 2 PDPE	6 (3.3)	4 (3.3)
Number of subjects with 3 PDPE	1 (0.5)	1 (0.8)

Table 13. Subjects hospitalized due to PDPE from Baseline through Week 26, study CF-302

	Mannitol N=184	Control N=121
Total subjects hospitalized due to PDPE n(%)	22 (12)	19 (15.7)
Duration of hospitalization (days)*		
Mean ±SD	12.09 ±7.91	15.42 ± 10.16
Median	10.0	14.0
Min, Max	2, 30	3, 39
No. of subjects with distinct hospitalizations due to PDPE, n (%):		
1 hospitalization	18 (9.8)	14 (11.6)
2 hospitalizations	3 (1.6)	5 (4.1)
3 hospitalizations	1 (0.5)	0 (0.0)
No. of subjects hospitalized by days:		
0 days	162 (88.0)	102 (84.3)
1-7 days	7 (3.8)	5 (4.1)
8-14 days	9 (4.9)	5 (4.1)
15-21 days	3 (1.6)	5 (4.1)
22 -28 days	1 (0.5)	1(0.8)
≥29 days	2 (1.1)	3(2.5)

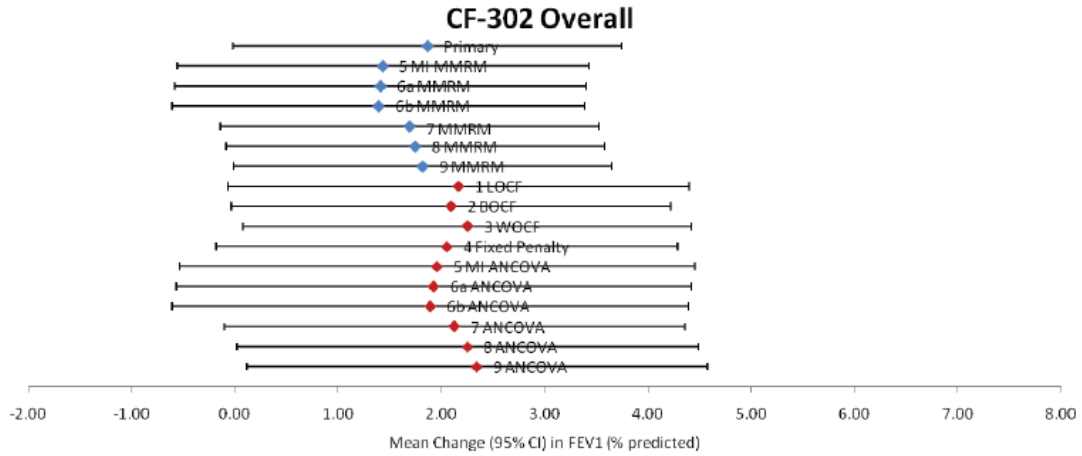
** For ongoing hospitalizations, duration is censored at the last follow-up date in the double blind phase*

There were no meaningful differences in mean change over baseline for either treatment group or between treatment groups for any of the QoL domains.

Ancillary analyses

In order to address the high number of patients discontinued from the study (though lower than in study CF-301), a sensitivity analysis was performed in order to handle missing data.

Sensitivity analysis for primary endpoint in study CF-302



Analysis of efficacy outcomes was conducted by the applicant by age subgroups.

Effect of treatment on absolute change in FEV_1 (ml) was 81.13 (95% CI -45.30 to 207.57, p=0.21) in children aged 6 – 11 years, -9.50 (95% CI -108.86 to 89.86, p=0.85) in adolescents aged 12 – 17 years and 85.94 (95% CI 4.63 to167.26, p=0.038) in adults.

Treatment effect on FVC (ml) in children was 71.63 (95% CI -63.8 to 207.1, p=0.299), in adolescents 6.64 (95% CI -100.3 to 113.6, p=0.903) and in adults 113.77 (95% CI 26.14 to 201.4, p=0.011).

Effect of treatment on FEF25-75 (ml/s) was 58.69 (95% CI-158.43 to 275.82, p =0.59) in children, -49.92 (95% CI -222.09 to 122.25, p=0.569) in adolescents and 71.51 (95%CI -69.40 to 212.42, p= 0.319) in adults.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14. Summary of Efficacy for trial DPM-CF-301

Title: Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study			
Study identifier	Protocol: DPM-CF-301 CTN number: 2007/165 Eudra CT numbers: 2007-001412-23		
Design	Double blind, randomised, controlled, interventional, multicentre clinical trial. This study consisted of two phases: a double blinded 26 week safety and efficacy Phase and an open label safety phase.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks N/A 26 weeks
Hypothesis	Superiority over control		
Treatment groups	Mannitol		Treatment: 400 mg mannitol twice daily Duration: 26 weeks Number randomized: 192
	Control		Treatment: 50 mg mannitol twice daily Duration: 26 weeks Number randomized: 132
Endpoints and definitions	Primary endpoint	Change in FEV_1 (ml)	Change from baseline in absolute FEV_1 at week 26 (descriptive) / Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 (effect estimation)
	Secondary endpoint	Change in FEV_1 (ml) in rhDNase users	Change from baseline in absolute FEV_1 in patients receiving rhDNase treatment at week 26 (descriptive) / Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 in patients receiving rhDNase treatment (effect estimation)

	Secondary endpoint	PE	Rate of pulmonary Exacerbations requiring the use of antibiotics
	Secondary endpoint	PDPE	Rate of protocol Defined Pulmonary Exacerbations meeting at least 4 of the predefined criteria and requiring use of intravenous antibiotics
Database lock	24 April 2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT): all subjects randomised who received at least one dose of study medication			
Descriptive statistics and estimate variability	Treatment group	Mannitol		Control	
		LS mean	95% CI	LS mean	95% CI
	Number of subjects	n=177		n=118	
	Primary endpoint: Change in FEV_1 (ml)	118.88	[85.61, 152.16]	26.00	[-11.61, 63.61]
	Number of subjects	n=96		n=67	
	Secondary endpoint: Change in FEV_1 (ml) in rhDNase users	81.03	[35.49, 126.56]	-27.78	[-78.17, 22.61]
	Number of subjects	n=177		n=118	
	Secondary endpoint: PE	incidence	36.7 %	incidence	50.8%
	Number of subjects	n=177		n=118	
	Secondary endpoint: PDPE	incidence	18.1 %	incidence	28.0 %

Effect estimate per comparison	Primary endpoint: Change in FEV_1 (ml)	Comparison groups	Mannitol - Control
		Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26	54.17
		95% CI	24.73, 83.60
		P-value	p<0.001
	Secondary endpoint: Change in FEV_1 (ml) in rhDNase users	Comparison groups	Mannitol - Control
		Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 in rhDNase users	53.82
		95% CI	14.03, 93.61
		P-value	P=0.008
	Secondary endpoint: PE	Comparison groups	Mannitol - Control
		Rate ratio	0.86

		95% CI	0.64, 1.17
		P-value	> 0.05
	Secondary endpoint: PDPE	Comparison groups	Mannitol - Control
		Rate ratio	0.74
		95% CI	0.47, 1.18
		P-value	> 0.05

Table 15. Summary of Efficacy for trial DPM-CF-302

Title: Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study			
Study identifier	Protocol: DPM-CF-302 Eudra CT number: 2008-002740-42		
Design	Double blind, randomised, controlled interventional, multicentre clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks N/A 26 weeks
Hypothesis	Superiority over control		
Treatment groups	Mannitol		Treatment: 400 mg mannitol twice daily Duration: 26 weeks Number randomized: 192
	Control		Treatment: 50 mg mannitol twice daily Duration: 26 weeks Number randomized: 126
Endpoints and definitions	Primary endpoint	Average treatment effect on FEV_1 (ml) across weeks 6, 14, 26	Change from baseline in absolute FEV_1 over 26 weeks (Estimate of the overall difference between mannitol and control with respect to the change from baseline based on (repeated) measurements of the response at Week 6, Week 14 and Week 26 to produce a treatment effect across 26 weeks of treatment)
	Secondary endpoint	Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 in rhDNase users	Change from baseline in absolute FEV_1 in patients receiving rhDNase treatment over 26 weeks (Estimate of the overall difference between mannitol and control with respect to the change from baseline based on (repeated) measurements of the response at Week 6, Week 14 and Week 26 to produce a treatment effect across 26 weeks of treatment)
	Secondary endpoint	PE	Rate of pulmonary Exacerbations requiring the use of antibiotics
	Secondary endpoint	PDPE	Rate of protocol Defined Pulmonary Exacerbations meeting at least 4 of the predefined criteria and requiring use of intravenous antibiotics

Database lock	09 June 2010				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (ITT): all subjects randomised who received at least one dose of study medication				
Descriptive statistics and estimate variability	Treatment group	Mannitol		Control	
		mean	95% CI	mean	95% CI
	Number of subjects	n=184		n=121	
	Primary endpoint: Average treatment effect on FEV_1 (ml) across weeks 6, 14, 26	106.53	62.43, 150.62	52.38	2.09, 102.68
	Number of subjects	n=137		n=92	
	Secondary endpoint: Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 in rhDNase users	78.6	27.64, 129.56	35.11	20.99, 90.21
	Number of subjects	n=184		n=121	
	Secondary endpoint: PE	incidence	57.6 %	incidence	62.8 %
	Number of subjects	N=184		N=121	
	Secondary endpoint: PDPE	incidence	15.2 %	incidence	19 %

Effect estimate per comparison	Primary endpoint: Change in FEV_1 (ml)	Comparison groups	Mannitol - Control
		Average treatment effect on FEV_1 (ml) across weeks 6, 14, 26	54.14
		95% CI	1.97, 110.26
		P-value	0.059
	Secondary endpoint: Change in FEV_1 (ml) in rhDNase users	Comparison groups	Mannitol - Control
		Average treatment effect on FEV_1 (ml) across weeks 0, 6, 14, 26 in rhDNase users	43.49
		95% CI	-19.8, 106.78
		P-value	0.177
	Secondary endpoint: PE	Comparison groups	Mannitol - Control
		Rate ratio	0.93
		95% CI	0.74, 1.17
		P-value	0.551

	Secondary endpoint: PDPE	Comparison groups	Mannitol - Control
		Rate ratio	0.85
		95% CI	0.51, 1.41
		P-value	0.520

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant has presented efficacy analysis across phase 3 trials. For the change in FEV_1 the results are presented below in comparison to the results of individual studies. For pooled data the overall treatment effect over 26 weeks is estimated for FEV_1 as 2.12 % predicted. However as the results of the two studies are not consistent a pooled analysis is not considered appropriate.

Table 16. Mean absolute (ml) and percent predicted (%) changes from baseline in FEV_1 across Phase 3 studies, ITT population

Analyzed:	DPM-CF-301a (N=272)			DPM-CF-302 (N=297)			Pooled DPM-CF-301 and DPM-CF-302 (N=569)		
Mean absolute change from baseline in FEV_1 (mL)*									
	LS Mean Estimate	95% CI	p-value	LS Mean Estimate	95% CI	p-value	LS Mean Estimate	95% CI	p-value
Difference over 26 weeks	94.45	(46.21, 142.70)	<.001	54.14	(-1.97, 110.26)	0.059	73.42	(36.19, 110.65)	<.001
Mannitol	121.35	(89.18, 153.51)	<.001	106.53	(62.43, 150.62)	<.001	114.05	(87.24, 140.86)	<.001
Control	26.9	(-10.15, 63.94)	0.154	52.38	(2.09, 102.68)	0.041	40.63	(9.90, 71.36)	0.01
Absolute change in FEV_1 percent predicted of normal									
Difference over 26 weeks	2.40	(0.94, 3.85)	0.001	1.87	(-0.02, 3.75)	0.052	2.12	(0.91, 3.33)	<.001
Mannitol	2.85	(1.88, 3.83)	<.001	3.13	(1.65, 4.62)	<.001	2.99	(2.12, 3.86)	<.001
Control	0.46	(-0.66, 1.57)	0.420	1.27	(-0.43, 2.96)	0.142	0.87	(-0.13, 1.87)	0.088

Model: DPM-CF-302 MMRM (with treatment group by visit interaction)

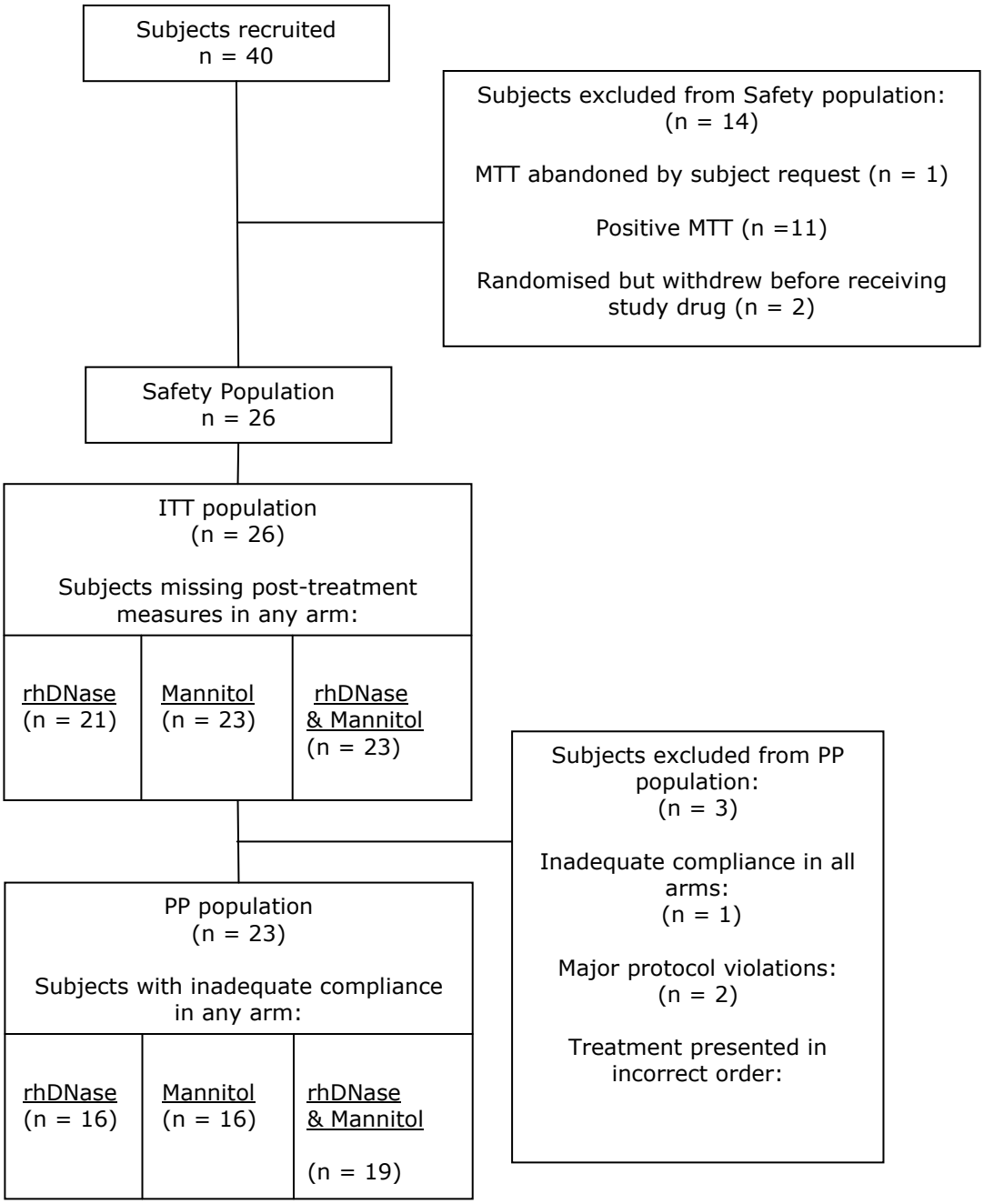
Clinical studies in special populations

One phase II study was conducted in children.

Study DPM-CF-203: A cross-over comparative study of inhaled Mannitol, alone and in combination with daily rhDNase, in children with cystic fibrosis

This was an open label, multicentre, randomised, cross-over, comparative study. After satisfying inclusion and exclusion criteria, subjects were given the mannitol tolerance test to screen for airway hyper-reactivity. Those with a negative MTT test result were randomised to one of three cross-over treatments in a 1:1:1 ratio to receive for 12 weeks either 400 mg Mannitol twice daily, 2.5 mg rhDNase daily, or 400 mg Mannitol twice daily plus 2.5 mg rhDNase daily according to one of six treatment schedules, which were also randomly assigned. All subjects received all three treatments. There was a two week washout period prior to each treatment.

Figure 17. Subject disposition in study DPM-CF-203

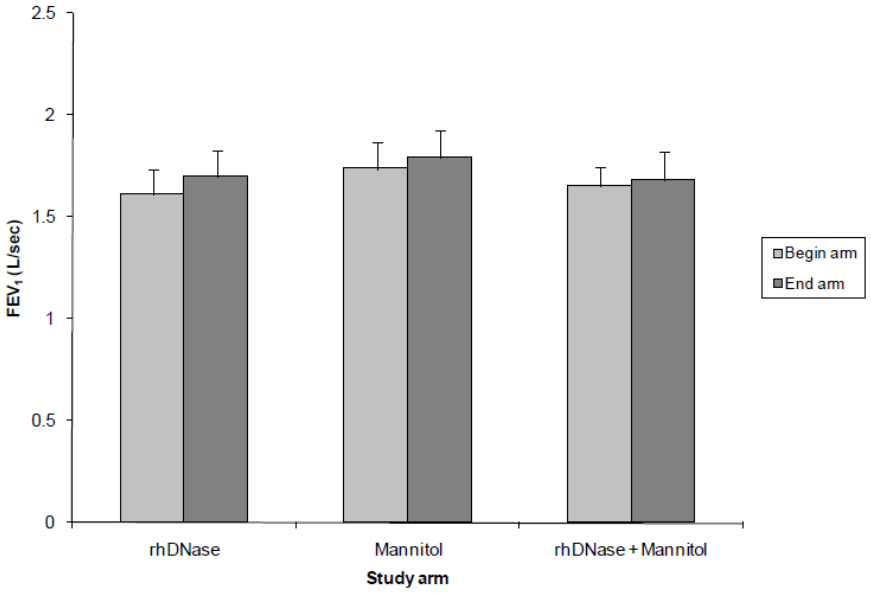


Results

No statistically significant differences in FEV_1 or FVC changes were observed when comparing rhDNase treatment to either Mannitol or rhDNase plus Mannitol treatment. No other spirometry results were significantly different between the arms. The change in FEV_1 was smaller in the Mannitol plus rhDNase arm than either the rhDNase or Mannitol alone arms (0.8% vs 9.1% vs 6.4% in ITT analysis and 1.0% vs 9.3% and 8.3% in the PP analysis). The rhDNase and Mannitol alone treatments resulted in similar spirometry improvements.

However, there was a trend for a smaller effect when rhDNase and mannitol were both used as compared to rhDNase used alone (mean percentage change in FEV_1 between mannitol+rhDNase and rhDNase alone = - 4.3 %; [95% CI: -14.1 to +6.5]). The same trends were also shown on FEF 25-75

Figure 18. FEV_1 (l) by visit and treatment arm in ITT population, study DPM-CF-203



No significant differences were noted in Quality of Life CFQ-R scores when the rhDNase treatment arm was compared to either of the Mannitol or rhDNase plus Mannitol arms. The Mannitol plus rhDNase arm showed the biggest reduction in score (worsening of symptoms). No significant differences were noted for any respiratory symptoms questions between the comparator treatment, rhDNase, and the other two treatment arms. The comparison between the rhDNase and Mannitol treatment arms for tiredness, while not significant, had a probability of 0.078, with subjects reporting less tiredness during the Mannitol treatment arm.

Sputum microbiology results showed no notable changes in microbial growth in any treatment arm.

The rhDNase arm had 3 (14.3%) patients who reported an exacerbation, while there were also 3 (13.0%) patients (p = 1.000) in the mannitol arm and 6 (26.1%) patients (p = 0.2568) in the rhDNase plus mannitol arm. These observations would rather suggest a lesser efficiency of the mucocilliary clearance when mannitol was associated to rhDNase.

Supportive study

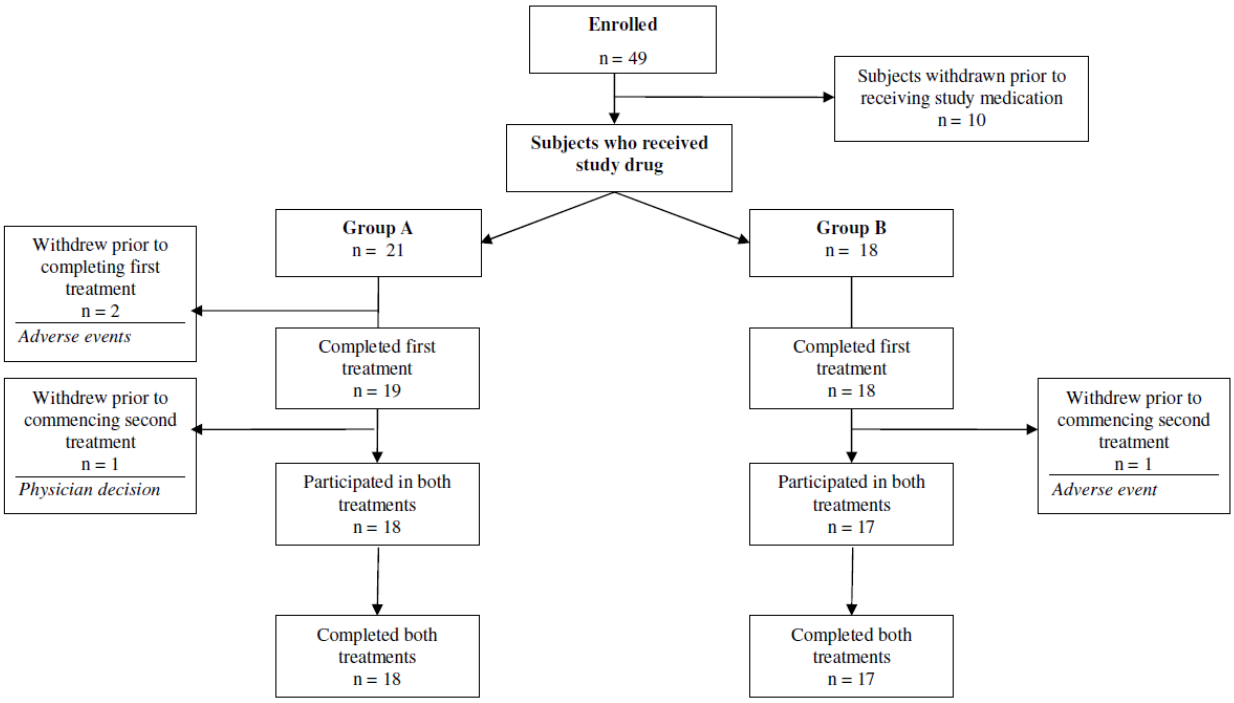
DPM-CF-201 A Phase 2 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol in Cystic Fibrosis

This was a randomised, multicentre, double-blinded, controlled, crossover, phase II study primarily determining the efficacy of inhaled mannitol in improving lung function and quality of life in subjects with cystic fibrosis. Study included subjects with a known diagnosis of cystic fibrosis, of either gender, aged ≥ 8 years, having a baseline FEV_1 of between 40% and 80% of the predicted normal value or a decline in FEV_1 of greater than 20% in the last twelve months. This study was conducted in a sample of 37 patients (ITT) aged from 8 to 48 years (mean: 19 years) who received 420 mg BD inhaled mannitol and non-respirable mannitol (average particle diameter 68 microns, fine particle fraction less than 2%) for 2 weeks in a cross over design. At visits 2 and 4 the initial dose of study medication was administered i.e. 30mg of Inhaled mannitol or control x 14 capsules (a dose of 420mg) twice a day. A bronchodilator (salbutamol 100 mcg, 4 puffs) was inhaled 15 minutes prior to a treatment. Dry powder inhaler devices were used for administration. The DPM-CF-201 protocol was amended twice before

enrolment commenced. The main changes in these amendments were the lowering of entry age to 8 years.

Primary Objective of the study was to determine the effect of two weeks twice daily treatment with Inhaled mannitol (inhaled mannitol) on FEV_1 in subjects with cystic fibrosis.

Figure 19. Subject Disposition in study DPM-CF-201



Treatment with Inhaled mannitol led to a 7.0 ± 1.9% (mean ± SE) increase in the FEV_1 ($p<0.001$) and this increase was significant compared to the change on placebo treatment ($p<0.01$). The absolute increase in FEV_1 on Inhaled mannitol treatment was 121 ± 33 ml (mean ± SE). The mean FEV_1 % of normal predicted increased from 62% at baseline to 66% i.e. LS mean FEV_1 (expressed as % of normal predicted value) change from baseline was + 3.86% (SD ± 1.08).

Although statistically significant ($p<0.01$) as compared to the control group (LS mean change from baseline in the control group= - 0.09), the improvement from baseline appeared very weak. The change from baseline of FEV_1 % of predicted was under the threshold of 5% usually considered as clinically significant. FEV_1/FVC, FEF_{25-75} and PEF increase were not significant on inhaled mannitol treatment group as compared to control ($p=0.3$). The differences in respiratory symptoms and respiratory domains of CF QOL questionnaire were very small and not clinically relevant.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Studies DPM-CF-301 and DPM-CF-302 are of identical design (multicenter, 26 week double blind, randomised, 2 parallel groups, controlled, trial to compare inhaled mannitol 400 mg twice daily to a control group receiving inhaled mannitol in a "subtherapeutic" dose of 50 mg twice daily).

Subjects less than 6 years of age were not considered for Phase 3 trials since mannitol tolerance test (MTT) and reliable spirometry measurements are not adequately achievable in children and infants

below this age. This is justified since children below 6 years of age are generally not able to use a dry powder inhaler.

During the assessment the applicant limited the proposed indication to adults (aged 18 years and above) only, however data on all age groups is being analysed in order to assess the consistency.

The doses of 400 mg for the active treatment and 50 mg for control group were chosen by the applicant based mainly on the results from the dose response 2 week Phase II trial DPM-CF-202 where the 400 mg dose was shown to be the most efficacious whereas the 40 mg dose did not demonstrate any efficacy. The applicant stated that the 40 mg fill capsules were chosen for the phase 3 studies as this was the largest dose that could effectively be delivered via the intended inhaler device. With consideration that utilizing more than 10 capsules may overly compromise subject's compliance with treatment, the applicant considered that 400 mg dose was the most appropriate balance between acceptability/tolerability and efficacy. Because the control had to be delivered across 10 capsules and 5 mg was the smallest available fill, a final dose of 50 mg (5 mg x 10) was selected as control group for this study. During study DPM-CF-202, however, the plateau was not reached and it is therefore not known, what effect higher doses would have.

In study DPM-CF-302 better training was provided to study personnel at the sites which led to fewer dropouts (a decrease from around 30% to around 15% in study DPM-CF-302). The other main difference between the two studies was the percentage of patients under 18 which was around 50% in study DPM-CF-302 compared to approximately 36% in study DPM-CF-301.

The population in study DPM-CF-301 included patients aged from 6 to 59 years. However no attempt was made to stratify the randomisation into different age ranges or to ensure that the sample size provided sufficient patients in each age group. However it was recognised that children (aged 6 - 11), adolescents (aged 12 – 17) and adults aged 18 years and above formed three clear subgroups. Furthermore it has been suggested in the literature that treatment for cystic fibrosis has improved considerably in recent years so that children born more recently will possibly have received better care immediately after diagnosis improving their lung function more than what was possible for patients born earlier. Also the choice of the primary endpoint based on lung function is problematic in such broad population as FEV_1 will naturally increase as children and adolescents grow in height, thereby increasing the size of lung.

Although the block size chosen for the randomisation scheme in study DPM-CF-301 was small and the majority (30) of the 40 centres recruited 5 or more patients, the randomisation was not stratified by centre resulting in an imbalance in the majority of centres. This is considered to be a serious deficiency in the study and prevents adjustment of the statistical analysis for any possible centre effects. Furthermore, no estimates of treatment difference by centre have been presented making it difficult to confirm the homogeneity of effect across the centres. No justification for use of region as a stratification factor instead of study centre has been provided by the applicant. In addition, it is unclear if other methods of stratification were considered such as division into centres recruiting children only, adults only or both age groups of patients by region.

Approximately 30% of patients discontinued study DPM-CF-301 before the end of the randomised treatment period of 26 weeks, while the statistical methods used for the analysis of the primary endpoint are not considered adequate to account for the large amount of missing data. Overall the handling of missing data was limited and a number of additional analyses and investigations are necessary to confirm that the results reported from the MMRM analysis are robust and reliable over the totality of this heterogeneous population. It is not accepted that the pre-specified MMRM model itself provided robust estimates of treatment differences in both studies (as claimed by the applicant) as it likely would overestimate the effect in Study DPM-CF-301 where a large percentage of patients discontinued early resulting in high levels of missing data.

The sensitivity analysis used 10 different methods to handle missing data. It should be noted that analysis Method 10 is not appropriate. Although for study DPM-CF-302 results this was used by the applicant to reanalyse the primary endpoint which had failed to achieve statistical significance in the pre-specified analysis, the reason for including the average of screening and baseline FEV_1 as a covariate is not accepted. The use of the baseline value as a covariate is considered the appropriate method of adjustment only for an endpoint based on change from baseline.

The indication sought by the applicant includes two distinct groups of patients and it is unclear how the findings reported apply to both. Furthermore, the investigation of the effect in different important subgroups has not been sufficiently carried out. Although the subgroups by rhDNase use have been analysed and suggest a difference in effect between the two, consistency of effect across subgroups according to age has not been established (see below).

The study design does not allow to establish whether rhDNase non users at baseline were indeed patients who did not derive benefit from rhDNase i.e. inadequately responsive to rhDNase as claimed in the indication of the proposed SPC. Study DPM-CF-203 is the only study with a direct comparison between rhDNase and Mannitol 400 mg bd in a cross over design. The results presented, however, do not allow to establish whether mannitol can be an alternative in those patients who will not obtain benefit with rhDNase since it is not known if included patients actually did not obtain benefit from rhDNase treatment. Furthermore, results indicate that combination of mannitol and rhDNase does not convey additional benefit. It therefore cannot be determined from this study whether or not mannitol will provide better benefit (or even worsening) in patients not fully responding to rhDNase.

It should be noted that the most appropriate presentation of the results for the overall population aged 6 years and over is considered to be in terms of FEV_1 as percent predicted normal not the unadjusted FEV_1 value that was applied according to study protocols.

Efficacy data and additional analyses

In the study DPM-CF-201, the effect of inhaled mannitol 420 mg appeared rather weak, although an effect is shown as compared to the control group. This study is presented by the applicant as a proof of concept study and no direct conclusion can be drawn as it was performed with different doses of mannitol (420 mg x 2 daily), different capsules of mannitol (filling with 30 mg powder), and different dry powder inhaler than those proposed for use in the present application for inhaled mannitol. About half of the studied population was treated with rhDNase at baseline (18 patients out of 39), but no interpretation can be provided on the results obtained in patients with concomitant use of RhDNase and those not using concomitant rhDNase as the study was not designed for this consideration.

The pivotal study DPM-CF-301 showed a statistically significant increase of 92 ml in FEV_1 by 26 weeks compared to the control group. This translates in an improvement of 2 to 3 % of FEV_1 as expressed as FEV_1 % predicted. The clinical relevance was questioned because of the large drop out rate, the statistical methods used to assess this change, and the large effect noted in the subgroup where mannitol was used in conjunction with rhDNase (change of 108 ml) compared with those using mannitol alone (69 ml).

The analysis of the primary endpoint in study DPM-CF-302, change from baseline in absolute FEV_1, in the overall population failed to achieve statistical significance (p=0.059) using the pre-specified statistical analysis method. Similarly the analysis of change from baseline of FEV_1 as percentage of predicted normal did not demonstrate a statistically significant difference (p=0.052). It is of note that the European guideline on multiplicity issues in clinical trials (CPMP/EWP/908/99) concludes that claims on statistically significant and clinically relevant findings based on subgroups are possible only after the primary objective has been achieved and if pre-specified. This is not the case in this study.

The applicant has argued that an unexpectedly large change between screening and baseline in the control group had contributed to a reduced treatment effect in the primary endpoint of study DPM-CF-302. Although this may be true, it is not acceptable to conduct a second analysis using a post-hoc baseline correction using the average of the screening and baseline values in order to obtain a significant result. As described in current European guidance on adjustment for baseline covariates (CPMP/EWP/2863/99) the analysis of change from baseline without adjusting in the model for baseline as a covariate is not appropriate. There is no scientific rationale to support the adjustment used in the post-hoc analysis which is not accepted.

It is unclear if the problem of high rates of missing data was limited to a particular subgroup of patients such as children or if it was distributed evenly across all subgroups of the population. This raises concerns over the quality of the data provided, especially by study DPM-CF-301.

Sensitivity analysis clearly indicates the lack of consistency of the estimated treatment difference in study DPM-CF-301. The discontinuation rate for study DPM-CF-302 is considerably lower than for study DPM-CF-301, although certainly not negligible, being slightly less than 15%. However the sensitivity analysis for study DPM-CF-302 presents more consistent estimates of treatment difference using the same analysis methods as applied for study DPM-CF-301, although somewhat lower around 2% in terms of change from baseline in percentage predicted normal FEV_1.

Thus it may be argued that the important issue is not which analysis method provides the most appropriate estimate but whether the different methods of handling the missing data have a profound effect on the estimate or whether it remains fairly consistent indicating that the results are robust. Therefore it is considered that due to the high discontinuation rate from study DPM-CF-301 the results are less reliable than those from study DPM-CF-302 where the applicant admits that higher levels of training were provided to the study centres based on the experience gained from the earlier study. As the quality of the two studies is considered to be different the pooled data does not necessarily provide better estimates of the treatment difference.

The relevance of the improvement in FEV_1 seen in the rhDNase and mannitol users' strata is not clear. As the actual use in the rhDNase strata during the study period is not clarified by the applicant, no reliable conclusion regarding the efficacy and safety of mannitol alone or as add on therapy to rhDNase can be drawn from the results presented by the applicant. If it is assumed that included patients maintained rhDNase use unchanged during the study, several issues arise.

Firstly, the sub therapeutic dose of the control group, inhaled mannitol 50 mg bid, is questionable. In the control group of rhDNase non users strata (assumed to correspond to mannitol 50 mg BD as the sole mucoactive drug being administered) least squares means estimates for FEV_1 absolute change from baseline at week 26 was 88.7 ml (95% CI 32.12, 145.27) in study DPM-CF-301 and 78.44 ml (95% CI -41.50, 198.38) in study DPM-CF-302. However, patients were pre-treated with a beta agonist, which might increase FEV_1 by 10-15%. In this subgroup, the change from baseline in absolute FEV_1 reached the threshold that was defined as clinically significant in the statistical analysis plan (>70 ml was the threshold of statistical hypothesis). Therefore the effect of 50 mg might not be sub-therapeutic, as a significant effect was observed. The adequacy of the control is questionable especially with regards to the between groups comparison of the incidences of adverse events, where the sensitivity would be limited and no reliable conclusion can be drawn on safety assessment. The dose of 50 mg is in the middle of the range used as a bronchoprovocation test and may induce bronchoconstriction during exacerbations even if initial falls in FEV_1 at screening were below 20%.

When considering the effect on change in absolute FEV_1 from baseline, the change from baseline with mannitol 400 mg bd appeared lower in the rhDNase users than in the rhDNase non user strata. This suggests that the addition of mannitol to rhDNase could possibly produce a smaller effect as compared to mannitol alone. This cannot be excluded, as it was evoked in the small phase II DPM-CF-203 study.

The only conclusion that would be allowed is that the combination of both treatments needs further evidence.

Moreover, there is a concern over the unexpected heterogeneity across the age groups, especially in study DPM-CF-302 where the applicant has been unable to explain the total lack of effect in the adolescent subgroup compared with the subgroups of children and adults.

The table below presents the number of patients in each subgroup by age and rhDNase use.

Table 17. Number of patients in subgroups by age and rhDNase use

	DPM-CF-301 N=295	**DPM-CF-302** N=305
Age in years n(%)		
6 - 11	48 (16.3)	59 (19.3)
12 – 17	57 (19.3)	95 (31.1)
≥ 18	190 (64.4)	151 (49.5)
rhDNase use n(%)		
User	163 (55.3)	229 (75.1)

Results for the overall population as well as the subgroups by age for the change from baseline in FEV_1 as percentage of predicted normal are summarised below. Although the table above indicates the numbers of patients in each subgroup, the numbers included in the analysis presented in the table below have not been provided by the applicant. As the trial has not been powered for individual subgroups by age, the p-values for the subgroups are not important. However, the lack of consistency of effect across age groups with different patterns in the two studies is clearly shown.

Table 18. Change from baseline in FEV_1 as percentage of predicted normal by age

DPM-CF-301a (N = 272)			**DPM-CF-302** (N = 297)		
Estimated difference	95% CI	p-value	Estimated difference	95% CI	p-value
Overall population					
2.40	(0.94, 3.85)	0.001	1.87	(-0.02, 3.75)	0.052
Children aged 6-11 years					
0.66	(-2.96, 4.27)	0.721	4.76	(0.55, 8.97)	0.027
Adolescents aged 12-17 years					
2.68	(-0.53, 5.88)	0.102	-0.43	(-3.77, 2.91)	0.801
Adults aged 18 years and over					
2.71	(0.88, 4.54)	0.004	2.33	(-0.40, 5.06)	0.095

It is important to note that although the percentage of children and adolescents in study DPM-CF-301 is relatively small with two thirds of the patients 18 years or over, in study DPM-CF-302 over 30% of the patients are in the adolescent subgroup with almost a further 20% under 12 years. Therefore, the subgroups by age are fairly well represented although the study is not powered for statistical significance in the subgroups.

A possible explanation could be lack of compliance in the adolescent population. Although information has been provided for the overall population which would suggest that average compliance was reasonably high at 94%, unfortunately this information has not been provided by age subgroup, but the data on compliance provided do not indicate there was an issue with it. Furthermore, estimation of compliance is possibly unreliable since it was based only on counting returned unused mediation and empty blister packaging. Moreover, lack of compliance cannot justify the differences in results seen in children under 12 in the two studies. A reasonable explanation for these heterogenic results seen in

patients under 18 can not be found; this renders the results of both phase III studies – including the results in the adults only group – unreliable, as there is not sufficient confidence that the consistency seen in adults was not by chance.

Overall, the FEF 25-75 mean changes from baseline were lesser in the mannitol 400 mg group as compared to the control group for both adolescent and paediatric groups. This observation is worthy to be considered since FEF25-75 is generally more accurate to assess the small airways. The evidence of improvement of clearance of mucus in distal and small airways is lacking. In the presented data in children the 50 mg dose has a significant effect on FEV_1 and overall the FEF25-75 results were lowered with the full dose of 400 mg mannitol as compared to mannitol 50 mg. It could also suggest that the mannitol 400 mg might be rather deleterious as compared to lower dose of 50 mg in children with small airways, maybe due to a elevated dose that would exert a "too great increased in viscosity" with inefficient mucociliary clearance. Clearly the appropriate dose in paediatrics need to be further investigated to be determined.

The pivotal studies (DPM-CF-301 and DPM-CF-302) do not provide adequate evidence of efficacy. The change in FEV_1 % predicted is very small (around 2-3%) and the clinical relevance of the effect observed on FEV_1 has not been established. The magnitude of the effect size is very small and not clinically significant. In clinical practice such small differences in FEV_1 are not detected and cumulative benefit was not demonstrated.

2.5.4. Conclusions on the clinical efficacy

In both pivotal Phase 3 studies the effect size for FEV_1 is very small and cannot be recognised as clinically significant.

The lack of consistency across the trials in the individual age groups questions the value of the pooled analysis. Moreover there is serious concern over the lack of consistency both within the trials across age groups and between the two studies.

There is a serious concern over the differences in effect across the age groups which have not been explained and therefore raise concerns about the confidence in results of pivotal studies in general.

Studies DPM-CF-301 and DPM-CF-302 do not establish the benefit of inhaled mannitol 400 mg BD as add on therapy to rhDNase, nor as alternative to rhDNase, in the claimed population of cystic fibrosis patients.

2.6. Clinical safety

Patient exposure

The use of 400 mg inhaled mannitol has been studied in Cystic Fibrosis patients in studies, DPM-CF-201, DPM-CF-202, DPM-CF-203, DPM-CF-301 and DPM-302 with a total of 511 patients exposed. The applicant has also been studying this dose in patients with bronchiectasis in studies DPM-B-201, DPM-B-202 and at dose of 320 mg bd in study DPM-B-301, with a total of 289 patients exposed. This indicates that the overall safety sample represents 800 patients. In the bronchiectasis study DPM-B-301 a further 99 patients were exposed to inhaled mannitol for 1 year.

The applicant has reported that as of February 2011 256 patients have received inhaled mannitol for treatment of Cystic fibrosis outside clinical studies.

Adverse events

Inhaled mannitol at a dose of 400 mg bd has been associated with adverse events which affect the respiratory tract (area it is delivered in) as well as the gastro-intestinal tract. The most common respiratory tract adverse event is cough, haemoptysis, pharyngolaryngeal pain. When mannitol is used in association with rhDNase there is a higher frequency of reports of cough, wheezing and haemoptysis (for the cough the difference is twice). Gastrointestinal tract associated adverse events are clearly linked to some of the inhaled mannitol being swallowed by the patient, abdominal pain being the most common event.

Table 19. Treatment-Emergent Adverse Events Experienced by ≥2% of Patients in Either Treatment Group or Overall in Blinded Phase of Combined Studies DPM-CF-301 and DPM-CF-302 (Safety Population)

MedDRA System Organ Class Preferred Term[1]	DPM-CF-301		DPM-CF-302		DPM-CF-301+DPM-CF-302	
	Bronchitol N=177 n (%)	Control N=118 n (%)	Bronchitol N=184 n (%)	Control N=121 n (%)	Bronchitol N=361 n (%)	Control N=239 n (%)
Patients with ≥ TEAE	**154 (87.0)**	**109 (92.4)**	**165 (89.7)**	**106 (87.6)**	**319 (88.4)**	**215 (90.0)**
Ear and labyrinth disorders	**8 (4.5)**	**4 (3.4)**	**5 (2.7)**	**0 (0.0)**	**13 (3.6)**	**4 (1.7)**
Ear pain	5 (2.8)	4 (3.4)	5 (2.7)	0 (0.0)	10 (2.8)	4 (1.7)
Gastrointestinal disorders	**55 (31.1)**	**33 (28.0)**	**52 (28.3)**	**43 (35.5)**	**107 (29.6)**	**76 (31.8)**
Abdominal pain	6 (3.4)	8 (6.8)	14 (7.6)	8 (6.6)	20 (5.5)	16 (6.7)
Abdominal pain upper	12 (6.8)	7 (5.9)	6 (3.3)	7 (5.8)	18 (5.0)	14 (5.9)
Constipation	6 (3.4)	5 (4.2)	1 (0.5)	3 (2.5)	7 (1.9)	8 (3.3)
Diarrhoea	9 (5.1)	1 (0.8)	8 (4.3)	5 (4.1)	17 (4.7)	6 (2.5)
Distal intestinal obstruction syndrome	3 (1.7)	0 (0.0)	1 (0.5)	3 (2.5)	4 (1.1)	3 (1.3)
Faecaloma	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	3 (1.3)
Intestinal obstruction	0 (0.0)	2 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	4 (1.7)
Nausea	4 (2.3)	5 (4.2)	3 (1.6)	2 (1.7)	7 (1.9)	7 (2.9)
Post-tussive vomiting	2 (1.1)	0 (0.0)	6 (3.3)	2 (1.7)	8 (2.2)	2 (0.8)
Stomach discomfort	1 (0.6)	3 (2.5)	1 (0.5)	3 (2.5)	2 (0.6)	6 (2.5)
Toothache	9 (5.1)	3 (2.5)	3 (1.6)	3 (2.5)	12 (3.3)	6 (2.5)
Vomiting	13 (7.3)	4 (3.4)	9 (4.9)	2 (1.7)	22 (6.1)	6 (2.5)
General disorders and administration site conditions	**76 (42.9)**	**54 (45.8)**	**93 (50.5)**	**62 (51.2)**	**169 (46.8)**	**116 (48.5)**
Chest discomfort	6 (3.4)	2 (1.7)	3 (1.6)	2 (1.7)	9 (2.5)	4 (1.7)
Condition aggravated	57 (32.2)	42 (35.6)	76 (41.3)	54 (44.6)	133 (36.8)	96 (40.2)
Chest pain	1 (0.6)	3 (2.5)	0 (0.0)	0 (0.0)	1 (0.3)	3 (1.3)
Fatigue	5 (2.8)	3 (2.5)	3 (1.6)	5 (4.1)	8 (2.2)	8 (3.3)
Influenza like illness	4 (2.3)	1 (0.8)	5 (2.7)	2 (1.7)	9 (2.5)	3 (1.3)
Malaise	3 (1.7)	3 (2.5)	3 (1.6)	0 (0.0)	6 (1.7)	3 (1.3)
Pyrexia	7 (4.0)	2 (1.7)	17 (9.2)	13 (10.7)	24 (6.6)	15 (6.3)

MedDRA System Organ Class Preferred Term[1]	DPM-CF-301		DPM-CF-302		DPM-CF-301+DPM-CF-302	
	Bronchitol N=177 n (%)	Control N=118 n (%)	Bronchitol N=184 n (%)	Control N=121 n (%)	Bronchitol N=361 n (%)	Control N=239 n (%)
Infections and infestations	**69 (39.0)**	**56 (47.5)**	**80 (43.5)**	**50 (41.3)**	**149 (41.3)**	**106 (44.4)**
Bronchitis	0 (0.0)	0 (0.0)	7 (3.8)	5 (4.1)	7 (1.9)	5 (2.1)
Pseudomonas infection	0 (0.0)	0 (0.0)	1 (0.5)	3 (2.5)	1 (0.3)	3 (1.3)
Influenza	2 (1.1)	1 (0.8)	6 (3.3)	5 (4.1)	8 (2.2)	6 (2.5)
Lower respiratory tract infection	15 (8.5)	20 (16.9)	7 (3.8)	4 (3.3)	22 (6.1)	24 (10.0)
Nasopharyngitis	25 (14.1)	17 (14.4)	11 (6.0)	6 (5.0)	36 (10.0)	23 (9.6)
Oral candidiasis	4 (2.3)	2 (1.7)	0 (0.0)	2 (1.7)	4 (1.1)	4 (1.7)
Pharyngitis	0 (0.0)	2 (1.7)	7 (3.8)	2 (1.7)	7 (1.9)	4 (1.7)
Rhinitis	0 (0.0)	2 (1.7)	6 (3.3)	1 (0.8)	6 (1.7)	3 (1.3)
Sinusitis	3 (1.7)	1 (0.8)	8 (4.3)	7 (5.8)	11 (3.0)	8 (3.3)
Tonsillitis	6 (3.4)	2 (1.7)	0 (0.0)	0 (0.0)	6 (1.7)	2 (0.8)
Upper respiratory tract infection	14 (7.9)	8 (6.8)	10 (5.4)	11 (9.1)	24 (6.6)	19 (7.9)
Viral infection	3 (1.7)	3 (2.5)	1 (0.5)	0 (0.0)	4 (1.1)	3 (1.3)
Viral upper respiratory tract infection	0 (0.0)	4 (3.4)	1 (0.5)	0 (0.0)	1 (0.3)	4 (1.7)
Investigations	**41 (23.2)**	**27 (22.9)**	**16 (8.7)**	**6 (5.0)**	**57 (15.8)**	**33 (13.8)**
Fungus sputum test positive	7 (4.0)	3 (2.5)	2 (1.1)	0 (0.0)	9 (2.5)	3 (1.3)
Bacteria sputum identified	33 (18.6)	22 (18.6)	6 (3.3)	5 (4.1)	39 (10.8)	27 (11.3)
Musculoskeletal and connective tissue disorders	**32 (18.1)**	**18 (15.3)**	**22 (12.0)**	**17 (14.0)**	**54 (15.0)**	**35 (14.6)**
Back pain	7 (4.0)	7 (5.9)	3 (1.6)	1 (0.8)	10 (2.8)	8 (3.3)
Musculoskeletal chest pain	5 (2.8)	2 (1.7)	2 (1.1)	3 (2.5)	7 (1.9)	5 (2.1)
Musculoskeletal pain	4 (2.3)	1 (0.8)	3 (1.6)	3 (2.5)	7 (1.9)	4 (1.7)
Pain in extremity	4 (2.3)	2 (1.7)	6 (3.3)	2 (1.7)	10 (2.8)	4 (1.7)
Arthralgia	12 (6.8)	7 (5.9)	2 (1.1)	0 (0.0)	14 (3.9)	7 (2.9)
Nervous system disorders	**43 (24.3)**	**30 (25.4)**	**28 (15.2)**	**29 (24.0)**	**71 (19.7)**	**59 (24.7)**
Dizziness	2 (1.1)	1 (0.8)	2 (1.1)	5 (4.1)	4 (1.1)	6 (2.5)
Headache	38 (21.5)	28 (23.7)	26 (14.1)	22 (18.2)	64 (17.7)	50 (20.9)
Migraine	3 (1.7)	1 (0.8)	2 (1.1)	3 (2.5)	5 (1.4)	4 (1.7)
Sinus headache	4 (2.3)	1 (0.8)	0 (0.0)	0 (0.0)	4 (1.1)	1 (0.4)
Psychiatric disorders	**4 (2.3)**	**2 (1.7)**	**8 (4.3)**	**2 (1.7)**	**12 (3.3)**	**4 (1.7)**
Insomnia	4 (2.3)	1 (0.8)	4 (2.2)	1 (0.8)	8 (2.2)	2 (0.8)
Reproductive system and breast disorders	**5 (2.8)**	**1 (0.8)**	**7 (3.8)**	**1 (0.8)**	**12 (3.3)**	**2 (0.8)**
Dysmenorrhoea	2 (1.1)	0 (0.0)	6 (3.3)	0 (0.0)	8 (2.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**91 (51.4)**	**54 (45.8)**	**70 (38.0)**	**35 (28.9)**	**161 (44.6)**	**89 (37.2)**
Cough	45 (25.4)	24 (20.3)	28 (15.2)	16 (13.2)	73 (20.2)	40 (16.7)
Epistaxis	5 (2.8)	2 (1.7)	5 (2.7)	3 (2.5)	10 (2.8)	5 (2.1)
Haemoptysis	21 (11.9)	10 (8.5)	13 (7.1)	3 (2.5)	34 (9.4)	13 (5.4)
Pharyngolaryngeal pain	24 (13.6)	5 (4.2)	19 (10.3)	13 (10.7)	43 (11.9)	18 (7.5)
Nasal congestion	4 (2.3)	4 (3.4)	4 (2.2)	3 (2.5)	8 (2.2)	7 (2.9)
Productive cough	12 (6.8)	7 (5.9)	5 (2.7)	2 (1.7)	17 (4.7)	9 (3.8)
Asthma	2 (1.1)	3 (2.5)	0 (0.0)	0 (0.0)	2 (0.6)	3 (1.3)
Rhinitis allergic	0 (0.0)	3 (2.5)	0 (0.0)	1 (0.8)	0 (0.0)	4 (1.7)
Rhinorrhoea	4 (2.3)	2 (1.7)	3 (1.6)	2 (1.7)	7 (1.9)	4 (1.7)
Wheezing	4 (2.3)	4 (3.4)	2 (1.1)	1 (0.8)	6 (1.7)	5 (2.1)
Skin and subcutaneous tissue disorders	**12 (6.8)**	**8 (6.8)**	**14 (7.6)**	**9 (7.4)**	**26 (7.2)**	**17 (7.1)**
Rash	4 (2.3)	4 (3.4)	4 (2.2)	2 (1.7)	8 (2.2)	6 (2.5)

Table 20. Treatment Emergent AEs ≥ 5% by SOC and PT Through the 26-Week Double-blind Phase, by rhDNase Use (Studies DPM-CF-301 and DPM-CF-302; Safety Population)

MedDRA System Organ Class Preferred Term[1]	rhDNase user		rhDNase non-user	
	Bronchitol N=233 n (%)	Control N=159 n (%)	Bronchitol N=128 n (%)	Control N=80 n (%)
At least one TEAE	**206 (88.4)**	**144 (90.6)**	**113 (88.3)**	**71 (88.8)**
Gastrointestinal disorders	**71 (30.5)**	**49 (30.8)**	**36 (28.1)**	**27 (33.8)**
Abdominal pain	12 (5.2)	10 (6.3)	8 (6.3)	6 (7.5)
Abdominal pain upper	11 (4.7)	11 (6.9)	7 (5.5)	3 (3.8)
Constipation	5 (2.1)	4 (2.5)	2 (1.6)	4 (5.0)
Stomach discomfort	1 (0.4)	1 (0.6)	1 (0.8)	5 (6.3)
Toothache	7 (3.0)	2 (1.3)	5 (3.9)	4 (5.0)
Vomiting	17 (7.3)	4 (2.5)	5 (3.9)	2 (2.5)
General disorders and administration site conditions	**120 (51.5)**	**83 (52.2)**	**49 (38.3)**	**33 (41.3)**
Condition aggravated	99 (42.5)	68 (42.8)	34 (26.6)	28 (35.0)
Pyrexia	16 (6.9)	11 (6.9)	8 (6.3)	4 (5.0)
Infections and infestations	**95 (40.8)**	**72 (45.3)**	**54 (42.2)**	**34 (42.5)**
Lower respiratory tract infection	12 (5.2)	14 (8.8)	10 (7.8)	10 (12.5)
Nasopharyngitis	21 (9.0)	13 (8.2)	15 (11.7)	10 (12.5)
Upper respiratory tract infection	15 (6.4)	14 (8.8)	9 (7.0)	5 (6.3)
Investigations	**38 (16.3)**	**19 (11.9)**	**19 (14.8)**	**14 (17.5)**
Bacteria sputum identified	25 (10.7)	15 (9.4)	14 (10.9)	12 (15.0)
Musculoskeletal and connective tissue disorders	**36 (15.5)**	**17 (10.7)**	**18 (14.1)**	**18 (22.5)**
Arthralgia	9 (3.9)	3 (1.9)	5 (3.9)	4 (5.0)
Nervous system disorders	**43 (18.5)**	**35 (22.0)**	**28 (21.9)**	**24 (30.0)**
Headache	41 (17.6)	31 (19.5)	23 (18.0)	19 (23.8)
Respiratory, thoracic and mediastinal disorders	**110 (47.2)**	**60 (37.7)**	**51 (39.8)**	**29 (36.3)**
Cough	55 (23.6)	27 (17.0)	18 (14.1)	13 (16.3)
Haemoptysis	25 (10.7)	10 (6.3)	9 (7.0)	3 (3.8)
Pharyngolaryngeal pain	29 (12.4)	11 (6.9)	14 (10.9)	7 (8.8)
Productive cough	14 (6.0)	7 (4.4)	3 (2.3)	2 (2.5)

[1] Patients are counted only once at the system organ class level. Within each system organ class, patients are counted once for each unique preferred term identified from the CRF verbatim text.

Of note spontaneous adverse event reports have been received for 21 patients (out of estimated 256 exposed) in named-patient and special access schemes.

Serious adverse event/deaths/other significant events

Three deaths have been reported (two in study DPM-B-301 due to pneumonia and acute myocardial infarction; one in study DPM-CF-302 after its completion due to pneumothorax), but were thought probably (pneumonia) or definitely (myocardial infarction and pneumothorax) not to be related to treatment.

In pivotal studies, during the 26-week randomised treatment phase, 77 (21.3%) and 65 (27.2%) patients in the inhaled mannitol and control groups, respectively, experienced SAEs. The most common by SOC were general disorders and administration site conditions with 60 (16.6%) and 45 (18.8%) patients in the inhaled mannitol and control groups, respectively, experiencing SAEs in this SOC, all of which were condition aggravated, which was the PT chosen to indicate an exacerbation of pulmonary

CF. Other common SAEs by PT included haemoptysis in 8 (2.2%) and 2 (0.8%) patients and lower respiratory tract infection in 4 (1.1%) and 5 (2.1%) patients in the inhaled mannitol and control groups, respectively.

Table 21. SAEs by SOC and PT through the 26-week double-blind phase (DPM-CF-301 and DPM-CF-302)

	DPM-CF-301		DPM-CF-302		DPM-CF-301+ DPM-CF-302	
MedDRA System Organ Class Preferred Term[1]	**Bronchitol N=177 n (%)**	**Control N=118 n (%)**	**Bronchitol N=184 n (%)**	**Control N=121 n (%)**	**Bronchitol N=361 n (%)**	**Control N=239 n (%)**
At least one SAE	**46 (26.0)**	**35 (29.7)**	**31 (16.8)**	**30 (24.8)**	**77 (21.3)**	**65 (27.2)**
Gastrointestinal disorders	**3 (1.7)**	**3 (2.5)**	**1 (0.5)**	**4 (3.3)**	**4 (1.1)**	**7 (2.9)**
Abdominal pain	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Constipation	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Distal intestinal obstruction syndrome	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.6)	1 (0.4)
Intestinal obstruction	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.8)
Pancreatitis	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Tooth impacted	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
General disorders and administration site conditions	**33 (18.6)**	**25 (21.2)**	**27 (14.7)**	**20 (16.5)**	**60 (16.6)**	**45 (18.8)**
Condition aggravated	33 (18.6)	25 (21.2)	27 (14.7)	20 (16.5)	60 (16.6)	45 (18.8)
Hepatobiliary disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Immune system disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Drug hypersensitivity	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Infections and infestations	**6 (3.4)**	**6 (5.1)**	**1 (0.5)**	**7 (5.8)**	**7 (1.9)**	**13 (5.4)**
Acute tonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Bronchopneumonia	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Cellulitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Lower respiratory tract infection	4 (2.3)	2 (1.7)	0 (0.0)	3 (2.5)	4 (1.1)	5 (2.1)
Lung infection pseudomonal	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Otitis media	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pilonidal cyst	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.8)
Pneumonia bacterial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)

MedDRA System Organ Class Preferred Term[1]	DPM-CF-301 Bronchitol N=177 n (%)	 Control N=118 n (%)	DPM-CF-302 Bronchitol N=184 n (%)	 Control N=121 n (%)	DPM-CF-301+ DPM-CF-302 Bronchitol N=361 n (%)	 Control N=239 n (%)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Viral infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Viral upper respiratory tract infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	**0 (0.0)**	**2 (1.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.8)**
Postoperative ileus	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Treatment noncompliance	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Investigations	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Bacteria sputum identified	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.6)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**2 (0.6)**	**0 (0.0)**
Diabetes mellitus	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.6)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**
Polymyositis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**9 (5.1)**	**4 (3.4)**	**2 (1.1)**	**3 (2.5)**	**11 (3.0)**	**7 (2.9)**
Asthmatic crisis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Bronchospasm	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Haemoptysis	6 (3.4)	2 (1.7)	2 (1.1)	0 (0.0)	8 (2.2)	2 (0.8)
Nasal polyps	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pleural effusion	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pleuritic pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)	1 (0.4)
Pneumothorax	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.8)
Surgical and medical procedures	**4 (2.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (1.1)**	**0 (0.0)**
Antibiotic prophylaxis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Catheterisation venous	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
Hospitalisation	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

[1] Patients are counted only once at the system organ class level. Within each system organ class, subjects are counted once for each unique preferred term identified from the CRF verbatim text.

More SAEs were experienced by rhDNase users than non-users in both treatment groups. The most common PT was condition aggravated, which occurred in 49 (21.0%) and 30 (18.9%) rhDNase users in the inhaled mannitol and control groups, respectively, and 11 (8.6%) and 15 (18.8%) rhDNase non-users in the respective treatment groups.

Table 22. SAEs by SOC and PT Through the 26-Week Double-blind Phase, by rhDNase Use (Studies DPM-CF-301 and DPM-CF-302; Safety Population)

MedDRA System Organ Class Preferred Term[1]	rhDNase user		rhDNase non-user	
	Bronchitol N=233 n (%)	Control N=159 n (%)	Bronchitol N=128 n (%)	Control N=80 n (%)
At least one serious TEAE	**58 (24.9)**	**45 (28.3)**	**19 (14.8)**	**20 (25.0)**
Gastrointestinal disorders	**2 (0.9)**	**5 (3.1)**	**2 (1.6)**	**2 (2.5)**
Abdominal pain	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Distal intestinal obstruction syndrome	1 (0.4)	1 (0.6)	1 (0.8)	0 (0.0)
Intestinal obstruction	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.3)
Pancreatitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Tooth impacted	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Vomiting	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**49 (21.0)**	**30 (18.9)**	**11 (8.6)**	**15 (18.8)**

MedDRA System Organ Class Preferred Term[1]	rhDNase user		rhDNase non-user	
	Bronchitol N=233 n (%)	Control N=159 n (%)	Bronchitol N=128 n (%)	Control N=80 n (%)
Condition aggravated	49 (21.0)	30 (18.9)	11 (8.6)	15 (18.8)
Hepatobiliary disorders	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Cholecystitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Drug hypersensitivity	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	**2 (0.9)**	**9 (5.7)**	**5 (3.9)**	**4 (5.0)**
Acute tonsillitis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Bronchopneumonia	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Lower respiratory tract infection	1 (0.4)	4 (2.5)	3 (2.3)	1 (1.3)
Lung infection pseudomonal	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Pilonidal cyst	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Pneumonia bacterial	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Viral upper respiratory tract infection	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**2 (1.3)**	**0 (0.0)**	**0 (0.0)**
Postoperative ileus	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Treatment noncompliance	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**
Bacteria sputum identified	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Metabolism and nutrition disorders	**2 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Diabetes mellitus	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**
Polymyositis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**7 (3.0)**	**6 (3.8)**	**4 (3.1)**	**1 (1.3)**
Asthmatic crisis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Bronchospasm	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Haemoptysis	5 (2.1)	1 (0.6)	3 (2.3)	1 (1.3)
Nasal polyps	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Pleural effusion	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pleuritic pain	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)
Pneumothorax	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Surgical and medical procedures	**2 (0.9)**	**0 (0.0)**	**2 (1.6)**	**0 (0.0)**
Antibiotic prophylaxis	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Catheterisation venous	1 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)
Hospitalisation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Patients are counted only once at the system organ class level. Within each system organ class, subjects are counted once for each unique preferred term identified from the CRF verbatim text.

Ten (2.8%) patients in the inhaled mannitol group and four (1.7%) patients in the control group, respectively, experienced at least one SAE considered possibly, probably or definitely related to study treatment. The most common SAEs by SOC were respiratory, thoracic and mediastinal disorders,

reported in 7 (1.9%) patients and one (0.4%) patient in the inhaled mannitol and control groups, respectively, of which all except one bronchospasm report were haemoptysis.

Table 23. Treatment-related SAEs by SOC and PT through the 26-week double-blind phase (DPM-CF-301 and DPM-CF-302)

	DPM-CF-301		DPM-CF-302		DPM-CF-301+DPM-CF-302	
MedDRA System Organ Class Preferred Term[1]	**Bronchitol N=177 n (%)**	**Control N=118 n (%)**	**Bronchitol N=184 n (%)**	**Control N=121 n (%)**	**Bronchitol N=361 n (%)**	**Control N=239 n (%)**
At least one Treatment-related SAE	**6 (3.4)**	**1 (0.8)**	**4 (2.2)**	**3 (2.5)**	**10 (2.8)**	**4 (1.7)**
General disorders and administration site conditions	**1 (0.6)**	**0 (0)**	**2 (1.1)**	**1 (0.8)**	**3 (0.8)**	**1 (0.4)**
Condition aggravated	1 (0.6)	0 (0)	2 (1.1)	1 (0.8)	3 (0.8)	1 (0.4)
Infections and infestations	**0 (0)**	**0 (0)**	**0 (0)**	**2 (1.7)**	**0 (0)**	**2 (0.8)**
Lower respiratory tract infection	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.4)
Pneumonia bacterial	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**5 (2.8)**	**1 (0.8)**	**2 (1.1)**	**0 (0)**	**7 (1.9)**	**1 (0.4)**
Bronchospasm	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)
Haemoptysis	4 (2.3)	1 (0.8)	2 (1.1)	0 (0)	6 (1.7)	1 (0.4)

[1] Patients are counted only once at the system organ class level. Within each system organ class, subjects are counted once for each unique preferred term identified from the CRF verbatim text.

Four fatal cases have been reported in named-patient and special access schemes, one involving respiratory failure. It is, however, difficult to determine inhaled mannitol's role in this fatality because there is no indication of the seriousness of the respiratory decline in the patient concerned.

Laboratory findings

There were no important abnormalities in laboratory tests in the data sets submitted.

Immunological events

There have been no immunological events reported.

Safety in special populations

66 paediatric patients and 88 adolescent patients received inhaled mannitol in Phase 3 CF trials. For all age groups, the three most commonly reported treatment related AEs were condition aggravated, headache and cough.

Table 24. Treatment emergent AEs ≥ 5% by SOC and PT through the 26-week double-blind phase by age (Studies DPM-CF-301 and DPM-CF-302 combined; Safety Population)

MedDRA System Organ Class Preferred Term[1]	Age 6-11 years		Age 12-17 years		Age ≥ 18 years	
	Bronchitol N=66 n (%)	Control N=41 n (%)	Bronchitol N=88 n (%)	Control N=64 n (%)	Bronchitol N=207 n (%)	Control N=134 n (%)
At least one TEAE	**58 (87.9)**	**40 (97.6)**	**83 (94.3)**	**60 (93.8)**	**178 (86.0)**	**115 (85.8)**
Ear and labyrinth disorders	**4 (6.1)**	**1 (2.4)**	**1 (1.1)**	**1 (1.6)**	**8 (3.9)**	**2 (1.5)**
Ear pain	4 (6.1)	1 (2.4)	1 (1.1)	1 (1.6)	5 (2.4)	2 (1.5)
Gastrointestinal disorders	**25 (37.9)**	**15 (36.6)**	**26 (29.5)**	**20 (31.3)**	**56 (27.1)**	**41 (30.6)**
Abdominal pain	8 (12.1)	4 (9.8)	6 (6.8)	8 (12.5)	6 (2.9)	4 (3.0)
Abdominal pain upper	5 (7.6)	0 (0.0)	5 (5.7)	6 (9.4)	8 (3.9)	8 (6.0)
Diarrhoea	3 (4.5)	1 (2.4)	7 (8.0)	1 (1.6)	7 (3.4)	4 (3.0)
Vomiting	8 (12.1)	1 (2.4)	3 (3.4)	2 (3.1)	11 (5.3)	3 (2.2)
General disorders and administration site conditions	**23 (34.8)**	**21 (51.2)**	**47 (53.4)**	**31 (48.4)**	**99 (47.8)**	**64 (47.8)**
Condition aggravated	17 (25.8)	19 (46.3)	39 (44.3)	22 (34.4)	77 (37.2)	55 (41.0)
Fatigue	2 (3.0)	3 (7.3)	1 (1.1)	1 (1.6)	5 (2.4)	4 (3.0)
Pyrexia	11 (16.7)	8 (19.5)	6 (6.8)	7 (10.9)	7 (3.4)	0 (0.0)
Infections and infestations	**34 (51.5)**	**21 (51.2)**	**46 (52.3)**	**28 (43.8)**	**69 (33.3)**	**57 (42.5)**
Bronchitis	3 (4.5)	3 (7.3)	3 (3.4)	2 (3.1)	1 (0.5)	0 (0.0)
Lower respiratory tract infection	3 (4.5)	3 (7.3)	2 (2.3)	4 (6.3)	17 (8.2)	17 (12.7)
Nasopharyngitis	10 (15.2)	3 (7.3)	8 (9.1)	5 (7.8)	18 (8.7)	15 (11.2)
Upper respiratory tract infection	7 (10.6)	2 (4.9)	9 (10.2)	7 (10.9)	8 (3.9)	10 (7.5)
Investigations	**10 (15.2)**	**5 (12.2)**	**15 (17.0)**	**12 (18.8)**	**32 (15.5)**	**16 (11.9)**
Bacteria sputum identified	6 (9.1)	4 (9.8)	8 (9.1)	11 (17.2)	25 (12.1)	12 (9.0)
Musculoskeletal and connective tissue disorders	**8 (12.1)**	**5 (12.2)**	**12 (13.6)**	**5 (7.8)**	**34 (16.4)**	**25 (18.7)**
Arthralgia	1 (1.5)	1 (2.4)	2 (2.3)	1 (1.6)	11 (5.3)	5 (3.7)
Nervous system disorders	**18 (27.3)**	**13 (31.7)**	**18 (20.5)**	**15 (23.4)**	**35 (16.9)**	**31 (23.1)**
Headache	16 (24.2)	11 (26.8)	16 (18.2)	13 (20.3)	32 (15.5)	26 (19.4)
Respiratory, thoracic and mediastinal disorders	**31 (47.0)**	**20 (48.8)**	**45 (51.1)**	**24 (37.5)**	**85 (41.1)**	**45 (33.6)**
Cough	13 (19.7)	10 (24.4)	21 (23.9)	14 (21.9)	39 (18.8)	16 (11.9)
Epistaxis	4 (6.1)	1 (2.4)	2 (2.3)	0 (0.0)	4 (1.9)	4 (3.0)
Haemoptysis	4 (6.1)	0 (0.0)	8 (9.1)	2 (3.1)	22 (10.6)	11 (8.2)
Nasal congestion	4 (6.1)	2 (4.9)	1 (1.1)	3 (4.7)	3 (1.4)	2 (1.5)
Pharyngolaryngeal pain	11 (16.7)	4 (9.8)	12 (13.6)	7 (10.9)	20 (9.7)	7 (5.2)
Productive cough	4 (6.1)	4 (9.8)	7 (8.0)	1 (1.6)	6 (2.9)	4 (3.0)

Safety related to drug-drug interactions and other interactions

There was no indication of safety concerns due to drug-drug interactions. It should, however, be noted that an increased reporting rate of some adverse events (such as wheezing) was observed when rhDNase and mannitol were used together. This observation requires further investigation.

Discontinuation due to adverse events

42 patients (11.6%) in the inhaled mannitol group and 15 (6.3%) in the control group withdrew from Phase 3 CF studies due to treatment-related adverse events.

Table 25. Frequency of Subjects with Adverse Events Leading to Study Withdrawal During the Double Blind Phase (Studies DPM-CF-301 and DPM-CF-302; Safety Population)

MedDRA System Organ Class Preferred Term[1]	DPM-CF-301		DPM-CF-302		DPM-CF-301+DPM-CF-302	
	Bronchitol N=177 n (%)	Control N=118 n (%)	Bronchitol N=184 n (%)	Control N=121 n (%)	Bronchitol N=361 n (%)	Control N=239 n (%)
At least one adverse event leading to study discontinuation	**29 (16.4)**	**10 (8.5)**	**13 (7.1)**	**5 (4.1)**	**42 (11.6)**	**15 (6.3)**
Cardiac disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**1 (0.4)**
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Gastrooesophageal reflux disease	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
General disorders and administration site conditions	**10 (5.6)**	**2 (1.7)**	**3 (1.6)**	**1 (0.8)**	**13 (3.6)**	**3 (1.3)**
Chest discomfort	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)
Condition aggravated	7 (4.0)	2 (1.7)	1 (0.5)	1 (0.8)	8 (2.2)	3 (1.3)
Fatigue	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hernia pain	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Oedema peripheral	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Infections and infestations	**0 (0.0)**	**2 (1.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.8)**
Lower respiratory tract infection	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pneumonia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Nervous system disorders	**0 (0.0)**	**1 (0.8)**	**1 (0.5)**	**0 (0.0)**	**1 (0.3)**	**1 (0.4)**
Headache	0 (0.0)	1 (0.8)	1 (0.5)	0 (0.0)	1 (0.3)	1 (0.4)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Morbid thoughts	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**20 (11.3)**	**6 (5.1)**	**12 (6.5)**	**3 (2.5)**	**32 (8.9)**	**9 (3.8)**
Asthma	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Bronchospasm	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
Cough	11 (6.2)	4 (3.4)	7 (3.8)	2 (1.7)	18 (5.0)	6 (2.5)
Haemoptysis	5 (2.8)	0 (0.0)	1 (0.5)	0 (0.0)	6 (1.7)	0 (0.0)
Hyperventilation	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Obstructive airways disorder	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Pharyngolaryngeal pain	2 (1.1)	0 (0.0)	1 (0.5)	0 (0.0)	3 (0.8)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Productive cough	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Throat irritation	0 (0.0)	1 (0.8)	1 (0.5)	0 (0.0)	1 (0.3)	1 (0.4)
Wheezing	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)

The frequency of withdrawal from the study due to adverse events was low and the causes are in line with what could be expected from use of the product. There, however, is a concern since the studies (especially DPM-CF-301) had high drop out rate.

Post marketing experience

Bronchitol has not been marketed. The applicant, however, has provided some post marketing surveillance data for product inhaled mannitol used for bronchoprovocation testing, which includes 8 spontaneous adverse reaction reports and raise no concerns. The exposure to inhaled mannitol for bronchoprovocation testing as of April 2010 is estimated to be 59,812 patients.

2.6.1. Discussion on clinical safety

No treatment related fatal or life threatening adverse events were reported in clinical trials. Respiratory, thoracic and mediastinal disorders were the most frequent disorders.

The applicant was requested by the CHMP to discuss in detail the adverse events of interest from the two phase 3 studies – namely haemoptysis and bronchospasm. The latter is important also because mannitol is also used to provoke bronchoconstriction.

Haemoptysis was reported in considerably more patients in the inhaled mannitol arm compared to the control arm. In studies DPM-CF-301 and DPM-CF-302 combined, any haemoptysis was reported in 9.4% in the inhaled mannitol arm compared to 5.4% in the control arm. Of these severe were 1.1% in the inhaled mannitol arm compared to 0.4% in the control arm. The applicant then examined the frequency of haemoptysis either as a stand alone AE or as a reported symptom of a pulmonary exacerbation (PE). The incidence of haemoptysis was similar in the two treatment groups (15.8% versus 14.6% for the Inhaled mannitol and control arms, respectively). However, as the applicant is claiming that inhaled mannitol reduces the rate of PE this should have lead to less reporting of haemoptysis due to PE following the reduction of the rate of PE. Therefore, there is a possible link between inhaled mannitol and haemoptysis and further close monitoring of haemoptysis is necessary.

The applicant has analysed the reports of bronchoconstriction and associated events such as wheezing, dyspnoea and chest discomfort from the safety population of studies DPM-CF-301 and DPM-CF-302. In the overall population events of this type were reported in 6.1% in the inhaled mannitol group compared to 5% in the control group. There appears to be a similar number of reports related to bronchoconstriction. Patients are advised to receive a dose of bronchodilator 5 to 15 minutes before each dose of inhaled mannitol. The CHMP had a concern whether with long term use patients may become sensitised and not respond to bronchodilators, therefore additional discussion was requested from the applicant. The applicant had included bronchodilator response tests both at weeks 0 and 26 to demonstrate whether airways are sensitised by chronic use of inhaled mannitol. There was no change in both arms in the majority of patients (<92%), but the data was dichotomised (change from <12% to ≥12% reversibility) and therefore did not show the actual magnitude of the changes, which would have been more informative. Therefore no definitive conclusion can be made on this issue.

2.6.2. Conclusions on clinical safety

The data so far does not indicate a big difference in events associated with bronchoconstriction between the two groups. However, since inhaled mannitol is being used to provoke bronchoconstriction risk of bronchoconstriction requires close further monitoring.

There appears to be a possible link between haemoptysis and use of mannitol, which requires close further monitoring.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

The RMP version 1.3 proposed additional pharmacovigilance activities and additional risk minimisation activities. During the evaluation the CHMP has questioned the methodology proposed to be used to verify the success of the additional risk minimisation activities and some aspects of the design proposed for the CF registry study.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at the time of adoption of CHMP opinion and in view of benefit-risk balance conclusions and CHMP recommendations in section 3 below.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Benefits

Beneficial effects

Inhalation treatment with mannitol is intended to improve mucociliary clearance by creating an osmotic gradient that leads to changes in surface properties in the airways. In the armamentarium of medicinal products for the treatment of cystic fibrosis, inhaled mannitol would therefore be placed as a mucolytic agent. In general, a clinically relevant improvement of lung function through measurement of FEV_1 is considered adequate for the demonstration of efficacy for such products.

Two phase 3 studies of similar design have been performed (DPM-CF-301 and DPM-CF-302), investigating the dose of inhaled mannitol 400 mg twice daily compared to a "subtherapeutic" dose of 50 mg twice daily. The studies allowed the use of rhDNase. Study DPM-CF-301 showed a statistically significant overall treatment effect of 54.17 ml in FEV_1 over 26 weeks compared to the control group ($p<0.001$). The pre-specified analysis of the primary endpoint in study DPM-CF-302 showed overall treatment effect over 26 weeks in change in absolute FEV_1 of 54.14 ml as compared to the control group, which was not statistically significant ($p=0.059$); additional post-hoc analyses were presented by the applicant.

Overall treatment with mannitol showed an improvement of approximately 2-3% compared with the control group over 26 weeks in terms of percent predicted FEV_1. The clinical relevance of this minor improvement has not been established. Compared to the effect size of other treatments, such as bronchodilators or inhaled tobramycin, the size of the effect of inhaled mannitol on lung function is considered small and with questionable clinical importance. Moreover, there was no significant difference on the secondary parameters as exacerbation rate, use of systemic antibiotics, hospitalisations and quality of life as compared to the comparator group.

Stratification by rhDNase at screening showed in study DPM-CF-301 a statistically significant difference in FEV_1 at week 26 in the so called rhDNase users stratum (108 ml) but not in the so called rhDNase non-users stratum (69 ml). In study DPM-CF-302 the difference was not statistically significant in

either stratum. There appears however in both studies to be a trend that the mean change in absolute FEV_1 was higher in the stratum of rhDNase non-users as compared to the stratum of rhDNase users.

Patients above the age of 6 years were included in these two studies. Based on the available data, and in the absence of stratification, there appear to be three subgroups in terms of treatment effect, 6-11 years, 12-17 years and adults. However, given the limitation of the data in the paediatric population, the applicant revised the claimed indication during the procedure to use only in adults.

Uncertainty in the knowledge about the beneficial effects

The major uncertainty is the fact that the reliability of the results from the two pivotal studies (DPM-CF-301 and DPM-CF-302) is questionable.

- Study DPM-CF-301 has failed to provide robust evidence of efficacy due to the high drop-out rate of approximately 30%. The pre-defined statistical methods are not deemed suitable for dealing with high drop-out rates seen in this study. Sensitivity analyses clearly indicate the lack of consistency of the estimated treatment difference in this study.
- Study DPM-CF-302 failed to reach statistical significance for its primary endpoint, which prevents from drawing conclusions about the results in study population subgroups. The post-hoc analysis proposed by the applicant was not considered acceptable. Furthermore, this study also demonstrated lack of consistency across age groups despite different groups being fairly well represented, which is a cause for concern since it questions the reliability of the estimates for both the overall population and the adult subgroup. The effect in children was found to be higher than in either adults or adolescents, with no effect in the adolescent subgroup.

Overall, there is a lack of consistency between the two studies in the estimated treatment effect in the overall population and, in particular, in children and adolescents (though the estimates for adults were similar between the two studies)". As the quality of the two pivotal studies is considered to be different, the pooled data is not expected to provide better estimates of treatment difference.

With regard to the comparator, the effect of 50 mg of inhaled mannitol might not be sub-therapeutic, as a significant effect was observed in rhDNase non users in study DPM-CF-302, which raises doubts about the adequacy of the chosen control medication dose.

The applicant claims an indication as add-on treatment to DNAse as well as the use in patients ineligible, intolerant, or inadequately responsive to rhDNase. However, the design of phase 3 studies has not defined the subgroup of rhDNase users the same way as in the proposed indication. During the studies it was not established upon inclusion of non-users of rhDNase if they would or would not benefit from it, were they taking rhDNase. The actual use of rhDNase by subjects during the pivotal trials is unknown; therefore no reliable conclusion regarding the efficacy and safety of mannitol alone or as an add-on therapy to rhDNase can be drawn from the results presented. In addition, the large effect in the subgroup of rhDNase non-users, as compared to the users, has not been sufficiently explained. This raises also concerns of a possible decrease in efficacy of inhaled mannitol when used in combination with rhDNase.

Given the uncertainties around the available efficacy data, the appropriateness of the actual dose of inhaled mannitol studied in the pivotal studies remains questionable. The potential effects of higher doses of inhaled mannitol have not been investigated.

3.2. Risks

Unfavourable effects

The most important adverse effects were respiratory, thoracic and mediastinal disorders.

Mannitol is already used in the EU as an inhaled product to test for bronchial hyper-responsiveness. Although a bronchocontrictor response to mannitol was used as an exclusion criterion in the main trials, the use of such an exclusion test may not be so rigorous outside a clinical trial. In addition, given that airway hyper-responsiveness is common in cystic fibrosis, a patient who is negative to such a challenge may become positive during an exacerbation, in which case treatment with mannitol would increase the potential severity of the exacerbation.

The major adverse event-related concern was an increase in bronchoconstriction when mannitol was used in patients receiving inhaled rhDNase. There was also a small increase in haemoptysis which was consistently seen in both pivotal studies.

Uncertainty in the knowledge about the unfavourable effects

The increase in wheezing/bronchoconstriction among patients receiving mannitol within rhDNase users' strata highlights the potential increased risk related to the use of these two therapies together. It is therefore uncertain whether the product should be used with or without rhDNase.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

There is a small potential benefit in FEV_1, without supporting clinical endpoint evidence, in two trials that have design limitations. The clinical relevance of this small potential benefit has not been established. The heterogeneity of the results seen across age groups in both studies raises serious concerns about the overall validity of the results, recognising that the claimed indication is in adults only. In addition, the benefits of the use together with rhDNase are uncertain given the observed inconsistencies.

There is an identified risk for potentially serious adverse events such as bronchoconstriction and haemoptysis, which with the uncertainties on the magnitude of effect renders the risk benefit balance negative.

The evidence of favourable risk benefit is lacking.

Benefit-risk balance

Given the uncertainties with efficacy in the claimed patient population and the identified risks of bronchoconstriction and haemoptysis the benefit-risk balance for inhaled mannitol in the proposed indication is considered negative.

3.3. Discussion on the Benefit-Risk Balance

Treatment of cystic fibrosis requires a multidisciplinary approach. With regard to the pulmonary management, the mainstay being inhaled and systemic antibiotics to prevent or treat pulmonary infections, and therapy with mucoactive drugs to improve airway mucosal clearance of lower-airway secretions and treat chronic obstructive pulmonary disease.

Inhaled mannitol was developed as mucus rehydrating drug for the treatment of cystic fibrosis. However, the two pivotal studies failed to demonstrate robust evidence of efficacy. In particular, the large drop out in study DPM-CF-301 limits the confidence in the effect size seen, which in any case was of questionable clinical relevance. Study DPM-CF-302 was essentially a failed study as statistical significance in the primary endpoint was not achieved using the pre-specified analysis. Furthermore, in this study the results were inconsistent across the age groups with little or no effect in adolescents and not consistent with the findings in study DPM-CF-301. Therefore there is considerable uncertainty on the robustness of the results seen in the two pivotal studies.

The applicant initially claimed the use of the product also in the paediatric population, but has subsequently restricted the use in adults only given the concerns expressed by the CHMP about the available data below the age of 18 years. With regard to the use with or without rhDNase as claimed by the applicant, i.e. add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase, the available evidence is considered insufficient and inconsistent.

Therefore, the CHMP concluded that the limited efficacy is considered not to outweigh the observed and potential safety concerns, relating primarily to bronchoconstriction events and haemoptysis, such that a favourable benefit-risk cannot be concluded.

Some CHMP members expressed a divergent view stating that available clinical data from the two pivotal studies show an effect on FEV_1 which is small but nevertheless considered to be of clinical relevance. This particularly because the product is complementary to existing expectorant treatments due to its mechanism of action hence providing an alternative treatment in a complex and individualised treatment strategy. The remaining uncertainties with respect to the magnitude of the effect are accepted in this context. The principal adverse events associated with its use, cough and minor haemoptysis may be considered as tolerability rather than safety problems and are not a sufficient ground to refuse an authorisation.

4. Recommendations

4.1. Outcome

Based on the CHMP review of data on quality, safety and efficacy for Bronchitol in the treatment of cystic fibrosis, the CHMP considered by majority decision that the efficacy of the above mentioned medicinal product was not sufficiently demonstrated, and, therefore recommended the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considered that:

The pivotal studies (DPM-CF-301 and DPM-CF-302) are considered not to provide adequate evidence of efficacy in the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase. In particular:

- The clinical relevance of the treatment effects observed on FEV_1 has not been established.
- Uncertainties remain in the magnitude of the effect following treatment with Bronchitol. In study DPM-CF-301 a high proportion of patient withdrawals complicates inference. The pattern of estimated treatment effects is inconsistent within each study across important subgroups defined by age (children, adolescents and adults) and the pattern of effects in each age group is inconsistent between studies. In light of the limited effects observed, these internal inconsistencies result in unacceptable uncertainty in the estimated treatment effect for the proposed population.

The limited efficacy, of uncertain magnitude, is considered not to outweigh the observed and potential safety concerns, relating primarily to bronchoconstriction events and haemoptysis, such that a favourable benefit-risk cannot be concluded.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and conditions to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

4.2. Re-examination of the CHMP opinion of 23 June 2011

Following the CHMP conclusion that Bronchitol was not approvable for the following indication: *"Treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase"*, the applicant submitted detailed grounds for the re-examination of the grounds for refusal on 19 August 2011.

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad-hoc expert meeting on 3 October 2011 inviting the experts, including patients representatives, to provide their views on the questions posed by the CHMP in relation to the marketing authorisation application, taking into account the applicant's response to the grounds for refusal.

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP on 17th October 2011.

4.2.1. Detailed grounds for re-examination submitted by the applicant

Ground 1: *The clinical relevance of the treatment effects observed on FEV_1 has not been established.*

<u>Applicant´s position:</u> (summarised)

The applicant provided the following evidence to support the clinical relevance of Bronchitol's treatment effects:

- The clinical relevance of the FEV_1 benefit noted in both pivotal studies in the overall population and across age subgroups is supported by expert opinion.
- A sustained FEV_1 benefit observed with Bronchitol is highly meaningful in the context of declining lung function in CF
- Bronchitol's size of effect in FEV_1 is comparable to existing CF therapies
- Secondary endpoints all support the primary FEV_1 including significant improvements in FVC, increased mucus clearance and reductions in exacerbations.

Although the last proposed indication at the time of the re-examination was for adults only, as the CHMP had concerns regarding restriction of the indication, overall population data was presented in the following sections alongside both age and rhDNase subgroup data.

<u>Estimated Treatment Effect size</u>

In the grounds for refusal the magnitude of the treatment effect obtained using Bronchitol has been questioned, rather than an absence of treatment effect. The uncertainty of exact treatment effect size then led to difficulty in determining clinical relevance

Data presented in the following sections was generated using the mixed model analysis of repeated measures as the estimate of Bronchitol's efficacy from this statistical analysis plan (SAP) defined primary model. It is representative of a number of sensitivity analyses performed to take into account missing data due to withdrawals. It is also supported using analyses based on last and baseline observation carried forward (LOCF & BOCF), as requested by CHMP.

Absolute change over study in FEV_1 % predicted normal

	Study 301			Study 302			Pooled		
	LS mean	95% CI	P value	LS mean	95% CI	P value	LS mean	95% CI	P value
Mannitol	2.85	1.88, 3.83	0.001	3.13	1.65, 4.62	<0.001	2.99	2.12,3.86	<0.001
Control	0.46	-0.66, 1.57	0.42	1.27	-0.43, 2.96	0.142	0.87	-0.13,1.87	0.088
Relative (%) change over study in FEV1% predicted normal									
Mannitol	4.82	3.12, 6.52	<0.001	6.73	4.12,9.33	<0.001	5.81	4.28,7.35	<0.001
Control	1.31	-0.64, 3.27	0.187	3.13	0.16, 6.10	0.039	2.26	0.50, 4.01	0.012

The treatment effects estimated by MMRM model from both studies are consistent with those estimated based on cross-sectional analysis (ANCOVA) of Week 26 data, which are imputed by LOCF or BOCF as requested by CHMP. All age and rhDNase subgroups from both studies provide estimates of treatment effect which consistently favour Bronchitol. The overlap of the 95% CIs among all subgroups is substantial, which indicates that there is no statistical evidence to support the concept that the treatment effects are not consistent across the subgroups.

The results consistently demonstrate Bronchitol's benefit on top of current standard of care (including rhDNase) in this orphan designated indication. The adult population similarly showed benefit in both the rhDNase user and rhDNase unsuitable subgroups. The observed relatively larger variation among children and adolescents subgroups is what would be expected with the small sample sizes included in these subgroups and expected sampling variation.

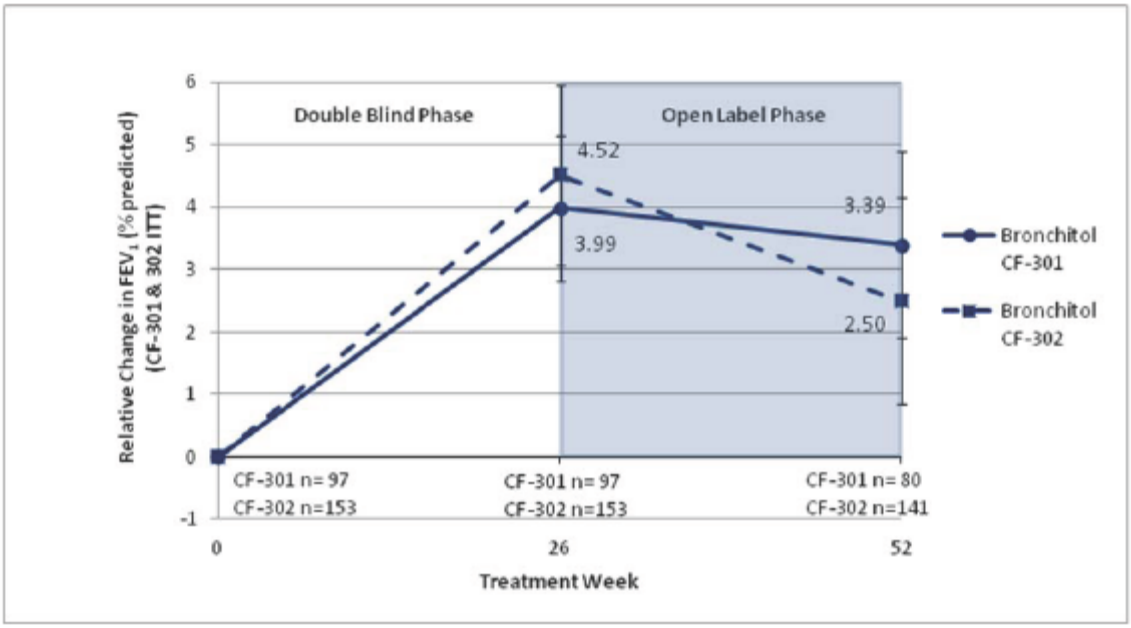
Both studies were designed to assess the treatment effect for the overall population and in light of the evidence above, Pharmaxis believe that the overall treatment effect of around 3.6% relative change in % predicted for both studies is representative of the best estimate of treatment effect for all subgroups in these studies.

Sustained FEV_1 benefit observed with Bronchitol

Another important component of the clinical relevance of Bronchitol's efficacy is that it has been demonstrated to be sustained out to 52 weeks in both pivotal studies. The FEV_1 change (in relative % predicted) in those patients who entered the open label phase of both pivotal studies was plotted over time to show a sustained improvement for the Bronchitol arm across 52 weeks (Figure 4).

Although the change in FEV_1 in the Bronchitol arm decreases from 26 to 52 weeks in both studies, the change in FEV_1 at week 52 is still well above 0 demonstrating the sustained improvement in FEV_1 over time. This is despite the predicted decline over one year expected in a CF population.

Figure 4: Relative change in FEV_1 % predicted in the Bronchitol Arm of Studies DPM-CF-301 and 302 over 1 year



Source: Appendix 7

Comparison of Bronchitol's size of effect in FEV_1 to existing CF therapies

Further evidence of the clinical relevance of Bronchitol's effect is provided when it is compared with other CF therapies currently used in the EU. The pooled effect of Bronchitol by change from baseline from both studies was comparable with rhDNase, and larger than that reported for hypertonic saline (HS) (Table 2).

Although inhaled antibiotics are less appropriate comparators, due to their antibacterial mode of action, these have been included here to demonstrate the variability in the FEV_1 benefit noted with tobramycin. When the original studies were performed large FEV_1 benefits (12%) were noted as patients were naive to treatment for *P. Aeruginosa*, whereas recent studies, which are more representative of how CF patients are currently treated, have shown more modest FEV_1 improvements (2.6%). More recent trials of inhaled aztreonam have examined only the first month of drug, when benefit may be most apparent. This is in contrast to Bronchitol which has shown continued benefit out to 52 weeks.

Table 2: Comparison of improvement in lung function by respiratory CF therapy

Drug	Bronchitol	Pulmozyme (rhDNase)	Hypertonic saline	Aztreonam		Tobramycin			
Source	Pooled Data	Fuchs *et al*, 1994 [17]	Elkins *et al*, 2006 [18]	Cayston EPAR		US FDA NDA 50,753 review		Konstan *et al*, 2011 [16]	
Duration	26 weeks	24 weeks	48 weeks	28 days	28 days	24 weeks, 28 day cycle			
Dose	400 mg b.i.d.	2.5 mg once daily	4 ml 7% b.i.d.	75 mg b.i.d. or t.i.d.	75 mg t.i.d.	TOBI (nebulised) 300 mg b.i.d.			TIP 112mg b.i.d.
Patient numbers (Active)	361	322	82	135	80	109	149	209	308
Age	Over 6	Over 5	Over 6	Over 6	Over 6	Over 6	Over 6	Over 6	Over 6
FEV_1% predicted, relative (%) change from baseline across the treatment period	5.8	5.5*	3.1*	4.1	8.4	12.0	8.7	2.7*	2.6*

* data derived from publications

Source: Appendix 9

Secondary Endpoints Support FEV_1 Improvement

Improvement in other spirometry measures

An increase in FVC reflects increased opening of airways as a result of the clearing of distal airway mucus blocking, and reduced air trapping behind this mucus. The tidal volume is also increased as a result, so potentially improving exercise capacity. The secondary endpoint of FVC (relative change in % predicted) from both pivotal studies and pooled data supports the primary endpoint of FEV_1. Both DPM-CF-301 and 302 showed statistically significant improvements of 3.03% (95% CI: 0.76, 5.29) and 3.07% (95% CI: 0.48, 5.66) relative change in % predicted FVC respectively compared to control across 26 weeks of treatment in the overall ITT population. Pooled data of both studies also showed an improvement of 3.00% (95% CI: 1.27, 4.74) relative change in % predicted. The FVC improvements correlate with FEV_1 changes, indicating that an improved lung capacity is driving the FEV_1 improvement.

Quantitative Microbiology

In study DPM-CF-302 based on quantitative microbiological results, Bronchitol treatment was shown to both reduce the incidence of *P. aeruginosa* infection and reduce the bacterial burden in those that were infected. The incidence of *P. aeruginosa* infection was 52.9% at baseline and 58.2% after 26 weeks on treatment in control patients, with the average bacterial burden in infected patients increasing from 6.1 to 6.3 log units (CFU/g). In contrast the incidence of infection fell over 26 weeks of treatment in the Bronchitol group from 48.1% to 41.5%, with a reduction in average bacterial burden from 6.9 to 6.4 log units (CFU/g) (from 7,943,282 CFU/g to 2,511,886 CFU/g).

Reduction in exacerbations

Exacerbation prevention is an important goal of CF therapy. Not only do exacerbations carry an immediate morbidity and mortality risk, but they have also been shown to lead to permanent declines in lung function. Exacerbations are relatively uncommon events so although clinically very important, are not a sensitive tool. Therefore exacerbation was included as a secondary variable, but the individual studies were not powered to test this endpoint. The larger population provided by the pooled data is therefore of particular importance. It was consistently observed that, compared with the

control, Bronchitol was associated with a reduction in pulmonary exacerbations, antibiotic use and hospitalisations. In the pooled studies, the incidence of exacerbations and associated rescue antibiotic use was reduced by 29% (relative risk 0.71, 95% CI: 0.51, 0.98, p=0.039) and 30% (relative risk 0.70, 95% CI: 0.50, 0.97, p=0.033), respectively in the Bronchitol group compared with control. This reduction in incidence is considered to be clinically meaningful, and similar to the reductions originally reported using rhDNase, at a time when other concomitant therapies were not available. The reduction in exacerbations was supported by trends in reduced hospitalisations (relative risk 0.78, 95% CI: 0.53, 1.16). These findings are generally consistent with the findings in the individual studies (Table 5).

Table 5: Relative Risk of Exacerbations, Rescue Antibiotic Use and Hospitalisations – DPM-CF-301, 302 and Pooled

Exacerbation Measures	Relative Risk (95% CI) (Bronchitol vs Control)		
	DPM-CF-301	DPM-CF-302	Pooled DPM-CF-301 and 302
Exacerbations	0.65 (0.42, 0.99) p=0.045	0.80 (0.48, 1.32) p=0.386	0.71 (0.51, 0.98) p=0.039
Rescue Antibiotic Use	0.63 (0.40, 0.97) p=0.036	0.80 (0.48, 1.32) p=0.386	0.70 (0.50, 0.97) p=0.033
Exacerbation related Hospitalisations	0.80 (0.46, 1.38) p=0.424	0.76 (0.43, 1.35) p=0.349	0.78 (0.53, 1.16) p=0.219

Source: Appendix 14

Ground 2: *Uncertainties remain in the magnitude of the effect following treatment with Bronchitol. In study DPM-CF-301 a high proportion of patient withdrawals complicates inference. The pattern of estimated treatment effects is inconsistent within each study across important subgroups defined by age (children, adolescents and adults) and the pattern of effects in each age group is inconsistent between studies. In light of the limited effects observed, these internal inconsistencies result in unacceptable uncertainty in the estimated treatment effect for the proposed population.*

Applicant´s position: (summarised)

In order to address the concerns regarding magnitude of effect size which were raised during the MAA assessment, the Applicant presented FEV_1 as relative change in % predicted. This is stated by the CHMP as the preferred endpoint.

Uncertainty Associated with Patient Withdrawal and Use of MMRM Model

While acknowledging that there is a treatment effect with Bronchitol, the CHMP stated in the grounds for refusal that "uncertainties remain in the magnitude of the effect following treatment with Bronchitol". These uncertainties arose due to a relatively higher than expected patient withdrawal rate, and the use of MMRM model and possible different effects in different subgroups.

Data from at least 90% of the patients contributed to the estimation of treatment effect. Although the overall withdrawal rate was higher than anticipated in study DPM-CF-301, there is a significant proportion of the subjects (Bronchitol: 89.8%, control: 95.8%) who contributed at least one post-baseline observation (Table 6).

This is similar to Study DPM-CF-302, where 96.2% of Bronchitol subjects and 99.2% of control subjects provided at least one post-baseline observation. The overall withdrawal rate underestimates

the amount of data included in the primary analysis, thus could over emphasize the potential impact of the withdrawals.

Table 6: The availability of data for the Studies DPM-CF-301 and 302

Post baseline data available	DPM-CF-301		DPM-CF-302	
	Bronchitol N=177	Control N=118	Bronchitol N=184	Control N=121
At least 1 post-baseline observation	159 (89.8%)	113 (95.8%)	177 (96.2%)	120 (99.2%)
At least 2 post-baseline observations	135 (76.3%)	104 (88.1%)	164 (89.1%)	116 (95.9%)
At least 3 post-baseline observations	114 (64.4%)	84 (71.2%)	157 (90.9%)	110 (90.9%)

As pointed out by CHMP and acknowledged by the applicant, the MMRM model could be associated with uncertainty in the estimation of the treatment effect, and missing data could further complicate the inference. In light of this, in order to assess the sensitivity of the primary analysis, missing data were imputed by various methods including last observation carried forward (LOCF) and baseline observation carried forward as requested by CHMP. The data were subsequently analyzed by Analysis of Covariance (cross-sectional analysis at Week 26) or MMRM (longitudinal analysis across the treatment period), to compare results with those from the primary analysis which were 3.51% (95% CI: 0.96, 6.06) and 3.59% (95% CI: 0.29, 6.90) respectively for studies DPM-CF-301 and 302. Comprehensive and systematic sensitivity analyses focused on the most relevant methods and results were reported to address possibly different missing mechanisms.

In this section, the following approaches were used to handle the missing data for the relative change in % of predicted FEV_1:

CHMP requested methods:

• LOCF: missing data at Week 26 were imputed by last observation carried forward. This is likely to be conservative in DPM-CF-301, particularly because – as recognized by CHMP – patients tended to withdraw earlier from the Bronchitol arm than the control arm. Hence, early withdrawals are more likely to have only minimal improvement from baseline. The imputed Week 26 data were then analyzed by Analysis of Covariance.

• BOCF: missing data at Week 26 were imputed by baseline observation carried forward. This will also be conservative in DPM-CF-301, but possibly even more so than LOCF. The imputed Week 26 data were then analyzed by ANCOVA.

Other methods:

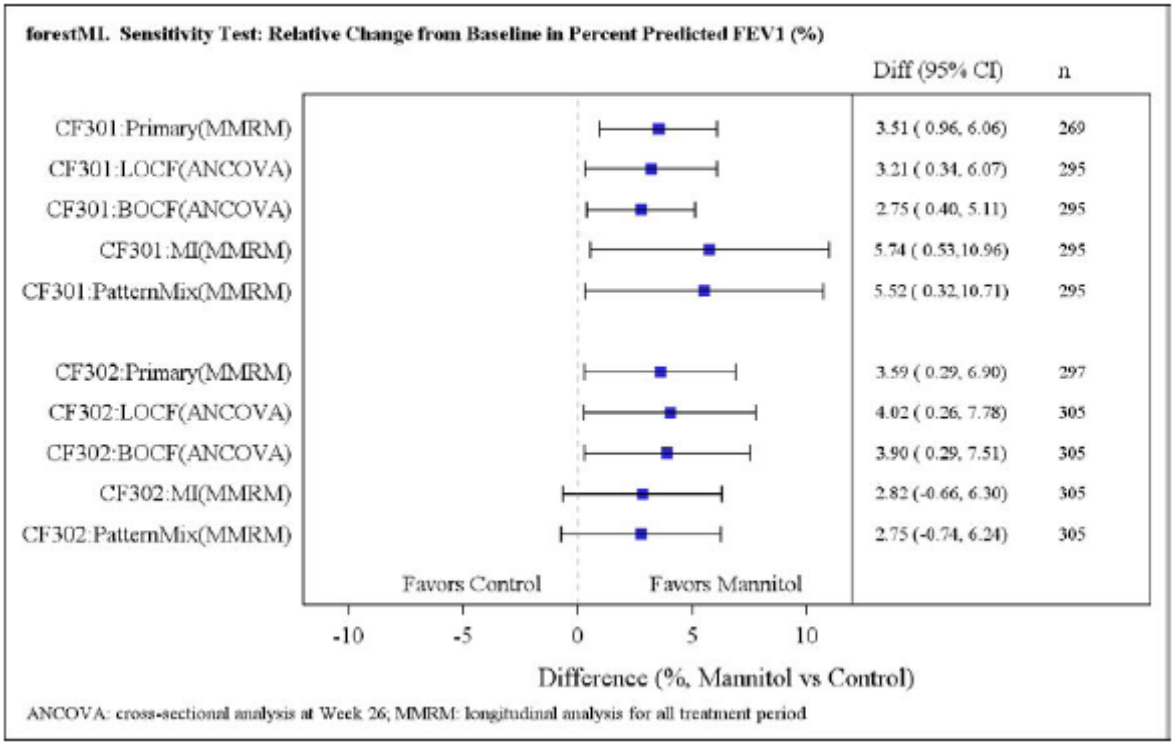
• MI: missing data across the treatment period, namely Week 6 to Week 26, were imputed by multiple imputation (MI) for 50 times. Each imputed longitudinal dataset was then analyzed by MMRM model. Finally the MMRM estimates of the 50 imputed datasets were combined for inference following the approach as reported by Rubin.

• Pattern Mixture Model (via Multiple Imputation): missing data across the treatment period, namely Week 6 to Week 26, were first imputed by multiple imputation for 50 times. Then a further penalty was given to patients with multiple missing data, as these patients could less likely benefit from the

treatment. That is 20mL was removed per missing visit (20mL at 1st missing visit, 40mL at 2nd missing visit, and 60mL at 3rd missing visit). The imputed longitudinal data were then analyzed by MMRM model as above.

The analysed results are plotted as forest plot in Figure 10.

Figure 10: Forest plot of results of sensitivity analyses – DPM-CF-301 & 302



It has been acknowledged by both CHMP and the applicant that no single correct way to impute the missing data exists. Therefore the above sensitivity analyses were conducted to assess the uncertainty associated with the estimates from the primary analysis using MMRM model. As mentioned above, LOCF and BOCF were requested by CHMP to be used to impute the missing data at Week 26, and then ANCOVA was used to analyse the imputed data at Week 26 cross-sectionally. Though not directly comparable between the longitudinal analysis (MMRM) and the cross-sectional analysis (ANCOVA), for both studies DPM-CF-301 and 302, the results based on LOCF (ANCOVA) and BOCF (ANCOVA) give similar estimates of effect size (of the order of 3% for study DPM-CF-301 and 4% for study DPM-CF-302). LOCF and BOCF do, however, still lead to the same conclusion as that based on the primary analysis (MMRM). Their results indicate that, at Week 26, there was a positive effect favouring Bronchitol for the comparison between Bronchitol versus control. Much of the uncertainty associated with the estimates from MMRM arises from possibly inappropriate assumptions of the MMRM model; the results based on LOCF (ANCOVA) and BOCF (ANCOVA) should alleviate those concerns.

Multiple imputation and pattern mixture model (via MI) were also used to account for the possible missing mechanisms in the data such as missing at random (MAR) or not missing at random (NMAR), which unfortunately cannot be directly tested or verified. As the imputed data were subsequently analysed by MMRM, the results are provided for reference purpose only. The imputation by MI and Pattern Mixture (via MI) introduced extra variation into the data to account for the uncertainty due to the imputation of missing data. Therefore, it is expected that their 95% CIs will be wider than other estimates. However, this is less applicable to DPM-CF-302, as the quantity of missing data for DPM-CF-

302 is far less than that for DPM-CF-301. Even with the presence of all these uncertainties mentioned above, the results based on MI and Pattern Mixture (via MI) still favour Bronchitol.

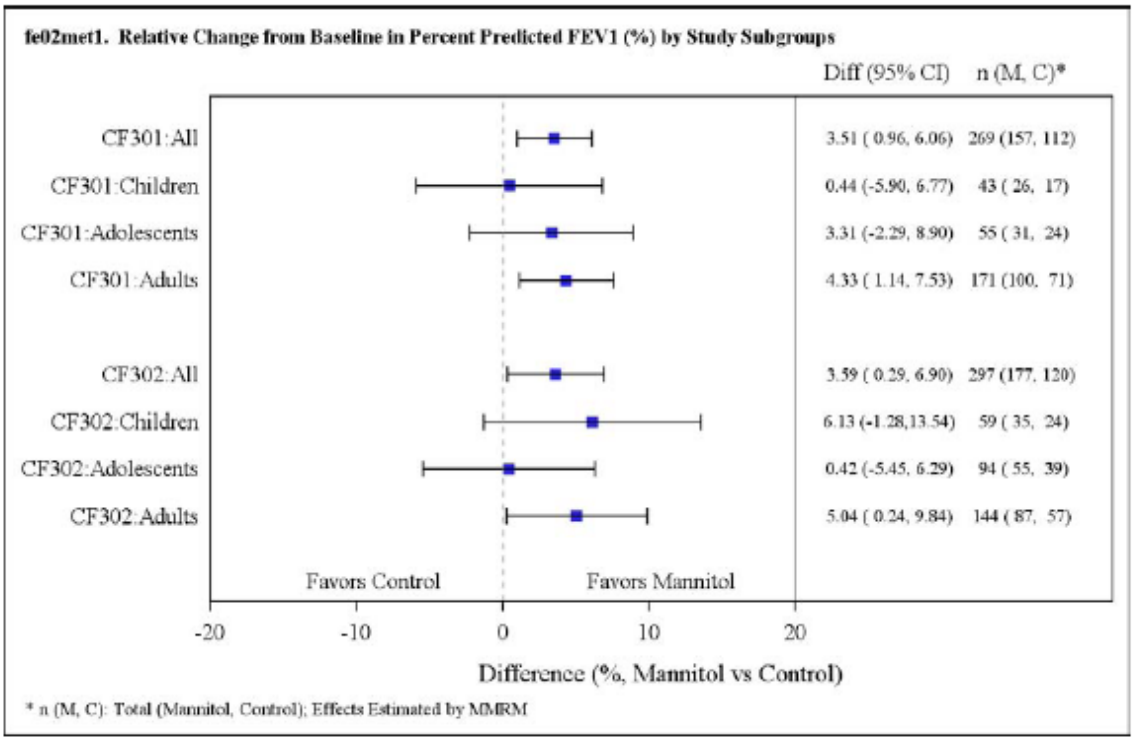
In summary, the applicant accepts the concern raised by CHMP with regards to the estimates based on the primary analysis using MMRM model. The withdrawals in both studies could further complicate the inference based on MMRM model. The applicant followed the analysis approaches requested by the CHMP – i.e. that the missing data at Week 26 should be imputed by LOCF or BOCF, and the data subsequently analysed by ANCOVA cross-sectionally. The methods recommended by the CHMP lead to the same conclusion as that from the primary analysis, which indicate that the treatment is effective and that this conclusion is reliable even with the presence of the uncertainty associated with the primary analysis. The evidence for the presence of the treatment effect is not highly dependent on the selected analysis methods.

Consistency of Estimated Treatment Effects Across Subgroups and Studies

A further CHMP concern regarding the magnitude of Bronchitol's effect was that "the pattern of estimated treatment effects is inconsistent within each study across important subgroups defined by age (children, adolescents and adults) and the pattern of effects in each age group is inconsistent between studies".

In an effort to demonstrate the consistency of the treatment effects across subgroups and studies, the applicant stated that the treatment effect as measured by the relative change in % of predicted FEV_1 was estimated for the age subgroups for both DPM-CF-301 and 302 studies, based on the estimates from the primary analysis using MMRM model. It is acknowledged that heterogeneity should not be claimed on the basis of the observed treatment-effect sizes within each subgroup alone, while there is uncertainty of these estimates. Therefore, the age subgroup data are plotted as a forest plot for initial visual inspection. The forest plot for the treatment effects of the three age subgroups in each of the two studies (DPM-CF-301 and 302) was presented by the applicant showing the actual number of patients used in the estimation of treatment effect (Figure 11).

Figure 11: Relative Change from Baseline in Percent Predicted FEV_1 by Study and Age Groups (MMRM)



To further address the concern of the uncertainty associated with the MMRM estimates, the applicant presented the subgroup estimates based on the ANCOVA analysis of Week 26 data imputed by LOCF or BOCF.

While acknowledging the uncertainty associated with the estimates from MMRM model, Figure 11 shows that the 95% CIs for the treatment effects of the six subgroups have substantial overlap with each other. More importantly, all the point estimates are well above unity of 0, except for the children in study DPM-CF-301 and adolescents in study DPM-CF-302. Due to the overlap in the 95% CIs among the subgroups, it should not be concluded that the effect of Bronchitol on children in study DPM-CF-301 or adolescents in study DPM-CF-302 are different from other subgroups. The sample sizes in the children and adolescents subgroups are quite small which, as would be expected, contributes to the larger uncertainty in the estimated treatment effects for these subgroups.

The patterns of the treatment effects for all subgroups, regardless of the imputation methods (LOCF or BOCF) are very similar to those observed in Figure 11. The treatment effects among the age subgroups all consistently favour Bronchitol. Therefore, it can be concluded that the treatment effects estimated among the subgroups are independent of the analysis methods.

In general, in the presence of an overall effect, real (as opposed to simply observed) discrepancies in subgroups are rare. When such discrepancies are seen, a usual approach to understanding whether or not they are real is to look at other studies and see if the discrepancy is replicated. Neither of the apparent discrepancies (the children in study DPM-CF-301 or the adolescents in study DPM-CF-302) is replicated in the complimentary study. Based on visual inspection of the forest plots, it should be concluded that the treatment effects in all age subgroups are largely consistent, and the pattern of treatment effects predominantly favours Bronchitol.

Statistical Assessment of Uniformity of Treatment Effects among Age Subgroups

Interaction Test

To formally assess whether the treatment effect is consistent across the age subgroups within each study, the interaction between treatment and age groups was tested for each of the studies. The results from the Summary of Clinical Efficacy are extracted as follows:

- DPM-CF-301: interaction between treatment and age group, p-value=0.551
- DPM-CF-302: interaction between treatment and age group, p-value=0.384

The above analyses were based on MMRM model. The interaction between treatment and age group has also been assessed by using ANCOVA to analyse Week 26 data imputed by LOCF or BOCF, as requested by CHMP. The p-values of these interaction tests are as follows:

Imputation Method	P-value of Interaction Between Treatment and Age Group (ANCOVA)	
	DPM-CF-301	DPM-CF-302
LOCF	0.656	0.392
BOCF	0.440	0.496

The interaction test takes into account the point estimate of the treatment effect and the variation associated with the estimates. It is acknowledged that the interaction test might suffer from the small sample size in each subgroup, and accordingly the test might not identify a true interaction due to lack of power. Therefore, despite the general agreement that an insignificant test result does not exclude the possibility of true interaction, nevertheless an insignificant interaction does not support that the treatment effect is heterogeneous across the age subgroups. The evidence from interaction tests supports a homogeneous treatment effect, regardless of the data or statistical models used.

Heterogeneity test

To further assess if there is heterogeneity of treatment effects across the studies and age subgroups, a heterogeneity test as proposed by Cochran (1954) was used, following the meta-analysis approach.

It is assumed that the treatment effects estimated from each subgroup are independent. Though this assumption is not strictly true in this case (as subgroup data were collected within the two studies separately), a minor violation of this assumption should not invalidate the test. Therefore, age subgroups from both studies are used for the heterogeneity test. The p-values for the heterogeneity test are 0.715, 0.558 and 0.682 respectively for LOCF, BOCF and the primary analysis. Although the heterogeneity test (like the interaction test) suffers from a small sample size (six subgroups in this case), there is no evidence to support an assertion that the treatment effect is not consistent across the studies and age groups.

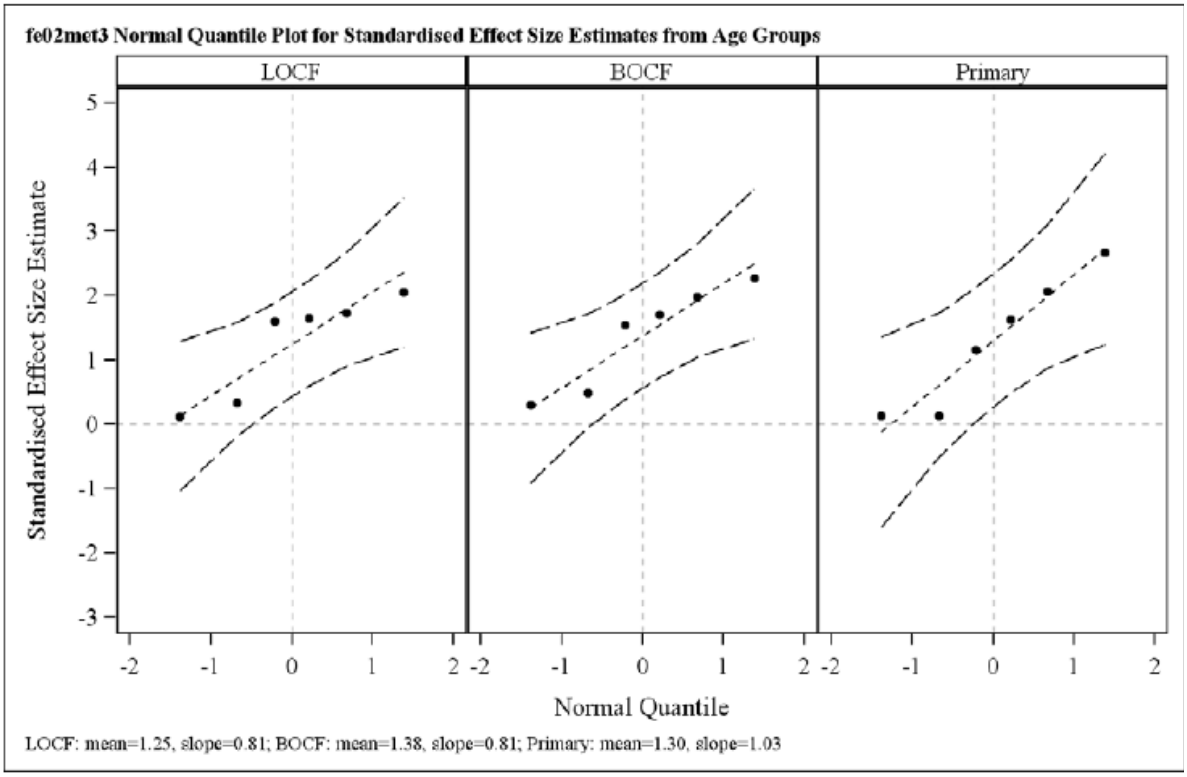
Normal Quantile Plot

The question of whether the underlying treatment effects from each age group can all be considered as being drawn from the same (single) population or from heterogeneous populations can be further explored with a normal quantile plot. In this method a standardised treatment effect (z-score) is calculated for each age group in each study. The standardised treatment effect is equal to the point estimate divided by the standard error of the estimate, so takes into account the uncertainty of the estimate.

Wang and Bushman (1998) show how a normal quantile plot can be used to assess whether subgroups are all from one population, or not. Each standardized effect-size estimate should have a standard deviation of 1. If the subgroups do all come from the same population, then the distribution of effect size estimates will be approximately normal. Thus, the plotted line in the normal quantile plot for the age subgroup data should be straight and should have a slope close to 1. If the slope is substantially less than one, this indicates unusually little variability between subgroups – a fact that in itself would be unexpected. The normal quantile plots for each of the missing data methods are reported in Figure 14.

For each of the different methods, all the observed standardised treatment effects fall within their 95% confidence bands and are close to their respective straight line. In all cases the mean of the standardised treatment effects is well above 0 (0 would indicate no treatment effect). The slopes of the regression line for LOCF and BOCF are less than 1 (both are approximately 0.81), as expected, because these two methods could reduce the variation in the data when change from baseline is calculated. The slope for the primary analysis is 1.03. Thus, it can be concluded that the treatment effects across the studies and age subgroups are from the same population.

Figure 14: Normal Quantile Plot for Standardised Effect Size Estimates from Age Groups



Monte Carlo Simulation

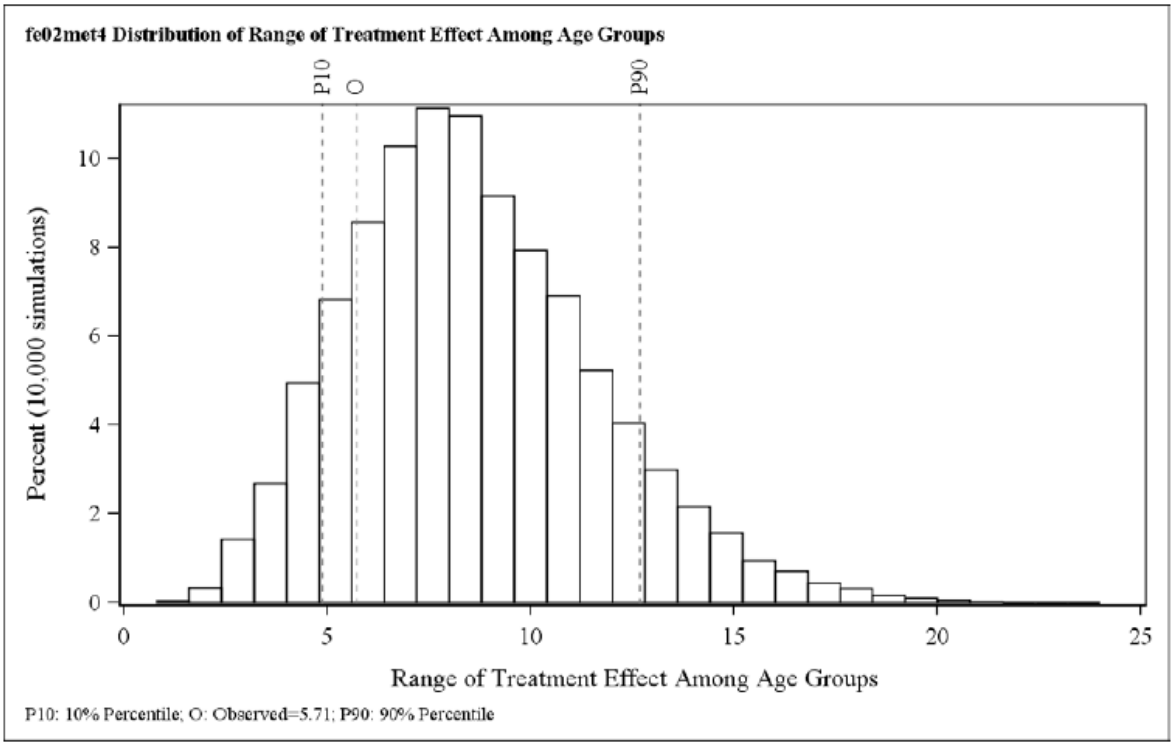
Finally, a simulation has been conducted to further explore whether or not the observed treatment effects among the six subgroups are from the same population. The mean (standard error) for the relative change in % of predicted FEV_1 was estimated to be 5.81 (0.78) and 2.26 (0.89) respectively for the Bronchitol and control groups, based on the MMRM analysis of the combined data. Individual patient data for each age group were drawn randomly from populations with the following distributions:

Bronchitol Normal (mean=5.81, standard deviation=0.78√361)

Control Normal (mean=2.26, standard deviation=0.89√239),

where 361 and 239 were the sample sizes for the Bronchitol and control groups, respectively, as reported in the combined studies. This generates samples assuming that all the age groups have the same underlying mean effect. In each sampling, the same number of patients as that reported in the studies was randomly drawn for each age subgroup. The treatment effect within each age subgroup and the range of the treatment effect (max minus min) among the six subgroups were calculated for each sampling. This process was repeated 10000 times. The observed range of treatment effects among the age subgroup in the trials is approximately 5.71 (6.13-0.42, Figure 11), which falls within the 10% and 90% percentiles of the simulation distribution. This shows that effect sizes as divergent as those seen, even when the true underlying effect size is the same in all subgroups, is wholly to be expected. Thus, this further supports the assertion that the treatment effects among the six subgroups are from the same population.

Figure 15: Distribution of Range of Treatment Effect Among Age Groups



In summary, although each single piece of evidence alone cannot be considered conclusive, the combined evidence from the forest plots, interaction tests, the heterogeneity tests, the normal quantile plots and the simulations do not support the conclusion that the treatment effect is not the same across studies and age groups. It is therefore concluded that the observed variation is due to expected sampling variation rather than true differences. All the evidence collectively supports that the

treatment effects are consistent across the studies and subgroups. Further, this supports the statistical validity of combining the two study populations for analysis.

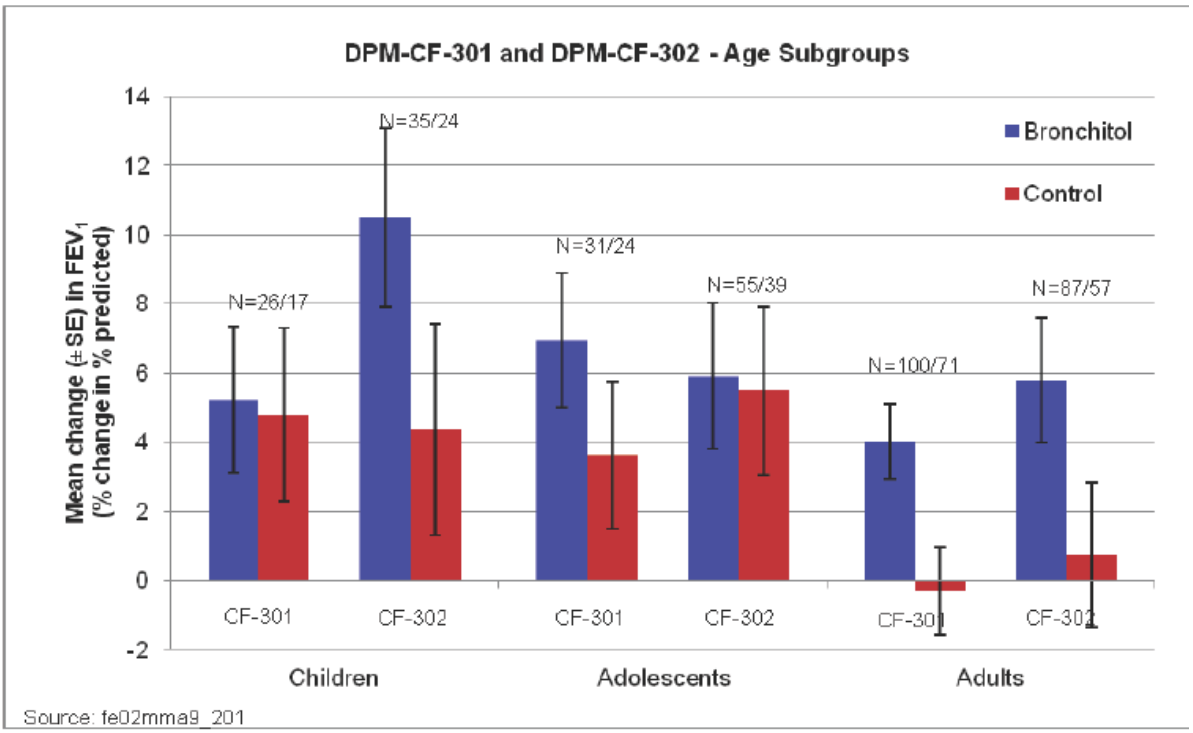
Assessing Possible Control Effect in Children and Adolescent Subgroups

As evidenced in the previous section, the variation noted in treatment effect estimates between subgroups and across studies is consistent with expected sampling variation.

When looking at the Bronchitol arm, there is consistently a significant improvement within all age subgroups across both studies showing a ≥4% relative change from baseline in % predicted FEV_1.

However, it is acknowledged that there does appear to be more variation in the control effect (Figure 16). Control in both pivotal studies comprised 50mg b.i.d. of respirable mannitol. Notably the adult subgroup which was the subject of the CHMP opinion did not show any control effect in either study, whereas there was a suggestion of a control effect in the younger age groups.

Figure 16: Bar Chart of FEV_1 Change by Treatment Group and Age Subgroup – DPM-CF-301 & 302



In the first pivotal study, DPM-CF-301, there was a suggestion that there may have been an effect at the lower dose in children (possibly due to their smaller lung size). However, when children and adolescents receiving control in DPM-CF-301 were examined by FEV_1 improvement against height (a surrogate for lung volume), no relationship was seen. This lack of correlation was supported by DPM-CF-302 data, where children showed a meaningful effect versus control, but adolescents did not. The earlier phase II, two week dosing studies did not show efficacy in children or adolescents at a dose of 40 mg b.i.d.

The more variable control response in children and adolescents is consistent with sampling variation alone but the applicant acknowledges that other explanations are possible. There are a number of additional hypotheses which could contribute to this type of control effect.

- Firstly, it is known that CF management in adolescents can be particularly erratic, although study drug compliance appeared to be similar between Bronchitol and Control arms in all age groups (Children – 86.5 vs 87.3%, Adolescents – 80.1 vs 83.0%, Adults – 78.3 vs 82.2% respectively). However, improved compliance in pre-existing therapy due to study participation could be contributing.
- Secondly, although study DPM-CF-202 suggested that the 50mg control dose was subtherapeutic in all ages, some effect in young patients over a longer time course cannot be excluded, and only a study in children and adolescents performed using non-respirable rather than respirable mannitol as placebo might confirm this. If the control did have an effect, then the effect size in patients under 18 would be an underestimation.
- Lastly, a control effect may be more apparent in children because of their inherent difficulty in initiating an effective, productive cough at will, to assist mucus clearance. As both doses of mannitol provoke some cough, this may have been more impactful in children, despite this being secondary to the main MCC mechanism of action.

Apparent treatment differences by age in cystic fibrosis are not unique to Bronchitol, and in a tobramycin pivotal study there were large differences in the placebo arm of children compared to adolescents (Ramsey et al, 1999).

It is also interesting to note that in studies DPM-CF-301 and DPM-CF-302 when patients switched to Bronchitol treatment after 26 weeks of control treatment an improvement in FEV_1 was noted during the subsequent 6 months during the open label phase.

The increase in FEV_1 attained in the Bronchitol treated ex-control arm in the open label phase is similar to the level of improvement noted with the Bronchitol arm in the double blind phase. This strongly suggests that control patients have not achieved maximal FEV_1 benefits on control and provides further evidence of Bronchitol's effectiveness.

In summary, Bronchitol's magnitude of effect can be determined with sufficient certainty to confirm it is clinically meaningful. It has been shown that the effect size provided by the DPM-CF-301 study has not been overestimated to any meaningful extent despite patient withdrawals, and regardless of which analyses model is used Bronchitol provides clear FEV_1 improvement. This is further confirmed by sensitivity analyses. There is no statistical evidence of internal inconsistencies amongst age groups or between studies, as the variability is consistent with expected sampling variation within this CF patient population.

CHMP position on grounds 1 and 2

The main studies in support of this application are studies DPM-CF-301 and DPM-CF-302, which included children, adolescents, and adults and used absolute change from baseline in lung function (FEV_1) as the primary efficacy variable. Mean (SD) baseline FEV_1 percent predicted in study DPM-CF-301 (safety population, N= 295) was 62.4 (SD:16.45) and 61.4 (SD:16.13) in the mannitol and control groups, respectively. These figures for study DPM-CF-302 (N=305) are as follows: 65.24 (SD:13.90) and 64.35 (SD:15.29). In study DPM-CF-301 64.4 % of the patient population were adults while in study DPM-CF-302 this figure was 49.5%. Fifty five % of patients were receiving rhDNase in study DPM-CF-301 while in study DPM-CF-302 this number was 75%. The percentage of patients receiving inhaled antibiotics was 55% in study DPM-CF-301 and 56% in study DPM-CF-302.

During the initial evaluation procedure, the CHMP raised a number of concerns regarding the methodology, conduct and interpretation of the two pivotal trials. The concerns remaining at the end of

that procedure, following a GCP inspection that raised no critical issues, related to the impact of the non-negligible amount of missing data due to patient withdrawals and the consequent uncertainty in understanding the true effect of treatment with Bronchitol, also to the apparent heterogeneity within the trial results. These uncertainties were considered unacceptable in light of the conclusion that the clinical relevance of the treatment effect was questionable. During the re-examination procedure, the view of CHMP on the clinical relevance of the results was changed following consultation of an ad-hoc expert group (discussed below). The applicant presented a range of statistical analyses to investigate the robustness of the estimated treatment effect to different assumptions on how to handle the data that were missing. In light of the revised view on the clinical relevance of the estimated effects, these analyses were accepted as comprehensively addressing concerns over the uncertainty introduced because of missing data due to patient withdrawal. The issue of apparent heterogeneity in the trial results is addressed below. From a methodological point of view, the applicant used a proper set of available statistical methodologies to explore these effects, 'interaction tests' and subgroup analyses, complemented by discussion on the biological plausibility of observing heterogenous results. These arguments were accepted by the CHMP to conclude that the effect demonstrated in adults, across multiple trials, was robust. Taking into account the arguments presented during the re-examination, the CHMP concluded that the studies were fit for purpose and any residual, minor methodological concerns were of no consequence to demonstration of efficacy, assessment of safety or judgement on benefit-risk.

The primary pre-specified endpoint i.e. the change from baseline in FEV1 (ml) in the modified ITT (mITT) population (n=269 and 297 in studies DPM-CF-301 and DPM-CF-302, respectively) compared to control over the 26 weeks period is provided in Table 1 alongside FEV_1 presented as absolute and relative change % predicted.

Table 1 – Change in FEV_1 from baseline over 26 weeks in the mITT and adult populations

	Effect size estimate			
	DPM-CF-301		**DPM-CF-302**	
	FEV_1 (95% CI)	**p value**	**FEV_1 (95% CI)**	**p value**
	Overall Population			
	N=269		**N=297**	
Absolute mL	**94.5** (46.2, 142.7)	**<0.001**	**54.1** (-1.97, 110.3)	**0.059**
Absolute % predicted	**2.4** (0.9, 3.9)	**0.001**	**1.9** (-0.02, 3.8)	**0.052**
Relative % predicted	**3.5** (1.0, 6.1)	**0.007**	**3.6** (0.3, 6.9)	**0.033**
	Adult Population			
	N=171		**N=144**	
Absolute mL	**108.5** (47.6, 169.4)	**<0.001**	**85.9** (4.6, 167.3)	**0.038**
Absolute % predicted	**2.7** (0.9, 4.5)	**0.004**	**2.3** (-0.4, 5.1)	**0.095**
Relative % predicted	**4.3** (1.1, 7.5)	**0.008**	**5.0** (0.2, 9.8)	**0.040**

According to the study reports of studies DPM-CF-301 and DPM-CF-302, the number of subjects with at least one protocol defined pulmonary exacerbation (PDPE, defined by the presence of at least 4 symptoms and signs plus the use of intravenous antibiotics) was 18.1% in the mannitol arm and 28% in the control arm in study DPM-CF-301 (ITT population). In study DPM-CF-302 15.2% of the subjects in the mannitol arm and 19% of the subjects in the control had a PDPE. The PDPE mean (SD) rate (events per subject per year) was 0.78 (1.976) in the mannitol group and 1.05 (2.148) events per subject per year (rate ratio [95% CI] 0.74 [0.47, 1.18]). In study DPM-CF-302 the rate ratio [95% CI] was 0.85, [0.51, 1.41]. This is consistent with a reduction in the incidence of PDPE in the mannitol arms by approximately 25% in study DPM-CF-301 and by 15% in study DPM-CF-302. However, a six-month period of treatment is not sufficiently lengthy as to permit an adequate assessment of this variable.

The change in FEV_1 can be measured as the absolute change from baseline (in litres), the relative change (as percent change from baseline), or the absolute change in percent predicted FEV_1. While the predefined primary endpoint in the two phase 3 pivotal studies is the change from baseline in FEV_1 (mL) in the response to the CHMP grounds for refusal, the results are discussed as the relative change in FEV_1 predicted of normal. This is also in line with the expert group's position received. They noted that the assessment based on relative % predicted change is better than the use of absolute change in mL, the latter being not considered appropriate for the study. However, the experts also noted that the absolute % predicted change would have been even better and this was endorsed by the CHMP.

It is not controversial that the effect size for FEV_1 observed in studies DPM-CF-301 and DPM-CF-302, which investigated the dose of 400 mg bid, is small. Overall treatment with mannitol showed an improvement of approximately 2-3% compared with the control group over 26 weeks in terms of percent predicted FEV_1. The clinical relevance of such a marginal effect size needs to be established in the overall context of CF management and prognosis. The experts group confirmed that benchmarking for a product impacting on sputum clearance like inhaled mannitol would need to consider the respective mode of action. In general, a comparison against antibiotics has limitations. Based on the expected effect on the volume of liquid on the airway surface it would appear that nebulised hypertonic saline (HS) seems the medicinal product most closely related to inhaled mannitol; however the use of nebulised HS in cystic fibrosis is not an approved therapy and all the evidence for the use of nebulised HS in patients with CF is limited to published studies. This view was shared by the expert group and subsequently endorsed by the CHMP.

The expert group confirmed that the effect size observed with inhaled mannitol is small and based on the available data it is difficult to ascertain whether the treatment effect is clinically relevant. Nevertheless the expert group unanimously agreed that in the overall treatment approach for cystic fibrosis patients any improvement in lung function can be of relevance in an individual patient given the deterioration of FEV_1 inherent to the disease progression. Since the lung function is progressively declining in cystic fibrosis patients over time, any intervention that slightly improves lung function can be of relevance for the long-term management of these patients in clinical practice. The CHMP accepted the experts' opinion that even the small improvement in lung function that was observed on average across the population included in the clinical trials, which might normally not be detectable in an individual patient in clinical practice, is of clinical importance to cystic fibrosis patients where lung function deteriorates over time.

Another issue raised by the CHMP was the heterogeneity between and within studies with respect to benefit on lung function. While study DMP-CF-301 showed a statistically significant benefit for FEV_1 (mL), study DPM-CF-302 did not, at least in terms of the primary analysis. Furthermore, there were differences in outcome for children, adolescents, and adults. The applicant has presented a number of statistical analyses to address the internal inconsistency observed in the pattern of effect across age groups and between studies. The limitations of any such approach have been acknowledged. It is

concluded that the inconsistencies seen in subgroups can be attributed to the inherent variability and to the fact that the overall effect size is small.

Based on the available data, any such effect can only be considered demonstrated in the adult population. In studies DPM-CF-301 and DPM-CF-302 relative % predicted FEV_1 compared to control in children (6-11 years) was improved by 0.44% (95% CI -5.90, 6.77, N=43) and 6.1% (95% CI -1.28, 13.54, N=59) over 26 weeks (p=0.892 and 0.104) respectively. In adolescents (12-17 years) relative change in % predicted FEV_1 compared to control improved by 3.31% (95% CI -2.29, 8.90, N=55) and 0.42% (95% CI -5.45, 6.29, N=94) over 26 weeks (p=0.245 and 0.888) respectively. In principle it is not expected that efficacy differs between children/adolescents and adults; however, the data from studies DPM-CF-301 and DPM-CF-302 do not support this. Particularly the results in adolescents were considered surprising by the expert group from a clinical perspective as this is the patient population where normally benefits are clearly demonstrated, which seems not to be the case across both pivotal studies. The available data in children and adolescents does however not demonstrate the benefit of inhaled mannitol in this population. During the evaluation procedure the applicant restricted the applied indication to the use in adults. It is therefore considered appropriate to limit any use of inhaled mannitol to the adult population, given that the effect size in the adult population was similar in the two pivotal studies and that this effect was consistent with the 2 supportive studies all showing a similar benefit in FEV_1 (for both Phase III studies there was a statistically significant benefit in the primary efficacy variable, change in FEV_1 from baseline to study end, for Bronchitol compared to control treatment arms). This suggests that the benefit is real, and is unlikely to be an artefact of the subgroup analyses presented by age. In addition it is considered that the effect has been measured with acceptable precision, and it is recognised by the ad-hoc expert group cystic fibrosis experts and the CHMP to be small, but of clinical relevance. Moreover, the differential response according to patients' age may be due to clinical trials conducted in a refractory disease, in a relatively small number of patients. Taking the above information into account, the CHMP concludes that the studies are considered reliable.

Nevertheless, it is recognized that the main studies DPM-CF-301 and DPM-CF-302 included children, adolescents, and adults, thereby the overall patient population relevant for the condition "cystic fibrosis". Given the prevalence in individuals below the age of 18 years, treatment of this population is of particular relevance. Whilst this is the population for which a clinical benefit can be established, it remains paramount from a clinical perspective and for the benefit risk assessment of the use of inhaled mannitol in this condition to further investigate the efficacy and safety of inhaled mannitol in children and adolescents with cystic fibrosis. The applicant is therefore requested as a condition to the marketing authorization to perform a study in this regard. A first draft synopsis was presented by the applicant during the evaluation; it was noted that it would be important to assess the effect of treatment by use of inhaled antibiotics, which are often used in an "on cycle" (4 weeks) and in an "off cycle" (4 weeks), and that the duration of the observation period would need to account for such treatment regimen. The study protocol shall be agreed with the CHMP prior to the start of the study and the final results provided to the CHMP and EMA by June 2015. The submission of the study protocol is envisaged for Q2 2012. It is highly recommended to obtain scientific advice for this study protocol.

It was also raised previously that the differentiation between rhDNAse users and non-users has limitations due to the study design and the results obtained. In rhDNase users in study DPM-CF-301 the relative change in FEV1 % predicted from baseline across 26 weeks of treatment was 2.83 (95% CI -0.62, 6.27). For non-users the relative change was 4.30 (95% CI 0.53, 8.07). In study DPM-CF-302 the relative change (95% CI) for rhDNase users and non-users was 3.21 (-0.61, 7.03) and 4.73 (-1.93, 11.40), respectively. It needs to be acknowledged that the studies were not powered for the analysis of these two subgroups. When experts were requested to provide their opinion on what would

constitute an adequate definition of patients intolerant to, or inadequately responsive to rhDNase, they stated that the criteria for the subgroups related to rhDNAse users and non-users were not pre-specified for both studies which rendered the interpretation of the results very difficult. Moreover, studies DPM-CF-301 and DPM-CF-302 were not powered to make such stratifications. From a clinical perspective, the proposed distinction between rhDNAse users and non-users appeared difficult given that in practice the (non-)use of rhDNAse is also subject to patient's choice, hence the definition of rhDNAse non-users appeared not appropriate. Therefore, to overcome this obstacle the claimed indication was changed by the applicant to refer to the add-on therapy to best standard of care. This change was deemed acceptable by the CHMP in light of the fact that although the effect size appears to be smaller in the rhDNase users, both rhDNase users and non-users can benefit from the addition of mannitol to their treatment regime. The clinical experts from the ad hoc expert group highlighted that even a small effect size can be considered relevant. The data on FEV_1 are given greater weight in the assessment than the QoL data, where the absence of effect is perhaps not surprising in light of the commonly accepted insensitivity of these scales.

Both Phase III studies demonstrated a clinically relevant benefit in the primary efficacy variable, change in FEV_1 from baseline to study end, for Bronchitol compared to the control treatment arms, for both rhDNase users and non-users. These data supersede the rather equivocal and difficult to interpret data from phase II studies given that the phase III studies are larger and better reflect clinical practice since both rhDNAse users and non-users were included. The CHMP conclusion is that the effect in rhDNAse users and non-users is established, that clinical benefit in both rhDNAse users and non-users is positive and that benefits in both groups are considered clinically relevant.

In conclusion, further to the assessment of the applicant's responses to the grounds for refusal the and to the advice provided by the ad-hoc expert group, the CHMP concluded that the grounds for refusal No. 1 and No. 2 had been adequately addressed.

Ground 3*: The limited efficacy, of uncertain magnitude, is considered not to outweigh the observed and potential safety concerns, relating primarily to bronchoconstriction events and haemoptysis, such that a favourable benefit-risk cannot be concluded.*

Applicant´s position: (summarised)

The overall AE incidence, including SAEs, was very similar between treatment groups, irrespective of age group or concomitant rhDNase use. The remaining safety concerns raised in the grounds for refusal related primarily to risks of bronchoconstriction or haemoptysis. The applicant wanted to demonstrate that the level of haemoptysis noted in pivotal studies is in line with that expected in a CF population and that the proposed initiation dose assessment and prophylactic bronchodilator use adequately minimises the risk of bronchoconstriction. The applicant believes that both of these safety concerns can be further allayed with the proposed SPC and RMP activities including close monitoring (with re-testing for bronchial hyper-reactivity after six weeks if indicated) and cumulative reviews of all adverse events associated with both of these AEs.

Bronchospasm is not a high risk

Inhaled mannitol is a known bronchoconstrictive agent, specifically in sensitive patients with bronchial hyper-responsiveness. Because of this, mandated steps were introduced to minimize risk in the Bronchitol development programme; namely, a mannitol tolerability screening test (MTT) to detect reactive bronchoconstriction to mannitol, and prophylactic bronchodilator use prior to administration of mannitol. While it is true that acute bronchoconstriction can potentially occur during treatment in

susceptible CF patients, the findings in the pivotal studies show bronchoconstriction is infrequent and if bronchoconstriction does occur, it is not severe, responds to treatment which is available to the patient (e.g. salbutamol), and is temporary.

The following issues raised by the CHMP were addressed by the applicant:

- Bronchitol does not increase the incidence of bronchoconstriction in patients more likely to be at risk
- Bronchitol does not increase the incidence of bronchoconstriction during exacerbations
- The risk of bronchial hyper-responsiveness (BHR) developing does not increase with chronic use of Bronchitol.

Wheeze and dyspnoea are features of airways disease in cystic fibrosis, and may result from bronchospasm as well as other causes of airway obstruction. Obstructive lung disease is a major source of disability in CF, and wheezing and exercise intolerance are commonly described. Although bronchial hyperreactivity may be present, in most patients the obstruction relates to excessive viscid secretions, inflammation of airway walls, and increased compressibility of airways during expiration. This contrasts with asthmatics, in whom bronchial hyper-reactivity leading to bronchoconstriction is the common factor. Because of this, Bronchitol would lead to a degree of bronchial narrowing in more than 80% of asthmatics if untreated with steroids or bronchodilators. This contrasts with an earlier Bronchitol study in cystic fibrosis (DPM-CF-202) in which patients did not receive pre-treatment bronchodilator, 12% of these CF patients (6/52) had an FEV_1 decrease exceeding 20% at screening. Furthermore, no fall exceeded 25%. In the two pivotal cystic fibrosis studies, in which pre-treatment bronchodilator was used, about 6% of patients failed a test of mannitol tolerability at screening.

A risk in the CF population is therefore recognized, but in the six month pivotal studies which mandated screening and prophylaxis, bronchospasm related events were infrequently reported and not severe in intensity.

Bronchoconstriction risk similar between study arms

Bronchospasm itself was a rare event in the Phase 3 studies, reported by only 2 patients. Both patients were adults in study DPM-CF-301, and both were in the Bronchitol group (1 rhDNase user and 1 non-rhDNase user). Both events were considered treatment-related and both led to study discontinuation. One of these events was reported as an SAE; the patient was symptom free and recovered to baseline FEV_1 within half an hour. He was an rhDNase non-user who had an FEV_1 fall of 16% from baseline (21% from post-bronchodilator FEV_1) after study drug at the time of first study drug administration. Notably the fall in FEV_1 was only 1 percent more than that considered acceptable to continue medication. There were no other bronchoconstriction related SAEs.

Since wheeze, chest discomfort and dyspnoea are signs or symptoms that can result from bronchoconstriction, these events were also closely examined and all found to be infrequent in the pooled Phase 3 data (Table 8). These have been grouped to the term 'bronchoconstriction related AEs' (although such AEs might also result from other causes). In the overall population of the pooled studies there was a similar incidence of bronchoconstriction related AEs between arms with 6.1% on Bronchitol vs 5.0% on control. There were no severe bronchoconstriction related AE's reported in either study.

There were no trends for these AEs that suggest greater risk for any age group.

Similar findings are seen in the rhDNase user subgroups. In rhDNase users, the incidence of bronchoconstriction related AEs was 7.3% on Bronchitol, and 5.0% on control. In rhDNase non-users the incidence was 3.9% on Bronchitol and 3.8% on control. Notably though in rhDNase users a medical

history of asthma was more common in Bronchitol than the control group (32.6% vs 20.1%), which would predict a higher incidence of bronchoconstriction related AE's in the Bronchitol arm during the studies.

Bronchoconstriction risk comparable to expected background rate

The incidence of bronchoconstriction or associated events is similar between Bronchitol and control arms. However, the CHMP have previously raised concerns that a control using subtherapeutic mannitol might lead to an underestimation of difference between groups, even though incidence is low. The expected background of bronchoconstriction can also be estimated from the placebo arms of other CF studies, in particular when they are of similar length and disease severity. It should be noted that the aztreonam data was collected over 4 weeks whereas 6 month data is presented for Bronchitol, tobramycin and rhDNase.

When Bronchitol is compared with studies using other inhaled CF agents (rhDNase, aztreonam, TOBI and TIP), the incidence of dyspnoea, wheeze, chest discomfort, or bronchospasm events on either Bronchitol (400 mg B.I.D.) or control (50 mg B.I.D.) did not exceed the background rates based on the placebo arms in other studies (shaded columns in Table 8).

Table 8: Favourable Pooled Safety Data Compared to Other CF Therapies and Placebos (AEs of Interest) - Incidence (%) of AEs Over 6 Months Except Aztreona

AE %	Bronchitol (DPM-CF-301+ 302) N=361	Bronchitol control (DPM-CF-301+ 302) N=239	rhDNase (once daily) N=322	rhDNase placebo N=325	TOBI N=258	TOBI placebo N=262	Aztreonam Pooled TID (4 week) N=146	Aztreonam Pooled placebo TID (4 week) N=160	TOBI (2010) N=209	TIP (2010) N=308
Dyspnoea	1	1	37	43	34	39	7	7	12	16
Wheeze	2	2	N/A	N/A	N/A	N/A	10	8	6	7
Chest Discomfort	2	2	18	16	26	30	6[2]	5[2]	3	7
Broncho-spasm	1 (0.8[1])	0 (0.8[1])	N/A	N/A	N/A	N/A	(3[2,3])	(3[2,3])	(5.3[1])	(5.2[1])

[1]Clinically significant post dose bronchospasm FEV_1 fall ≥20%, not necessarily reported as AE; N/A –Not Available;
[2] data available from one study – Not pooled; [3]Clinically significant post dose bronchospasm FEV_1 fall ≥15%
Sources: Appendix 25; [16, 17, 26-29]

In addition, Bronchitol, tobramycin and aztreonam trial data allowed comparison of acute falls in FEV_1 immediately after study drug administration. The data suggests that Bronchitol results in a lower incidence of significant acute FEV_1 falls than either tobramycin or aztreonam (Table 8).

In summary, the overall incidence of bronchoconstriction events does not suggest any increased risk of Bronchitol over control, and these rates are consistent with that expected in a CF population.

However, there were concerns that the prolonged use of Bronchitol, or particularly susceptible patients or disease exacerbations may increase the risk. Assessment of these issues did not show any evidence that these posed any particular risks for bronchoconstriction as summarised in the following sections.

Bronchoconstriction events are not increased after long term treatment

If the sensitivity to bronchoconstriction increased with long term treatment, then acute falls in FEV_1 after Bronchitol administration would also be expected to increase over time. However, the FEV_1 falls post dose at the early study visits were similar to those observed during visits after 26 weeks of treatment. In the pooled studies, 246 patients could be analysed and the majority (135 (54.9%)) had a smaller fall in FEV_1 after 26 weeks of treatment. Consistent with this, the overall mean falls in FEV_1

at each of these visits were similar. Thus, the data is not suggestive of increased bronchial reactivity after long term Bronchitol treatment.

As supportive evidence, similar results were seen when looking at bronchodilator reversibility at the beginning and end of the treatment period. Increasing reversibility over time to a bronchodilator might also suggest an increase in BHR. In the combined studies, 7/246 (2.8%) Bronchitol patients and 11/170 (6.5%) control patients changed from < 12% reversibility to ≥ 12% reversibility in FEV_1 from Week 0 to Week 26. In contrast, 12/246 (4.9%) Bronchitol patients and 1/170 (0.6%) control patients changed from ≥ 12% reversibility to < 12% reversibility in FEV_1 from Week 0 to Week 26. Thus falls in FEV_1 after drug administration and reversibility to bronchodilator shows no evidence of increased susceptibility to bronchoconstriction after long term use of Bronchitol.

Bronchoconstriction events are not increased significantly during exacerbations

Patients with meaningful reactivity to mannitol at screening were excluded from the studies, and the patient group continuing with therapy did not then exhibit bronchial reactivity while on treatment. However it is conceivable that increased bronchial hyper-reactivity could become apparent with worsening airway inflammation at the time of pulmonary exacerbations. However, it was found that Bronchitol does not worsen the degree of bronchoconstriction at the time of CF exacerbations.

Falls in FEV_1 in response to Bronchitol at the time of exacerbations (within 7 days) were examined, as a meaningful number of patients (N=64) experienced exacerbations within a week of study visits.

Only in five patients out of 58 (2 out of 30 in Bronchitol group and 3 out of 28 in control group) did FEV_1 fall more than 10% following Bronchitol or control drug administration at the time of an exacerbation. Falls of 10% are not considered excessive, thus only two patients (6.7%) experienced notable falls in FEV_1 around the time of an exacerbation while on Bronchitol treatment. In no case did the fall exceed 20% and most were close to 10%.

Further to the lack of increased FEV_1 falls in response to study drug, falls in FEV_1 and dyspnoea were also recorded as components of an exacerbation, and these were both reported in similar proportions of patients experiencing exacerbations in the Bronchitol and control arms. If there was increased bronchial reactivity in the Bronchitol arm at the time of an exacerbation it would be expected that they would therefore show a higher frequency of these events. The data is not indicative of this.

In addition, out of the 64 patients experiencing an exacerbation in either treatment arm, only 7 (10.9%) had bronchoconstriction related AEs reported at the same time, which is similar to the rates of these events seen outside the period of exacerbations.

Thus, while reasonable hypothetical concerns were raised regarding increased airway-reactivity at the time of exacerbations, there is no evidence of a higher frequency or greater severity of bronchoconstriction events during exacerbations.

Patients with potential susceptibility show no increased risk of bronchoconstriction

Patients who might potentially be most at risk of increased hyper-reactivity during the study were also specifically examined i.e. those patients with a degree of bronchoconstriction (FEV_1 fall ≥10%) during the screening test dose of mannitol but who still went into the study. Patients with a less than 10% fall in FEV_1 after the test dose had a similar incidence of bronchoconstriction related AEs to those with at least a 10% fall in FEV_1 (6.3% vs 6.5% respectively) indicating no increase in bronchoconstriction risk in this group.

Furthermore, patients who had post mannitol falls in FEV_1 of 10% or more during their mannitol tolerability test at screening, had long-term FEV_1 improvements that were similar to the rest of the study population. In this group the falls in FEV_1 post-dose at all visits were similar, and showed no

change in average fall in FEV_1, despite hypothetically being more vulnerable to lung function drops on treatment.

In conclusion an evaluation of more than six hundred patients in both pivotal trials for risks associated with bronchospasm, found that the MTT appeared to be a safe and effective screening procedure, since bronchoconstriction events during the treatment period were not notable. Although bronchoconstriction remains a potential risk, if the recommended strategy of a screening test to assess tolerability in addition to the prophylactic use of a pre-treatment bronchodilator is used, then the apparent risk of bronchospasm with therapeutic Bronchitol is low. The applicant suggested a reference to the initiation dose assessment in section 4.2 of the SPC which is expected to provide an effective safety measure in the post authorisation setting.

Since bronchospasm during and after the initiation dose assessment and also during long term use were identified as potential risks, a precaution was proposed in section 4.4 of the SPC.

In addition to the SPC precaution outlined above, it is proposed to include in the product information, as part of a stopping rule, that physicians will enquire whether patients experience an increase in bronchoconstriction symptoms at the end of the initial treatment period. If symptoms are present then it will be recommended that the patient is re-assessed for bronchial hyperresponsiveness to inhaled mannitol by taking a further tolerability test prior to continuing with treatment. If this test is positive treatment would be stopped. This would further minimise the risk of bronchospasm.

Furthermore, routine and additional pharmacovigilance and risk minimisation activities have been outlined in the RMP (Module 1.8.2) addressing the risk of bronchospasm during and after the assessment as well as during long-term use. These include as additional risk minimisation activities a healthcare professional leaflet addressing definition, identification/monitoring and information related to these potential risks.

In summary, bronchospasm is an event uncommonly reported across both phase 3 studies and bronchoconstriction related events are reported at similar levels between treatment groups in all age and rhDNase subgroups assessed. Furthermore an assessment of bronchoconstriction risk with long term treatment and in at-risk situations such as during exacerbations, confirmed that there is not an increased risk of bronchoconstriction. However, bronchospasm during and after the initiation dose assessment and during long term use are identified as potential risks in the Bronchitol RMP. The proposed labelling includes the assessment for bronchial hyperresponsiveness to inhaled mannitol and prophylactic bronchodilator use. These, together with RMP activities including close monitoring and cumulative reviews, will minimise any potential risks.

Haemoptysis risk is not high

Haemoptysis is common for patients with CF, although typically the bleeding is scant or mild. CF patients have chronically inflamed and friable airways and in this pathological situation haemoptysis is to be expected, and is not an unusual occurrence. Haemoptysis can be of varying cause for concern depending on the extent of bleeding occurring; sputum streaking has very different implications to a large haemorrhage. Massive haemoptysis occurs more commonly in older patients with more advanced lung disease.

Overall the incidence of haemoptysis was similar between the two treatment groups (15.8% versus 14.6% for the Bronchitol and control groups, respectively) in the pooled Phase 3 studies. Haemoptysis was reported as an AE that was outside an exacerbation more frequently in the Bronchitol group (6.1%) than in the control group (3.8%). However, haemoptysis is frequently associated with CF exacerbations. Indeed, two-thirds (61/92) of the total incidence of haemoptysis was associated with pulmonary exacerbation. Haemoptysis occurring during an exacerbation was commonly captured as a symptom of the exacerbation, and not therefore reported as a separate AE. When all events were

appropriately included, the total incidence of haemoptysis was similar between treatment groups (Table 9).

Table 9: Occurrence of Haemoptysis Reported as an AE and/or as a Symptom of Pulmonary Exacerbation of CF During the Double-blind Phase – Pooled Safety Population

Patients with Haemoptysis:	DPM-CF-301+DPM-CF-302	
	Bronchitol (N=361) n (%)	Control (N=239) n (%)
Reported as AE (no exacerbation)	22 (6.1)	9 (3.8)
Related to Exacerbations	35 (9.7)	26 (10.9)
Total	57 (15.8)	35 (14.6)

Source: Appendix 29

Most of the haemoptysis events noted with Bronchitol were mild or moderate, with only 1.1% and 0.4% of patients reporting severe events of haemoptysis in the Bronchitol and Control arms respectively. Treatment emergent massive haemoptysis occurred infrequently, in study DPM-CF-301 there was one case in each arm and in study DPM-CF-302 one case in the Bronchitol arm. This is consistent with the expected rate of massive haemoptysis of 0.9%/year based on reviews published in CF.

Haemoptysis incidence consistent with background rate

As well as the incidence being similar in the Bronchitol and control arms, the incidence of haemoptysis does not exceed expected background rates based upon incidence observed in the placebo arms of published therapeutic studies. In patients of similar disease severity, the incidence of haemoptysis was 21% and 31% over 6 months with rhDNase and TOBI placebo groups respectively, and was already 8% in the Aztreonam placebo group after 1 month (shaded columns in Table 10). Thus the data suggest that the incidence of haemoptysis in the Bronchitol development program is not a significant risk associated with Bronchitol treatment, but rather a risk consistent with the disease state.

Table 10: Comparison of Haemoptysis Incidence (%) with other CF Therapies and Placebos

AE %	Bronchitol (CF-301 +CF-302) (6 months) N=361	Bronchitol control (CF-301 +CF-302) (6 months) N=239	rhDNase (once daily) (6 months) N=322	rhDNase placebo (6 months) N=325	TOBI (6 months) N=258	TOBI placebo (6 months) N=262	Aztreonam Pooled TID (1 month) N=146	Aztreonam Pooled placebo (1 month) N=160
Haemoptysis	16[1]	15[1]	17	21	27	31	5	8

[1] Includes events reported as exacerbation symptom.
Sources: Appendix 25; [15, 17, 26-28]

Although the risk of haemoptysis does not appear elevated, it is an identified risk. Therefore a precaution is proposed in section 4.4 of the SPC.

Furthermore, routine and additional pharmacovigilance and risk minimisation activities have been outlined in the RMP (Module 1.8.2) addressing the identified risk of haemoptysis.

In summary, although the level of haemoptysis noted in pivotal studies is in line with that expected in CF, this is an identified risk in the Bronchitol RMP. Therefore the proposed labelling and RMP activities including close monitoring and cumulative reviews are in place to minimise this risk.

Optimisation of benefit/risk – justification for a stopping rule

The applicant believes that adequate benefit/risk has already been demonstrated in the overall population of the pivotal studies. However, there are approaches which might allow further enhancement that is either reliably identifying patients who are more likely to respond, or limiting long term therapy to those who demonstrate a response.

Firstly, pre-treatment criteria (predicting whether or not a patient will respond long-term to treatment based upon baseline characteristics) were explored. For any criteria to be useful it should reduce the exposure to drug for patients that will not experience any benefit, but also ensure that patients who can potentially experience meaningful benefit are not excluded.

The second approach, to minimise any potential risks and increase benefit, involves a stopping rule after a trial of therapy to ensure that patients achieve a minimum level of response before continuing further treatment with Bronchitol. A formal review of response is also an opportunity to question patients specifically for signs or symptoms of bronchoconstriction, and investigate further if required.

Following an evaluation of over 16 variables including age, disease severity, and lung infection comorbidity, no pre-treatment criteria were found in which both the sensitivity and specificity were high enough to be clinically useful. The alternative approach of a trial of therapy with a stopping rule was therefore explored, and this is described in the following section. It was found that an FEV_1 response after 6 weeks of treatment was highly predictive of response over the whole 6 months of the double blind studies, and a stopping rule at 6 weeks for patients showing early signs of response therefore offers an attractive option.

Trial of Therapy with Stopping Rule

A trial of therapy with a stopping rule is particularly applicable if an early response can be shown to reasonably predict a long term response. This in turn minimises exposure in non-responding patients, and hence only patients who are likely to continue to respond ('responders') continue with treatment.

To increase objectivity, the assessment was based on an improvement from baseline in FEV_1, after a fixed period of time. For Bronchitol, a treatment period of 6 weeks was explored to assess its sensitivity and specificity to predict a sustained response, as this was the earliest time point assessed in the pivotal studies, but is also reasonably in keeping with the timing in clinical practice for a first follow-up assessment of a new therapy, and does not expose non-responders to unreasonable risk.

Currently there is no globally accepted threshold for FEV_1 improvement in CF, and CHMP guidelines do not define a threshold. European CF experts consulted considered that because lung function is continually declining in CF, any statistically significant benefit in lung function is meaningful. Therefore a range of response thresholds were explored from > 0 to ≥ 12% relative improvements in % predicted FEV_1.

Calculations have been performed regarding the sensitivity and specificity of each threshold for a responder from the pooled clinical studies, thereby providing a measure of how predictive the week 6 response was for a sustained response out to week 26. This data suggests that most of the thresholds explored are reasonable; for example, a response of ≥ 6% provides a good balance of sensitivity (86.5%) and specificity (83.0%), and would lead to 41.3% of patients continuing Bronchitol beyond 6 weeks. As experts view any sustained benefit as meaningful, thresholds above 6% are unnecessarily high to ensure meaningfulness, and also start to lose sensitivity, without much gain in specificity.

Continuing with the same example, (i.e. a 6% threshold), when the mean relative change from baseline in % predicted in the Bronchitol arm of the overall pooled ITT population was compared with that using the 6% threshold, the mean relative change from baseline in % predicted over the 26 week study period increased from 4.8% to 16.3%. This provides an indication of the enhanced level of

effectiveness in FEV_1 which can be expected over 26 weeks in a responder population, if the example of a stopping rule using a 6% threshold at 6 weeks was introduced.

The applicant proposes to implement the stopping rule by amending the product information. It is proposed that patients undergo a trial of therapy for 6 weeks, at the end of which the change from baseline in FEV_1 will be assessed. Only if the threshold (to be determined) is met, will patients continue with therapy.

It is also proposed to include an additional safety step in the product information as part of the stopping rule to further minimise bronchospasm risk. Physicians will ask patients at the end of the initial 6 week treatment period whether they have experienced new or increased signs or symptoms of bronchoconstriction. If present, it will be recommended that the patient be re-assessed for bronchial hyperresponsiveness to inhaled mannitol by taking a further tolerability test prior to continuing Bronchitol.

In conclusion, using a stopping rule which includes a response threshold (to be determined) after 6 weeks of treatment increases positive benefit/risk by stopping treatment in non-responders and ensuring patients being treated meet a level of FEV_1 improvement considered clinically meaningful. The inclusion of a re-test for bronchial hyper-reactivity if bronchoconstriction signs or symptoms arise will further reduce the risk of bronchospasm. This type of approach also addresses concerns regarding inconsistency of effect as patients are assessed for effectiveness and only proceed if the threshold is met, irrespective of age or concomitant rhDNase use. Therefore, the response threshold with a stopping rule provides an approach that improves the certainty of response, minimises risk and is in line with the individualised treatment strategy which is used for CF patients.

CHMP position on ground 3

The two main safety issues identified by the CHMP were bronchoconstriction and haemoptysis.

Since inhaled dry powder mannitol is known to cause bronchoconstriction in susceptible patients, all patients underwent a mannitol tolerance test (MTT) prior to randomised treatment. In study DPM-CF-301, 378 subjects were enrolled and underwent the MTT. Of these 324 were randomised to treatment. Of those that failed to progress to randomisation, 27 had a >20% fall in FEV_1 following the MTT (7.5% of those tested), despite premedication with 400mcg salbutamol (mean maximum fall in FEV_1 26.4%, range 18 – 39). In addition there were 19 subjects who failed to complete the mannitol tolerance test, with cough (9/19), bronchoconstriction symptoms (5/19) and nausea (4/19) being the most common symptoms associated with incomplete testing.

Of the 342 patients who underwent MTT in study DPM-CF-302, 18 (5.3%) had a positive MTT and 8 patients had an incomplete test due to mannitol induced cough or other unspecified reasons. The mean maximum fall in FEV_1 was 26.3%. The most frequently reported adverse events reported in association with the MTT were cough (12.6%) and wheeze (0.9%). Bronchoconstriction was an expected effect during the MTT and was not considered as an adverse event unless the bronchoconstriction caused a >50% fall in FEV_1 or the subject desaturated to <89%. If at any other time during or immediately following the administration of the mannitol/control powder, the subject experienced a fall in FEV_1 of >20% due to bronchoconstriction, the subject was monitored for 30 minutes before having the FEV_1 measurement repeated. Subjects who had not recovered their FEV_1 to < 20%, at this point and provisos 1 and 2 (below) had been met, did not receive further study medication.

1) A suitable bronchodilator was taken prior to administration of the mannitol/control;

2) The investigator determined that the fall in FEV_1 was bronchoconstriction and not due to mucus plug or floppy airway collapse. This was to be tested by administering positive pressure via a PEP mask or Acapella device or similar and repeating the FEV_1 manoeuvres.

The applicant concludes that the MTT appeared to be a safe and effective screening procedure since subsequent airway reactivity during the treatment period was not a notable event, i.e. there were 2 cases of bronchospasm in the phase III trials, both in the Bronchitol group, that lead to treatment discontinuation. However, bronchoconstriction related events (wheeze, chest discomfort and dyspnoea) had a similar incidence in both treatment groups (6.1% in patients on Bronchitol and 5.0% on control).

The applicant has provided a table comparing the frequency of bronchospasm and bronchoconstriction related events of Bronchitol with that of other inhaled agents for CF (rhDNase, TOBI, aztreonam, tobramycin inhalation powder).

Furthermore, the applicant argued that bronchospasm events are consistent with rates to be expected in a CF population and arise from the underlying disease rather than its treatment. According to the expert group bronchospasm is probably inherent to the treatment with inhaled mannitol and not to the disease; nevertheless, the panel concluded that this safety issue is manageable in clinical practice.

Overall, the CHMP is of the view that the data provided suggest that bronchoconstriction can reasonably be prevented with the use of the mannitol tolerance test and a pre-treatment bronchodilator. Whether patients with pulmonary exacerbations are at increased risk of this adverse event cannot be completely ruled out but the overall frequency of reporting does not suggest it. In addition to the instructions given in section 4.2 in relation to the performance of the mannitol tolerance test, the use of a bronchodilator pre-treatment etc. prior the initiation of treatment with Bronchitol, the applicant proposed that all patients should be formally reviewed after approximately six weeks of Bronchitol treatment to assess for signs and symptoms suggestive of drug induced bronchospasm. This precautionary measure in section 4.4 of the proposed SPC is endorsed.

Bronchospasm is considered as an identified risk in the Risk Management Plan. Routine pharmacovigilance for monitoring this adverse event as well as several risk minimisation activities (statements in the SPC, educational pack - healthcare professional leaflet) are proposed. These measures cover the occurrence of such events during and after the initiation dose assessment, as well as during long-term (chronic) use of inhaled mannitol. Therefore, the CHMP considers that this identified risk is adequately addressed.

With regard to haemoptysis, the overall incidence was similar in patients on Bronchitol and on control (15.8% and 14.6% respectively) in the pooled main studies. However, when haemoptysis was reported as a stand alone AE (outside of pulmonary exacerbations) the incidence was higher in the Bronchitol group (6.1% versus 3.8%) suggesting that haemoptysis may be related to treatment rather than the disease. Similar percentages, however, are shown for haemoptysis related to exacerbations (9.7% for patients on Bronchitol and 10.9% in patients in the control group).

To explore how haemoptysis in the Bronchitol and control group compares with that reported in other trials a table quoting the percentage of haemoptysis for different inhaled medicinal products commonly used by patients with cystic fibrosis is provided. Comparisons across trials may provide some insight but the data should be considered with caution due to limitations related to the trial population, disease severity and whether patients with previous antecedents of haemoptysis were permitted to be enrolled in these trials or not.

Co-administered inhaled products which have been associated with reports of haemoptysis include dornase alpha and hypertonic saline. Hypertonic saline was not permitted in studies DPM-CF-301 and DPM-CF-302. The Clinical Study Reports provide the following information: in study DPM-CF-301 haemoptysis was reported by 13 (13.5%) and 7 (10.4%) rhDNase users and 8 (9.9%) and 3 (5.9%)

non-users in the mannitol and control groups respectively. In study DPM-CF-302, 12 of the 13 subjects who had haemoptysis recorded as an adverse event in the mannitol group in the overall safety population were rhDNase users. Therefore, the co-administration of dornase alpha increases the incidence of haemoptysis (and also that of other adverse events such as cough).

The expert group was of the opinion that haemoptysis as seen in the main studies is manageable in clinical practice. Hence it is considered that haemoptysis needs to be monitored in patients receiving inhaled mannitol hence a precautionary statement is included in section 4.4 of the SPC. Haemoptysis is considered as an identified risk in the Risk Management Plan. Routine pharmacovigilance for monitoring this adverse event as well as several risk minimisation activities (statements in the SPC, educational pack - healthcare professional leaflet) are proposed. The above-mentioned view of the experts was endorsed by the CHMP and therefore considered that this identified risk is adequately addressed.

To further optimise the benefit risk balance of the product, the applicant proposed the introduction of a stopping rule using an early predictor of long-term response. Based on an evaluation of data from studies DPM-CF-301 and DPM-CF-302 and the analysis of a variety of variables to serve as predictor, a stopping rule after a trial of therapy was proposed based on the change in FEV_1 after 6 weeks as this was identified as highly predictive of response over the whole 6 months of double-blind treatment. However, further to considering the above-mentioned proposal from the applicant, the CHMP concluded that this stopping rule, which is based on post-hoc review of the data, cannot be considered as a valid instrument for the intended purpose. In fact, the proposed stopping rule was considered more to reflect clinical practise rather than a product specific approach. The proposal was therefore not accepted. Nevertheless, the two main safety issues – namely bronchoconstriction and haemoptysis – can be addressed adequately through the risk minimisation activities discussed above, and without such stopping rule.

The CHMP agreed that the collection of post-marketing safety data through the UK CF registry is an important additional pharmacovigilance activity. During the procedure, the applicant provided a study synopsis, which is part of the Risk Management Plan.

The applicant is requested to submit periodic analysis of the CF study every 6 months for 3 years and annually for 2 years. The final report is expected in Q1 2018.

In conclusion, further to the assessment of the applicant's responses to the grounds for refusal and to the advice provided by the ad-hoc expert group, the CHMP concluded that the ground for refusal No. 3 had been adequately addressed.

4.2.2. Ad Hoc Expert Group meeting

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad-hoc expert meeting on 3 October 2011 inviting the experts, including patients representatives, to provide their views on the questions posed by the CHMP in relation to the marketing authorisation application, taking into account the applicant's response to the grounds for refusal. The above-mentioned questions, together with the experts' conclusions, are shown below:

Experts' input on the CHMP questions:

Mechanism of action

1. The applicant considers that the mechanism of action is through the osmotic properties of mannitol increasing airways epithelial lining fluid, and thus reducing sputum viscosity. However, an alternative mechanism which could contribute to sputum clearance is through increase in cough. Could the group comment?

Experts' response: It is the unanimous view of the experts that the predominant mechanism of action is the change in osmolarity hence the hypothesis of hyperosmolarity due to administration of inhaled mannitol leading to reduced sputum viscosity is accepted. With regard to cough there is a need to differentiate between productive and reactive events. Productive cough can be supportive as it can contribute to sputum clearance. Reactive cough is solely a side effect.

Efficacy

2. There is considerable heterogeneity between and within studies with respect to benefit on lung function. Study DPM-CF-301 showed a statistically significant benefit for FEV_1 (mL). Study DPM-CF-302 did not, at least in terms of the primary analysis. Furthermore, there were differences in outcome for children, adolescents, and adults. From a clinical point of view, are the observed differences surprising or expected (e.g. as a result of small study numbers and varied demographics)? If the heterogeneity is surprising, could the group say why?

Experts' response: There is heterogeneity between the subgroups in studies DPM-CF-301 and DPM-CF-302 and depending on the type of analysis performed (absolute change in FEV_1, relative % predicted, absolute % predicted). However, the experts noted that the two studies were not powered for such subgroup analysis hence this heterogeneity is not considered of relevance. At the same time, the experts indicated that the studies should ideally have been stratified for such subgroup analysis since it is clinically plausible to detect differences.

Furthermore for the present application, the group did not consider the inconsistency of the results seen in the different age groups as an issue since the claimed indication is restricted to adults only. In contrast, the experts raised concerns about the fact that the indication proposed by the applicant includes rhDNAse users and non-users even if the studies were not powered for the analysis of these two subgroups (see below).

3. In both pivotal Phase 3 studies the effect size for FEV_1 is small and of debatable clinical relevance. The applicant argues that any improvement in lung function in the population studied is clinically relevant. Please provide your opinion on the clinical relevance of the observed treatment effect for

each population (children, adolescents and adults) as well as the overall population. The experts are also invited to discuss whether the rate of the decline in lung function in CF patients changed over the past years and what should be the benchmark for a product impacting on sputum clearance (and not an antibiotic) like inhaled mannitol.

Experts' response: The effect size is considered small and based on the available data it is difficult to ascertain whether the treatment effect is clinically relevant. However, the experts also noted that even a small benefit can be of relevance in an individual patient given the deterioration of FEV_1 inherent to the disease progression. The results in adolescents were considered surprising from a clinical perspective as this is the patient population where normally benefits are clearly demonstrated, which seems not to be the case across both pivotal studies.

Regarding benchmarking the experts agreed that the mechanisms of action need to be considered. Therefore, for inhaled mannitol a different approach should be taken compared to antibiotics. Acting on sputum clearance constitutes an additional approach but this cannot be compared versus antibiotics. In general the experts indicated that FEV_1 remains an important outcome parameter for studies in cystic fibrosis; from a patients' perspective a relief in symptoms is very important.

4. The change in FEV_1 can be measured as the absolute change from baseline (in litres), the relative change (as percent change from baseline), or the absolute change in percent predicted FEV_1. While the predefined primary endpoint in the two phase 3 pivotal studies is the change from baseline in FEV_1 (mL) in the response to the CHMP grounds for refusal the results are discussed as the relative change in FEV_1 predicted of normal. While using FEV_1 (% predicted) is endorsed if children and adolescents are considered it is believed that the results to be taken into consideration are those corresponding to the absolute change in percent predicted FEV_1. Could the experts provide their opinion on the above issue?

Experts' response: The assessment based on relative % predicted change is better than the use of absolute change in mL, the latter being not considered appropriate for the study. However, the experts also noted that the absolute % predicted change would have been even better.

5. The applicant claims an indication for the use either as an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to, rhDNase. The experts are invited to discuss whether from the clinical perspective the data in all or part of these subgroups related to rhDNase use are compelling. Additionally, while analysis by non-use/use of rhDNase was predefined in the statistical analysis plans of studies DMP-CF-301 and 302 there was an assumption that all non rhDNase users would reflect, and therefore be representative of the subpopulation of non rhDNase users who were "intolerant to, or inadequately responsive to rhDNase". Could the experts provide their opinion on what would constitute an adequate definition of patients intolerant to, or inadequately responsive to rhDNase?

Experts' response: The criteria for the subgroups related to rhDNAse users and non-users were not pre-specified for both studies, which renders the interpretation of the results very difficult. Moreover, studies DMP-CF-301 and DMP-CF-302 were not powered to make such stratifications. From a clinical perspective, the proposed distinction between rhDNAse users and non-users appear difficult given that in practice the (non-)use of rhDNAse is also subject to patient's choice, hence the definition of rhDNAse non-users appears not appropriate.

As mentioned above, a general issue is the fact that the studies were powered only for the overall population but the indication claims an effect on both rhDNAse users and non-users. It may be more appropriate not to specifically indicate in the indication the rhDNAse use.

Safety

6. Bronchospasm and haemoptysis occurred more frequently in the Bronchitol than the control treatment arms of the studies. The applicant argues that these events are consistent with rates to be expected in a CF population and arise from the underlying disease rather than its treatment. Could the group provide their view?

Experts' response: It is likely that bronchospasm is inherent to the treatment with inhaled mannitol and not to the disease. Regardless of this, the safety issues observed are not a major problem from the clinicians' point of view. It was noted however that patients might be concerned by an event of haemoptysis hence education is necessary.

4.2.3. Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant in writing and in the oral explanation and considered the views of the ad-hoc expert group.

The applicant has conducted two six month, placebo controlled, phase III clinical trials of dry-powder inhaled mannitol in the treatment of cystic fibrosis involving a total of 600 patients. Studies DPM-CF-301 and DPM-CF-302 included children, adolescents, and adults and used absolute change from baseline in lung function (FEV_1) as the primary efficacy variable. The studies show an effect of inhaled mannitol on lung function.

The uncertainties regarding the methodology, conduct and interpretation of the two pivotal trials identified by the CHMP in the initial assessment were considered unacceptable in light of the conclusion that the clinical relevance of the treatment effect was questionable. During the re-examination procedure, the view of CHMP on the clinical relevance of the results was changed following consultation of an ad-hoc expert group and the statistical analyses presented by the applicant were accepted as comprehensively addressing concerns over the uncertainty introduced because of missing data due to patient withdrawal. Regarding the issue of apparent heterogeneity in the trial results, the applicant used a proper set of available statistical methodologies to explore these effects, 'interaction tests' and subgroup analyses, complemented by discussion on the biological plausibility of observing heterogenous results. These arguments were accepted by the CHMP to conclude that the effect demonstrated in adults, across multiple trials, was robust. Taking into account the arguments presented during the re-examination, the CHMP concluded that the studies were fit for purpose and any residual, minor methodological concerns were of no consequence to demonstration of efficacy, assessment of safety or judgement on benefit-risk.

The predominant mechanism of action of inhaled mannitol is understood to be the change in osmolarity, particularly the hyperosmolarity due to administration of inhaled mannitol leading to reduced sputum viscosity. Productive cough can be supportive as it can contribute to sputum clearance and reactive cough is solely a side effect. These assumptions were confirmed by the expert group.

In both main studies the effect size for FEV_1 is small. Overall, the treatment with mannitol showed an improvement of approximately 2-3% compared with the control group over 26 weeks in terms of percent predicted FEV_1. The clinical relevance of such a marginal effect is difficult to acertain. Therefore, this critical question was posed to an ad-hoc expert group. Acknowledging that the effect

size is small, the experts nevertheless agreed unanimously that any improvement in lung function in the population studied can be of relevance in an individual patient given the deterioration of FEV_1 inherent to the disease progression. The above was subsequently endorsed by the CHMP.

The CHMP had raised concerns regarding the observed heterogeneity between and within studies with respect to benefit on lung function. While study DPM-CF-301 showed a statistically significant benefit for FEV_1 (mL), study DPM-CF-302 did not, at least in terms of the primary analysis. Furthermore, there were differences in outcome for children, adolescents, and adults. From the view of the expert group the fact that the study was not stratified for the various sub-groups is a limitation since certain variability is clinically plausible. The inconsistency across age groups was considered less of a concern. This is because the effect size in the adult population was similar in the two pivotal studies and was consistent with the 2 supportive studies, all showing a similar benefit in FEV_1 and it was considered that the available data could support an indication in adults (for both Phase III studies there was a statistically significant benefit in the primary efficacy variable, change in FEV_1 from baseline to study end, for Bronchitol compared to control treatment arms). This suggests that the benefit is real, and is unlikely to be an artefact of the subgroup analyses presented by age. In addition it is considered that the effect has been measured with acceptable precision, and it is recognised by the ad-hoc expert group cystic fibrosis experts and the CHMP to be small, but of clinical relevance. Moreover, the differential response according to patients' age may be due to clinical trials conducted in a refractory disease, in a relatively small number of patients. Taking the above information into account, the CHMP concluded that the studies are considered reliable.

The previously claimed indication made a difference between rhDNAse users and non-users. This proposal has limitations from a methodological view point in terms of definition and stratification, as well as from the results. In clinical practice the definition of rhDNAse users appears not appropriate, as stated by the experts. The applicant changed the proposed indication to add-on therapy to best standard of care, which the CHMP considered acceptable; there was evidence of efficacy, which is regarded as being of clinical relevance, also in this subgroup although the effect size appeared smaller in the RhDNase subgroup.

Both Phase III studies demonstrated a clinically relevant benefit in the primary efficacy variable, change in FEV_1 from baseline to study end, for Bronchitol compared to the control treatment arms, for both rhDNase users and non-users. These data supersede the rather equivocal and difficult to interpret data from phase II studies given that the phase III studies are larger and better reflect clinical practice since both rhDNAse users and non-users were included. The CHMP conclusion is that the effect in rhDNAse users and non-users is established, that clinical benefit in both rhDNAse users and non-users is positive and that benefits in both groups are considered clinically relevant.

Children and adolescents were included in the patient population in the two main studies. However, based on the available data the efficacy in this paediatric population has not been demonstrated. From a clinical perspective – given the demographics of CF patients – such reliable data in the paediatric population appears paramount; these data will further establish the benefit risk of the product. The applicant is therefore requested by the CHMP as a condition to the marketing authorisation to conduct a study to investigate efficacy and safety data of Bronchitol in children and adolescents with cystic fibrosis.

With regard to the safety of Bronchitol, two main safety issues have been identified by the CHMP: bronchoconstriction and haemoptysis.

Regarding the risk of bronchoconstriction, the CHMP is of the view that the data provided suggest that can reasonably be prevented with the use of the mannitol tolerance test and a pre-treatment bronchodilator. Furthermore, the product information includes an additional measure, i.e. that physicians should formally review patients after approximately six weeks of Bronchitol treatment. If

symptoms of Bronchitol induced bronchospasm are presented patients should undergo the mannitol tolerance test again; if this test is positive treatment would be stopped. This would further minimise the risk of bronchospasm. According to the expert group bronchospasm is probably inherent to the treatment with inhaled mannitol and not to the disease; nevertheless, the panel concluded that this safety issue is manageable in clinical practice. Overall, bronchospasm is considered as an identified risk in the Risk Management Plan. Routine pharmacovigilance for monitoring this adverse event as well as several risk minimisation activities (statements in the SPC, educational pack - healthcare professional leaflet) are proposed. These measures cover the occurrence of such events during and after the initiation dose assessment, as well as during long-term (chronic) use of inhaled mannitol. Therefore, the CHMP considers that this identified risk is adequately addressed.

The expert group concurred that haemoptysis as seen in the main studies is manageable in clinical practice. Hence it is considered that haemoptysis needs to be monitored in patients receiving inhaled mannitol hence a precautionary statement is included in section 4.4 of the SPC. Haemoptysis is considered as an identified risk in the Risk Management Plan. Routine pharmacovigilance for monitoring this adverse event as well as several risk minimisation activities (statements in the SPC, educational pack - healthcare professional leaflet) are proposed. Therefore, the CHMP considers that this identified risk is adequately addressed.

For additional post-marketing safety data collection, the applicant has proposed a study using the UK CF registry. This proposal is endorsed by the CHMP.

At the time of the initial, negative CHMP opinion, there was a quality issue that was not fully addressed by the applicant. The issue relates to the preservative efficacy of mannitol and its potential as a microbiological growth substrate in an in-use context for cystic fibrosis pathogens e.g. Burkholdaria cepacia, Aspergillus fumigatus, etc. No data were provided in the MAA that explicitly address this issue. However, considering that the inhaler device is to be used for 7 days only and that clear instructions on how to clean the device are included in the package leaflet, this issue was not considered a major objection at the time of neither the first CHMP opinion nor the re-examination CHMP opinion, as it does not compromise change the positive benefit-risk conclusion. It is therefore not considered necessary to have the results from this study prior to authorisation.

Nevertheless, due to the potential risk of "Microbial infection via a contaminated inhaler device" the preservative efficacy of mannitol should be monitored through additional studies and data collection through risk management. Therefore, the applicant should investigate whether potentially pathogenic species for CF patients could survive and whether they could replicate within the residual mannitol in the inhaler. The applicant should perform appropriate in-vitro microbiological studies reflecting 'in-use' conditions to assess the duration of survival and changes in numbers of organisms to help evaluate the potential risk that important species such as Burkholderia spp. and Aspergillus spp. could be transmitted to patients from the inhaler.

In conclusion, the clinical relevance of the small treatment effect observed on FEV_1 is considered established given the deterioration of FEV_1 inherent to the disease progression of this chronic condition. This is accepted for the use in adults in the dose of 400 mg bid on top of best standard of care. The safety issues are considered adequately addressed with the proposed pharmacovigilance and risk minimisation activities, respectively, and are manageable in clinical practice. The benefit/risk conclusion for inhaled mannitol is therefore deemed positive.

4.2.4. Risk Management Plan

The MAA submitted a revised risk management plan, which included a risk minimisation plan.

Summary of the EU risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified Risks		
Haemoptysis	• Routine pharmacovigilance - Standard AE collection form and predefined targeted follow-up questions. - Routine review of new events and monthly surveillance activities. - Specific analysis in PSURs.	• Routine risk minimisation activities - Section 4.4 of the SmPC - Warning regarding haemoptysis and the requirement for monitoring this risk. - Section 4.8 of the SmPC - Details on haemoptysis ADRs.
	• Additonal pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Additional risk minimisation activities - An Educational Pack - healthcare professional leaflet.
Bronchospasm during and after the initiation dose assessment.	• Routine pharmacovigilance - Standard AE collection form and predefined targeted follow-up questions. - Routine review of new events and monthly surveillance activities. - Specific analysis in PSURs. • Additional pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.2 of the SmPC - Details that the patients' initiation dose must be used under the supervision and monitoring of an experienced physician or other health professional appropriately trained and equipped to perform spirometry, monitor SpO_2, and manage acute bronchospasm including appropriate use of resuscitation equipment. - Section 4.4 of the SmPC - Warning regarding bronchospasm and the requirement for monitoring this risk. - Section 4.8 of the SmPC - Details on bronchospasm ADRs. • Additional risk minimisation activities - An Educational Pack - healthcare professional leaflet.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Bronchospasm during long-term use	• Routine pharmacovigilance - Standard AE collection form and predefined targeted follow-up questions. - Routine review of new events and monthly surveillance activities. • Additonal pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.2 of the SmPC - Instructions for use of inhaler, including the importance of training patients to practice correct inhaler technique during the initiation dose assessment and the requirement for use of a bronchodilator 5 to 15 minutes before Bronchitol administration. - Section 4.4 of the SmPC - Warning regarding bronchospasm and the requirement for monitoring this risk. - Section 4.8 of the SmPC - Details on bronchospasm ADRs. • Additional risk minimisation activities - An Educational Pack - healthcare professional leaflet.

Potential Risk		
Cough-related sequelae	• Routine pharmacovigilance - Follow-up all SAEs with predefined questions to determine if cough was a predisposing factor of the SAE. • Additonal pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.8 of the SmPC - Details on Cough ADRs. • Additional risk minimisation activities - An Educational Pack - healthcare professional leaflet.
Pulmonary abscess on continued use	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities. • Additonal pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.2 of the SmPC – Instruction to replace the inhaler device after one week of use. If the inhaler does require cleaning, it is to be washed in warm water and before re-use, allowed to thoroughly air dry. -
Septicaemia on continued use	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities. • Additonal pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.2 of the SmPC – Instruction to replace the inhaler device after one week of use. If the inhaler does require cleaning, it is to be washed in warm water and before re-use, allowed to thoroughly air dry. -

Off-label use in non-CF bronchiectasis	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities from: • Study DPM-B-305. • SAS and named patient supply. - Monitoring off-label use from spontaneous reporting.	• Routine risk minimisation activities - The prescription of the initiation dose of the product will be restricted to specialist CF treatment centres. - Section 4.4 of the SmPC - Warning that efficacy and safety have not been established in non-CF bronchiectasis therefore treatment with Bronchitol is not recommended in non-CF bronchiectasis patients.
Off-label use in paediatric/ adolescent CF patients (aged 6-17 years)	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities. • Additional pharmacovigilance: • Safety data from DPM-CF-302 Open Label Phase • Safety data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents	• Routine risk minimisation activities - Section 4.2 of the SmPC – Warning that Bronchitol is not recommended for use in children/adolescents below 18 years of age due to insufficient data on safety and efficacy.
Microbial infection via a contaminated inhaler device	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities. • Additional pharmacovigilance • Safety data from DPM-CF-302 Open Label Phase • Safety and qualitative sputum microbiology data from DPM-B-305 • Analysis of Compassionate use (SAS) • Analysis of post-marketing safety data from CF Registry Study. • Safety Data from Phase III study in Children and Adolescents • In-vitro microbiological study	• Routine risk minimisation activities - Section 4.2 of the SmPC – Instruction to replace the inhaler device after one week of use. If the inhaler does require cleaning, it is to be washed in warm water and before re-use, allowed to thoroughly air dry.
Missing Information		
Patients who have had significant haemoptysis in last 3 months	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities.	• Routine risk minimisation activities - Section 4.4 of the SmPC - Warning regarding haemoptysis and the requirement for monitoring this risk.
Patients requiring home oxygen or needing assisted ventilation	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities.	• Routine risk minimisation activities - Section 4.4 of the SmPC - Warning regarding use in patients with impaired lung function.

Children < 6 years of age	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities.	• Routine risk minimisation activities - Section 4.2 of the SmPC – Warning regarding use in children < 6 years of age.
Patients with < 30% predicted FEV_1	• Routine pharmacovigilance - Routine review of new events and monthly surveillance activities.	• Routine risk minimisation activities - Section 4.4 of the SmPC - Warning regarding use in patients with < 30% predicted FEV_1. - Section 2 of the Package Leaflet- Warning regarding use in patients with < 30% predicted FEV_1.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The applicant should further investigate the efficacy and safety of Bronchitol in children and adolescents with cystic fibrosis. The study protocol shall be agreed with the CHMP prior to the start of the study and the final results provided to the CHMP and EMA by June 2015.	June 2015
The applicant is requested to submit periodic analysis of the CF study every 6 months for 3 years and annually for 2 years. The final report is expected in Q1 2018.	Q1 2018
The applicant is requested to provide safety results of DPM-B-305 including qualitative sputum microbiology analysis. Final report Q3 2013.	Q3 2013
The applicant should perform appropriate in-vitro microbiological studies reflecting 'in-use' conditions to assess the duration of survival and changes in numbers of organisms to help evaluate the potential risk that important species such as Burkholderia spp. and Aspergillus spp. could be transmitted to patients from the inhaler. Appropriate study design Q2 2012;Conduct of testing Q3 2012.final report Q4 2012	Q4 2012

The following additional risk minimisation activities were required:

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Bronchitol are provided with an educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet

- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a leaflet that includes information on the following key elements:

- The risk of bronchospasm during treatment
    - The need to perform the Bronchitol initiation dose assessment to identify patients who have bronchial hyperresponsiveness in response to inhaled mannitol by measuring the degree of bronchoconstriction that occurs following sequential administrations of mannitol.
    - How to perform the Bronchitol initiation dose assessment safely and how long to monitor the patient for.
    - How to interpret the results of the Bronchitol initiation dose assessment as Pass, Fail or Incomplete.
    - That therapeutic doses of Bronchitol should only be prescribed if the patient has passed the initiation dose assessment.
    - The need of pre-medication by a bronchodilator 5-15 minutes before the Bronchitol initiation dose assessment and before each therapeutic administration of Bronchitol.
    - The need to check that the patient knows how to correctly use the bronchodilator.
    - The need to review the patient after approximately six weeks to assess for signs and symptoms of bronchospasm.
    - The risk of bronchospasm during long term treatment even if the Bronchitol initiation dose assessment was initially passed and the need to reiterate it in case of doubt.
- The risk of haemoptysis during treatment
    - That Bronchitol has not been studied in patients with a history of significant haemoptysis (>60 ml) in the previous three months.
    - The need for monitoring and when to withhold treatment.
- The potential risk of cough related sequelae during treatment
    - The need to train the patient to minimise cough during administration in using the correct inhalation technique.

4.2.5. Recommendations following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Bronchitol in the "t*reatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Divergent positions are presented in Appendix I.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in v. 1.10 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Bronchitol are provided with an educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a leaflet that includes information on the following key elements:

- The risk of bronchospasm during treatment
    - The need to perform the Bronchitol initiation dose assessment to identify patients who have bronchial hyperresponsiveness in response to inhaled mannitol by measuring the degree of bronchoconstriction that occurs following sequential administrations of mannitol.

- How to perform the Bronchitol initiation dose assessment safely and how long to monitor the patient for.
- How to interpret the results of the Bronchitol initiation dose assessment as Pass, Fail or Incomplete.
- That therapeutic doses of Bronchitol should only be prescribed if the patient has passed the initiation dose assessment.
- The need of pre-medication by a bronchodilator 5-15 minutes before the Bronchitol initiation dose assessment and before each therapeutic administration of Bronchitol.
- The need to check that the patient knows how to correctly use the bronchodilator.
- The need to review the patient after approximately six weeks to assess for signs and symptoms of bronchospasm.
- The risk of bronchospasm during long term treatment even if the Bronchitol initiation dose assessment was initially passed and the need to reiterate it in case of doubt.

- The risk of haemoptysis during treatment
  - That Bronchitol has not been studied in patients with a history of significant haemoptysis (>60 ml) in the previous three months.
  - The need for monitoring and when to withhold treatment.
- The potential risk of cough related sequelae during treatment
  - The need to train the patient to minimise cough during administration in using the correct inhalation technique.

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The applicant should further investigate the efficacy and safety of Bronchitol in children and adolescents with cystic fibrosis. The study protocol shall be agreed with the CHMP prior to the start of the study and the final results provided to the CHMP and EMA by June 2015.	June 2015
The applicant is requested to submit periodic analysis of the CF study every 6 months for 3 years and annually for 2 years. The final report is expected in Q1 2018.	Q1 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

- Prior to launch of the product in the Member State, the national competent authority shall agree the content and format of the educational material with the Marketing Authorisation Holder. The Marketing Authorisation Holder (MAH) should ensure that at launch all Healthcare Professionals who are expected to use and/or prescribe Bronchitol are provided with an educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a leaflet that includes information on the following key elements:

- The risk of bronchospasm during treatment
    - The need to perform the Bronchitol initiation dose assessment to identify patients who have bronchial hyperresponsiveness in response to inhaled mannitol by measuring the degree of bronchoconstriction that occurs following sequential administrations of mannitol.
    - How to perform the Bronchitol initiation dose assessment safely and how long to monitor the patient for.
    - How to interpret the results of the Bronchitol initiation dose assessment as Pass, Fail or Incomplete.
    - That therapeutic doses of Bronchitol should only be prescribed if the patient has passed the initiation dose assessment.
    - The need of pre-medication by a bronchodilator 5-15 minutes before the Bronchitol initiation dose assessment and before each therapeutic administration of Bronchitol.
    - The need to check that the patient knows how to correctly use the bronchodilator.

- The need to review the patient after approximately six weeks to assess for signs and symptoms of bronchospasm.
- The risk of bronchospasm during long term treatment even if the Bronchitol initiation dose assessment was initially passed and the need to reiterate it in case of doubt.

- The risk of haemoptysis during treatment
  - That Bronchitol has not been studied in patients with a history of significant haemoptysis (>60 ml) in the previous three months.
  - The need for monitoring and when to withhold treatment.

- The potential risk of cough related sequelae during treatment
  - The need to train the patient to minimise cough during administration in using the correct inhalation technique.

APPENDIX 1

DIVERGENT POSITIONS

Divergent Positions

The undersigned members of the CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Bronchitol.

The reasons for divergent opinion were as follows:

The pivotal studies (301 and 302) are considered not to provide adequate evidence of efficacy in the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care. In particular:

- the clinical relevance of the treatment effects observed on FEV_1 has not been established.
- uncertainties remain in the magnitude of the effect following treatment with Bronchitol. In Study 301 a high proportion of patient withdrawals complicates inference. The pattern of estimated treatment effects is inconsistent within each study across important subgroups defined by age (children, adolescents and adults) and the pattern of effects in each age group is inconsistent between studies. In light of the limited effects observed, these internal inconsistencies result in unacceptable uncertainty in the estimated treatment effect for the proposed population.

The limited efficacy, of uncertain magnitude, is considered not to outweigh the observed and potential safety concerns, relating primarily to bronchoconstriction events and haemoptysis, such that a favourable benefit-risk cannot be concluded.

London, 16 February 2012

Pierre Demolis	Harald Enzmann
Robert Hemmings	Ian Hudson
Hubert Leufkens	Romaldas Mačiulaitis
Jan Mueller-Berghaus	Conception Prieto Yerro
Ruiz Sol	Barbara van Zwieten-Boot

The Icelandic and Norwegian CHMP Members also did not agree with the CHMP's final Opinion regarding Bronchitol (mannitol) for the same above-mentioned reasons.

_____	_____
Kolbeinn Gudmundsson	Karsten Bruins Slot