CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202049Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Summary Review

Date	October 30, 2020
Authors	Khalid Puthawala, M.D., Medical Officer Robert H. Lim, M.D., Cross-Discipline Team Leader Sally Seymour, M.D., Division Director
Subject	Summary Review
NDA/BLA # **Supplement#**	NDA 202049 Original submission May 18, 2012 (SDN 0, sequence# 0000) Resubmission December 19, 2018 (SDN 25, sequence #0022) Resubmission May 1, 2020 (SDN 43, sequence# 0040)
Applicant	Chiesi USA Inc.
Date of Submission	May 1, 2020
PDUFA Goal Date	October 30, 2020
Proprietary Name / Established (USAN) names	Bronchitol
Dosage forms / Strength	Oral dry powder inhaler/ 400mg twice daily
Proposed Indication(s)	Add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis. Use BRONCHITOL only in adults who have passed the BRONCHITOL Tolerance Test.
Recommended Regulatory Action	Approval

DPACC Summary Review
NDA 202049, Bronchitol (DPM, dry powder mannitol)
Khalid Puthawala, M.D., Robert Lim, M.D., Sally Seymour, M.D.

1. Introduction

This application is for inhaled dry powder mannitol (DPM) as add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis. The proposed dose is 400mg (10×40 mg capsules) twice daily for a maximum daily dose of 800mg. As an inhaled product, mannitol inhalation powder is a bronchoprovocation agent approved in the United States as part of a kit (Aridol) for the assessment of bronchial hyperresponsiveness. Inhaled mannitol can cause severe bronchospasm in susceptible individuals. As such, the proposed population is limited to those patients who can tolerate DPM based on a mannitol tolerance test (MTT) in which patients are given sequentially increasing doses of mannitol in a stepwise manner, up to 400mg, by a healthcare provider and monitored for decreases in oxygen saturation and pulmonary function.

The current submission, dated May 1, 2020, is the Applicant's complete response to a Complete Response (CR) action taken on June 19, 2019. While, during the previous review cycle, the risk-benefit assessment was determined to be favorable in the patients who passed the MTT, the CR action was taken because results from human factors studies had not demonstrated that healthcare providers (HCP) could reliably perform the MTT to identify CF patients who could safely take this medication. In this submission, the Applicant has submitted a new completed human factors (HF) validation study and revisions to the user interface to address the CR deficiencies. No new clinical data were submitted.

2. Regulatory History

On May 18, 2012, the Applicant submitted the initial NDA for the use of inhaled DPM for the management of CF in patients 6 years of age and older to improve pulmonary function. During this initial review cycle, the NDA received a CR action as the data submitted from the two phase 3 studies, studies 301 and 302, did not provide a favorable benefit-risk for the proposed population due to lack of substantial evidence of efficacy as well as safety concerns particularly in pediatric patients. Results from study 302 were not statistically significant for the primary endpoint of change from baseline in FEV_1 over 26-weeks when comparing DPM to control patients. While study 301 did appear to demonstrate a statistically significant increase for the primary endpoint (change from baseline in FEV_1) based on the Applicant's prespecified analysis, the results could have been biased by substantial missing data and differential withdrawal for which the prespecified analysis did not account. Multiple additional sensitivity and responder analyses were performed which failed to confirm substantial evidence of a treatment effect of DPM for the primary endpoint. Moreover, the estimated FEV_1 treatment effect was modest/small and there was no support from other clinically relevant secondary endpoints. With regard to safety, there was a small, but clear safety signal for hemoptysis, particularly in the pediatric population.

This was discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting, in which the PADAC voted unanimously against approval. After considering the input from the PADAC

meeting and review of the clinical data, the Division took a CR action on March 18, 2013. Post-CR, the Division recommended that the Applicant conduct at least one additional study that addressed the statistical, safety, and efficacy issues raised in the initial 2012 review cycle (see reviews from Dr. Kimberly Witzmann, Dr. Anthony Durmowicz, and Dr. Badrul Chowdhury dated February 11, 2013, February 25, 2013, and March 18, 2013, respectively, and statistical review from Dr. Feng Zhou dated February 19, 2013). Based on these recommendations, the Applicant conducted an additional phase 3 study, very similar in design to the prior two studies, that addressed these concerns (steps taken to minimize missing data, study population limited to adults).

To address the deficiencies in the 2013 CR action, on December 27, 2018, the Applicant submitted data from an additional phase 3 study (study 303) as well as *post-hoc* analyses of the adult data from the prior two phase 3 studies (301 and 302). Additionally, the indication was limited to only CF patients ≥18 years of age. Studies 301, 302, and 303 were largely similar in design in that they all included a double-blind, randomized, controlled 26-week treatment period. Across all three trials, the primary endpoint was change from baseline in FEV_1 over the 26-week treatment period (assessed at week 6, 14, and 26), and secondary endpoints included exacerbation-related and symptom-related endpoints. Relevant differences included that study 303 had specific provisions to minimize missing data (even if a patient discontinued treatment, they continued to be followed) and only enrolled adult patients due to the hemoptysis safety concern. Review of study 303 demonstrated a modest (51 ml), but statistically significant improvement in the primary endpoint (change from baseline in FEV1 over 26 weeks). Results from *post-hoc* analyses from the adult populations in studies 301 and 302 demonstrated point estimates of 78 mL across both studies and 95% CI excluding null. While these results are generally consistent with study 303, they must be interpreted with caution given their *post-hoc* nature and missing data issues. Overall, based primarily on study 303 results, with some support from the *post-hoc* adult analyses of studies 301 and 302, the Division concluded that DPM treatment resulted in modest improvement in FEV_1 over the 26-week treatment period. However, secondary endpoint results for endpoints such as exacerbation and symptoms were not statistically significant and did not offer additional support for efficacy. Moreover, point estimates for exacerbations favored the control arm, accentuated in *post-hoc* subgroup analysis of U.S. only patients. This accentuation may be explained by a higher percentage of DPM treated U.S. patients versus U.S. control treatment patients having a history of >1 exacerbation in the previous 12 months (a known risk factor for exacerbation). Safety analyses of exacerbation related adverse events were consistent with the exacerbation efficacy endpoint. These data were discussed at a PADAC meeting on May 8, 2019, in which the majority of PADAC panelists favored approval (9 vs. 7).

After considering the PADAC panel discussion and reviewing clinical trial data, the Division ultimately concluded that there was adequate demonstration of safety and efficacy for DPM in the proposed population (i.e., adult CF patients who passed the MTT) (see NDA 202049 Multi-Disciplinary Review and Evaluation dated June 19, 2019). However, there were significant concerns with the appropriate identification of the indicated population by use of the MTT. As

reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) during the review cycle of the December 27, 2018 submission, there were use errors with critical tasks in the human factors (HF) validation study which could result in unindicated patients receiving DPM. In light of these concerns, the Division took a CR action on June 19, 2019, recommending revisions to the user interface and a repeat HF validation study to assess the effectiveness of the revisions to the user interface.

3. Current Submission

To address the deficiencies in the June 19, 2019 CR letter, the current submission, dated May 1, 2020, includes results from a new HF study (P3235-R-007 v 1.1) and product labeling which includes a revised user interface for the MTT (i.e., MTT HCP Instructions for Use [HCP-IFU]).

As previously noted, the MTT is designed to determine which patients tolerate DPM and are candidates for DPM therapy. During the MTT, patients are given sequentially increasing doses of mannitol in a stepwise manner, up to 400mg, by a healthcare practitioner (HCP). Between each step of the sequentially increasing mannitol dose administration, a patient's oxygen saturation and pulmonary function are assessed. If at any step a patient experiences a decrease in oxygen saturation or pulmonary function (forced expiratory volume in 1 second; FEV1) of greater than a prespecified amount from that day's baseline (i.e., the "Stop" value – 80% baseline FEV1, 90% baseline oxygen saturation), the patient has failed the MTT and should not receive DPM.

The new HF study was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). Their review of the study is summarized here; for full details see DMEPA review dated October 22, 2020. In brief, the HF study included 45 study participants consisting of 15 untrained healthcare HCPs, 15 untrained respiratory therapists, and 15 trained HCPs. Each participant participated in a simulated use session, simulating performing the MTT with a patient actor. Prior to the simulated use session each participant was given, on average, 15 minutes to acclimate themselves to the product user interface with the option to review the MTT user interface (including revised MTT HCP-IFU), the fact sheet, an instructional video, prescribing information, medication information phone line, and a patient chart similar to what they may see in practice. During the simulated use session, each participant had access to the following materials: simulated clinic office, MTT user interface, spirometer, pulse oximeter, inhaled short-acting beta-agonist bronchodilator, spacers, nose clips, timer, calculator, paper, pen hand sanitizer, stethoscope, blood pressure cuff, and medications and equipment to manage acute bronchospasm were it to occur (e.g. bronchodilator, crash cart).

Results of the HF study showed that despite revisions to the MTT user interface, some MTT use errors remained. These included improper calculation/recording of "Stop" values, improper timing of FEV1/oxygen saturation measurement, and improper timing of administration of

inhaled short acting beta-agonists and stopping MTT prior to completion. While these use errors do result in some residual risk, these would not be expected to result in direct/immediate patient harm as they would likely result in erroneously concluding that a patient failed the MTT (e.g., errors would result in stopping for more conservative decreases in FEV1 and oxygen saturations), rather than erroneously concluding that the patient had passed. While such errors may result in patients who are eligible to receive DPM to be excluded from therapy, in clinical practice, such patients may be screened again if clinically indicated. These types of use errors are not a significant clinical safety concern. However, it was observed that some study participants failed to correctly identify that the patient was not a DPM candidate, despite oxygen saturation and FEV1 values that were "stop" criteria. These study participants were generally limited to the respiratory therapists and not an HCP who would write the actual DPM prescription. Additionally, the oxygen saturation and FEV1 values were properly recorded; thus, in clinical practice, the prescribing HCP would have the relevant information to determine that the patient was not a DPM candidate. Thus, the residual risk of a patient inappropriately passing the MTT and being prescribed DPM is low and acceptable. Additionally, some study participants did not confirm that patients returned to baseline for oxygen saturation/FEV1 in situations where these values decreased. This could potentially result in harm. However, in the simulated HF study setting, these patients were not exhibiting symptoms of respiratory discomfort or distress. This is in contrast to a true clinical setting where it is likely that a patient would exhibit overt symptoms and be treated accordingly until medically stable. It was also observed that some participants failed to administer the correct number of capsules during the MTT or recorded oxygen saturation values prior to the instructed 1-minute post-mannitol dose. Such errors could potentially result in recording incorrect less conservative "stop" values. However, as these patients would be monitored in a clinical setting and given the Applicant amended the user interface to address this, the residual risk associated with these errors is low and acceptable.

The MTT is complicated and despite modifications to the user interface, use errors continued to be noted in the repeat HF study. As described above and in the DMEPA review, some of these errors could result in an erroneous conclusion that a patient passed the MTT and has the potential to result in patient harm. Given the complexity of the MTT, further enhancement of the user interface is not expected to completely eliminate the use errors. While these errors result in residual risk and some uncertainty, the likelihood of serious harm is low. Patients are to pre-medicate with albuterol before administration of Bronchitol. If bronchospasm does occur, patients can treat with albuterol. Additionally, the vast majority of U.S. patients with CF are closely followed at specialized medical centers by multidisciplinary clinical care teams skilled in the care of patients with CF and management of CF patient safety. Taken together, despite the observed errors, the residual risk of patient harm associated with errors in administration of the MTT are acceptable given potential benefit in this patient population. The

results of the HF study have adequately addressed the deficiency to revise the user interface and repeat the HF study conveyed in the CR letter dated June 18, 2019.

With regard to product labeling, additional measures were taken to optimize patient safety. Specifically, the Applicant proposed labeling in section 2 was edited to more clearly and concisely convey the importance of performing the MTT prior to prescribing DPM and that it was required to identify patients suitable for DPM maintenance therapy. Additionally, given the known difficulties with administering the MTT, the Applicant's proposed (b) (4) (b) (4) in section 2 were deleted and reference was made to the MTT HCP-IFU (user interface). This was done to decrease potential confusion that may arise from (b) (4) (b) (4) Moreover, the MTT HCP-IFU had been formally assessed by HF studies and DMEPA (b) (4) The sponsor had also initially proposed to include the MTT user interface as a (b) (4) rather than an HCP-IFU, which would not have been included in the SPL label. To increase oversight of the user interface and to allow for its inclusion in the SPL label, the (b) (4) was re-titled as an HCP-IFU. To ensure that the operational characteristics for the HCP-IFU remained the same, the format of the HCP-IFU was identical to the (b) (4) aside from the title.

Given the exacerbation related safety concerns raised during the previous review cycle, section 6 of the label was also edited to communicate these concerns to prescribers, in particular, the numerical imbalance in exacerbations reported as serious adverse event observed in the U.S. adult subpopulation. While the numerical differences in the U.S. adult subpopulation are included in the labeling; it should be noted that this observation in U.S. patients may be explained by a higher percentage of DPM treated U.S. patients versus U.S. control treatment patients having a history of >1 exacerbation in the previous 12 months (a known risk factor for exacerbation), this difference was not observed in the non-U.S. population, and CF standard of care is largely similar between U.S. and non-U.S. populations at the time the trials were conducted. As such, while this is a potential safety concern that warrants inclusion in labeling, it does not rise to the level of a warning and precaution, nor does it warrant a PMR study.

In addition to edits to the Applicant's proposed labeling, to further optimize patient safety and avoid confusion, the Applicant was instructed to include the HCP-IFU only with the MTT kit presentation. The Applicant agreed. Further, as the MTT must be administered only by an HCP, the Applicant was instructed that the MTT kits should not be directly provided to patients. The Applicant agreed and stated that MTT kits would be provided to the prescribing HCP, rather than directly to the patient.

4. Conclusions and Recommendations

In summary, the deficiencies that resulted in the previous CR action have adequately been addressed and the recommendation is Approval of DPM as add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis who

have passed the MTT at a dose of 400mg (10×40 mg capsules) twice daily (maximum daily dose 800mg).

The previously submitted and reviewed phase 3 studies (301, 302, and 303) taken as a whole provide substantial evidence of efficacy and safety of DPM in the indicated population. The results of the HF validation study included in the current submission have adequately demonstrated that the HCPs can reliably perform the MTT to identify patients who are suitable for DPM therapy. While there remains some residual risk of error in administration of the MTT, that residual risk is acceptable as patients will be clinically monitored during MTT, the Applicant has mitigated the risks to the extent possible, and in the context of the patient population. The HF validation study has adequately addressed the deficiencies convey in the June 19, 2019 CR letter. The recommendation is Approval.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF IMMUNOLOGY AND INFLAMMATION
DIVISION OF PHARMACOLOGY AND TOXICOLOGY FOR IMMUNOLOGY AND INFLAMMATION

PHARMACOLOGY/ TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 202,409
Supporting document/s:	043
Applicant's letter date:	May 1, 2020
CDER stamp date:	May 1, 2020
Product:	Bronchitol (D-mannitol) Dry Powder
Indication:	Cystic fibrosis
Applicant:	Chiesi Pharmaceuticals
Review Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Carol Galvis, Ph.D.
Division Director:	Sally Seymour, M.D.
Project Manager:	Angela Ramsey

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202,049 are owned by Chiesi or are data for which Chiesi has obtained a written right of reference. Any information or data necessary for approval of NDA 202,049 that Chiesi does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202,049

LABELING REVIEW

Edits to the nonclinical sections and subsections of the proposed Bronchitol (NDA 202,049) label are recommended. The edits are made to ensure that the Bronchitol label complies with the current Agency labeling policies. Briefly, edits are recommended in the following sections: 8.1, 8.3, 12.1, and 13.2. The recommended edits include a) text edits in Sections 8.1, b) removal of Sections 8.3 and 13.2, and c) rewrite of Section 12.1. Annotated and clean versions of the recommended labeling are provided at the end of the document.

I. INTRODUCTION AND BACKGROUND INFORMATION

This labeling review evaluates the nonclinical sections/subsections of the Bronchitol (mannitol) labeling proposal submitted by Chiesi (the Applicant) on May 1, 2020 (NDA #202,049, SDN 043).[1] The proposal was a part of resubmission of the application (SDN 025 submitted on December 19, 2018), for which the Agency issued a Complete Response (CR) Letter on June 19, 2019. The CR-Letter contained no outstanding nonclinical issues.

This review evaluates specifically the following sections of the labeling proposal: 8.1, 8.3, 12.1, 13.1, and 13.2. The review finds necessary to edit content and/or text of the proposed language of these sections. The edits are made to ensure that the Bronchitol label complies with the current Agency labeling policies. The review discusses rationales and justifications for the recommended edits.

The review discusses the history of labeling review of inhaled mannitol products because the Division of Pulmonology, Allergy, and Critical Care (DPACC, previously known as DPARP) has evaluated previously the nonclinical data relevant to this review. The Division approved a Physician Labeling Rule (PLR)-compliant label of Aridol (inhaled mannitol) on October 5, 2015 (NDA 22-368). Further, the review evaluates the necessity of revising mannitol dose ratios between animals and humans in the Bronchitol label because Bronchitol and Aridol differ in the maximum recommended total daily dose of mannitol in humans (i.e., 800 and 635 mg for Bronchitol and Aridol, respectively). The evaluation concludes unnecessary to revise the dose ratios.

I.1 Labeling Review History

This is the first labeling review of the Bronchitol application (NDA 202,049). A nonclinical labeling review in the original submission was deemed unnecessary because of the Complete Response action taken on the application.

Although no labeling review was completed in the current application, the Division completed a comprehensive nonclinical labeling review of mannitol (the active

[1] Chiesi Pharmaceuticals is the current owner of NDA 202,409. Pharmaxis (previous owner) submitted the original NDA on May 18, 2012. Chiesi took over the ownership on April 25, 2018.

pharmaceutical ingredient, API) previously for the Aridol application (NDA 22-368). See a nonclinical labeling review completed by Dr. Luqi Pei in the Aridol application on November 13, 2009. Aridol was approved on October 5, 2010.

Both Bronchitol and Aridol contain mannitol as the API as alluded to earlier. Also, both products use the same set of nonclinical data from the literature to support their product approval. Chiesi (the Applicant) owns both products. Dr. Pei's review dated November 13, 2009 will be used to support this label under NDA 202,049.

I.2 Dose Ratios

This review discusses mannitol dose ratios between animals and humans in the Bronchitol label because Aridol and Bronchitol differ in mannitol doses as alluded to earlier. The review finds that the proposed dose ratios between animals and humans are acceptable because Bronchitol is to-be-approved for adults use only. Chiesi proposed the same dose ratios between animals and humans for the nonclinical sections of Aridol and Bronchitol labels, although the two products have different clinical doses. Specifically, the maximum recommended mannitol dose in humans is 635 and 800 mg/day in Aridol and Bronchitol, respectively. Because the dose ratios were derived from the same set of nonclinical data, an increase in clinical dose in the Bronchitol case (approximately 20%) would result in smaller dose ratios in the same animal dose (Table 1). However, Aridol and Bronchitol also differ in patient populations: ≥ 6 years and adults for Aridol and Bronchitol, respectively. Because the Aridol dose ratios provide more conservative coverage for both Aridol and Bronchitol populations, the proposed dose ratios for the Bronchitol label are acceptable and no revisions are necessary. (b) (4)

Table 1: Animal-to-Human Dose Ratios for Bronchitol Labeling

Section	Description	Species	mg/kg	Km	mg/m^2	Animal-to-Human Ratio [a]		
						Bronchitol [b]		Aridol label
						Calculated [c]	Round to [d]	
8.1	Pregnancy	Mouse	1600	3	4800	9.7	10	10
		Rat	1600	6	9600	19.5	20	20
13.1	Carcinogenicity	Mouse	7500	3	22500	45.6	(b) (4)	30
		Rat	7500	6	45000	91.2		55

a. Dose ratio between animals and humans on a mg/m^2 basis.
b. Dose ratio for adults. These ratios were derived from a daily dose of 800 mg mannitol for a 60-kg subject (493 mg/m^2). Derived from the maximum recommended human inhalation dose of 493 mg/m^2/day (or 800 mg/day) in an adult subject.
c. Calculated values were rounded to nearest integer of 5 or 10s.
d. Dose ratios in the Aridol label and in the currently proposed label for Bronchitol. The ratios in Aridol label were based on a pediatric dose of 739.8 mg/m^2 (or 635 mg/day for a 6-year old child with a 20-kg body weight).

I.3 Labeling Evaluation in General

Contents of the nonclinical sections of the proposed label are generally acceptable because they were adopted from the Aridol label, which was PLR-compliant.[2] The recent requirement for labels to be PLLR (Pregnancy and Lactation Labeling Rule) - compliant renders it necessary to review the Aridol label again. It is expected that the Aridol label will be converted to a PLLR-compliant format after Bronchitol is approved. In this review, highlights indicate recommended edits to the proposed label. Underline indicates addition while strikethrough indicates deletion.

II. PREGNANCY (SECTION 8.1)

The review recommends edits to both Risk Summary and Animal data in this section. In the Risk Summary section, the review recommends adding a statement summarizing the nonclinical findings. In the animal data subsection, the review recommends rewording the statement (b) (4)

Risk Summary

There are no adequate and well-controlled studies of BRONCHITOL in pregnant women. The available data on BRONCHITOL use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. Based on animal reproduction studies, no evidence of structural alterations was observed when mannitol was administered to pregnant rats and mice during organogenesis at doses up to approximately 20 and 10 times, respectively, the maximum recommended daily inhalation dose (MRDID) in humans [*see Data*]. There are risks to the mother associated with cystic fibrosis in pregnancy *[see Clinical Considerations].* BRONCHITOL should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Cystic fibrosis may increase the risk for preterm delivery.

Data

Animal Data

In animal reproduction studies, oral administration of mannitol to pregnant rats and mice during the period of organogenesis did not cause fetal structural alterations. The

[2] See http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022368S000lbl.pdf.

mannitol dose in rats and mice was approximately 20 and 10 times the maximum recommended human daily inhalation dose (MRDID) in humans, respectively, (on a mg/m^2 basis at maternal doses of 1600 mg/kg/day in both species).

(b) (4)

(b) (4)

IV. MECHANISM OF ACTION (SECTION 12.1)

The review recommends edits to the proposed text for Section 12.1 MECHANISM OF ACTION. Specifically, the review recommends (b) (4)

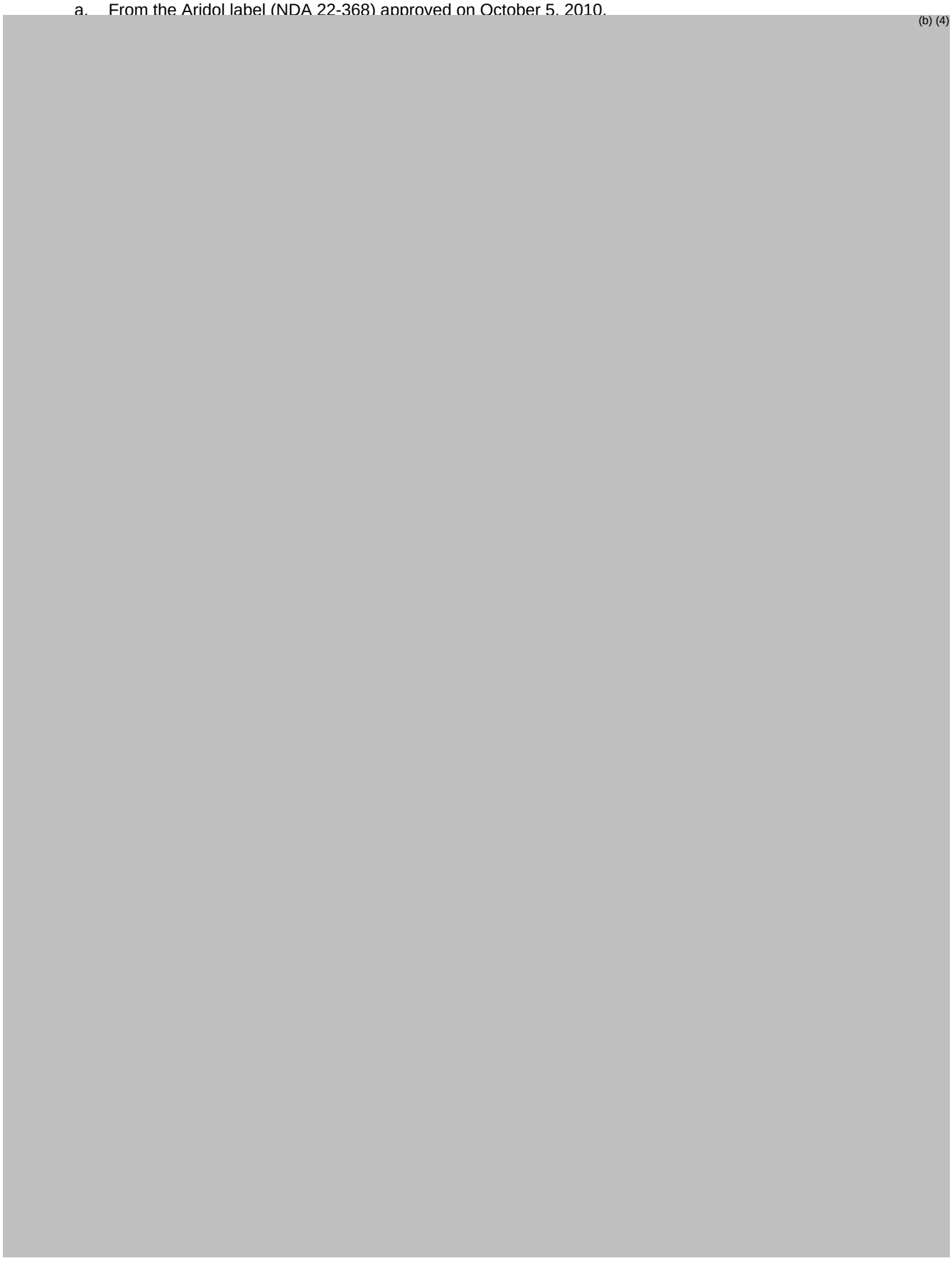
The recommendation was based on the Aridol label and available data. Table 2 presents both the approved Aridol label and the proposed label for Bronchitol. It appears that a slight modification to the Aridol label would also be sufficient for Bronchitol as discussed below.

Table 2: Labels for Aridol (approved) and Bronchitol (proposed)

Aridol [a]	Bronchitol
The precise mechanisms (b) (4) inhaled mannitol cause (b) (4) are not known.	(b) (4)

a. From the Aridol label (NDA 22-368) approved on October 5, 2010.

(b) (4)



(b) (4)

Overall, the review finds that the applicant's arguments are inadequate to support the proposed text for the Mechanism of Action from the nonclinical perspective. The review recommends revising the text in Section 12.1 as below:

12.1 Mechanism of Action:

The precise mechanism of action of BRONCHITOL in improving pulmonary functions in cystic fibrosis patients is not known.

V. NONCLINICAL TOXICOLOGY (SECTION 13)

The proposed text for Subsection 13.1 is identical to that of the Aridol label and is considered acceptable. However, Subsection 13.2 should be deleted. (b) (4)

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were approximately 55 and 30 times the MRHDID, respectively, on a mg/m^2 basis.

Mutagenesis

Mannitol tested negative in the following assays: bacterial gene mutation assay, *in vitro* mouse lymphoma assay, *in vitro* chromosomal aberration assay in WI-38 human cells, *in vivo* chromosomal aberration assay in rat bone marrow, *in vivo* dominant lethal assay in rats, and *in vivo* mouse micronucleus assay.

Impairment of Fertility

The effect of inhaled mannitol on fertility has not been investigated.

(b) (4)

VI. OVERALL LABELING RECOMMENDATIONS

Suggested labeling:

The following is a clean copy of the suggested text for the nonclinical sections of the Bronchitol label.

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BRONCHITOL in pregnant women. The available data on BRONCHITOL use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. Based on animal reproduction studies, no evidence of structural alterations was observed when mannitol was administered to pregnant rats and mice during organogenesis at doses up to approximately 20 and 10 times, respectively, the maximum recommended daily inhalation dose (MRDID) in humans [*see Data*]. There are risks to the mother associated with cystic fibrosis in pregnancy *[see Clinical Considerations].* BRONCHITOL should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Cystic fibrosis may increase the risk for preterm delivery.

Data

Animal Data

In animal reproduction studies, oral administration of mannitol to pregnant rats and mice during the period of organogenesis did not cause fetal structural alterations. The mannitol dose in rats and mice was approximately 20 and 10 times the maximum recommended human daily inhalation dose (MRDID) in humans, respectively, (on a mg/m^2 basis at maternal doses of 1600 mg/kg/day in both species).

12.1 Mechanism of Action:

The precise mechanism of action of BRONCHITOL in improving pulmonary functions in cystic fibrosis patients is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were approximately 55 and 30 times the MRHDID, respectively, on a mg/m^2 basis.

Mutagenesis

Mannitol tested negative in the following assays: bacterial gene mutation assay, *in vitro* mouse lymphoma assay, *in vitro* chromosomal aberration assay in WI-38 human cells, *in vivo* chromosomal aberration assay in rat bone marrow, *in vivo* dominant lethal assay in rats, and *in vivo* mouse micronucleus assay.

Impairment of Fertility

The effect of inhaled mannitol on fertility has not been investigated.

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/s/

LUQI PEI
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CAROL M GALVIS
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I concur.

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	202049
Priority or Standard	Priority
Submit Date(s)	December 19, 2018
Received Date(s)	December 19, 2018
PDUFA Goal Date	June 19, 2019
Division/Office	Division of Pulmonary Allergy Rheumatology Products, Office of New Drugs
Review Completion Date	June 19, 2019
Established/Proper Name	Inhaled Mannitol
(Proposed) Trade Name	Bronchitol
Pharmacologic Class	
Code name	
Applicant	Chiesi
Dosage form	Dry powder for inhalation
Applicant proposed Dosing Regimen	400mg inhaled twice daily
Applicant Proposed Indication(s)/Population(s)	The management of cystic fibrosis (CF) in patients 18 years of age and older to improve pulmonary function in conjunction with standard therapies.
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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Nonclinical Reviewer	Luqi Pei, PhD
Nonclinical Team Leader	Carol Galvis, PhD
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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The proposed product reviewed in this document is inhaled dry powder mannitol (DPM). Mannitol is a well-known, naturally occurring sugar alcohol found in many vegetables. As an inhaled product, mannitol inhalation powder is a bronchoprovocation agent approved in the United States as part of a kit (Aridol) for the assessment of bronchial hyperresponsiveness. Inhaled mannitol can cause severe bronchospasm in susceptible individuals and caution is advised in patients with conditions that may increase sensitivity to bronchoconstriction.

The current submission, submitted on December 19, 2018, is the Applicant's complete response to a Complete Response (CR) action taken following the initial submission (May 18, 2012) of the new drug application (NDA). In this complete response to CR, the Applicant has submitted new clinical data to support DPM for the proposed indication of the management of cystic fibrosis (CF) in patients 18 years of age and older to improve pulmonary function in conjunction with standard therapies at a dose of 400 mg (10×40 mg capsules) twice daily. As DPM can cause severe bronchospasm in susceptible individuals, the proposed population is further limited to those patients who can tolerate DPM based on a mannitol tolerance test (MTT) in which patients are given increasing doses of mannitol, up to 400mg, by a healthcare provider and monitored for decreases in oxygen saturation and pulmonary function.

On May 18, 2012, the Applicant submitted the initial NDA for the use of inhaled DPM for the management of CF in patients 6 years of age and older to improve pulmonary function. The proposed dose was 400 mg twice daily. During the initial NDA review cycle for DPM, the NDA received a Complete Response (CR) action as the data submitted from the two phase 3 studies, studies 301 and 302, did not provide a favorable benefit-risk for the proposed population due to lack of substantial evidence of efficacy as well as safety concerns particularly in pediatric patients. Results from study 302 were not statistically significant for the primary endpoint of change from baseline in FEV_1 over 26-weeks when comparing DPM to control patients. While study 301 did appear to demonstrate a statistically significant increase for the primary endpoint (change from baseline in FEV_1) based on the Applicant's prespecified analysis, the results could have been biased by substantial missing data and differential withdrawal for which the prespecified analysis did not account. Multiple additional sensitivity and responder analyses were performed which failed to confirm substantial evidence of a treatment effect of DPM for the primary endpoint. Moreover, the estimated FEV_1 treatment effect was modest/small and there was no support from other clinically relevant secondary endpoints. With regard to safety, there was a small, but clear safety signal for hemoptysis, particularly in the pediatric population. This was discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting, in which the PADAC voted unanimously against approval. After considering the input from the PADAC meeting and review of the clinical data, the Division took a CR action. At a post-CR interaction with the Applicant, the Division recommend that the Applicant conduct at

least one additional study that addresses the statistical, safety, and efficacy issues raised in initial NDA review cycle. Since the CR action and based on recommendations made by the Division following the CR action, the Applicant conducted an additional phase 3 study, study 303, to address the concerns raised in the initial review cycle. Due to the pediatric safety concern, this new study included only adult CF patients (≥18 years of age) and took specific steps to minimize missing data, but was otherwise very similar in design to studies 301 and 302. Study 303 data, as well as *post-hoc* analyses of the adult data from studies 301 and 302, were submitted in the Applicant's complete response to the CR action to support the benefit-risk of this product in the proposed population. The Applicant also proposed to limit the indication to include only CF patients ≥18 years of age. The focus of this review is to evaluate the benefit-risk of this product in light of the new data.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the clinical safety and efficacy data submitted from the phase 3 studies, the recommended regulatory action from the Cross Discipline Team Leader (CDTL) and Division Director is Approval for the management of cystic fibrosis (CF) in patients 18 years of age and older to improve pulmonary function in conjunction with standard of care therapies. However, due to an issue regarding human factors testing, in which healthcare providers were unable to consistently properly administer the MTT (see section 4.5) and determine which patients were eligible to receive DPM, the Division will take a CR action.

To support the current submission, the Applicant (Chiesi) submitted data from one recently completed phase 3 placebo controlled, 26-week treatment period efficacy/safety study in adult patients (study 303), as well as *post-hoc* analyses of adults only from two phase 3 studies (studies 301 and 302) which were submitted in the previous review cycle. Studies 301, 302, and 303 were largely similar in design in that they all included a double-blind, randomized, controlled 26-week treatment period. Across all three trials, the primary endpoint was change from baseline in FEV_1 over the 26-week treatment period (assessed at week 6, 14, and 26), and secondary endpoints included exacerbation-related and symptom related endpoints. Relevant differences included that study 303 had specific provisions to minimize missing data (even if a patient discontinued treatment, they continued to be followed) and only enrolled adult patients due to the hemoptypsis safety concern.

Given the issues identified with studies 301 and 302 during the previous review cycle (see section 3 for an in-depth discussion), as well as the fact that the adult only analyses were *post-hoc*, study 303 is considered the primary support for efficacy and is the focus of this review. However, given that the current proposed indication is the adult population, data from the *post-hoc* analyses of adults from studies 301 and 302 is taken into consideration.

With regard to the primary endpoint of change from baseline in FEV_1 over 26-weeks, results

from study 303, demonstrated a modest, but statistically significant treatment effect of 55 mL (95% CI: 9 to 101mL; p-value=0.018) based on the Applicant's prespecified analysis and imputation procedure; sensitivity analyses using a Pattern Mixture Model approach demonstrated similar results (Table 8 and Table 9). It is also worth noting that in study 303, there were no significant issues with regard to missing data or differential drop-out. Additional sensitivity analyses including a two dimensional tipping point analysis support the statistical robustness of the primary endpoint results. Data from study 303 support a modest treatment effect for DPM in the studied population. Results from *post-hoc* analyses from the adult populations in studies 301 and 302 demonstrated point estimates of 78 mL across both studies and 95% CI excluding null (Table 12). While these results are generally consistent with study 303, they must be interpreted with caution given their *post-hoc* nature and missing data issues. Overall, based primarily on study 303 results, with some support from the *post-hoc* adult analyses of studies 301 and 302, DPM treatment appears to result in modest improvement in FEV_1 over the 26-week treatment period.

Responder analyses were also performed using various FEV_1 cut-offs. In study 303 responder analyses, at the cut-offs of 100 mL, 200 mL, and 300 mL, a larger proportion of DPM patients were responders compared to control patients with odds ratios of greater than 1 and 95% CI excluding null (Table 22). Similar numerical trends were also noted for responder analyses from studies 301 and 302, however, for the most part 95% CI did not exclude null. The data from study 303 suggest that while the treatment may be modest in the overall population, some patients appear to derive larger magnitude FEV_1 benefit.

As DPM would be chronically administered, durability of effect is an important consideration. As such, change from baseline in FEV_1 at weeks 6, 14, and 26 was assessed. In study 303, the magnitude of treatment effect appeared to decline over time, with change from baseline in FEV_1 for DPM versus control at these timepoints of 60 mL, 56 mL, and 39 mL, respectively (Table 16). These data suggest that the FEV_1 effect may decline over time, alternatively, this may represent normal fluctuations in pulmonary function. While there was no similar decline observed in the *post-hoc* adult analyses of studies 301 and 302 (Table 16), given the issues with missing data and patient drop-out, that does not alleviate concerns with potential decline in treatment effect over time.

Study 303 also included a range of clinically relevant secondary endpoints related to protocol defined pulmonary exacerbations (PDPE) and respiratory symptoms as measured by the Cystic Fibrosis Questionnaire – Revised respiratory domain score (CFQ-RRD). In terms of PDPE, for time to first PDPE and PDPE rate, the point estimates for the hazard ratio (HR) and adjusted rate ratios (ARR) using the Applicant's prespecified analyses were 1.14 and 1.55 with 95% CI including the null value. In sensitivity analysis of PDPE using the PMM, results were similar with an ARR of 1.35 and 95% CI excluding null. PDPE results from study 303 do not support efficacy with a numerical trend favoring control. In a *post-hoc* adult analysis of PDPE rate for studies 301 and 302, with the noted limitations, point estimates for the ARR were 0.77 and 1.35 with 95% CI including the null value. In *post-hoc* subgroup analysis of U.S. only patients from study

303, trends favoring control for PDPE rate were accentuated (Table 19). A similar trend was observed for study 302 (data not shown). However, as a higher percentage of DPM treated patients versus control patients in both studies 302 and 303 had a history of >1 exacerbation in the previous 12 months (Table 34), this could at least in part account for this accentuation as a history of exacerbation is predictive of subsequent exacerbations. Additionally, as these were *post-hoc* analyses of a subgroup, definitive conclusions cannot be made. While none of the PDPE results offer additional support for efficacy, they do not demonstrate that DPM treatment results in increased exacerbations.

With regard to CFQ-RRD, in study 303, there were no statistically significant differences between DPM and control groups. Findings were similar in the *post-hoc* adult analyses of studies 301 and 302. These results offer no additional support for efficacy.

While clinically relevant secondary endpoints (i.e. PDPE and symptoms) do not offer additional support for efficacy, overall, DPM has demonstrated a treatment benefit in terms of FEV_1 in adults with CF. Across all studies, point estimates for this effect have been consistently modest ranging from approximately 50-80 mL. Although modest, responder analyses suggest that some DPM treated patients may have a larger magnitude of benefit and, as articulated at the May 8, 2018 PADAC (see section 9), even a 50-80 mL improvement may be clinically meaningful and discernible to some patients, especially those with low lung function and/or severe disease. With regard to the observed small decrease in the magnitude of FEV_1 benefit over time, this may have been related to normal fluctuation in pulmonary function, though some decrease over time cannot be ruled out. Overall, the FEV_1 data supports a modest treatment benefit in terms of lung function only.

The evaluation of safety was primarily based on the pooled analysis of adults from studies 301, 302 and 303. While there were some numerical differences in certain adverse events, overall the differences between arms did not raise major safety concerns for patients ≥18 years of age. Across the three phase 3 studies, two deaths occurred, both in control treated adult patients. With regard to SAEs, overall, they were balanced between arms. AEs leading to treatment discontinuation were more common in DPM treated patients compared to control, with cough and CF exacerbations accounting for the majority of events. This suggests that there may be tolerability issues associated with DPM. Common AEs occurring more frequently in DPM patients than control were cough, oropharyngeal pain, hemoptysis, bacteria sputum identified, and pyrexia.

With regard to the previous safety concern of hemotysis, when analyzing the adult only data for hemoptysis, there were no concerning imbalances between DPM and control groups (Table 31). CF exacerbation reported as adverse events was also specifically analyzed in terms of safety given the disease process as well as the fact that for PDPE related efficacy endpoint, point estimates for some of the hazard and rate ratios were >1 . CF exacerbation, coded as condition aggravated, was the most common AE across the phase 3 studies and was slightly greater in frequency in DPM patients compared to controls in serious adverse events (AE), AEs leading to

study and drug discontinuation, and severe AEs. This finding was accentuated when examining CF exacerbation in U.S. patients. Taken together with the PDPE efficacy data, this suggests a potential exacerbation related safety concern for DPM. When this issue was discussed at the May 8, 2019 PADAC, some committee members were concerned and suggested additional investigation into the potential safety signal, though acknowledging that it would difficult to do so in the context of standard post-marketing safety reporting. However, others did not find the numerical differences concerning. Overall, while there is the potential exacerbation related safety concern, it is not sufficient to conclude that DPM is unsafe in the proposed population. However, further investigation in the setting of a post-marketing required study may be warranted.

Overall, we (CDTL and Division Director) find the benefit-risk for this product favorable and recommend Approval. It should be noted that our recommendation is in contrast to the recommendation of the primary clinical reviewer and statistical team, who have recommended a CR action. The CR recommendation of the primary clinical reviewer and statistical team was primarily based on the modest effect on FEV_1 through the 26-week treatment period, numerically smaller effect at week 26, and lack of support from other clinically relevant endpoints; coupled with a potential exacerbation related safety concern. While we acknowledge the recommendations of the primary medical revivewer and statistical team and do not dispute the safety and efficacy data, based on several factors, we have a different recommendation. First, while the FEV_1 benefit is modest, as articulated by PADAC members, even a small increase may be clinically meaningful to some patients. Additionally, responder analyses also suggest that some patients may receive a larger magnitude treatment benefit. With regard to the observed numerical decline in treatment effect in study 303, it is possible that that represented normal fluctuation in pulmonary function. As such, we find that the FEV_1 data support the efficacy of the product. While we also conclude that there was no support from clinically relevant secondary endpoints, this does not preclude a recommendation of Approval as the stated indication is somewhat limited in that it specifies “to improve pulmonary function.” Additionally, our recommendation considers the input given at the PADAC from PADAC members, CF patients/family members, and CF care providers. Specifically, that treatment options for inhaled mucolytics are limited, current treatment options require a significant amount of time to administer drug and clean the delivery device, such treatments also require access to a power source, and compliance can be suboptimal with currently available inhaled mucolytics. DPM could address these points. As such, while the treatment effect is modest and limited to FEV_1, DPM does offer a benefit to CF patients. This benefit is not outweighed by the safety findings and thus our recommendation is Approval. That being said, given PDPE data, CF exacerbation adverse event data, and input from PADAC members, we recommend a post-marketing required study to further investigate safety in terms of CF exacerbation.

The recommendation is Approval with a PMR study to further investigate CF exacerbation related safety concerns.

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Cystic fibrosis (CF) is a debilitating illness with significant morbidity, mortality, and no cure. CF results from mutations in and abnormal functioning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR aids in the regulation of salt and water absorption and secretion throughout the body, and thus its malfunctioning leads to difficult to mobilize tenacious respiratory secretions leading to recurrent infections and lung damage. The leading cause of death in CF is respiratory related. Many respiratory treatment options are focused on treating symptoms and sequelae. There is currently a single approved medication aimed at improving respiratory secretions and pulmonary toilet, Dornase alpha. Hypertonic saline (7%) is also use clinically as a mucolytic to improve pulmonary toilet, but is not FDA approved for this indication. Both are administer via nebulization. Recently approved medications, are directed at the more proximal cause of disease, the CFTR protein, and have changed the treatment landscape considerably for those patients with CF with eligible mutations. The products are sometimes referred to as CFTR "modulators." Their recent approvals (2012-2018) were based on improvement in lung function and support from secondary endpoints.

The Applicant has submitted a complete response to a Complete Response (CR) action for inhaled dry powder mannitol (DPM). In the airway, DPM is thought to decrease the thickness of respiratory secretions and result in improved pulmonary toilet, which in turn is postulated to to improve pulmonary function. The proposed indication is for the management of CF patients 18 years of age and older to improve pulmonary function in conjunction with standard therapies. The proposed dose is 400mg inhaled twice daily. In the initial NDA review cycle, the Applicant proposed a similar indication, though included patients ≥6-years of age. A CR action was taken at that time due to lack of substantial evidence of efficacy and safety concerns largely in the pediatric population (<18 years of age) based on data from two phase 3 studies. To support this complete response to CR, the Applicant submitted data from an additional recently completed phase 3 placebo controlled, 26-week treatment period efficacy/safety study in adults (study 303). *Post-hoc* analyses of adults only from the two previously reviewed phase 3 studies of similar design and duration (studies 301 and 302) were also submitted (prior studies include patients ≥6 years of age). All phase 3 studies were in CF patients.

From an efficacy standpoint, in studies 301, 302, and 303, the improvement in adults for the primary endpoint, change from baseline in FEV_1 over 26 weeks, ranged from approximately 50mL to 80mL depending on the statistical analysis method used. Secondary endpoints included clinically meaningful measures such as exacerbation related endpoints and symptom related scores [Cystic Fibrosis Questionairre – Revised respiratory domain (CFQ-RRD) score]. Secondary endpoints, such as exacerbation and symptoms did not provide additional support to the primary endpoint. In fact, several measures of exacerbation demonstrated trends in favor of control patients, with trends magnified in the US

subpopulation. Additionally, no clear durability of FEV_1 effect was seen.

From a safety standpoint, while prior studies had raised hemoptysis as a safety concern in the younger patients, this was not seen in the most recent study in adults. However, there was suggestion of a slightly increased number of CF exacerbations in several safety categories. These differences were magnified in the US subpopulation.

The primary clinical reviewer and statistical team do not recommend approval of inhaled DPM for the proposed indication based upon concerns related to the small treatment effect on FEV1, durability of effect for a potentially chronic medication, lack of support from clinically relevant secondary endpoints and questions related to the potential for an increase in pulmonary exacerbations. We (CDTL and Division Director) acknowledge the recommendation for a CR action from the primary clinical reviewer and statistical team; however, we have a more favorable view of the benefit risk assessment of DPM. We acknowledge the discussion at the May 8, 2019 Pulmonary-Allergy Drug Advisory Committee meeting in which the AC panel was split regarding the recommendation for approval of DPM. So, it is not surprising that there are some differences in recommendations amongst the review team members. Our assessment is that the available clinical data supports approval of DPM for patients with CF; however, because of issues related to human factors studies regarding administration of the mannitol tolerance test (MTT), a complete response action is planned. The following is a discussion of our benefit risk assessment for DPM for use in patients with CF.

The DPM clinical program provides evidence of a consistent effect of DPM on FEV_1 with an estimated effect size ranging from a mean of 50-80mL. We acknowledge that while there is not a predefined threshold for clinically meaningful treatment effect in FEV_1 for patients with CF, the treatment effect of DPM raises questions regarding whether it is clinically meaningful. CF is a progressive disease with a decline in pulmonary function over time, so preservation or improvement in lung function is important. As discussed during the May 8, 2019 PADAC meeting (see section 9), even a 50-80 mL improvement may be clinically meaningful and discernible to some patients, especially those with low lung function and/or severe disease. We also found the responder analyses compelling. The responder analyses showed that some DPM treated patients had a larger benefit, which would be clinically meaningful (e.g., >100 mL, >200mL, > 300mL) compared to control.

With regard to the observed small decrease in the magnitude of FEV_1 benefit over time, this does raise questions regarding the durability of the treatment effect. However, this decrease was not consistently observed across all 3 studies. In addition, the Applicant's responder analysis at week 26 in Study 303 did show there was a greater proportion of patients who had a response > 100mL in the DPM group compared to control.

Secondary measures of efficacy, such as exacerbations or CFQ-RRD, did not provide additional support for the efficacy of DPM. We typically would expect important secondary endpoints to support the efficacy of a product. This was not the case for DPM. While the trend for PDPE

did not favor DPM in study 303, the data do not show that DPM increases the risk of pulmonary exacerbations; however, given the limitations of the data, a post-marketing study to further evaluate the risk of exacerbations with DPM is warranted.

There are additional benefits of DPM that should be considered in the benefit risk assessment. Treatment options for inhaled mucolytics are limited. Current treatment options require a significant amount of time to administer drug and clean the delivery device. These nebulized treatment options also require access to a power source and bulky equipment. Because of these issues, compliance can be suboptimal with currently available inhaled mucolytics. Patient testimony at the PADAC meeting noted these issues and they expressed the benefit of a convenient, portable treatment option for airway clearance. While DPM may have only demonstrated efficacy in terms of an improvement in pulmonary function and not reduction in exacerbations, it does provide another option that may be suitable for some patients.

In terms of safety, hemoptysis was not an issue in study 303, so it appears to be primarily an issue with patients less than 18 year old age. There were tolerability issues with DPM, which is not surprising given the mechanism of action. The question regarding an increase in exacerbations was also noted in the safety analyses. The data do not clearly show that DPM increases the risk of exacerbations, but given the concern, a post-marketing study to evaluate exacerbations will be required.

Overall, we find the benefit risk assessment of DPM favorable as it will provide benefit to some patients with CF. While it may offer only a modest FEV_1 benefit, it does provide an option that healthcare providers and patients can consider. Labeling will need to clearly describe the available data so healthcare providers understand that DPM does not reduce exacerbations or improve patient symptoms. The benefit is limited to pulmonary function and convenience. The MTT is described in the Dosage and Administration section of the product label and screening patients is important to identify those patients who may have bronchospasm with DPM. Therefore, it is important that the instructions are clear so healthcare providers can screen patients appropriately. Because human factor studies identified issues with the instructions for the MTT, additional human factor testing is necessary. This will preclude approval at this time; thus a CR action is planned. Once the human factors issues are resolved, labeling can be completed and the NDA can be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CF is a serious disease with considerable morbidity, mortality, and no cure. • CF is a multiorgan disease however respiratory related disease accounts for the the majority of morbidity and mortality. This is primarily driven by the difficulty in clearing secretions that cause repeated infections. • CF exacerbations and respiratory symptoms play an important role in decreasing patients quality of life	• CF is a debilitating illness causing significant morbidity and mortality. • The Applicant's use of measures to assess lung function, exacerbations, and symptoms in their clinical studies is reasonable.
Current Treatment Options	• Many treatments are directed at treating symptoms and sequelae of the disease. From a respiratory standpoint, this involves use of therapies to decrease viscosity of airway secretions to improve airway clearance/pulmonary toilet. Current treatment options for such agents include dornase alpha and hypertonic saline. Only dornase alpha is FDA approved in CF. Both take time to administer and to clean the delivery device, and require access to a power source. • Newer treatments are directed at the more proximal cause of the disease, the CFTR protein. These treatments are approved for a growing but limited number of patients based on genetic mutations, and have changed the treatment landscape.	• Multiple current respiratory treatments are used to address symptoms and sequelae of the disease as well as newer agents acting on a more proximal cause. • Tthere are limited options for inhaled treatments aiming to improve viscosity of airway secretions. • DPM would represent an additional treatment option that would be relatively fast to administer and not require access to a power source.
Benefit	• The submitted data across multiple studies has demonstrated a modest treatment benefit in terms of $FEV_{1.}$ • No effect on endpoints such as exacerbation or respiratory symptoms was demonstrated. • DPM administration time is shorter than other clinically used mucolytics and does not require access to a power source.	• While DPM has not demonstrated an effect on exacerbation or symptoms, it has demonstrated efficacy in terms of a modest benefit in pulmonary function. • This benefit may be clinically meaningful to some patients. • DPM would also provide an additional treatment option for CF patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety program for inhaled mannitol demonstrated possible concerns for increased CF exacerbations • No REMS is proposed	• Analysis of safety raise concerns regarding exacerbation. • A postmarketing required study is warranted to further investigated this risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
	X	□	Patient reported outcome (PRO)	CFQ-R (8.1.2)
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
X	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	X	Other: (Please specify): Patient testimony at Open Public Hearing at the May 8, 2019, PADAC meeting		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

CF is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[a], and approximately 70,000 children and adults worldwide[b]. CF affects all ethnic and racial groups but is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is in the forties.[1]

CF results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which leads to decreased amount or abnormal function of CFTR protein. The CFTR protein is an epithelial chloride ion channel present on the apical surface of epithelial cell membranes. CFTR aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. Over time, the CF lung is exposed to a cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure. Because it is a recessive genetic disease, in order to present with clinical CF disease, one must have two mutations in the *CFTR* gene. To date, approximately 2,000 mutations in CFTR have been identified, with over 300 identified as disease causing.[c]

The Applicant proposes that their inhaled DPM product will improve mucus clearance in patients with CF due to the osmotic properties of mannitol remaining in the extracellular compartment to cause an outflow of water into surrounding tissues, and thus reduce the thickness and stickiness of CF mucus secretions.

2.2. Analysis of Current Treatment Options

There are no FDA approved products for CF that act in a manner similar to DPM. Hypertonic saline, which is widely used by CF patients, may work in a similar manner, but is not FDA

[a] Cystic Fibrosis Foundation Patient Registry 2016 Annual Data Report
[b] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cystic Fibrosis 2008;7(5):450-453.
[c] US CF Foundation, Johns Hopkins University, The Hospital for Sick Children, The Clinical and Functional Translation of CFTR (CFTR2). Accessed at http://cftr2.org on June 11, 2018.

approved. A number of drugs are used to treat the symptoms and sequelae of CF, as well as several which treat the underlying cause of CF. Medications used to treat CF patients are summarized in Table 1. Note that not all are FDA approved for use in CF.

Table 1: Treatments for Cystic Fibrosis (CF)

Active Ingredient	Trade Name	FDA-Approved for CF Indication?
CFTR modulator		
Ivacaftor	Kalydeco	Yes: one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay*
Lumacaftor/Ivacaftor	Orkambi	Yes: homozygous for *F508del* mutation mutations
Tezacaftor/Ivacaftor	Symdeko	Yes: homozygous for the *F508del* mutation or at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.**
Inhaled antibiotics for the treatment of pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	TIP	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled treatments used as mucolytics		
Dornase alpha (rhDNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Oral pancreatic enzyme supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase, Pertzye, Viokace, Ultresa	Yes
Inhaled bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-inflammatory agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No

*Includes G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D, 2789+5G→A, 3272-26A→G, 3849+10kbC→T mutations

** Includes E56K, R117C, A455E, S945L, R1070W, 3272-26A→G, P67L, E193K, F508del, S977F, F1074L, 3849+10kbC→T, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N,
D110H, R352Q, E831X, A1067T, 2789+5G→A mutations. *F508del* must be present in two copies or with at least one copy of these above-mentioned mutations to be indicated.

Source: Approved labeling data from Drugs@FDA.gov (accessed on March 8, 2019)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mannitol is generally recognized as safe (GRAS) as an oral supplement. Inhaled mannitol (Aridol) has also been in use since its approval in 2010 and is indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age and older who do not have clinically apparent asthma.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History Summary
This NDA was initially submitted to the Agency on May 18, 2012, for the proposed indication of the management of cystic fibrosis (CF) in patients 6 years of age and older to improve pulmonary function. To support efficacy, the Applicant submitted two phase 3 trials (301 and 302) that include CF patients ≥6 years of age. During the initial NDA review cycle, a Complete Response (CR) action was taken. This was because substantial evidence of efficacy had not been demonstrated as well as safety concerns primarily in the 6-year-old to <18-year-old age group. With regard to efficacy, study 302 did not demonstrate a statistically significant increase in absolute change from baseline in FEV_1 across the 26-week treatment period (primary endpoint) when comparing DPM treated patients to control patients. While Study 301 did appear to demonstrate a statistically significant increase in terms of the primary endpoint based on the Applicant's prespecified analysis (mixed model for repeated measures, MMRM), the results could have been biased by substantial missing data and differential withdrawal of patients in the active treatment group which the MMRM statistical analysis method did not account for. Multiple sensitivity and responder analyses were conducted and resulted in a range of possible treatment effects of DPM on FEV_1. These additional analyses failed to confirm a demonstration of substantial evidence of a treatment effect of DPM on the primary efficacy endpoint for either study 301 or 302. Moreover, there was no significant support for efficacy from secondary endpoint analyses (analysis of which suffered from the same statistical issues as those for the primary analysis). With regard to safety, there was a small but clear signal for hemoptysis in the overall population. This was of particular concern in the youngest age group of 6- to 11-year-olds, raising issues of safety specifically for pediatric patients.

As a result of these concerns, a Pulmonary Allergy Drug Advisory Committee (PADAC) was convened where these issues were discussed (see section clinical review by Dr. Kim Witzmann dated February 11, 2013). The PADAC convened on January 30, 2013 and on the question of whether there was substantial evidence of efficacy, the majority of the PADAC voted "No" (No:11, Yes:3). In the discussion of efficacy, committee members noted concern over the relatively small effect size and difficulty in knowing the true treatment effect given the differential withdrawal between DPM and control groups. Some also commented that there was not strong statistical evidence for efficacy of DPM that would meet the regulatory

definition of substantial evidence. The lack of support from secondary endpoints was also cited as a concern. However, several committee members commented that there did seem to be some evidence of efficacy in the adult population. On the question of whether the safety profile was sufficient to support approval, the majority of the PADAC also voted "No" (No:11, Yes: 3). In the discussion of safety, committee members expressed concern over the high occurrence of hemoptysis in patients receiving DPM, especially in children. For the question of whether the safety and efficacy data provided substantial support for approval, the PADAC voted "no" unanimously.

Following the PADAC meeting, a Complete Response (CR) action was taken on March 18, 2013. In the CR letter, the deficiency was as follows:

> *The submitted data do not provide a favorable benefit-risk balance to support the use of inhaled mannitol in patients with cystic fibrosis 6 years of age and older. The determination of efficacy based on the two submitted trials are not adequate because of the treatment-related frequent early dropouts in trial 301 for which the primary statistical analyses did not account and the lack of statistical significance in trial 302 for the primary endpoint. Sensitivity analyses conducted on data from study 301 either fail to confirm a treatment effect on the primary efficacy or are problematic in that they attribute a good outcome to some patients who discontinue treatment, or they impute a single score without accounting properly for variability. In addition, there was lack of support for efficacy from secondary endpoints in both the studies. Assessment of safety findings show that, compared to control, subjects treated with mannitol 400 mg had a high occurrence of hemoptysis, particularly in pediatric patients, which is concerning and does not balance favorably with the submitted efficacy data, especially in the pediatric population.*

To address the above deficiency, the CR letter stated the following:

> *To support approval of inhaled mannitol for the treatment of cystic fibrosis, conduct a clinical program including at least one adequate clinical trial to show substantial evidence of efficacy in patients with cystic fibrosis and balancing safety findings…. In the clinical trial include specified criteria that address the specific safety concern of hemoptysis.*

Following the CR action, a post-action meeting (type A) between the Applicant and the Agency occurred to discuss a path forward for the development program. At that meeting, the Agency agreed that a primary endpoint of change from baseline in FEV_1 over 6 months was acceptable to provide substantial evidence of efficacy provided that the FEV_1 change is found to be statistically significant and clinically meaningful. Additionally, to support efficacy, exacerbations would be expected to trend in a positive direction. It was also communicated to the Applicant that conducting a third trial similar in design to the previously completed studies may be the

most expedient path forward. This new study should be designed to minimize missing data and patient drop-out and exclude pediatric patients due to safety concerns.

Following completion of the new study (Study 303), a pre-NDA meeting was held on November 29, 2016. During the meeting the Agency recommended that the Applicant conduct an additional supportive analysis evaluating FEV_1 *at* 26 weeks (in addition to "over 26 weeks") and noted that this would be important from a regulatory perspective. The Agency also recommended a two-dimensional tipping point analysis and that CFQ-R respiratory domain (CFQ-RRD) score be included as one of the hierarchical secondary endpoints. The Agency also reiterated that secondary endpoints such as exacerbation and CFQ-RRD score would be important in the evaluation of efficacy.

The applicant submitted their complete response to the CR action on December 19, 2018.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections were requested for this review cycle, as inspections were performed during the previous review cycle.

4.2. Product Quality

The drug product, Bronchitol (mannitol) Inhalation Powder, 40 mg, is proposed for treatment of cystic fibrosis. The same formulation (neat mannitol) was approved in 2010 with a diagnostic kit (also from Pharmaxis) for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 022368, Aridol Inhalation Powder).

The Bronchitol drug product is a non-sterile dry powder inhaler with formulation pre-metered in hard-gelatin capsules, each containing 40 mg of spray-dried mannitol. The capsules are packaged into aluminum foil-foil blisters and co-packaged with one or more inhalation devices, the Plastiape RS01 Inhaler Model 7 HR, which is a high-resistance inhaler. The to-be-marketed inhaler Model 7 HR is manufactured from the same plastic materials as inhaler Model 7 LR (low resistance) which is approved with Aridol Inhalation Powder diagnostic kit of NDA 022368, however there is difference in the air inlets (refer to page 59 of CMC review #1) to account for the difference in device resistances, and there are different color piercing buttons (blue for HR and red for LR). The mechanism of action for both inhaler models is the same and is described below, however the Aridol inhaler is labeled for less use (57 capsules) than the Bronchitol inhaler (140 capsules). Upon insertion of the capsule into the inhaler, it is pierced from both ends, and the patient inhales from the mouthpiece, which results in the spinning of the capsule and release of the powder by entrainment into the air-stream. The *in vitro* emitted dose, at 60 L/min for 2 L air volume, is 32.2 mg (target emitted delivery). Three package configurations are proposed for marketing, a Bronchitol Tolerance Test packaged with a Training Kit (10 capsules and a device), a 7-day Treatment Pack (140 capsules and 1 device), and a 4-week Treatment Pack (560 capsules and 4 devices). Daily dosage is inhalation of 10 capsules twice a day.

The drug substance, which comprises the entire formulation, is a sugar alcohol with IUPAC name (2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol and the USAN name mannitol. It is a white, crystalline powder of free flowing granules. It is freely soluble in water (22 g/100 mL) and very slightly soluble in alcohol. (b) (4) (b) (4) (b) (4) The retest period of the drug

substance is (b) (4) and is supported by the stability data. The specification controls for the drug substance include appearance, appearance of solution, assay, related substances, (b) (4) (b) (4) melting range, conductivity, specific rotation, endotoxins, microbial limits, (b) (4) (b) (4) and residue on ignition.

For the drug product manufacture, the mannitol is (b) (4) (b) (4) The regulatory specification controls for the drug product include purity of mannitol and testing for related substances, identification by infrared spectroscopy, (b) (4), appearance, bacterial endotoxin limit, microbial limits, aerodynamic particle size distribution, and delivered dose uniformity (DDU).

At the end of the initial review cycle, the CMC team considered the application approvable pending a decision by the Office of Compliance regarding the GMP status of the various sites supporting the CMC for the drug product. Ultimately, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) issued a complete response (CR) letter to the applicant on 18-MAR-2013. The main issue leading to the CR letter was the GMP deficiencies found during investigation of a packaging and labeling facility (b) (4)

The CMC team conveyed additional recommendations for the sponsor to consider for the resubmission, although it does not appear that the subjects of these were considered to be approvability issues. These comments and recommendations related to drug product specification (DDU), stability, manufacturing hold times, formulation conditioning, device ruggedness, drug holdup and device cleaning, stability of fine particle fraction (measured by cascade impaction), the post-approval stability protocol, and data supporting an improved foreign particulate method. Note that the applicant has now been producing their approved Aridol Inhalation Powder drug product for more than 8 years. This drug product also uses the same mannitol formulation prepared by the same process and the same device (but with a lower resistance) as for the Bronchitol Inhalation Powder drug product of this application. As a result, there is a substantially larger amount of data from process validation, clinical, and stability batches available now to gauge the production process and product stability, and these and other data provided in the resubmission mitigate the concerns outlined in the recommendation CMC comments included in the CR letter. In summary:

- The applicant has revised the DDU test acceptance criteria as requested.
- Regarding the Agency suggestion to consider adding (b) (4) to the manufacturing process, the applicant has provided additional data indicating that:

- Regarding hold times for drug product (b) (4) the applicant has updated the process description accordingly.
- Regarding device robustness and the drug hold-up issue, the applicant has revised the product presentation so that it now includes a device with each 7-day supply of capsules (no cleaning will be required).
- Updated stability data now support a 36 month expiry period and the applicant states that any extension of the expiry will be done via a prior-approval supplement as opposed to the typical submission via annual report.
- The post approval stability protocol is revised as requested, to include testing of assay and (b) (4) at the 3 month time-point.
- An updated and validated method for the determination of foreign particulates has now been provided as requested.

In summary, with this resubmission, the applicant has adequately addressed the quality-related recommendations and the GMP issues have been resolved. The evaluation of the resubmission is captured below in the reviews from the drug substance, drug product, process & facilities, and CDRH Office of Compliance teams.

RECOMMENDATION TO DPARP FROM OPQ/CMC: Approval

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

None.

4.5. Human Factors

As DPM can cause severe bronchospasm in susceptible individuals, the proposed population is limited to those patients who can tolerate DPM based on a mannitol tolerance test (MTT) in which patients are given increasing doses of mannitol, up to 400mg total, by a healthcare provider and monitored for decreases in oxygen saturation and pulmonary function (see 8.1.1). Given the importance of using the MTT in identifying patients who could safely tolerate DPM, it was vital that the Applicant provide data to support that a healthcare provider could reliably perform the MTT and correctly identify patients who could tolerate DPM. To support this, the Applicant submitted data from two separate human factor (HF) studies. Both were problematic.

The DMEPA/HF review team identified serious issues with the methodology and results of the Applicant's HF studies. The results of the HF validation studies demonstrated several use errors and use difficulties with critical tasks that could result in harm to the patient. For example, study results showed several use errors and use difficulties that occurred with critical tasks of healthcare providers performing the MTT (see 15.3 for tabular summary of identified issues). These use errors and use difficulties could lead the healthcare providers arriving at an incorrect clinical conclusion to prescribe DPM. This incorrect clinical decision could lead to unindicated patients receiving DPM, which could result in patient harm (e.g. bronchospasm, hypoxia, pulmonary compromise).

Because of this, additional revisions to the product user interface to address the errors seen in the HF validation studies are necessary. Additional HF validation study(ies) with appropriate study methodology will then be necessary to demonstrate that the additional mitigations are effective and that they do not introduce new risks. As a result of these identified issues and the need for a revised product user interface with subsequent additional HF study(ies) using the revised user interface, the DMEPA/HF review team recommends a Complete Response action. See review by DMEPA/HF review team for full details.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This resubmission contained no nonclinical data. The nonclinical data in support of the approval of the application was previously submitted to the original submission of the current application and/or the reference product application (NDAs 202049 and 22-368, respectively). The nonclicnial team has completed detailed reviews of the data and recommended approval in the original submission of the current application. See nonclinical reviews completed by Dr. Luqi Pei on February 5, 2013 for NDA 202049 (DARRTS Reference ID# 3255351) and on October 30, 2009 for NDA 22-368.

Briefly, Bronchitol is an inhalation drug product that contains D-mannitol as the ative pharmaceutical ingredient. The toxicological profile of inhaled mannitol has been well characterized. The compound is non-genotoxic, non-carcinogenic, and non-teratogenic. These properties have been described in the label of Aridol inhalation powder, the currently marketed mannitol inhalation product. A product labeling review of Bronchitol will be completed later.

5.2. Referenced NDAs, BLAs, DMFs

This application references to NDA 22-368 (Aridol) and DMF (b) (4) (Mannitol).

6 Clinical Pharmacology

6.1. Executive Summary

This resubmission contained no new clinical pharmacology data. All clinical pharmacology data in support of the approval of the current application was previously submitted to the original application. The following are the key findings from the original clinical pharmacology review.

1. Following single-dose administration of 635 mg mannitol dry powder by inhalation to healthy male sujects, the absolute bioavailability of inhaled mannitol was 59% as compared to intravenously administered mannitol. The relative bioavailability of inhaled mannitol as compared to orally administered mannitol was 96%. The median time to reach the mannitol peak serum concentration (T_{max}) was 1.5 (1 – 2) hr and dose normalized peak serum concentration (C_{max}) was 10,792 ng/mL for inhaled mannitol. The mean terminal half-life ($t_{1/2}$) of mannitol was approximately 5 hr regardless of route of administration (Study DPM-PK-101).
2. Following BID dosing of 400 mg inhaled mannitol in patients with cystic fibrosis aged 6 and older for 7 days, serum mannitol levels peaked approximately 0.75 to 2.54 hr post dosing. Variability in mean C_{max} values between adults, adolescents and pediatric subjects was moderate to high ranging from 15 to 51%. Between subject variability in mean AUC_{inf} values (Day 1) ranged from 22 to 47%. Serum mannitol concentrations accumulated following multiple BID dosing over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, pediatric (older), and pediatric (younger) subjects, respectively (Day 7/Day 1 AUC_{0-12} ratio) (Study DPM-PK-102).
3. In the Phase 2 Study, inhaled dry powder mannitol demonstrated a dose-dependent increase in FEV1 and FVC in patients with CF, at doses of 40, 120, 240 and 400 mg BID. Although the higest possible dose was not formally established, the use of more than 10 mannitol capsules for each dose ws considered by the Applicant to compromise compliance (Study DMP-CF-202).

For details, see clinical pharmacology review by Dr. Arun Agarwal dated February 8, 2013 for NDA 202049.

7 Sources of Clinical Data and Review Strategy

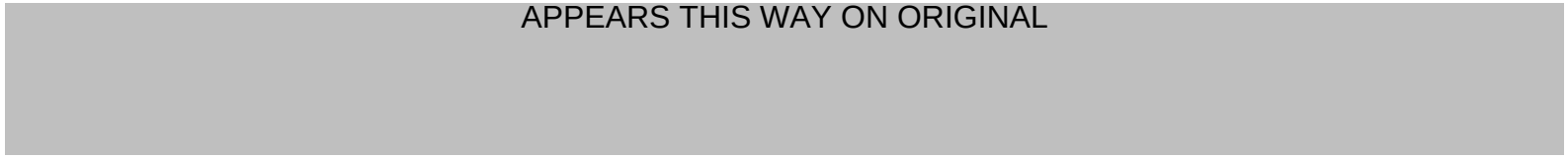
7.1. Table of Clinical Studies

The sources of clinical data reviewed in this document are derived from the phase 3 confirmatory studies. These are summarized in Table 2. Studies 301 and 302 were included in the original application and are highlighted in grey. Study 303 was submitted in the complete response to the CR.

Table 2: Phase 3 Studies

Study	Study years	Study Design	Duration	Population	Treatments	N	Countries*
301	2007-2010	R, DB, PG with OLE 52 weeks	26 week controlled treatment period	CF patients, ages 6 and older, FEV1 30-90%	DPM 400mg BID DPM 50mg BID (control)	177 118	UK, Australia
302	2008-2010	R, DB, PG with OLE 26 weeks	26 weeks controlled treatment period	CF patients, ages 6 and older, FEV1 40-90%	DPM 400mg BID DPM 50mg BID (control)	184 121	US, Germany, Canada, Argentina,
303	2014-2017	R, DB, PG	26 weeks controlled treatment period	CF patients, ages 18 and older, FEV1 40-90%	DPM 400mg BID DPM 50mg BID (control)	209 214	US, Poland, Russia, Ukraine

Abbreviations: DPM=dry powder mannitol; R=randomized; DB=double blinded; PG=parallel group; OLE=open label extension; BID=two times per day; CF=cystic fibrosis; FEV1=forced expiratory volume in one second
**countries contributing ≥10% subjects listed*



7.2. Review Strategy

For efficacy, the double-blind phase (DBP) of studies 301, 302, and 303 serve as the primary support. As studies 301 and 302 were previously reviewed, the focus of this document is study 303 data. However, data from studies 301 and 302 will be discussed and presented when relevant (for details regarding protocol review and results for studies 301 and 302, see Dr. Kim Witzmann's primary clinical review from February 11, 2013). Given the change in the target population to patients ≥18 years of age, efficacy data from the prior studies in the subgroup of patients ≥18 years are presented when appropriate along with study 303 results.

The assessment of safety is primarily based on data from the DBP of studies 301, 302; and study 303, in patients who were randomized and received at least one dose of study drug. Studies 301 and 302 included patients ≥6 years of age and study 303 included patients ≥18 years of age. As the proposed indication includes only those ≥18 years of age, this document only reviews and presents safety data from the ≥18-year-old population in these studies. While safety data from studies 301 and 302 were reviewed in the previous NDA cycle, that review did not include separate analyses of the ≥18-year-old subgroup. As such it is presented here. Long term safety is supported by the 52 and 26 -week open label extension phases (OLP) of studies 301 and 302, respectively; study 303 lacked an extension phase. The DBP of studies 301, 302, and 303 were very similar in design and study population. Therefore, these studies were pooled for safety analyses.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study DPM-CF-303

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

Study Dates: Sept 17, 2014 to February 21, 2017
Study sites: 101 sites in 21 countries [North America (41), Western Europe (10), Eastern Europe (22), South America (2), Australia/New Zealand (4), Russia (5)]

Study Objectives:

Primary objective: To determine whether inhaled mannitol (400 mg twice daily (BID)) was superior to control (inhaled mannitol 50 mg BID) for improving lung function in adult patients with cystic fibrosis (CF).

Secondary objective: To determine whether inhaled mannitol (400 mg twice daily (BID)) was superior to control (inhaled mannitol 50 mg BID) for improving exacerbation related outcomes (antibiotic usage, hospitalizations, number of exacerbations, and time to exacerbations) and quality of life/ symptom related outcomes.

Trial Design

Study 303 was a 26-week treatment period, double-blind, randomized, parallel group, multicenter, controlled study in adults with cystic fibrosis. Eligible patients were randomized 1:1 to receive either dry powder mannitol (DPM) 400 mg BID or matched control for 26-weeks. Randomization was stratified by recombinant human deoxyribonuclease (rhDNase) use, and by country. Patients who discontinued study treatment were encouraged to continue to participate in the study, rather than withdraw. Patients were screened for eligibility at the screening visit (week -5 to -2) – see the description of the mannitol tolerance test below. At Visit 1, (week 0) patients were randomized and the 26- week treatment period began. Patients were subsequently seen in clinic at weeks 6, 14, and 26 (visits 2-4), at which time safety and efficacy assessments were performed. Between clinic visits, patients were contacted via telephone at weeks 2, 4, 8, 12, 16, 20, 24, and 27. The schedule of assessments is summarized in Figure **1**.

Figure 1: Study 303, Schedule of assessments

Event	Screening Visit 0	☎	Visit 1	☎	☎	Visit 2	☎	☎	Visit 3	☎	☎	☎	Visit 4	☎	Study drug discontinuation visit[1]
Week	-5 to- 2	-1	0[2]	2	4	6	8	12	14	16	20	24	26	27	
Visit window		± 1 day		± 3 days	± 3 days	± 7 days	± 3 days	± 3 days	± 7 days	± 3 days	± 3 days	± 3 days	- 7 days to + 28 days	± 1 day	Within 2 weeks of study drug discontinuation
Informed consent	X														
Inclusion/exclusion criteria	X														
Medical history/demographics	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/ vital signs	X		X			X			X				X		X
Pulmonary function tests	X		X			X			X				X		X
Urine pregnancy test	X														
Pulmonary exacerbations review			X			X			X				X		X
MTT procedure	X														
Randomize subject			X[3]												
Dispense study drug and bronchodilator			X			X			X						
Administer treatment dose in clinic			X			X			X				X		
Sputum qualitative microbiology	X														

Event	Screening Visit 0	☎	Visit 1	☎	☎	Visit 2	☎	☎	Visit 3	☎	☎	☎	Visit 4	☎	Study drug discontinuation visit[1]
Week	-5 to- 2	-1	0[2]	2	4	6	8	12	14	16	20	24	26	27	
Visit window		± 1 day		± 3 days	± 3 days	± 7 days	± 3 days	± 3 days	± 7 days	± 3 days	± 3 days	± 3 days	- 7 days to + 28 days	± 1 day	Within 2 weeks of study drug discontinuation
Screening blood sample	X														
Issue Subject Diary	X														
Review Subject Diary			X			X			X				X		X
Collect Subject Diary													X		
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ease of expectoration VAS			X			X			X				X		X
CFQ-R respiratory domain			X			X			X				X		X
Study drug compliance and accountability[4]						X			X				X		
Discuss adherence to treatment (if subject has discontinued study drug, schedule study drug discontinuation visit within 2 weeks of last study drug)				X	X		X	X		X	X	X			
Remind subject of next visit or phone call, withholding periods, to complete Subject Diary, and to return study drug (if applicable)[5]		X	X	X	X	X	X	X	X	X	X	X	X		X
Discharge subject from trial														X	

CFQ-R=Cystic Fibrosis Questionnaire-Revised; MTT=mannitol tolerance test; VAS=visual analogue scale

[1] The study drug discontinuation visit was used for all subjects who discontinued study drug early, but were remaining in the trial.
[2] Subjects had to have been stable and clear of pulmonary exacerbations for at least 2 weeks prior to Visit 1. If a subject had an exacerbation after Visit 0 (screening), Visit 1 should have occurred 2 to 5 weeks from the end of the treatment of the exacerbation or the end of the adverse event, whichever was later.
[3] Eligible subjects were to be randomized if compliance with maintenance therapies (antibiotic and rhDNase) was at least 80% in the 2 weeks prior to Visit 1.

[4] Study drug accountability and collection was to occur at the next scheduled visit for any subject who withdrew from the trial or discontinued from study drug early.
[5] The Subject Diary was to be collected for all subjects, including those who withdrew early from the trial.

Source: Study 303 CSR p 35-36

As inhaled mannitol can induce bronchospasm, to be eligible for participation, patients had to pass a mannitol tolerance test (MTT). The MTT entails receiving successively increasing doses of

dry powder mannitol from 40 mg to 160 mg (40 mg, 80 mg, 120 mg, and 160 mg for a cumulative dose of 400 mg). If a patient experienced an SpO_2 <89% within 1 minute after any dose of dry powder mannitol, the patient failed the MTT. If a patient experienced a drop in FEV_1 ≥ 20% of baseline within 60 seconds after the 80 mg, or 120 mg dose, the patient failed the MTT. For the final 160 mg dose, if a patient experienced a drop in FEV_1 of ≥50%, the patient failed the MTT. However, if, at the 160 mg dose, the patients experienced a drop in FEV_1 of 20-50%, the patient was reassessed in 15 minutes. If after 15 minutes the patient continued to have an FEV_1 drop of ≥20%, the patient failed the MTT.

Overall the design of study 303 was largely similar to 301 and 302. All included 26-week double-blind treatment periods, the same treatment arms, and a largely similar MTT. However, study 303 included additional features to minimize patient drop-out and missing data, such as encouraging patients to remain in study even if discontinuing from study treatment, as well as additional telephone contact with patients.

Study population

The planned sample size for this study was 350 patients with a confirmed diagnosis of CF (175 patients in each arm).

Key inclusion criteria:

1. Confirmed diagnosis of CF (positive sweat chloride value ≥60 mEq/L) and/or genotype with two identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype
2. At least 18 years old
3. Having an FEV_1 >40% and <90% predicted
4. Stable medication use within 1 month prior to screening. No rhDNase or maintenance antibiotics were allowed to be started during the trial

Key exclusion criteria:

1. Lung transplant eligible or s/p lung transplant
2. Use of hypertonic saline
3. Hemoptysis >60 mL in the 3 months prior
4. A myocardial infarction, cerebrovascular accident, or uncontrolled hypertension in the 3 months prior
5. Having had major ocular, abdominal, chest, or brain surgery in the 3 months prior
6. Pregnancy or unreliable contraception

Failure or incompletion of the MTT

Study Treatments

During the 26-week treatment period the treatment arms were as follows:

Test product: DPM 400 mg BID delivered via 10 capsules (40 mg each) for inhalation from a single-dose dry powder inhaler. One capsule was taken at a time.

Control product: inhaled mannitol 50 mg BID delivered via 10 capsules (5 mg each) for inhalation from a single-dose dry powder inhaler model. One capsule was taken at a time. The control was chosen given the sweet taste of mannitol in the test product and based on results of the dose ranging study (202), which showed no efficacy for the 40 mg dose. Study drug was given during clinic visits on the visit days and self-administered on non-clinic days.

All CF related medications were permitted and continued except inhaled hypertonic saline (HTS) and oral nonselective beta-blockers. Patients on maintenance antibiotics or rhDNase were required to have been on the medication for at least 1 month and to continue the maintenance medications through the entire treatment period. HTS and oral non-selective beta blockers were discontinued at screening.

The order in which inhaled treatments were given was as follows:

1. Bronchodilator
2. DPM/control
3. Physiotherapy/exercise
4. rhDNase (if used)
5. Inhaled antibiotics (if used)
6. Inhaled corticosteroid (if used)

It should be noted that before taking study medication, patients were instructed to take a bronchodilator.

Study Endpoints

Primary Endpoint:

The primary efficacy endpoint for study 303 was the mean absolute change from baseline in FEV_1 over the 26-week treatment period (measured at weeks 6, 14, and 26). This primary endpoint is identical to that used in studies 301 and 302. FEV_1 is a fairly typical primary endpoint measure for CF studies.

Secondary Endpoints:

The secondary endpoints were divided into those that were part of a prespecified analysis hierarchy and those that were not. The secondary endpoints which were assessed in a statistical hierarchical manner are as follows (in order):

1. Forced vital capacity (FVC)
2. Time to first protocol defined pulmonary exacerbation (PDPE)
3. Number of days on antibiotics due to PDPE
4. Number of days in hospital due to PDPE
5. Rate of PDPE

Other secondary endpoints not included in the analysis hierarchy are as follows:

1. Incidence of PDPE
2. Ease of expectoration using the change in VAS score over the 26 weeks
3. CFQ-R respiratory domain score change from baseline over the 26 weeks

PDPE was defined as having occurred when a pulmonary exacerbation was treated with IV antibiotics for four or more of the following signs or symptoms:

1. Change in sputum production (volume, color, consistency);
2. Increased dyspnea;
3. New or increased hemoptysis;
4. Malaise, fatigue, or lethargy;
5. Fever (≥38°C, i.e., ≥100.4°F);
6. Anorexia or weight loss;
7. Sinus pain or tenderness;
8. Change in sinus discharge;
9. FVC or FEV_1 decrease by >10% from previous recorded value;
10. Radiographic signs indicative of pulmonary infection;
11. Increased cough;
12. Changes in physical examination of the chest.

This definition for CF exacerbation is reasonable. It is the same as used in studies 301 and 302, and similar definitions have been used in development programs for other CF products.

With regard to the secondary endpoints, FVC has not typically been used to support efficacy in CF development programs, nor has ease of expectoration. However, exacerbation related endpoints are recognized as clinically meaningful and have been used to support efficacy for CF products. CFQ-R respiratory domain scores, as an assessment of respiratory symptoms, have also been used to support efficacy for CF products.

Statistical Analysis Plan

Analysis Sets

The following analysis sets were defined in the Statistical Analysis Plan (SAP):

- Safety Set (SAF): This set included patients who were administered at least one dose (or part thereof) of randomized study medication. Patients in this set were grouped according to study medication received. This set was used for all analyses of safety endpoints.
- Intent-to-Treat Set (ITT): This set included all randomized patients. Patients were grouped according to randomized study medication. This set was used for all analyses of efficacy endpoints.

- Per Protocol Set (PP): This set included all randomized patients who did not have deviations from the protocol that may have affected the assessment of response to study medication.

Analysis Definitions for Periods

For Safety Data:

- On-treatment period: period of time while the patient was on study medication; it started with the first dose of study medication after randomization and ended 28 days after the last dose of study medication.

For Efficacy Data:

- On-treatment period: period of time while the patient was on study medication; it started with the first dose of study medication after randomization and ended 7 days after the last dose of study medication.
- Off-treatment period: period of time while the patient was not on study medication; it started the eighth day after the last dose of study medication and ended on the date of last participation in the study.

Estimands

The SAP referred to the de facto estimand as Estimand 1 in Mallinckrodt et al.[4], which was defined as the "difference in outcome improvement at the planned endpoint for all randomized participants". This estimand was targeted in the primary analysis of the primary efficacy endpoint. No other estimands were referenced or defined. The SAP did not specify the estimands being targeted by analyses of other endpoints.

Primary Efficacy Endpoint

Primary Analysis: Absolute change from baseline over the 26-week treatment period (with measurements at Week 6, 14, and 26) in Forced Expiratory Volume in 1 second (FEV_1) was compared between the two treatment groups with a restricted maximum likelihood based Mixed Model for Repeated Measures (MMRM) approach. This model included the fixed categorical effects of treatment group, rhDNase use, pooled country, visit, and an interaction term between treatment group and visit, as well as the continuous, fixed covariates of baseline FEV_1 and baseline percent predicted FEV_1. Patient was included in the model as a random effect. An unstructured covariance structure was used to model the within-patient variability. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The SAP stated that least squares (LS) means for each treatment group and mean treatment group difference, standard error (SE), 95% confidence intervals (CIs) and the p-value for the treatment group effect averaged across the different study visits, with the same weight applied to each visit, were to be presented. However, the analysis actually estimated a treatment group

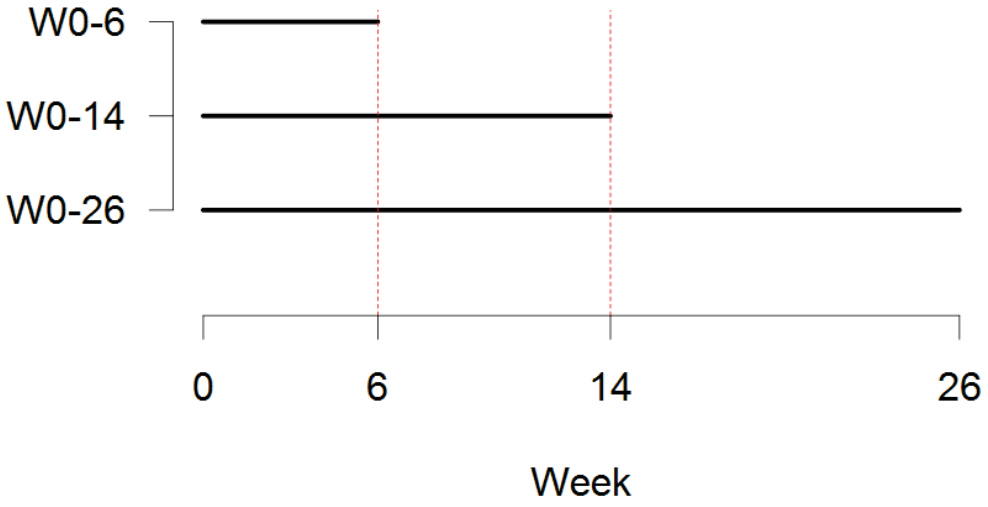
[4] Mallinckrodt, Craig H., et al. "A structured approach to choosing estimands and estimators in longitudinal clinical trials." Pharmaceutical Statistics 11.6 (2012): 456-461.

effect averaged across change from baseline to the different study visits, with the same weights applied to change from baseline to each visit. Prior to this analysis, missing data were handled in the following manner:

- All available on-treatment and off-treatment period data were included.
- Missing baseline values were imputed with screening values, if available.
- Post-baseline measurements that were missing because of study withdrawal due to adverse events (AEs), death, physician decision, or lack of efficacy were imputed using a Baseline Observation Carried Forward (BOCF) approach.
- Post-baseline measurements that were missing because of study withdrawal due to other causes (i.e., loss to follow-up, relocation, pregnancy, major protocol deviation, sponsor decision, withdrawal of consent, or other) were not imputed. As a result, these measurements were assumed to be Missing at Random.
- Missing data at intermediate visits (i.e., where data were available at a later visit) were not imputed. As a result, these measurements were assumed to be Missing at Random.

It is worth noting that in this analysis and in other analyses that gave equal weight to change from baseline to each visit in FEV_1, change occurring in earlier time periods was given substantially more weight than change occurring at later time periods. This weighting is illustrated in Figure 2, with each of the horizontal lines (representing change from baseline at each of Weeks 6, 14, and 26) being given equal weight. The dashed vertical red lines separate the 26-week period into incremental periods of Week 0 to Week 6, Week 6 to Week 14, and Week 14 to Week 26. This figure makes clear that in the primary efficacy endpoint, change occurring from Week 0 to Week 6 was counted three times (for an effective weight of 50%), change occurring from Week 6 to Week 14 was counted twice (for an effective weight of 33%), and change occurring from Week 14 to Week 26 was counted only once (for an effective weight of 17%). This endpoint therefore puts a weight of 83% on change occurring during the first 14 weeks of the 26-week period, and a weight of only 17% on change occurring during the last 12 weeks of the 26-week period.

Figure 2: Visual Representation of Weighting in Change from Baseline Over 26 Weeks in FEV_1



Abbreviations: W0-X=Week 0 to Week X
Source: FDA Statistical Reviewer

Letting FEV_1^{WX} denote the FEV_1 measurement at Week X, the primary efficacy endpoint can be reexpressed in the following form:

$$\frac{3(FEV_1^{W6} - FEV_1^{W0}) + 2(FEV_1^{W14} - FEV_1^{W6}) + (FEV_1^{W26} - FEV_1^{W14})}{3}$$

Given the heavy weighting of this endpoint toward earlier time periods, any loss of efficacy at later time periods such that the treatment effect is not durable is downweighted by this endpoint.

Sensitivity Analysis 1 (Pattern Mixture Model): Absolute change from baseline in FEV_1 (averaging over change to Weeks 6, 14, and 26) was compared between the two treatment groups with an Analysis of Covariance (ANCOVA) model including as covariates treatment group, rhDNase use, pooled country, baseline FEV_1, and baseline percent predicted FEV_1. Prior to this analysis, missing data were imputed (resulting in 1000 multiply imputed datasets) in the following manner:

- As a preliminary step, post-baseline missing data at intermediate visits (i.e., where data were available at a later visit) were imputed using a joint modeling approach in order to obtain monotone missing data patterns assuming Missingness at Random (MAR), with an imputation model including as covariates treatment group, rhDNase use, pooled country, and FEV_1 at screening, at baseline, and at Weeks 6, 14, and 26.
- Regardless of treatment group, post-baseline data that were missing because of study withdrawal due to adverse events, death, physician, or lack of efficacy were imputed using a regression model for baseline FEV_1 including as covariates rhDNase use, pooled

country, and FEV_1 at screening, estimated on data from patients with non-missing baseline FEV_1 values.

- Within each treatment group, post-baseline data that were missing because of study withdrawal due to other reasons were imputed using a regression model including rhDNase use, pooled country, and FEV_1 at screening, baseline, and at Weeks 6, 14, and 26, using data from patients in the same treatment group who completed the study.

Sensitivity Analysis 2 (Tipping Point Analysis): Absolute change from baseline in FEV_1 (averaging over change to Weeks 6, 14, and 26) was compared between the two treatment groups using the same model as in Sensitivity Analysis 1. Prior to this analysis, missing data were imputed (resulting in 1000 multiply imputed datasets) in the following manner:

- As a preliminary step, post-baseline missing data at intermediate visits (i.e., where data were available at a later visit) were imputed in the same manner as with Sensitivity Analysis 1
- Then, a regression-based imputation was performed for the remaining FEV_1 values, regardless of the reasons for withdrawal from the study. The imputation model included as covariates treatment group, rhDNase use, pooled country, and FEV_1 at screening, at baseline, and at Weeks 6, 14, and 26. Measurements for patients in the control group that were imputed in this step had their values shifted downward by one of the following values (in liters): 0, -0.02, -0.04, -0.06, -0.08, or -0.10. For each of the aforementioned values, the measurements for patients in the mannitol group that were imputed in this step were shifted downward in increments of 0.02 liters (starting at -0.02 liters) until the results tipped from having statistical significance to lacking statistical significance. For each of the six aforementioned shift values for the control group, the shift value for the mannitol group at which the results tipped was to be reported.

The results presented in the 303 CSR according to the prespecified reporting approach were not very informative, so the Applicant was asked to redo the analysis to present a two-dimensional table instead. For each scenario considered in the tipping point analysis, the table includes a point estimate for the treatment effect, as well as the corresponding 95% confidence interval and p-value.

Sensitivity Analysis 3: This analysis was the same as the primary analysis for the primary efficacy endpoint, except that data were not imputed, and any missingness was assumed to be at random. Because this assumption for the missingness mechanism is rather strong, results for Sensitivity Analysis 3 are not presented in this document.

Sensitivity Analysis 4: A responder analysis was performed where a patient was considered to be a responder if (1) the data to determine the change from baseline to Week 26 in FEV_1 were not missing; and (2) the change from baseline to Week 26 in FEV_1 was above a certain

threshold. The thresholds considered were (in liters) 0.050, 0.075, and 0.100. The proportion of responders were summarized and compared between treatment groups using a logistic regression model that included the same covariates as in the model for the primary analysis. The treatment group effect odds ratio, as well as the corresponding 95% CI and p-value, were to be presented.

Multiplicity Control Procedure

A hierarchical testing procedure was used, in that if results from the primary analysis for an endpoint were found to be statistically significant at the two-sided significance level of 0.05, the following endpoint in the hierarchy was to be tested at the same significance level in its primary analysis. If results for any of these endpoints were found to not be statistically significant, formal hypothesis testing was not performed for any remaining endpoints in the hierarchy. The procedure began with the primary efficacy endpoint, and the hierarchy was as shown below:

- Absolute change from baseline over 26 weeks in FEV_1
- Absolute change from baseline over 26 weeks in Forced Vital Capacity (FVC)
- Time to first protocol defined pulmonary exacerbation (PDPE)
- Number of days on antibiotics (oral, inhaled, or IV) due to PDPEs
- Number of days in hospital (admissions only) due to PDPEs
- PDPE Rate (per person year)

Primary Analyses for Hierarchical Secondary Efficacy Endpoints

Change from Baseline Over 26 Weeks in Forced Vital Capacity: This endpoint was analyzed in the same manner as in the primary analysis of the primary efficacy endpoint, using the same missing data handling methods.

Time to First PDPE: Number of days to the first PDPE was analyzed using a Cox Proportional Hazards Model which included as covariates treatment group, pooled country, rhDNase use, and number of IV antibiotic treated pulmonary exacerbations (PEs) in the year prior to screening. For this analysis, each patient who did not have a PDPE by the date of his or her last participation in the study were censored at that date. The treatment group hazard ratio, as well as the corresponding 95% CI and p-value, were to be presented.

Number of Days on Antibiotics Due to PDPEs, Number of Days in Hospital Due to PDPEs, and PDPE Rate: Each of these three endpoints was compared between treatment groups using a negative binomial model that included as covariates treatment group, pooled country, rhDNase use, and the number of IV antibiotic treated PEs in the year prior to screening. An offset variable of the natural log of follow-up duration (in years) was used in each model to adjust for different lengths of follow-up. For each endpoint, the rate ratio, as well as the corresponding 95% CI and p-value, were to be presented.

For PDPE rate, if a patient withdrew from the study before Week 14 with no observed instances of a PDPE, the number of PDPEs was imputed using half the patient's historical (previous 12 months) PE count rounded up to the nearest whole number, and their follow-up duration was imputed as 26 weeks. If a patient withdrew from the study after Week 14 with no observed instances of a PDPE, the number of PDPEs was imputed using one quarter the patient's historical (previous 12 months) PE count rounded up to the nearest whole number, and their follow-up duration was imputed as 26 weeks.

Primary Analysis for Other Secondary Efficacy Endpoints:

Change from Baseline Over 26 Weeks in CFQ-R Respiratory Domain Score: This endpoint was analyzed in the same manner as in the primary analysis of the primary efficacy endpoint, using the same missing data handling methods.

Safety Analyses

In general, safety analyses were descriptive in nature. No inferential statistical testing was planned on the safety data.

Key Differences in SAP Compared to Studies 301 and 302

- Analysis Population Definitions
  - Studies 301 and 302
    - The SAPs for Studies 301 and 302 defined the ITT population to include all randomized patients who received at least one dose of study medication
- Primary Analysis for Change from Baseline Over 26 Weeks in FEV_1
  - Studies 301 and 302
    - The SAPs did not reference or define the estimand being targeted
    - Missing measurements for FEV_1 were not imputed, and all missingness was assumed to be at random
    - Treatment discontinuation was not distinguished from study withdrawal
    - The SAPs did not state whether off treatment data would be included
  - Study 301
    - Patients with no post-baseline assessments of FEV_1 were excluded
  - Study 302
    - The SAP did not state whether patients with no post-baseline assessments of FEV_1 would be included
- Primary Analysis for PDPE Rate
  - Studies 301 and 302
    - No imputation was performed for any patients who withdrew from the study, regardless of the number of observed instances of a PDPE
- Family-Wise Type I Error Control
  - Studies 301 and 302
    - Because of a prespecified interim analysis, the primary efficacy endpoint was tested at the two-sided significance level of 0.0498
  - Study 301

        - There was no multiplicity control procedure for the primary efficacy endpoint and the secondary efficacy endpoints
    - Study 302
        - Instead of using an analysis hierarchy, key secondary efficacy endpoints were tested using the Holm's method of correction, at the one-sided significance level of 0.025

Protocol Amendments

Protocol version 1.8 was the first version used dated March 27, 2014. The second version, version 2.0, was dated Oct 13, 2014.
Differences between the two protocol versions were

- The addition of a study drug discontinuation visit 2 weeks after study drug discontinuation (but not study withdrawal)
- Rephrasing of the PP definition set
- Clarification of procedures and administrative changes

8.1.2. Study Results

Study results for study 303 are discussed here along with pertinent results from studies 301 and 302 from the prior review cycle when appropriate.

Compliance with Good Clinical Practices

The trial was monitored according to ICH guidelines for GCP and conducted in accordance with the ethical principles consistent with GCP.

Documented approval was obtained from IRBs and IECs prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with GCP, CFR, and the Declaration of Helsinki. No foreign clinical studies are noted.

Financial Disclosure

There are no financial conflicts of interest noted nor has the sponsor entered into any financial arrangements with any investigators.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted and verifies that no compensation is linked to study outcome. The PIs did not disclose any proprietary interest to the sponsor.

Patient Disposition

A total of 486 patients were screened for eligibility. Of these, 32 (5%) failed the MTT and an additional 31 did not meet other eligibility criteria. Thus, 423 patients were randomized (209 DPM, 214 control). Of those randomized, approximately 88% completed the study; the study withdrawals were balanced in the two treatment arms. Treatment discontinuation (without study withdrawal) occurred in 19% of patients and was also balanced in the two treatment arms.

The reasons for study withdrawal were balanced between the treatment arms. The most common reason was withdrawal of consent. Other reasons included AEs, lack of efficacy, loss to follow-up, pregnancy, relocation, and other. With regard to treatment discontinuations, adverse events were the common reason, with "subject decision" being the second most common. Other reasons were similar to the reasons noted for study withdrawal. These data are summarized in Table 3.

Table 3: Study 303, Disposition

Disposition	Study 303	
	DPM (N=209)	Control (N=214)
Randomized	209	214
Completed study	183 (87.6)	190 (88.8)
Early study withdrawal		
Total	26 (12.4)	24 (11.2)
Withdrawal of consent	12 (5.7)	13 (6.1)
AE	10 (4.8)	6 (3.3)
Death	0	1 (0.5)
Lack of efficacy	2 (1)	1 (0.5)
Lost to follow-up	1 (0.5)	1 (0.5)
Other (relocation, pregnancy, unspecified)	1 (0.5)	2 (1)
Early treatment discontinuation		
Total	37 (17.7)	44 (20.6)
AE	20 (9.6)	18 (8.4)
Lack of efficacy	2 (1)	4 (1.9)
Relocation	1 (0.5)	0
Physician decision	0	1 (0.5)
Pregnancy	0	1 (0.5)
Other*	14 (6.7)	20 (9.3)

*Most frequent reason "subject decision" approximately 10 patients (5%) each arm

Source: study 303 CSR, Table 14.1.1.2, p.143; reviewer verified (ADSL study 303, ITTFL=Y, COMPLFL=Y, DCSREAS tabulated by TRT01P)

Withdrawal of consent was explored further, as it was the most common reason for study withdrawal. Reviewer analysis (Study 303 ADSL, ITTFL=Y, TRT01P,WCREAS tabulated) did not reveal an imbalance in reasons cited for withdrawal of consent, which included logistical

reasons (insufficient time, travel, study schedule), the desire to take an alternate medication (hypertonic saline or Orkambi), or patient decision without further clarification.

Note that the study completion data from study 303 are in contrast to those of the prior studies, particularly study 301. In the entire study population (including non-adults) for study 301, only 63% of DPM and 73% of control patients completed the 26-week treatment period. In study 302, the findings were similar, though not as pronounced, where 83% of DPM and 88% of control patients completed the 26-week treatment period. The study completion rate in studies 301 and 302 for adults as compared to the overall population was even lower. Primary reasons for study withdrawal in studies 301 and 302 were similar to study 303. These data are summarized in Table 4.

Table 4: Studies 301, 302, Disposition, Adults only, ITT, DBP

	Study 301		Study 302	
	DPM (N=124)	Control (N=85)	DPM (N=97)	Control (N=60)
Randomized	124	85	97	60
Completed study (DBP only)	71 (57.3)	52 (61.2)	70 (72.2)	50 (83.3)
Early study withdrawal*				
Total	53 (42.7)	33 (38.8)	27 (27.8)	10 (16.7)
Withdrawal of consent	18 (14.5)	17 (20)	10 (10.3)	6 (10)
Adverse event	24 (19.4)	12 914.1)	9 (9.3)	2 (3.3)
Physician decision	5 (4)	1 (1.2)	2 (2.1)	1 (1.7)
Sponsor decision	5 (4)	2 (2.4)	0	0
Protocol violation	0	1 (1.2)	1 (1)	0
Lost to follow-up	0	0	2 (2.1)	0
Randomization error	0	0	1 (1)	0
Other (unspecified)	1 (0.8)	0	2 (2.1)	1 (1.7)
*Early treatment discontinuation led to study withdrawal, not shown separately				

Source: SCS, Table 19, p.75

Importantly, in studies 301 and 302 when patients withdrew or discontinued treatment, they were no longer followed for efficacy endpoint data. This resulted in issues related to missing data which complicated analyses and interpretation of efficacy from these studies, as the Applicant's prespecified analysis plan used a mixed model for repeated measures (MMRM). This approach assumes that data missingness occurred at random, which did not appear to be the case for DPM, given the observed differential drop-out and that the product has known side effects which can make it difficult to tolerate for some patients. Given the lower and non-differential withdrawal in study 303, this was not as much of a concern for interpretation and analysis of the efficacy data.

Overall, the percentage of patients who withdrew from study 303 was reasonable for a 26-week study. Additionally, withdrawals were balanced between treatment arms. As such, the concerns raised in the analyses of studies 301 and 302 are likely less prominent for study 303.

Protocol Violations/Deviations

In the ITT set, 21 patients in the DPM group (10%) and 31 patients in the control group (14.5%) had major protocol deviations (MPDs) (Table 5). The most common protocol deviation was concomitant medication use (5% DPM, 7% control), of which starting and stopping maintenance antibiotics were the main medication class (12 of 15 control patients, 6 of 10 DPM patients, Source: Study 303 CSR, Table 14.1.2.1, p.153).

Table 5: Study 303 Major Protocol Deviations

	Study 303	
	DPM (N=209)	Control (N=214)
Total	21 (10%)	31 (14.5%)
Concomitant medication	10 (4.8%)	15 (7%)
Compliance <60%	9 (4.3%)	12 (5.6%)
Non-compliance with maintenance medications	2 (1%)	4 (1.9%)
Randomized but not dosed	2 (1%)	1 (0.5%)

Source: study 303 CSR p.69

The next most common MPD was inadequate compliance (<60%) (4% DPM, 6% control). Other deviations were violation of inclusion criteria for maintenance medications and lack of dosing post randomization.

Overall, given the balanced MPDs and the nature of the MPDs, it is unlikely that this impacted the efficacy analysis.

Demographics and Baseline Characteristics

In study 303, the demographic characteristics between the two arms were fairly balanced with minimal differences. As expected given the nature of CF, this was a predominantly young (mean age 28) Caucasian (97%) population. The mean height and weight at screening (not shown) were also fairly balanced and reasonable. The geographic contributions from the study sites are shown; US sites were the largest single country contributor at over 25%. The next highest contribution came from Ukraine, Russia, and Poland at >10% each. Demographic data are summarized in Table 6.

Table 6: Study 303, Demographics

	Study 303	
	DPM (N=209)	Control (N=214)
Age		
Mean	26.8 (7.6)	28.6 (10.8)
Median (min,max)	25 (18,59)	25 (18,78)
Geography (≥3% contributors)		
US	57 (27)	59 (28)
Non-US	152 (73)	155 (72)
Ukraine	31 (15)	32 (15)
Russia	21 (10)	20 (9)
Poland	22 (11)	22 (10)
Hungary	9 (4)	8 (4)
Slovakia	8 (4)	9 (4)
Canada	7 (3)	6 (3)
Italy	7 (3)	8 (4)
Bulgaria	6 (3)	7 (3)
Gender		
Female	92 (44)	107 (50)
Race		
Caucasian	202 (97)	209 (98)
African	4 (2)	2 (1)

Source: Study 303 CSR, Table 10-2,11-2

In comparing these demographics to the prior studies 301 and 302, differences in age and geography were noted. The mean and median ages were lower in studies 301 and 302, which is not surprising, as these studies included patients <18 years of age, who accounted for approximately 40-50% of the study 301 and 302 population. Also, study 301 had no U.S. patients (UK ~60%, Australia ~25%) and study 302 had the largest U.S. contribution (59%). No significant gender or race differences were noted.

With regard to baseline disease characteristics, in study 303, these were similar between treatment groups. Mean time since CF diagnosis was approximately 20 years, mean baseline FEV_1 percent predicted was 63%, just under half were colonized with *P. aeruginosa*, and the majority (67%) carried at least one *F508del* mutation (Table 7). These baseline characteristics are fairly typical for an adult CF population. However, it should be noted that in the U.S. CF population a larger percentage of patients carry at least one *F508del* mutation (86%). This difference may be related to the fact that approximately 70% of patients were non-U.S. where the mutational composition of the population may differ. Baseline disease characteristics are summarized in Table 7.

Table 7: Study 303, Baseline Disease Characteristics

	Study 303	
	DPM (N=209)	Control (N=214)
Mean Time to Diagnosis	20 years	20 years
Mean Age at Diagnosis	7 years	9 years
CFTR mutation		
Homozygous F508del	55 (26)	48 (22)
Heterozygous F508del	91 (44)	89 (42)
Other known mutation	28 (13)	37 (17)
Both unknown	35 (17)	40 (19)
Number of Hospitalizations associated with exacerbation in previous 12 months		
0	121(58)	135 (63)
1	57 (27)	43 (20)
2	20 (10)	23 (11)
3	11 (5)	9 (4)
>3	0	4 (2)
Screening Hemoptysis history		
History of Hemoptysis	68 (33)	60 (28)
Multiple prior hemoptysis events	38 (56)	27 (45)
Prior massive* hemoptysis events? yes	3 (4)	5 (8)
Lung function at baseline		
Mean FEV1	2.45L	2.38 L
FEV1 % predicted, mean	63%	63%
CFQ-R respiratory domain scaled score		
Mean	65.4	65.1
Median (min,max)	66.7 (16.7,100)	66.7 (5.6, 100)
Screening sputum microbiology		
Pseudomonas aeruginosa (any)	93 (44.5)	93 (43.5)
Pseudomonas aeruginosa (mucoid)	66 (32)	62 (29)
Pseudomonas aeruginosa (non-mucoid)	41 (20)	46 (22)
Pseudomonas spp. (other)	6 (2.9)	10 (4.7)
*Massive hemoptysis defined as ≥240 mL in a 24-hour period and/or recurrent bleeding ≥100 mL per day over several days		

Source: Study 303 CSR, Tables 11-3, 11-4, 11-6, 11-7, pp. 73-77

Baseline characteristics of patients in study 303 were generally similar to studies 301 and 302 with some minor differences expected based on age and geography; certain aspects were not captured at screening in the older studies and cannot be compared. Sputum *Pseudomonas* percentage, *F508del* mutation percentage (302 data only), and FEV_1 % predicted were largely similar across all three studies; CFQ-R respiratory domain scores, hemoptysis details, and hospitalization information was not uniform or present in the prior studies to allow comparison.

Hemoptysis was a significant safety concern in the prior review cycle (see Section 3). As such, the hemoptysis history at screening was reviewed. No significant imbalances in frequency, timing, or severity of prior events were noted; minor differences were present showing DPM patients to have a slightly higher frequency of prior multiple hemoptysis events (Table 7). Hemoptysis frequency in study 303 was slightly higher than the previous studies (<20%), understandably given the age differences of the population.

In review of baseline and concomitant medications, these were fairly balanced between DPM and control arms in study 303. However, more new systemic corticosteroid use was reported in DPM patients during the treatment period compared to control (10.5% DPM vs. 5.6% control). The reason for this difference is not apparent, however, one possibility is that, given that inhaled mannitol is known to cause bronchospasm/wheeze in susceptible individuals, it is possible that the increase in new steroid use is related to episodes of wheeze/bronchospasm. Although it should be acknowledged that based on adverse event analysis, no large differences were observed between groups with regard to wheeze/bronchospasm.

Efficacy Results – Primary Endpoint

The primary endpoint for study 303 was change from baseline in FEV_1 over the 26-week treatment period. FEV_1 is a fairly typical primary efficacy variable used in CF drug development programs, and has historically been used to support regulatory decision making. There was a statistically significant difference in change from baseline in FEV_1 over 26 weeks, when comparing DPM to placebo (p=0.018). The adjusted mean difference between DPM and placebo was 55 mL (95% CI: 9 to 101 mL) (Table 8).

Table 8: Study 303, FEV1 Over 26 Weeks, BOCF Imputation Using Dropout Reason, ITT

	Study 303	
	DPM (N=209)	Control (N=214)
Change from baseline in FEV_1 over 26 weeks (days 43, 99, and 183)		
Adjusted mean change from baseline	65 mL	10 mL
Adjusted mean difference (95% CI) p-value	55 mL (9 to 101 mL) p=0.018	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; BOCF=baseline observation carried forward
Note: These results reflect "on study" estimates, as they include data collected after treatment discontinuation.
Source: FDA Statistical Reviewer

Multiple sensitivity analyses were performed for the primary endpoint, including an analysis that utilized a Pattern Mixture Model (PMM) approach with multiple imputation. The Pattern Mixture Model approach with multiple imputation handles missing data most appropriately among the prespecified sensitivity analyses, from a regulatory and statistical perspective. It assigns bad scores to bad outcomes such as dropout due to adverse events or lack of efficacy, and assumes that missingness is at random for dropouts due to other reasons likely unrelated

to treatment, such as moving. Multiple imputation accounts for statistical uncertainty in parameter estimation due to data missingness. These results were consistent with those of the primary analysis (Table 9).

Table 9: Study 303, Primary Endpoint. FEV1 Over 26 Weeks, Pattern Mixture Model with MI Using Dropout Reason, ITT

	Study 303	
	DPM (N=209)	Control (N=214)
Change from baseline in FEV_1 over 26 weeks (days 43, 99, and 183)		
Adjusted mean change from baseline	63 mL	12 mL
Adjusted mean difference (95% CI) p-value	51 mL (6 to 97 mL) p=0.028	

Abbreviations: MI=multiple imputation; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol
Note: These results reflect "on study" estimates, as they include data collected after treatment discontinuation. For each imputed dataset, a linear regression model was fit, and Huber-White sandwich estimates for the standard errors were used for the confidence intervals and p-values.
Source: FDA Statistical Reviewer

Results of an "on-treatment" sensitivity analysis for this endpoint was also performed and did not produce substantially different results.

A tipping point analysis was also performed to evaluate the robustness of the primary analysis results across varying missing data assumptions. In the analysis, missing data with monotone missingness patterns were multiply imputed assuming that missingness was at random among those in the same treatment group and country group, with the same rhDNase use, and with comparable FEV_1 values from screening through Week 26. These imputed values were then shifted for each patient by a value δ that corresponded to the patient's treatment arm. The results over a range of reasonable by-arm shift (δ) values are summarized in Table 10. For the majority of scenarios (shaded in green), though not all (shaded in red), the statistical significance was maintained. This suggests that the primary analysis results are somewhat robust to violations of missing data assumptions, which was expected from relatively low and proportionate missingness rates between treatment groups. If FEV_1 values after study discontinuation in the control arm followed the same trend as those of comparable control patients who remained in the study through Week 26, then in order to tip to a lack of statistical significance, FEV_1 values after study discontinuation in the DPM arm, on average, would have had to be 100 mL lower than those of comparable DPM patients who remained in the study through Week 26. The results of the sensitivity analyses supported the robustness of the primary analysis to violations of assumptions regarding data missingness mechanisms.

Table 10: Study 303, FEV1 Over 26 Weeks, Tipping Point Analysis, ITT

		δ_t				
		-100 mL	**-50 mL**	**0 mL**	**50 mL**	**100 mL**
δ_c	**100 mL**	40 mL (-7 to 87) p=0.093	44 mL (-3 to 90) p=0.066	47 mL (1 to 94) p=0.045	51 mL (5 to 97) p=0.031	55 mL (9 to 101) p=0.020
	50 mL	43 mL (-4 to 89) p=0.073	46 mL (0 to 93) p=0.051	50 mL (4 to 96) p=0.034	54 mL (7 to 100) p=0.023	57 mL (11 to 103) p=0.015
	0 mL	45 mL (-1 to 92) p=0.057	49 mL (3 to 95) p=0.039	53 mL (6 to 99) p=0.026	56 mL (10 to 102) p=0.017	60 mL (14 to 106) p=0.011
	-50 mL	48 mL (1 to 95) p=0.044	52 mL (5 to 98) p=0.030	55 mL (9 to 102) p=0.019	59 mL (13 to 105) p=0.012	63 mL (17 to 109) p=0.008
	-100 mL	51 mL (4 to 97) p=0.034	54 mL (8 to 101) p=0.022	58 mL (12 to 104) p=0.014	62 mL (15 to 108) p=0.009	65 mL (19 to 111) p=0.006

Note: Missing data with monotone missingness patterns were multiply imputed assuming that missingness was at random among those in the same treatment group and country group, with the same rhDNase use, and with comparable FEV_1 values from screening through Week 26. The imputed values for patients in the DPM group were then shifted by δ_t, while the imputed values for patients in the Control group were instead shifted by δ_c, before analyzing the imputed datasets.
Source: Applicant's Response to FDA Request dated February 13, 2019

While the results for the primary endpoint were statistically significant based on the pre-specified analysis and supported by the sensitivity analyses, the magnitude of the effect size was small, corresponding to approximately 1.2% in terms of percent predicted FEV_1.

Studies 301 and 302

The primary endpoint for each of studies 301 and 302 was identical to that for study 303. While these studies were reviewed during the previous NDA cycle, they are presented here for consideration of the totality of the available efficacy data. During the previous NDA review cycle, the Agency found that the effect sizes estimated using Applicant's prespecified MMRM analysis method were unreliable and likely overestimated due to issues regarding missing data. First, the primary analyses excluded patients who had no post-baseline FEV_1 values. In study 301, the number of such patients was notable with over 10% in DPM group and with about 5% in control group, and these patients withdrew mostly due to adverse events within the first month. Second, the MMRM model assumed that data missingness was at random, such that patients maintained a treatment benefit even after they discontinued from study, likely also discontinuing treatment. The assumption was not supported by trial data. About 37% of the DPM group withdrew from study before 26 weeks, while about 27% of the control group withdrew from study. Last, unlike in study 303, valid use of a treatment policy estimand in these studies for inference was not possible, due to patients being withdrawn from study once they discontinued treatment, with no further data collection that would facilitate the targeting

of this estimand, which is an important consideration from a regulatory viewpoint (see section 3.8 FDA Division Memorandum From January 2013 PADAC Meeting for a summary of the statistical issues). Primary endpoint results based on the Applicant's pre-specified MMRM approach for studies 301 and 302 are summarized in Table 11. Note that this includes patients <18 years of age.

Table 11: Studies 301 and 302, FEV1 Over 26 Weeks, Patients ≥6 Years, No Imputation, MITT

Study 301	**DPM (N=157)**	**Control (N=112)**
Adjusted mean change from baseline	118 mL	35 mL
Adjusted mean difference (95% CI) p-value	83 mL (40 to 127 mL) p<0.001	
Study 302	**DPM (N=177)**	**Control (N=120)**
Adjusted mean change from baseline	107 mL	52 mL
Adjusted mean difference (95% CI) p-value	54 mL (-2 to 110 mL) p=0.059	

Abbreviations: CI=confidence interval; DPM=dry powder mannitol
Note: These results were calculated using data from patients of age ≥6 years. These results reflect "on treatment" estimates, as the studies were not designed to collect data after treatment discontinuation. MITT was defined as all ITT patients who had at least one post-baseline FEV_1 value, and ITT was defined as all randomized who received at least one study medication.
Source: Pulmonary-Allergy Drugs Advisory Committee Meeting January 30, 2013 briefing document, Table 4, p. 14

The results for the primary endpoint for study 302 were not statistically significant; and while the results for the primary endpoint for study 301 were statistically significant, as noted during the previous review cycle, the Applicant's pre-specified primary analysis was problematic due to statistical issues as noted above. Because of these issues, multiple sensitivity analyses were performed. Based on these analyses, significant concerns were raised regarding the robustness of the treatment effect on FEV_1. Moreover, during review and at the previous PADAC (January 30, 2013), additional concerns were raised due to the relatively modest effect sizes observed in studies 301 and 302. This concern played a role in the PADAC's recommendation against approval in the last review cycle. In that context, it is worth noting that the FEV_1 effect size observed in study 303 is numerically smaller than that observed in study 301 and similar to that of study 302.

Studies 301 and 302 – Adults Only (post-hoc)
Because in this review cycle, the Applicant has revised their target patient population to include only patients ≥18 years of age, the Division has performed an analysis in the ≥18-year-old patients from study 301 and 302. With the caveats that the concerns regarding missing data and differential drop-out still apply and given that this is a *post-hoc* analysis, results of ≥18-year-old patients in studies 301 and 302 are summarized in Table 12. Note that randomization in studies 301 and 302 was 3:2 (DPM: control). The PMM model with multiple imputation was used in this analysis, as this was felt to handle missing data most appropriately among the proposed sensitivity analyses from the regulatory and statistical perspective. Furthermore, Huber-White sandwich estimates for the standard errors were used to relax the homoscedasticity assumption in the model fits. These results are generally consistent with

those of the overall population, though the FEV_1 effect size appears somewhat larger. However, it should be noted that given the *post-hoc* nature of this analysis and previously noted issues with studies 301 and 302, interpretation of these results should be guarded.

Table 12: Studies 301 and 302, FEV1 Over 26 Weeks, Pattern Mixture Model with MI, ITT, Patients ≥18 Years

Study 301	DPM (N=124)	Control (N=85)
Adjusted mean change from baseline	93 mL	15 mL
Adjusted mean difference (95% CI) p-value	78 mL (21 to 135 mL)	
Study 302	**DPM (N=97)**	**Control (N=60)**
Adjusted mean change from baseline	75 mL	-2 mL
Adjusted mean difference (95% CI) p-value	78 mL (2 to 153 mL)	

Abbreviations: MI=multiple imputation; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol
Note: For each imputed dataset, a linear regression model was fit, and Huber-White sandwich estimates for the standard errors were used for the confidence intervals.
Source: FDA Statistical Reviewer

In summary, for the primary endpoint, only trials 301 and 303 demonstrated statistically significant treatment effect based on the respective, pre-specified primary analyses. However, as noted above, due to differential drop-out and missing data, results from study 301 for the overall population (≥6-year-olds) were not statistically robust. Additionally, across all studies, the effect size was consistently modest across multiple analyses. Given these observations, other clinically relevant endpoints must be carefully considered in assessing the clinical benefit of DPM.

Data Quality and Integrity

No clear issues were uncovered in data quality or data integrity.

Efficacy Results – Secondary endpoints

The secondary endpoints for study 303 were as follows:

1. FVC change from baseline over 26 weeks
2. Time to 1st PDPE
3. Days on antibiotics (oral, inhaled, intravenous) due to PDPE
4. Days hospitalized due to PDPE
5. Rate of PDPE over 26 weeks
6. CFQ-R respiratory domain score

Secondary endpoints 1-5 (key secondary endpoints) were analyzed in a hierarchical manner such that if the previous endpoint failed to reach statistical significance, the subsequent

endpoints were not considered statistically significant. CFQ-R respiratory domain score was a non-hierarchical secondary endpoint.

FVC over 26 weeks

For the first secondary endpoint of change from baseline in FVC over 26-weeks, there was a 36 mL (95% CI: -15 to 87 mL) difference between the DPM group compared to control, based on the FDA statistician's analysis. This was not statistically significant (p=0.169). Given the hierarchical analysis structure, all subsequent secondary endpoints were not considered statistically significant.

Exacerbation related endpoints

In CF development programs, exacerbation related endpoints, when exacerbation is appropriately defined in the protocol, are considered clinically meaningful and weigh heavily in evaluations of efficacy. In study 303, the definition used for exacerbation for PDPE is appropriate, and statistically significant findings for the PDPE related endpoints would have been considered clinically meaningful.

Results for the primary analyses of PDPE related secondary endpoints for study 303 are summarized in Table 13. As the first hierarchical secondary endpoint failed, none of the PDPE related endpoints can be considered statistically significant. The analyses for these endpoints were performed according to the prespecified primary analysis methods described in the SAP for study 303. This includes the prespecified imputation procedure in the analysis for PDPE rate, for patients who withdrew from the study with no observed PDPEs. The results in Table 13 are consistent with results presented in the Applicant's clinical study report for this study.

Table 13: Study 303, Exacerbation Related Secondary Endpoints, ITT, Treated

Secondary Endpoint	DPM (N=209)	Control (N=214)	Ratio	95% CI
Time to 1st PDPE			HR: 1.14	0.67 to 1.94
Days on antibiotics (oral, inhaled, IV) due to PDPE	6.0 days	7.9 days	ARR: 0.75	0.20 to 2.85
Days in hospital due to PDPE	1.2 days	0.9 days	ARR: 1.27	0.32 to 5.15
PDPE rate per patient per year (Rate of PDPE over 26 weeks)‡	0.349	0.226	ARR: 1.55	0.99 to 2.41

Abbreviations: ITT=intention to treat: all subjects randomized; HR=hazard ratio; ARR=adjusted rate ratio; DPM=dry powder mannitol; PDPE=protocol defined pulmonary exacerbations; IV=intravenous; CI=confidence interval
‡ This analysis implemented the imputation procedure prespecified for the primary analysis in the statistical analysis plan for study 303 for patients who withdrew from study with no PDPE.
Note: Only treated patients are included in the statistical analysis using negative binomial model.
Source: FDA Statistical Reviewer

Results across all exacerbation related endpoints were consistent in that none were statistically significant, and 95% CIs included the null for all parameters. For time to first exacerbation and days in hospital due to exacerbation, results do not suggest a clinical benefit, with a hazard ratio (HR) and adjusted rate ratio (ARR) of 1.1 and 1.3, respectively, and 95% CIs that contain the null value of 1. For PDPE rate, rates also trended higher for DPM patients compared to control, with a 95% CI lower limit near 1 [adjusted rate ratio 1.55 (95% CI 0.99, 2.41)]. For days on antibiotics, the point estimate for the rate ratio is <1. However, the 95% CI was wide and contained the null value of 1. It is also worth noting that the difference in number of days between DPM and control for antibiotics (6 versus 8 days) are minimal. Moreover, in the clinical care of patients with CF, choices regarding length of antibiotic treatment are often based on factors outside of a patient's clinical status.

The prespecified imputation procedure for the primary analysis of PDPE rate assumed that patients with no observed PDPEs who withdrew from the study before Week 26 would have PDPE rates after study withdrawal similar to their historical (prior 12 months) pulmonary exacerbation rate. However, because this was a single imputation approach, the resulting confidence intervals and p-values may have overestimated the precision in parameter estimation. Because of this, a *post-hoc* analysis of PDPE rate was performed using a Pattern Mixture Model multiple imputation procedure.

In this analysis, for each patient who withdrew from the study before Week 26, the number of PDPEs between the time of withdrawal and Week 26 was imputed. There were two imputation models used: (1) one for patients who withdrew from the study due to adverse events, death, physician decision, or lack of efficacy, to be applied regardless of treatment arm; and (2) one for patients who withdrew from the study due to other reasons, to be applied to each treatment arm separately. Each imputation model included as covariates rhDNase use and country group. However, the former model assumed that the number of imputed PDPEs would follow a rate similar to historical (prior 12 months) pulmonary exacerbation rates of comparable patients, while the latter model assumed that the number of imputed PDPEs would follow a rate similar to the PDPE rate of comparable study completers within the same treatment arm. The results in Table 14 were computed from one thousand such imputed datasets.

Table 14: Study 303, PDPE Rate, PMM, ITT

	Study 303	
	DPM (N=209)	Control (N=214)
PDPE Rate		
Adjusted Rate	0.27	0.20
Adjusted Rate Ratio (95% CI)	1.35 (0.81 to 2.26)	

Abbreviations: PDPE=Protocol Defined Pulmonary Exacerbation; PMM=Pattern Mixture Model; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol
Source: Applicant's Response to FDA Request dated May 21, 2019

With this analysis, the adjusted rate ratio for PDPE rate is estimated to be 1.35, when comparing DPM to control. The data are consistent with the adjusted rate ratio being between 0.81 and 2.26. The results of this *post-hoc* analysis are somewhat consistent with the results of the prespecified primary analysis.

Taken as a whole, the exacerbation data are not supportive of efficacy, with the majority of the exacerbation related endpoints trending in favor of control.

Studies 301 and 302 also include PDPE rate as a secondary endpoint. The definition used for exacerbation was the same as in study 303. Results from studies 301 and 302 provide context for the study 303 exacerbation related results. Of note, these analyses from 301 and 302 suffered from the same issue as the Applicant's primary analyses for the primary endpoint, as they were done without accounting for the unequal differential drop out of patients seen in studies 301 and 302. The adjusted rate ratio for PDPE rate per person per year in patients ≥6 years of age (ITT) was 0.74 (0.47,1.18) for study 301 and 0.95 (0.57,1.58) for study 302; however, the numerical difference in exacerbation rate between DPM and control could be a result of the differential early discontinuation rates. Other exacerbation related secondary endpoints were included in studies 301 and 302, however, these data are not presented as there was no correction for multiplicity and results were consistent with PDPE rate (adjusted odds/rate ratios with 95% CI including null). Given the focus on adults, an analysis of this subpopulation for studies 301 and 302 for PDPE rate is presented (Table 15).

Table 15: Studies 301 and 302, Adjusted PDPE Rate per Person per Year, No Imputation, ITT, Treated, Patients ≥18 Years

Study 301	**DPM (N=114)**	**Control (N=76)**
Mean rate	0.73	0.95
Adjusted rate ratio (95% CI)	0.77 (0.47 to 1.26)	
Study 302	**DPM (N=93)**	**Control (N=58)**
Mean rate	0.32	0.24
Adjusted rate ratio (95% CI)	1.35 (0.56 to 3.24)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol
Note: Only treated patients are included in the statistical analysis using negative binomial model.
Source: FDA Statistical Reviewer

While for studies 301 and 302, adjusted rate ratios for PDPE had point estimates of <1 in the overall populations and for the adult population in study 301, given the noted statistical issues with studies 301 and 302, interpretation is confounded. As such one cannot make definitive conclusions, other than that these exacerbation data from studies 301 and 302 are not clearly supportive of efficacy.

To summarize, based on the exacerbation related endpoint results, none of the three studies provide strong supportive evidence for efficacy. In fact, some of the exacerbation endpoints in study 303 show a negative numerical trend on exacerbation effect in DPM treated patients.

CFQ-R respiratory domain score

The CFQ-R is a patient reported outcome that captures quality of life information for CF patients. The respiratory domain specifically assesses for respiratory symptoms. The CFQ-R respiratory domain (CFQ-RRD) score is used commonly in clinical studies evaluating CF therapies and has been included in approved labeling for some CF products.

In Study 303, while the CFQ-RRD score increased in DPM patients (0.308) and decreased in control patients (-0.562), the difference was neither statistically nor clinically meaningful based on the SAP-specified analysis. The difference between DPM and control treated patients was 0.87 (95% CI: -1.4, 3.1, p=0.53).

These CFQ-RRD data are consistent with that observed in study 301 and 302, where there were no statistically significant differences between DPM and control treated patients. CFQ-RRD data across all three studies are not supportive of a treatment benefit.

In summary, results across all the reviewed secondary endpoints are consistent in that none demonstrated a statistically significant benefit of DPM over control. These secondary endpoint results do not provide additional support for efficacy.

Dose/Dose Response

Dose response was not evaluated in study 303, and dose exploration and dose ranging studies were reviewed in the prior review by Dr. Kimberly Witzmann dated February 11, 2013. Briefly, study 202 served as a pivotal dose ranging study and demonstrated the 400mg dose twice daily to have the largest effect and a 40mg dose twice daily to have no effect or slight worsening. In light of the absent response with the 40mg twice daily dose, 50 mg twice daily was chose as control for the phase 3 studies, in order to match the sweet taste of mannitol.

Durability of Response

As CF is a chronic condition and DPM would be a chronic therapy, efficacy data should support that the treatment benefit is durable over time. As noted in Section 8.1.1 of this review, the primary efficacy endpoint of Change from Baseline Over 26 Weeks in FEV_1 puts a weight of 83% on change occurring during the first 14 weeks of the 26-week period, and a weight of only 17% on change occurring during the last 12 weeks of the 26-week period.

Therefore, to assess durability of response, the FEV_1 effect was assessed using landmark analyses (e.g. change from baseline at the end of the 26-week treatment period). In study 303, the change from baseline in FEV_1 at 26 weeks was such that the 95% CI included the null, and the observed treatment effect size was numerically lower in magnitude than that for the primary endpoint and for FEV_1 at the Week 6 and Week 14 timepoints. These data from study 303 suggest that the FEV_1 effect may lack durability. A similar *post-hoc* analysis was performed for adults in studies 301 and 302. In contrast to study 303, in studies 301 and 302, such a

waning of effect over time was not observed. Change from baseline in FEV_1 at weeks 6, 14, and 26 in patients ≥18 years are summarized in Table 16.

Table 16: Studies 301, 302, and 303, FEV1 at Weeks 6, 14, and 24. Pattern Mixture Model with MI, ITT, Patients ≥18 Years

Week	FEV_1	Study 301		Study 302		Study 303	
		DPM N=124	Control N=85	DPM N=97	Control N=60	DPM N=209	Control N=214
Week 6	Change from baseline, mean	115 mL	64 mL	117 mL	29 mL	78 mL	18 mL
	Difference 95% CI	51 mL (-13 to 115 mL)		88 mL (15 to 161 mL)		60 mL (11 to 109 mL)	
Week 14	Change from baseline, mean	86 mL	-2 mL	50 mL	7 mL	72 mL	17 mL
	Difference 95% CI	88 mL (14 to 163 mL)		43 mL (-42 to 129 mL)		56 mL (2 to 109 mL)	
Week 26	Change from baseline, mean	78 mL	-18 mL	60 mL	-42 mL	38 mL	0 mL
	Difference 95% CI	95 mL (13 to 178 mL)		102 mL (-16 to 219 mL)		39 mL (-18 to 96 mL)	

Abbreviations: MI=multiple imputation; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; FEV_1=forced expiratory volume in one second
Note: For each imputed dataset, a linear regression model was fit, and Huber-White sandwich estimates for the standard errors were used for the confidence intervals.
Source: FDA Statistical Reviewer

Using an "on-treatment" approach for study 303, results at week 6, week 14, and week 26 for change from baseline in FEV_1 were similar.

Persistence of Effect

There are no data to support a persistence of effect after treatment discontinuation. Also, given the known MOA and pharmacokinetics of DPM, it is not considered likely that an effect would persist after treatment discontinuation.

Efficacy Results – Exploratory COA (PRO) endpoints

Refer to CFQ-RRD section in the above *Efficacy Results - Secondary Endpoint* section. No other clinically relevant PRO endpoints are noted in phase 3 studies.

Additional Analyses Conducted on the Individual Trial

Subpopulations:

U.S. versus non-U.S.: FEV_1

Additional analyses were performed for subgroups of patients according to whether they were or were not from U.S. sites. These *post-hoc* analyses were undertaken because the U.S. population is ultimately the population of interest, and it is possible that regional differences in standard of care could impact the treatment effect. It appears that the effect size in terms of FEV_1 over 26 weeks in the U.S. population is somewhat numerically larger than that observed in the non-U.S. population, however, the magnitude remains modest, and it may be due to decreases in the control group. As these were *post-hoc* analyses on a relatively small subset of patients, the ability to make definitive conclusions is limited. These data are summarized in Table 17

Table 17: Study 303, FEV1 Over 26 Weeks by Region, BOCF Imputation Using Dropout Reason, ITT

U.S. Population	DPM (N=57)	Control (N=59)
Adjusted mean change from baseline	57 mL	-11 mL
Adjusted mean difference (95% CI)	68 mL (-21 to 156 mL)	
Non-U.S. Population	**DPM (N=152)**	**Control (N=155)**
Adjusted mean change from baseline	77 mL	27 mL
Adjusted mean difference (95% CI)	50 mL (-3 to 104 mL)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; FEV_1=forced expiratory volume in one second; BOCF=baseline observation carried forward
Note: Results were calculated using the primary analysis model, except that an interaction term between treatment and region was included. These results reflect "on study" estimates, as they include data collected after treatment discontinuation.
Source: FDA Statistical Reviewer

A similar *post-hoc* subgroup analysis was performed for the subgroup of adult patients from U.S. sites from study 302. This analysis was not performed for study 301, as study 301 was entirely non-U.S. As in study 303, the effect size in terms of FEV_1 over 26 weeks in the U.S. population is somewhat larger to that observed in the non-U.S. population. This is summarized in Table 18.

Table 18: Study 302, FEV_1 Over 26 Weeks by Region, Pattern Mixture Model with MI, ITT, Patients ≥18 Years

U.S. Population	DPM (N=57)	Control (N=36)
Adjusted mean change from baseline	63 mL	-21 mL
Adjusted mean difference (95% CI)	84 mL (-1 to 169 mL)	
Non-U.S. Population	**DPM (N=40)**	**Control (N=24)**
Adjusted mean change from baseline	87 mL	19 mL
Adjusted mean difference (95% CI)	68 mL (-69 to 206 mL)	

Abbreviations: MI=multiple imputation; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; FEV_1=forced expiratory volume in one second
Note: Results were calculated using the original Pattern Mixture Model, except that an interaction term between treatment and region was included.
Source: FDA Statistical Reviewer

These results are consistent with the primary analysis, but may also suggest that the FEV_1 effect size in both the U.S. population may be somewhat larger in magnitude compared to non-U.S. population, however, it is still modest in magnitude. As these were *post-hoc* subgroup analyses in a relatively small subset of patients, the ability to make any definitive conclusion is limited.

U.S. versus non-U.S.: Exacerbation

Given that the subgroup analyses suggested a potential larger effect size in U.S. patients in terms of FEV_1, *post-hoc* analyses of the U.S. and non-U.S. population were also performed for each of the exacerbation related secondary endpoints for study 303. These results are summarized in Table 19.

Table 19: Study 303, Exacerbation Related Secondary Endpoints, by Region and Overall, ITT, Treated

Endpoint	U.S. Population		Non-U.S. Population		Overall	
	DPM (N=56)	Control (N=59)	DPM (N=151)	Control (N=155)	DPM (N=207)	Control (N=214)
Time to first PDPE, HR (95% CI)	2.02 (0.78 to 5.22)		0.87 (0.46 to 1.66)		1.14 (0.67 to 1.94)	
# Days on antibiotics due to PDPE, ARR (95% CI)	0.96 (0.09 to 10.51)		0.70 (0.15 to 3.09)		0.75 (0.20 to 2.85)	
# Days in hospital due to PDPE, ARR (95% CI)	1.39 (0.10 to 18.67)		1.24 (0.27 to 5.78)		1.27 (0.32 to 5.15)	
PDPE rate, ARR (95% CI)‡	2.93 (1.36 to 6.32)		1.06 (0.61 to 1.86)		1.55 (0.99 to 2.41)	
PDPE rate, ARR (95% CI)*	2.29 (0.89 to 5.89)		1.05 (0.56 to 1.97)		1.35 (0.81 to 2.26)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; PDPE=protocol defined pulmonary exacerbations; HR=hazard ratio; ARR=adjusted rate ratio
Note: Only treated patients are included in the statistical analysis using a negative binomial model. To get by-region estimates, the model was refit with the addition of an interaction term between treatment and region.
‡ This analysis implemented the imputation procedure prespecified for the primary analysis in the statistical analysis plan for study 303 for patients who withdrew from study with no PDPE.
* This post-hoc analysis implemented the same Pattern Mixture Model multiple imputation procedure as for the analysis used to generate results for Table 14.
Sources: FDA Statistical Reviewer and Applicant's Response to FDA Request dated May 21, 2019

Contrary to the FEV_1 data, for all exacerbation related endpoints, the response was numerically worse in the U.S. versus non-U.S. population. This was most notable for PDPE rate, where in the prespecified primary analysis the adjusted rate ratio doubled to 2.93 with a 95% CI that excluded the null. When a similar analysis was performed for study 302 for PDPE rate and time to first PDPE in adult patients, results were similar, in that the response was numerically worse in U.S. adult patients compared to non-U.S. adult patients, though the 95% CIs did not exclude the null. Similar trends were observed in an additional analysis of PDPE rate in study 303 that incorporated a Pattern Mixture Model multiple imputation approach. As noted previously, as these are *post-hoc* analyses in a relatively small subset of patients, the ability to make definitive conclusions is limited.

U.S. versus non-U.S.: CFQ-R Respiratory domain (CFQ-RRD) score

A *post-hoc* subgroup analysis was also performed on the CFQ-RRD score for U.S. versus non-U.S. population. Results were consistent with the exacerbation subgroup analyses with a

numerically diminished treatment effect in the U.S. population. These data are summarized in Table 20. The difference in change from baseline in CFQ-RRD score for DPM versus control in U.S. patients was negative suggesting worsening of symptoms, whereas for non-U.S. patients this difference was positive. However, as these are *post-hoc* analyses in a relatively small subset of patients, the ability to make definitive conclusions is limited.

Table 20: Study 303, Change in CFQ-R Respiratory Domain Scores, by Region and Overall, ITT

CFQ-RRD	U.S. Population		Non-U.S. Population		Overall	
Endpoint	DPM (N=56)	Control (N=59)	DPM (N=151)	Control (N=155)	DPM (N=207)	Control (N=214)
Adjusted mean change from baseline	-1.79	1.01	1.20	-1.05	0.36	-0.54
CFQ-R respiratory domain score difference (95% CI)	-2.80 (-7.21 to 1.61)		2.25 (-0.41 to 4.91)		0.90 (-1.38 to 3.19)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; CFQ-R=Cystic Fibrosis Questionnaire–Revised
Note: By-region results were calculated by refitting the primary analysis model with the addition of an interaction term between treatment and region.
Source: FDA Statistical Reviewer

Subgroup analysis limitations notwithstanding, taken as a whole, the subgroup analyses of U.S. versus non-U.S. patients does not offer additional support for efficacy in terms of FEV_1, CFQ-RRD, and exacerbation, and may raise some safety concern given the exacerbation results.

Other subpopulations

The sample estimates of the treatment effect in change from baseline in FEV_1 over 26 weeks among subgroups (specifically, age, gender, region, rhDNase use, and percent predicted FEV_1) were based on a linear regression model using Huber-White sandwich estimates, adjusting for treatment effect. There were some random highs and random lows in sample estimates of subgroup treatment effects due to the number of subgroups considered and the large variability for some subgroups. This review includes shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates, i.e., the estimated mean change from baseline in FEV_1 over 26 weeks comparing DPM to control, is the sum of the within-subgroup variability of the sample estimator and the across-subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The same flat prior was used to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i \in \{1, 2, \ldots\}$, Y_i represents the estimated mean change from baseline in FEV_1 over 26 weeks in a subgroup level i, assuming the distribution of Y_i is approximately $N(\mu_i, \sigma_i^2)$, where

- σ_i^2 is the estimated variance of the change from baseline in FEV_1 over 26 weeks in subgroup level i
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 200^2), \frac{1}{\tau^2} \sim Gamma(0.001, 0.001)$

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups, are presented in Table 21. The sample sizes were not sufficient to conduct multi-way subgroup analyses. Therefore, results were presented for marginal subgroups. These subgroup analysis results by demographic subgroups were largely consistent with findings in the overall population, based on change from baseline in FEV_1 over 26 weeks.

Table 21. Subgroup Analysis for Age, Gender, Region, rhDNase Use, and Percent Predicted FEV_1, for Change from Baseline in FEV_1 (mL) Over 26 Weeks

Subgroup	N	Sample Treatment Effect Estimate (95% CI)	Shrinkage Treatment Effect Estimate (95% PI)
Overall	423	51 (6 to 97)	--
At Least Median Age	230	65 (9 to 120)	56 (11 to 102)
Below Median Age	193	37 (-41 to 115)	53 (3 to 102)
Female	199	-15 (-65 to 36)	-1 (-56 to 54)
Male	224	110 (37 to 183)	83 (-3 to 168)
US	116	59 (-27 to 145)	52 (-2 to 105)
Non-US	307	48 (-6 to 103)	51 (3 to 98)
rhDNase Use	286	27 (-26 to 79)	40 (-9 to 90)
No rhDNase Use	137	103 (12 to 195)	58 (-13 to 129)
Percent Predicted $FEV_1 \geq 50\%$	326	31 (-20 to 82)	43 (-5 to 90)
Percent Predicted $FEV_1 < 50\%$	97	122 (18 to 227)	65 (-18 to 148)

Abbreviations: CI = confidence interval; PI=prediction interval
[Source: Statistical Reviewer]

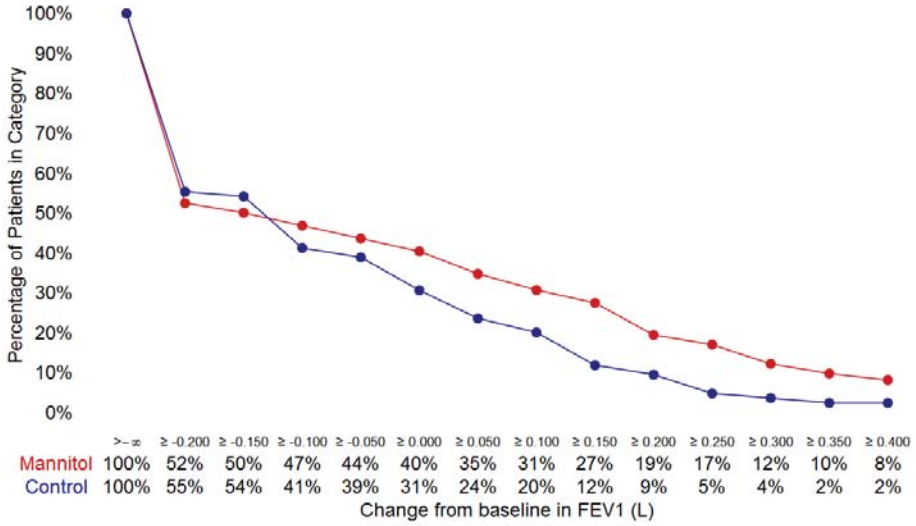
Subgroup analyses were also performed based on similar parameters for studies 301 and 302.

Continuous Responder Analyses:

To thoroughly evaluate the treatment response in the setting of the significant dropout related statistical issues for the prior studies, continuous responder analyses were performed for studies 301, 302, and 303 (Figure 3, Figure 4, Figure 5, Table 22). These analyses included only those patients ≥18 years of age given the Applicant's target population. For each analysis, a patient is classified as having been successfully or unsuccessfully treated according to a specific threshold for the change from baseline in FEV_1 at week 26, in this case from -200 to +400 mL. The x-axis displays the thresholds required to classify a subject as a successfully treated subject while

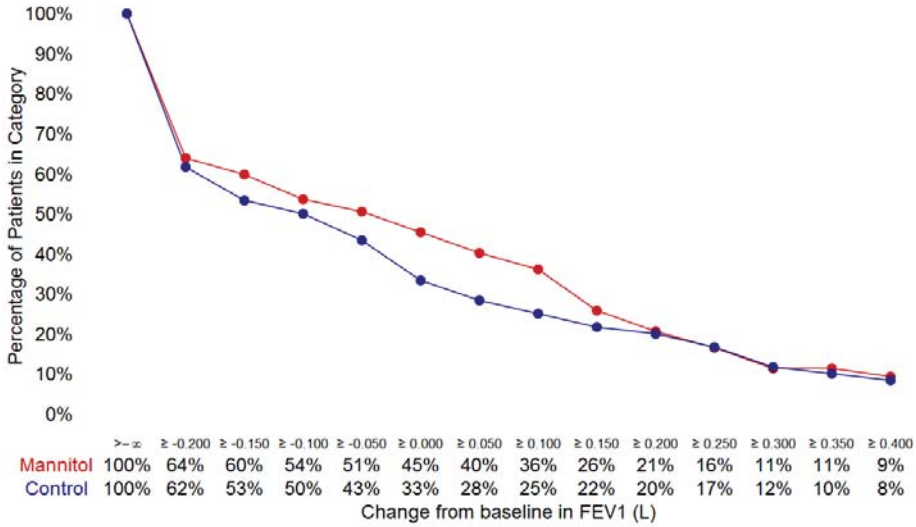
the y-axis represents the proportion of ITT subjects who achieved the corresponding threshold. The proportion of DPM treated patients achieving each threshold is represented by the red line and proportion of control subjects by the blue line.

Figure 3: Study 301 Continuous Responder Analysis, Patients ≥18 Years, ITT



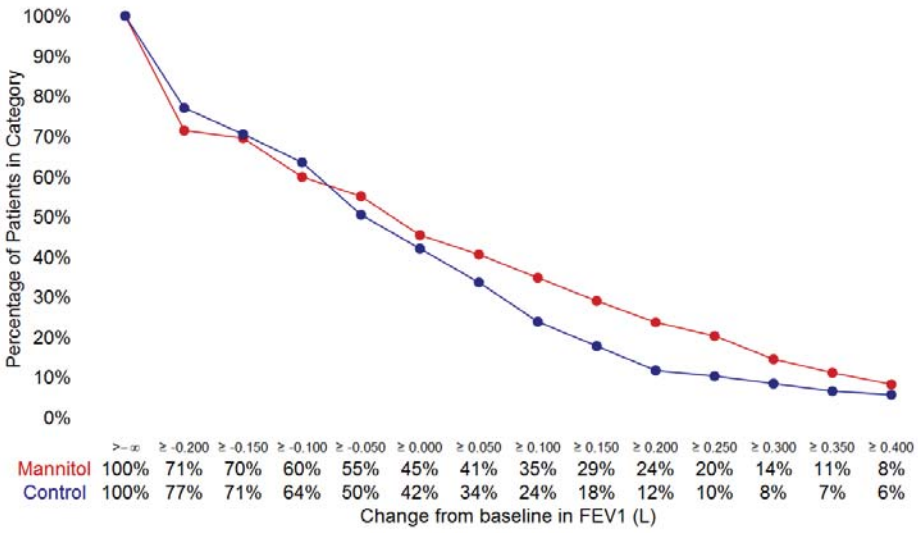
Abbreviations: ITT=intention to treat: all subjects randomized
Source: FDA Statistical Reviewer

Figure 4: Study 302 Continuous Responder Analysis, Patients ≥18 Years, ITT



Abbreviations: ITT=intention to treat: all subjects randomized
Source: FDA Statistical Reviewer

Figure 5: Study 303 Continuous Responder Analysis, ITT



Abbreviations: ITT=intention to treat: all subjects randomized
Source: FDA Statistical Reviewer

In studies 301 and 302, there is an initial sharp drop from 100% to approximately 50-60% in the y-axis corresponding to the proportion of patients who dropped out or whose FEV_1 change from baseline was a decrease of more than 200 mL. This was not as pronounced for study 303. After the initial drop, some separation between groups is evident. The DPM group has a numerically higher proportion of patients who achieve the increasing change from baseline in FEV_1 thresholds than does the control group [red line (DPM) generally lies above the blue line (control)]. This numerical difference is sustained in the 301 and 303 curves, however for 302, at the higher cut-offs, the lines converge. For many of the thresholds across all three studies, the 95% CI for the odds ratio of DPM to control groups included the null (see Table 22 for the 50, 75, 100, 200, 300, and 400 mL thresholds). As such, these continuous responder analyses, while generally consistent with the primary analyses for their respective studies, do not provide additional support for efficacy.

Table 22: Studies 301, 302, and 303, Responder Analyses, ITT, Patients ≥18 Years

Study	Threshold	DPM	Control	Adjusted Odds Ratio (95% CI)
Study 301		N=124	N=85	
	50 mL	43 (34.7%)	20 (23.5%)	1.67 (0.89 to 3.20)
	75 mL	40 (32.3%)	18 (21.2%)	1.71 (0.90 to 3.37)
	100 mL	38 (30.6%)	17 (20.0%)	1.70 (0.88 to 3.40)
	200 mL	24 (19.4%)	8 (9.4%)	2.23 (0.97 to 5.63)
	300 mL	15 (12.1%)	3 (3.5%)	3.62 (1.14 to 16.07)
	400 mL	10 (8.1%)	2 (2.4%)	3.42 (0.85 to 22.86)
Study 302		N=97	N=60	
	50 mL	39 (40.2%)	17 (28.3%)	1.72 (0.86 to 3.54)
	75 mL	37 (38.1%)	15 (25.0%)	1.86 (0.92 to 3.92)
	100 mL	35 (36.1%)	15 (25.0%)	1.70 (0.83 to 3.58)
	200 mL	20 (20.6%)	12 (20.0%)	1.03 (0.46 to 2.38)
	300 mL	11 (11.3%)	7 (11.7%)	0.97 (0.35 to 2.84)
	400 mL	9 (9.3%)	5 (8.3%)	1.13 (0.36 to 3.93)
Study 303		N=209	N=214	
	50 mL	84 (40.6%)	72 (33.6%)	1.35 (0.91 to 2.01)
	75 mL	76 (36.7%)	62 (29.0%)	1.43 (0.95 to 2.15)
	100 mL	72 (34.8%)	51 (23.8%)	1.71 (1.12 to 2.63)
	200 mL	49 (23.7%)	25 (11.7%)	2.36 (1.40 to 4.05)
	300 mL	30 (14.5%)	18 (8.4%)	1.86 (1.01 to 3.51)
	400 mL	17 (8.2%)	12 (5.6%)	1.51 (0.71 to 3.32)

Abbreviations: CI=confidence interval; DPM=dry powder mannitol, ITT=intention to treat: all subjects randomized
Source: FDA Statistical Reviewer

Integrated Review of Effectiveness

This review focuses mainly on study 303. As noted in the prior sections, the prior review cycle dealt with studies 301 and 302 however problems raised in that cycle were such that the target population was changed to adults only. As noted in the regulatory history, the Applicant was asked to submit one additional study, a "tie breaker" study, and resubmit.

As noted in the above efficacy sections, results from studies 301 and 302 from the prior review cycle were discussed for context in addition to study 303. As this review focuses mainly on study 303 as the most recently submitted study in the current review cycle, but draws on post-hoc analyses from studies 301 and 302, a separate integrated review of effectiveness for study 303 is not present. Please refer to section 8.1.3.

8.1.3. Integrated Assessment of Effectiveness

The evaluation of efficacy in the ≥18-year-old population is based on three phase 3 studies (301, 302, and 303), two of which (301 and 302) were reviewed in the previous NDA cycle. Studies 301 and 302 included patients ≥6 years of age, and study 303 included patients ≥18 years of age. Based on the Applicant's pre-specified analyses, results from 302 did not achieve statistical significance in the overall population for the primary endpoint of change from baseline in FEV_1 over 26-weeks, whereas studies 301 (overall population) and 303 did. However, study 301 results are complicated by the extent of differential missing data due to differential drop-out raising concerns regarding the statistical robustness of the results. For the ≥18-year-old population in studies 301 and 302, while *post-hoc* analyses may have suggested a treatment effect in terms of FEV_1, these were *post-hoc* analyses of a trial that lost (302) and a trial with significant statistical issues (301). Moreover, regardless of the analysis used, the treatment effect size across all studies was modest. Additionally, the durability of the treatment effect, an important consideration for medication intended for chronic use, as assessed by landmark analyses at 26 weeks in study 303, was not supportive, with results suggesting a decrease in the already modest treatment effect size at 26-weeks versus earlier timepoints. Given the above, secondary endpoints were evaluated for additional support for efficacy.

The exacerbation and symptom related secondary endpoints, across all three phase 3 studies, offered little support for efficacy. In no cases were differences between DPM and control statistically significant. Additionally, in the most statistically robust study (303), for the majority of these endpoints (time to first PDPE, days hospitalized for PDPE, PDPE rate) results numerically favored control over DPM. Additionally, in subgroup analyses of U.S. patients, these unfavorable trends were accentuated.

In summary, while studies 301 (overall population) and 303 achieved statistically significant results for the FEV_1 primary endpoint based on the Applicant's pre-specified analysis, due to missing data and patient drop-out issues, interpretation of study 301 is complicated. Additionally, while *post-hoc* analyses of patients ≥18 years of age from studies 301 and 302 may suggest a treatment effect in terms of FEV_1, these were *post-hoc* analyses of a trial that lost (302) and a trial with significant statistical issues (301). Moreover, the treatment effect size is modest across all studies. Importantly, these modest in magnitude "wins" on the primary spirometric endpoint are not supported by the exacerbation or symptom related secondary endpoint measures in any of the phase 3 studies. As such, in the opinions of the primary clinical reviewer and statistical reviewer, these data do not provide substantial support for efficacy for this product in the indicated population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The assessment of safety is primarily based on data from the double-blind phase (DBP) of studies 301, 302; and study 303, in patients who were randomized and received at least one dose of study drug. Studies 301 and 302 included patients ≥6 years of age and study 303 included patients ≥18 years of age. As the proposed indication includes only those ≥18 years of age, this document only reviews and presents safety data from the ≥18-year-old population in these studies. While safety data from studies 301 and 302 were reviewed in the previous NDA cycle, that review did not include separate analyses of the ≥18-year-old subgroup. As such it is presented here. Long term safety is supported by the 52 and 26 -week open label extension phases (OLP) of studies 301 and 302, respectively; study 303 lacked an extension phase. The DBP of studies 301, 302, and 303 were very similar in design and study population. Therefore, these studies were pooled for safety analysis.

8.2.2. Review of the Safety Database

Overall Exposure

In the phase 3 studies, 414 patients were exposed to DPM 400 mg BID and 347 patients to control during the DBP with a median exposure of approximately 6 months across studies (mean range 4-6 months). Of the 207 patients who received DPM in studies 301 and 302, 130 patients continued receiving DPM in the OLP. Of the 134 control patients, 94 switched to DPM in the OLP. The median exposure in the OLP was an additional 6 months (mean range: 5.9-6.6). Exposure data during the DBP are summarized in Table 23.

Table 23: Studies 301, 302, and 303 Pooled, Overall Exposure, Double Blind Phase Only, Patients ≥18 Years

Exposure (Months)	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Mean (SD)	5.1 (2.1)	5.4 (1.8)
Median (min, max)	6 (0, 7.8)	6 (0, 7.8)
Duration		
≤1	40 (9.7)	20 (5.8)
>1–2	26 (6.3)	14 (4)
>2–3	12 (2.9)	8 (2.3)
>3–4	14 (3.4)	19 (5.5)
>4–5	6 (1.4)	7 (2)
>5–6	112 (27.1)	93 (26.8)
>6	204 (49.3)	186 (53.6)

Abbreviations: SD=standard deviation; DPM=dry powder mannitol
Source: SCS; Table 11, p.36

While mean and median exposures were similar between DPM and control groups, a higher percentage of DPM patients had durations of exposure of ≤3 months compared to control patients. This is likely reflective of the differential and early drop-out observed in studies 301 and 302 previously reviewed and may suggest tolerability issues. However, it is worth noting that in study 303, this was not observed.

Adequacy of the safety database:

Given the disease, the safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The sponsor provides assurance that GCP training sessions were provided to the study staff at all sites. No issues were noted regarding data integrity or submission quality.

Categorization of Adverse Events

The definitions used for adverse events (AEs) and serious AEs (SAEs) were per 21 CFR 312.32. Treatment emergent AEs (TEAEs) were defined as AEs that occurred from treatment day 1 until 28 days after last study drug. AEs that started after the MTT but worsened on or after treatment day 1 were categorized as TEAEs even if they began prior to treatment day 1. AEs that began after the MTT but ended prior to treatment day 1 were not considered in this review.

AEs were originally coded using MedDRA v 9.1 for study 301, v 11.0 for study 302, and v 11.1 for study 303; re-coding of the earlier studies 301 and 302 was done to MedDRA v 11.1. The only exception to this was for pulmonary exacerbations. These were coded to 'exacerbation of disease' LLT linked to PT 'condition aggravated' according to MedDRA version 9.0, to maintain consistency with studies 301 and 302.

Investigators made causality and severity assessments.

Severity assessments were as follows:

- Mild: The patient had an awareness of a sign or symptom, but it was easily tolerated and did not alter normal activity;
- Moderate: The sign or symptom caused discomfort and/or interference with the patient's usual activity;
- Severe: The sign or symptom caused significant impairment of function or incapacitation, and/or the patient was unable to perform usual activities.

Routine Clinical Tests

Sputum microbiology and other standard labs (CBC, BMP, kidney and liver function assessments, electrolytes) were performed at screening and per the schedule of assessments (Figure 1).

8.2.4. Safety Results

Deaths

There were two deaths in the phase 3 studies; both in the control groups during the DBP for studies 302 and 303. Only one of these deaths was in a patient ≥18 years of age.

In study 303, one death occurred in the control arm in a 19-year-old Caucasian male diagnosed with CF at the age of 13. His screening FEV_1 was 48% predicted. The adverse event that lead to death was exacerbation (preferred term: condition aggravated). This occurred 219 days after the first dose of the control and 3 days after last dose.

In study 302, one death occurred in the control arm in a 15-year-old male diagnosed with CF at the age of 1. His screening FEV_1 was 36% predicted. The patient experienced a pneumothorax 135 days after the first dose of the control. The pneumothorax did not resolve, and the patient underwent partial pneumonectomy with subsequent pleurodesis. His clinical status continued to worsen, and he underwent lung transplant but ultimately died due to multiple organ failure 3 months after study drug was discontinued.

In study 301, there were no deaths during the course of the study. There were no deaths

during the OLP of the two phase 3 studies (301 and 302).

Given that the deaths occurred in the control group, these deaths do not raise safety concerns for DPM.

Serious Adverse Events

During the DBP of studies 301, 302, and 303, in patients ≥18years of age, approximately 18% of DPM and control patients experienced SAEs. The types of SAEs reported were generally consistent with the study population. CF exacerbation (reported as condition aggravated) was the most commonly reported SAE. SAE data are summarized in Table 24.

Table 24: Studies 301, 302, and 303 Pooled, Serious Adverse Events in ≥1% of Patients, Patients ≥18 Years

SOC/PT	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Any SAE	78 (18.8)	64 (18.4)
General disorders and administration site conditions	55 (13.3)	39 (11.2)
CF exacerbation (condition aggravated)	55 (13.3)	39 (11.2)
Infection and infestations	12 (2.9)	14 (4)
Pneumonia*	8 (1.9)	11 (3.2)
Respiratory, thoracic, and mediastinal disorders	9 (2.2)	7 (2)
Hemoptysis	6 (1.4)	4 (1.2)
Gastrointestinal disorders[a]	6 (1.4)	9 (2.6)
Surgical and medical procedures[b]	4 (1)	0

Abbreviations: SOC=system organ class, PT=preferred term, DPM=dry powder mannitol, SAE=serious adverse event, CF=cystic fibrosis

* Combined terms: Lower respiratory tract infection, pneumonia, lung infection, lobar pneumonia, lung infection pseudomonal, pneumonia bacterial

[a] Acute pancreatitis, intestinal obstruction, and abdominal pain terms account for majority of SOC counts noted

[b] Central venous catheterization accounts for majority of SOC count noted

Source: SCS, Table 38, p.100

In general, while there were some numerical differences in SAEs between DPM and control groups, these were small in magnitude; less than a 1% difference between arms (unless control arm was higher), with the only exception CF exacerbations (DPM 2% higher than control). This observation is somewhat consistent with the efficacy results regarding protocol defined pulmonary exacerbations (PDPE), where across multiple PDPE related endpoints trends favored control. Results from the OLP portion of studies 301 and 302 were generally consistent with the DBP results. As hemoptysis had been raised as a safety concern in the prior review cycle, it

is worth noting that in the analysis of SAEs in patients ≥18 years of age, the difference between DPM and control groups for hemoptysis was small, though still numerically higher in DPM. A more in-depth discussion of hemoptysis and exacerbations can be found in Section 3.6.8.

Dropouts and/or Discontinuations Due to Adverse Effects

During the DBP of studies 301, 302, and 303, in patients ≥18years of age, approximately 11% of DPM and control patients discontinued treatment due to AEs. The types of AEs that resulted in discontinuation were consistent with the known airway effects of inhaled mannitol and the disease state. Cough and CF exacerbation were the most commonly reported AEs that resulted in treatment discontinuation. These data are summarized in Table 25.

Table 25: Studies 301, 302, and 303 Pooled, AEs Leading to Permanent Treatment Discontinuation, >2 Patients in Any Arm, Patients ≥18 Years

SOC/PT	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Any TEAE leading to treatment discontinuation	51 (12.3)	30 (8.6)
Respiratory, thoracic, and mediastinal disorders	35 (8.5)	18 (5.2)
Cough	21 (5.1)	9 (2.6)
Hemoptysis	7 (1.7)	4 (1.2)
Wheezing	1 (0.2)	3 (0.9)
General disorders and administration site conditions	18 (4.3)	12 (3.5)
CF exacerbation (condition aggravated)	13 (3.1)	9 (2.6)
Chest discomfort	4 (1)	3 (0.9)
Infections and infestations	2 (0.5)	4 (1.2)
Psychiatric disorders	2 (0.5)	3 (0.9)
Nervous system disorders	2 (0.5)	3 (0.9)

Abbreviations: TEAE=treatment-emergent adverse event, SOC=system organ class, PT=preferred term, DPM=dry powder mannitol, CF=cystic fibrosis
Source: SCS; Table 40, p.107

Overall, more DPM patients discontinued study treatment due to AEs versus control patients suggesting that some patients may have difficulty tolerating DPM. This is not necessarily surprising given the known properties of inhaled mannitol. Generally, when considering individual TEAEs, more DPM patients had respiratory TEAEs than control but the difference between arms was minimal (<1%), with the exception of cough. Similar to SAEs, more DPM patients had reported a CF exacerbation and hemoptysis as a cause for treatment discontinuation, however, the difference between arms was small.

Results from the OLP portions of 301/302 were generally consistent with the DBP results. The total number of adult OLP patients with TEAEs leading to study withdrawal was 15 of 224

(6.7%). This included 11 of 94 (11.7%) DBP control patients who transitioned to DPM during the OLP and 4 of 130 (3.1%) patients on DPM during the DBP who remained on DPM during the OLP. A possible explanation for this may be that at the end of the DBP the remaining DPM patients were "tolerant" moving forward into the OLP portion thus accounting for low study withdrawal in the OLP (3.1%), whereas control patients who transitioned to DPM in the OLP were not "tolerant" and withdrew at rates similar to DPM in the DBP. Consistent with the DBP, the most frequent AEs in the OLP leading to discontinuation included CF exacerbations, albeit with a lower percentage (1.3%).

Overall these data suggest that DPM may not be tolerated in some patients, which is not necessarily surprising given the known effects of inhaled mannitol.

Significant Adverse Events

During the DBP of studies 301, 302, and 303, in patients ≥18years of age, 13% of DPM and control patients had severe TEAEs. CF exacerbation was the most commonly reported severe TEAE. Between treatment groups, total severe AEs were relatively balanced. These data are summarized in Table 26.

Table 26: Studies 301, 302, and 303 Pooled, Severe TEAEs, ≥1% Any Arm, Patients ≥18 Years

PT	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Patients with ≥1 severe TEAE	55 (13.3)	44 (12.7)
CF exacerbation (condition aggravated)	20 (4.8)	10 (2.9)
Cough	7 (1.7)	4 (1.2)
Oropharyngeal pain	4 (1)	0
Lower respiratory tract infection	0	4 (1.2)

Abbreviations: TEAE=treatment-emergent adverse event, PT=preferred term, CF=cystic fibrosis, DPM=dry powder mannitol
Source: SCS; Table 37, p.98

With regard to specific preferred terms, CF exacerbation severe TEAEs were more frequent in DPM patients than control. Similar trends were also noted for SAEs and AEs leading to treatment discontinuation. As noted previously, this observation is consistent with the PDPE efficacy data, where DPM patients had numerically more PDPE compared to control. This is further discussed in Section 3.6.8. Oropharyngeal pain and cough were reported more often in the DPM groups compared to control. Cough and oropharyngeal pain are likely related to the known effects of inhaled mannitol. Other severe TEAEs were fairly balanced between treatment arms or were more frequent in control groups.

Results from the OLP portions were consistent with the DBP results. Approximately 15% of adult OLP patients had a severe TEAE, of which CF exacerbations were the most common (5.8%). A small numerical increase in exacerbations was noted in control patients transitioning from control to DPM in the OLP (4.5% DBP to 5.3% OLP).

The safety analysis of severe TEAEs was consistent with the previously discussed AE data.

Treatment Emergent Adverse Events and Adverse Reactions

During the DBP of studies 301, 302, and 303, in patients ≥18 years of age, 76% of DPM and control patients had at least one TEAE. Many of the more common TEAEs were consistent with inhaled mannitol's known action and the patient population. CF exacerbation was the most commonly reported TEAE. These data are summarized in Table 27.

Table 27: Studies 301, 302, and 303 Pooled, TEAEs, >5% Any Arm OR >2% Difference Between Arms, Patients ≥18 Years

PT	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Patients with ≥1 TEAE	321 (77.5)	256 (73.8)
CF exacerbation (condition aggravated)	132 (31.9)	114 (32.9)
Cough	62 (15)	37 (10.7)
Headache	44 (10.6)	48 (13.8)
Hemoptysis	43 (10.4)	33 (9.5)
Nasopharyngitis	30 (7.2)	25 (7.2)
Oropharyngeal pain	29 (7)	15 (4.3)
Bacteria sputum identified	28 (6.8)	16 (4.6)
Upper respiratory tract infection	23 (5.6)	21 (6.1)
Pyrexia	19 (4.6)	8 (2.3)
Lower respiratory tract infection	18 (4.3)	18 (5.2)
Abdominal pain*	23 (5.6)	24 (6.9)

Abbreviations: TEAE=treatment-emergent adverse event; DPM=dry powder mannitol, PT=preferred term, CF=cystic fibrosis
*Abdominal pain upper and Abdominal pain combined
Source: SCS; Table 35, p. 93

The most common TEAEs were relatively similar between arms (CF exacerbation, cough, hemoptysis, and headache). There were some TEAEs that were reported more commonly in DPM versus control patients (cough, oropharyngeal pain, bacteria sputum identified, pyrexia, hemoptysis). Cough and oropharyngeal pain were likely related to known effects of inhaled mannitol. Bacteria sputum identified in the setting of CF and pyrexia in isolation are not of clear clinical significance and differences were not observed in other AE analyses (deaths, SAEs, AEs leading to treatment discontinuation, and severe AEs). Moreover, they can be managed relatively easily. Hemoptysis, a prior review cycle concern, is further discussed in Section 3.6.8.

Review of the OLP data was consistent with the DBP data. The overall incidence of TEAEs was similar between the OLP and DBP. The most frequent TEAEs in the OLP were generally similar to the DBP.

The safety analysis of all TEAEs was consistent with the previously discussed AE data and does not raise new safety concerns.

Laboratory Findings

Because only screening hematology and chemistry evaluations were performed in study 303, there is no analysis of abnormal laboratory findings (clinical chemistry, hematology, hepatic function). Because the primary mechanism of action for DPM is based on local airway effects, this is not unreasonable.

Sputum microbiology was also tested at screening only, therefore, it is unknown if any changes in the patients sputum microbiology occurred due to study treatment.

Vital Signs

There were no significant imbalances in vital signs measured at week 6, 14, or 26 between the two arms. This includes measurements of SBP, DBP, heart rate, respiratory rate, and oxygen saturation.

Electrocardiograms (ECGs)

Given the patient population, the disease process, the known mechanism of action of the product, and safety information from the prior studies, no ECG related safety analysis was performed.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Hemoptysis

Hemoptysis was identified as a safety concern in the initial review cycle based on review of safety data in all patients (pediatric and adult) from studies 301 and 302. Despite the exclusion of patients with >60 mL hemoptysis in the 3 months prior to screening in these studies, hemoptysis AEs, SAEs, and discontinuations due to hemoptysis were consistently observed more frequently in DPM versus control patients. This small but clear signal for hemoptysis occurred even in the youngest age group of 6- to 11-year-olds, raising issues of safety

specifically for pediatric patients. While no patients died from hemoptysis events in the safety population during the conduct of studies 301 and 302, the long-term effect of the 2-to-4-fold increase in hemoptysis, when projected to chronic use over the course of a CF patient's lifetime, is unknown. A summary of the safety data from studies 301 and 302 regarding the hemoptysis safety concern is shown in Table 28.

Table 28: Studies 301 and 302, Hemoptysis by Age

Age Group	Studies 301 and 302 Pooled	
	DPM	Control
All subjects	**N=361**	**N=239**
Any hemoptysis	34 (9.4)	13 (5.4)
Severe AE	4 (1.1)	1 (0.4)
SAE	8 (2.2)	2 (0.8)
AE leading study withdrawal	6 (1.7)	0
Pediatric (6–11 yrs)	**N=66**	**N=41**
Any hemoptysis	4 (6.1)	0
Severe AE	1 (1.5)	0
SAE	0	0
AE leading study withdrawal	0	0
Adolescent (12–17 yrs)	**N=88**	**N=64**
Any hemoptysis	8 (9.1)	2 (3.1)
Severe AE	1 (1.1)	0
SAE	3 (3.4)	1 (1.6)
AE leading study withdrawal	0	0
Adult (≥18 yrs)	**N=207**	**N=134**
Any hemoptysis	22 (10.6)	11 (8.2)
Severe AE	2 (1)	1 (0.7)
SAE	5 (2.4)	1 (0.7)
AE leading study withdrawal	6 (2.9)	0

Abbreviations: AE=adverse event; SAE=serious adverse event; DPM=dry powder mannitol; yrs=years
Source: AC briefing document Division Memorandum 2013, Table 7 and 8

In light of the safety concern identified in the previous NDA review cycle, hemoptysis was evaluated as an adverse event of special interest (AESI) in study 303. It was reported separately, even if part of an exacerbation or alternate process; and data on volume (investigator estimated) and prior frequency were collected in an attempt to better characterize hemoptysis. Hemoptysis data from study 303 are summarized in Table 29.

Table 29: Study 303, Hemoptysis AEs, Patients ≥18 Years

Hemoptysis	Study 303	
	DPM (N=207)	Control (N=213)
Any hemoptysis	21 (10.1)	22 (10.3)
Severe AE	0	0
SAE	1 (0.5)	3 (1.4)
AE leading to drug discontinuation	1 (0.5)	4 (1.9)
AE leading to study withdrawal	0	0

Abbreviations: AE=adverse event; SAE=serious adverse event; DPM=dry powder mannitol
Source: SCS Table 44, p.119

In contrast to the prior studies, hemoptysis AEs in study 303 were not increased in the major safety categories, particularly SAEs and AEs leading to drug discontinuation.

Analysis of hemoptysis events based on volume and prior history are summarized in Table 30.

Table 30: Study 303, Hemoptysis Details, Patients ≥18 Years

Hemoptysis		Study 303	
		DPM (N=207)	Control (N=213)
Patients with ≥1 TEAE hemoptysis		21 (10.1)	22 (10.3)
Total estimated hemoptysis volume (mL)	Mean	42.6 mL	65.9 mL
	Median	5 mL	17.5 mL
Estimated volume			
Scant (<5 mL within 24 hr)		12 (57.1)	8 (36.4)
Mild (5–60 mL within 24 hr)		8 (38.1)	10 (45.5)
Moderate (60–240 mL within 24 hr)		1 (4.8)	3 (13.6)
Massive (>240 mL within 24 hr or >100 mL x >1 day)		0	1 (4.5)
Screening history			
History of hemoptysis		68 (32.5)	60 (28)
Multiple prior hemoptysis events		38 (55.9)	27 (45)
Prior massive* hemoptysis events? yes		3 (4.4)	5 (8.3)

Abbreviations: TEAE=treatment-emergent adverse event; DPM=dry powder mannitol
* acute bleeding ≥240 mL in a 24-hour period and/or recurrent bleeding ≥100 mL per day over several days
Source: Study 303 CSR; Tables 11-4, 12-8

Hemoptysis volume was lower in DPM versus control (mean and median) and more DPM patients reported scant hemoptysis versus control. These data suggest that DPM does not result in larger volume hemoptysis despite a slightly higher percentage of DPM patients having a history of any hemoptysis and of multiple hemoptysis events at screening.

While in studies 301 and 302, notable imbalances in hemoptysis events were observed when examining the overall population (patients ≥6 years of age), these imbalances were diminished when examining only those patients ≥18 years of age. In study 303, which included only patients ≥18 years of age, no imbalances were noted. Taken as a whole, these data suggested that in the ≥18-year-old population, hemoptysis was less of a safety concern. Hemoptysis data in the ≥18-year-old patients across studies 301, 302, and 303 are summarized in Table 31.

Table 31: Studies 301, 302, and 303 Pooled, Hemoptysis AEs, Patients ≥18 Years

Hemoptysis	Studies 301 and 302 Pooled		Study 303		Studies 301, 302, 303 Pooled	
	DPM (N=207)	Control (N=134)	DPM (N=207)	Control (N=213)	DPM (N=414)	Control (N=347)
Any hemoptysis	22 (10.6)	11 (8.2)	21 (10.1)	22 (10.3)	43 (10.4)	33 (9.5)
Severe AE	2 (1)	1 (0.7)	0	0	2 (0.5)	1 (0.3)
SAE	5 (2.4)	1 (0.7)	1 (0.5)	3 (1.4)	6 (1.4)	4 (1.2)
AE leading to drug discontinuation	6 (2.9)	0	1 (0.5)	4 (1.9)	7 (1.7)	4 (1.2)
AE leading to study withdrawal	6 (2.9)*	0*	0	0	6 (1.4)	0

Abbreviations: AE=adverse event; SAE=serious adverse event; DPM=dry powder mannitol
* drug discontinuation led to automatic study withdrawal
Source: SCS Table 44, p.119

Exacerbations

CF exacerbations were common throughout the treatment period and given the significant morbidity and impact on quality of life that exacerbations can have on CF patients, a safety concern, if present, for this category would be of clear clinical importance. Thus, exacerbations were reviewed as an AE of special interest.

CF exacerbations (coded as condition aggravated) were discussed in prior sections that included SAEs, AEs leading to treatment discontinuation, severe TEAEs, and all TEAEs. In all of those sections, exacerbations were the most common AE observed and were, except for common TEAEs, reported more frequently in DPM versus control patients. Exacerbation related adverse event data are summarized in Table 32.

Table 32: Studies 301, 302, and 303 Pooled, CF Exacerbations, Patients ≥18 Years

CF Exacerbations	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
SAEs	55 (13.3)	39 (11.2)
AEs leading to drug discontinuation	13 (3.1)	9 (2.6)
AEs leading to study withdrawal*	11 (2.7)	5 (1.4)
Severe AEs	20 (4.8)	10 (2.9)
Any exacerbation	132 (31.9)	114 (32.9)

Abbreviations: SAE=serious adverse event; AE=adverse event; DPM=dry powder mannitol
* drug discontinuation led to automatic study withdrawal in studies 301 and 302
Source: Study 303 CSR; Table 12-5; SCS; Table 46

The increased frequency of CF exacerbations reported as adverse events in DPM versus control treated patients, albeit small, is consistent with the secondary efficacy endpoint data from studies 302 and 303 where for some PDPE related endpoints, results favored control (notwithstanding study 302 dropout related efficacy impact). Additionally, given the known airway effects of inhaled mannitol (bronchospasm), it is conceivable that chronic use could potentially predispose a patient to exacerbation. Taken together this may suggest a potential exacerbation related safety concern for DPM.

Given the regional differences noted in the PDPE efficacy analyses, a similar exacerbation-specific analysis comparing U.S. to non-U.S. subpopulations of adults from studies 301, 302, and 303 was performed for CF exacerbation adverse events. Results are shown in Table 33.

Table 33: Studies 301, 302, and 303 Pooled, Exacerbations, U.S. and Non-U.S. Subpopulations, Patients ≥18 Years

CF Exacerbations	Studies 301, 302, 303 Pooled			
	U.S. Population		Non-U.S. Population	
	DPM (N=110)	Control (N=93)	DPM (N=304)	Control (N=254)
SAEs	23 (20.9)	10 (10.8)	32 (10.5)	29 (11.4)
AEs leading to drug discontinuation	7 (6.4)	4 (4.3)	6 (2)	5 (2)
AEs leading to study withdrawal*	5 (4.5)	1 (1.1)	6 (2)	4 (1.6)
Severe AEs	7 (6.4)	2 (2.1)	13 (4.3)	8 (3.1)
Any exacerbation	42 (23.8)	33 (35.5)	90 (29.6)	81 (31.9)

Abbreviations: SAE=serious adverse event; AE=adverse event; DPM=dry powder mannitol
* drug discontinuation led to automatic study withdrawal in studies 301 and 302
Source: FDA Reviewer analysis

Results for serious CF exacerbations were striking. In the U.S. population, 21% of DPM versus 11% of control patients experienced a serious CF exacerbation. This is in contrast to the non-U.S. and overall population where the differences were much smaller. Similar trends, though

not as marked, were observed for AEs leading to drug discontinuation, AEs leading to study withdrawal, and severe AEs. While similar findings were not observed for the category "any exacerbation", these findings still raise exacerbation related safety concerns. It is also worth noting that these exacerbation related safety findings are consistent with the PDPE efficacy data.

To explore this further, an analysis of the demographics and baseline characteristics of the US patients from the pooled phase 3 study adult population was performed. This is summarized in Table 34.

Table 34: Studies 302 and 303 Pooled, Baseline characteristics of U.S. Subpopulation, Patients ≥18 Years

	Studies 302 and 303 Pooled	
	U.S. Population	
	DPM (N=110)	Control (N=93)
Age		
Mean	28.8	31.8
Gender		
Female	46 (41.8)	41 (44.1)
Race		
White	106 (96.4)	90 (96.8)
Number of Hospitalizations associated with exacerbation in previous 12 months		
0	60 (54.5)	58 (62.4)
≥1	50 (45.5)	35 (37.6)
≥2	22 (20)	13 (14)
Lung function at baseline		
FEV1 % predicted, mean	62.8%	62.2%
Screening Sputum microbiology		
Pseudomonas aeruginosa (any)	71 (64.5)	55 (59.1)
Medication use at screening		
rhDNase use	90 (81.8)	76 (81.7)
CFTR Mutation		
Homozygous F508del	35 (31.8)	35 (37.6)
Heterozygous F508del	55 (50)	41 (44.1)
Other known mutation	11 (10)	12 (12.9)
Both unknown	9 (8.2)	5 (4.5)

Source: Clinical Information Request May 17 2019, Table 1-2, p.6- 8

U.S. DPM patients had a higher frequency of hospitalizations due to CF exacerbations in the 12 months prior to screening; this was additionally supported by the observation of DPM patients

having a higher frequency of exacerbations treated with IV antibiotics in the 12 months prior to screening (data not shown). Other relevant baseline characteristics were generally balanced.

While this imbalance in the prior history of exacerbations may certainly have contributed to the serious CF exacerbation increase noted in U.S. DPM patients versus controls, as previous history of exacerbation generally predicts future occurrence; the magnitude of the difference in the overall US population may not fully explain the magnitude of the difference seen for serious CF exacerbations in US patients using DPM compared to control (nearly double). Therefore, an analysis of the baseline characteristics of those 33 US patients with serious CF exacerbations was also performed.

In that analysis, many baseline characteristics were balanced (results not shown), however, the prior history of hospitalizations due to exacerbations and IV antibiotic usage due to exacerbations were found to be significantly higher in the US DPM patients with serious exacerbations (Table 35).

Table 35: Studies 302 and 303 Pooled, Baseline characteristics of U.S. Subpopulation, Patients ≥18 Years Who Experienced a Serious CF Exacerbation

Serious CF Exacerbations	Studies 302 and 303 Pooled	
	U.S. Population	
	DPM (N=23)	Control (N=10)
Number of Hospitalizations associated with exacerbation in previous 12 months		
0	2 (8.7)	4 (40)
≥1	21 (91.3)	6 (60)
≥2	17 (73.9)	3 (30)
Number of exacerbations treated with IV antibiotics in previous 12 months		
0	1 (4.3)	3 (30)
≥1	22 (95.7)	7 (70)
≥2	18 (78.3)	3 (30)

Source: Reviewer Analysis, ADSL pooled phase 3 studies, ADAE pooled phase 3 studies, DBPFL=Y, TRTEMLFL=Y, AESER=Y, COUNGR1=United States, AGE≥18,

Given the small subgroup sizes, conclusions are unable to be drawn. Those limitations notwithstanding, the U.S. DPM patients with serious CF exacerbations had more baseline exacerbations in the 12 months preceding screening than the US control patients with serious CF exacerbations.

Given the known predisposing contribution that prior exacerbations can have in future exacerbations, these findings of a higher baseline number of prior exacerations in the US population may have played a role in the increased number of serious CF exacerbations seen in the US DPM patients, albeit not entirely explanatory.

Other

Given the known airway effects of inhaled mannitol, analysis of cough events was performed. This analysis was performed grouping the preferred terms "cough" and "productive cough." Based on this grouping the overall frequency of cough events was 14.7%. in pooled studies 301, 302, and 303. In the pooled safety data from all three studies, cough events were seen more frequently in DPM patients versus control. While there were no serious cough events reported, drug discontinuations and study withdrawal due to cough were more frequent with DPM patients. These findings are not unexpected but do suggest some patients may have difficulty tolerating DPM due to cough. These results are summarized in Table 36.

Table 36: Studies 301, 302, and 303 Pooled, Cough, Double Blind Phase Only, Patients ≥18 Years

Cough[†]	Studies 301, 302, 303 Pooled	
	DPM (N=414)	Control (N=347)
Any cough	69 (16.7)	43 (12.4)
Severe AE	7 (1.7)	4 (1.2)
SAE	0	0
AE leading to drug discontinuation	22 (5.3)	9 (2.6)
AE leading to study withdrawal*	18 (4.3)	6 (1.7)

Abbreviations: DPM=dry powder mannitol, AE=adverse event, SAE=serious adverse event
*drug discontinuation led to automatic study withdrawal in studies 301 and 302
[†] PT terms "cough" and "productive cough" were grouped
Source: SCS; Table 42, p.115

As severe bronchospasm is a known labeled warning with Aridol (inhaled mannitol), similar analyses across safety categories were performed for bronchospasm events assessing multiple potentially related preferred terms (preferred terms evaluated included "bronchospasm", "bronchial hyperreactivity", "laryngospasm", "wheezing", and "respiratory tract irritation"). No concerning findings were noted between treatment arms. The overall number of patients with events were low. However, bronchospasm events were reported more commonly in DPM versus control patients. As with cough, this finding is not surprising.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

US subgroup exploration of CF exacerbations discussed in section 8.2.5.

8.2.8. Specific Safety Studies/Clinical Trials

For this submission no additional safety studies were performed.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. This product is not approved in the U.S. Postmarket experience from Australia and other countries include approximately 8000 patient information with no clear safety concern being noted.

Expectations on Safety in the Postmarket Setting

Not applicable

8.2.11. Integrated Assessment of Safety

The safety information for this review was derived from three phase 3 studies: 301, 302, and 303. Given the similar design and duration of these three studies, these safety results were pooled; more specifically, results from adults from the earlier two studies (studies 301 and 302) were pooled with study 303 (adult only). With this pooling, there were 414 adult CF patients treated with DPM and 347 adult CF patients given control. As such, the overall exposure and size of the safety database for this disease were adequate.

While there were some numerical differences in certain adverse events, overall the differences between arms did not raise major safety concerns for patients ≥18 years of age. Across the three phase 3 studies, two deaths occurred, both in control treated patients. With regard to

SAEs, overall, they were balanced between arms, however, for the SAE CF exacerbations, events were slightly more common in the DPM versus control treated patients. AEs leading to treatment discontinuation were more common in DPM treated patients compared to control, with cough and CF exacerbations accounting for the majority of events. This suggests that there may be tolerability issues associated with DPM. For severe AEs, overall events were similar between groups, however, there were slightly more severe CF exacerbations in DPM treated patients than control. Common AEs occurring more frequently in DPM patients than control were cough, oropharyngeal pain, hemoptysis, bacteria sputum identified, and pyrexia.

Focused analyses of hemoptysis, cough, bronchospasm, and CF exacerbations were also performed. Hemoptysis had been a concern in the prior review cycle (primarily in patients <18 years of age) due to imbalances observed in DPM versus control patients. However, in the analyses of the pooled studies of patients ≥18 years of age and in study 303 alone, the differences were smaller suggesting that hemoptysis is less of a concern in the ≥18-year-old population. Cough occurred more frequently in DPM patients than control, particularly in events that led to study and drug discontinuation. Given the known airway effects of mannitol, bronchospasm was also explored but that analysis did not reveal major differences between groups.

With regard to CF exacerbation, it was the most common AE across the phase 3 studies and was slightly greater in frequency in DPM patients compared to controls in most of the safety categories (SAEs, AEs leading to study and drug discontinuation, and severe AEs). This finding was accentuated when examining CF exacerbation in U.S. patients, however, may be possibly explained by baseline exacerbation history. These exacerbation-related safety data were also consistent with PDPE data from two of the three phase 3 studies where results numerically favored control. Taken together, the data may suggest a potential exacerbation related safety concern for DPM.

Overall, the pooled adult safety data from the phase 3 studies are sufficient to evaluate the safety of DPM in the proposed population. Based on these data, DPM may have tolerability issues in some patients and is likely associated with cough. Additionally, these data also suggest an exacerbation related safety concern based on differences between DPM and control treated patients. The primary safety concern of hemoptysis raised in the previous NDA review cycle appears to have been largely addressed.

8.3. Statistical Issues

The main statistical issue during the review of results from study 303 was that some of the prespecified primary analyses for key efficacy endpoints did not properly account for uncertainty in parameter estimation due to data missingness. Some examples include the primary analysis for Change from Baseline Over 26 Weeks in FEV1 carrying the baseline observation forward for some patients with missing data, and the primary analysis for PDPE Rate imputing the 26-week number of PDPEs for some patients using those patients' historical

pulmonary exacerbation rate. Each of these approaches was a single imputation procedure, potentially resulting in confidence intervals that were unduly narrow and p-values that were unduly small. For this reason, analyses using other missing data handling methods were also considered.

In this review cycle, all analyses for data from studies 301 and 302 were *post-hoc*, and therefore interpretation of results from each of these analyses is limited. Furthermore, missingness rates in study 301 (and to a lesser extent, in study 302) are high such that analysis results are valid to the extent that missingness mechanisms assumed in the analyses resemble the true underlying missingness mechanisms. Finally, study 302 was a "failed" study.

8.4. Conclusions and Recommendations

Prior to the resubmission of this application, the efficacy expectations communicated to the applicant were that "tiebreaker" study 303 would have (1) statistically and clinically significant results in favor of DPM with respect to change from baseline over 26 weeks in FEV_1; (2) support from an analysis of change from baseline in FEV_1 at Week 26; and (3) point estimates from analyses of important secondary endpoints trending in favor of DPM. Of these expectations, only statistically significant results in favor of DPM with respect to change from baseline over 26 weeks in FEV_1 are present in study 303. Furthermore, there is some concern that DPM may have unfavorable effects with respect to PDPE Rate. Because of these considerations, and because of the limited ability to draw conclusions from study 301 and 302 results in adults only due to the statistical issues in these two studies, we (primary clinical reviewer and statistical team) conclude that in adult cystic fibrosis patients there is not substantial evidence of efficacy necessary for approval.

The pooled adult safety data from the phase 3 studies were sufficient to evaluate the safety of DPM in the proposed population. Based on these safety data, DPM may have tolerability issues in some patients and is likely associated with cough. The primary safety concern of hemoptysis raised in the previous NDA review cycle appears to have been largely addressed. However, these data suggest an exacerbation-related safety concern based on differences between DPM and control treated patients, most pronounced in the US subpopulation.

Due to the lack of sufficient evidence of efficacy and the potential concerns with respect to safety as discussed above, there is insufficient evidence to conclude that the benefits of DPM outweigh the risks in, adults with cystic fibrosis. Therefore, the primary clinical reviewer and statistical team recommend that a Complete Response action be taken.

Note that while the primary clinical reviewer and statistical team recommend a Complete Response (CR) action, the Cross-Disciplinary Team Leader and Division Director recommend Approval, though a CR action will be taken due to issues with the Human Factors studies (see sections 1 and 14).

9 Advisory Committee Meeting and Other External Consultations

A Pulmonary Allergy Drugs Advisory Committee (PADAC) was convened on May 8th, 2019 to discuss information covered in this review.

There were two discussion questions and three voting questions:

1. DISCUSSION: Discuss the efficacy of dry powder mannitol (DPM) for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. Include the following topics in your discussion:
    a. Effect on FEV_1, including effect size and durability of effect
    b. Secondary endpoints, particularly exacerbations and the Cystic Fibrosis Questionnaire – Revised respiratory domain score
    c. Statistical persuasiveness

2. DISCUSSION: Discuss the safety data for DPM for the proposed use in patients with cystic fibrosis 18 years of age and older, particularly exacerbation and hemoptysis.

3. VOTE: Do the data provide substantial evidence of efficacy for DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?

    VOTE: YES: 10 NO 6

4. VOTE: Are the safety data adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?

    VOTE: YES: 10 NO 6

5. VOTE: Does the benefit-risk profile support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?

    VOTE: YES: 9 NO 7

In terms of efficacy, the majority of panel members noted sufficient evidence being present to support efficacy, however, panel members voting “no” stated reasons such as lack of clinical meaningfulness, small effect size, lack of secondary endpoint support, statistical problems with prior studies (studies 301 and 302), and potential lack of durability. Members voting “yes” felt that two studies had demonstrated statistical significance and that the treatment effect size on

FEV_1 was sufficient and clinically meaningful.

In terms of safety, the majority of the panel members voted in favor of sufficient safety being present, however, panel members voting “no” were primarily focused on the possibility of exacerbation increases, accentuation in the U.S. subpopulation, or difficulty differentiating DPM related CF exacerbations from routine CF exacerbations. Members voting “yes” noted that the prior cycle safety concerns of hemoptysis being lessened was sufficient, that exacerbations were a routine aspect of CF, or that CF care as delivered through specialty centers and specialized clinicians in the U.S. would quickly identify a true safety signal if present.

When considering the overall benefit-risk profile, the panel members were somewhat divided with a slight majority favoring approval. Reasons cited by those recommending approval included improved patient adherence with a more convenient medication, the need for increased treatment options for patients, any small increase in lung function being beneficial to patients, and confidence in U.S. CF care delivery being sufficiently robust such that CF clinicians could best decide on the benefit-risk for each individual patient. Of note, several panel members noted they recommended approval with the understanding that a post-marketing study requirement should accompany approval to better assess exacerbation risk. Panel members voting against approval raised concerns with substitution of existing standard-of-care medications with DPM as a more convenient option potentially causing a relative increase in exacerbation risk (hypertonic saline was the example discussed by panel members), marginal efficacy not balanced by possible safety concerns, and issues previously discussed above.

10 Pediatrics

The target population was changed from patients 6 and older to patients 18 and older for this current resubmission. Data from the original submission regarding pediatric efficacy and safety are discussed in detail in Dr. Witzmann's primary review.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Not applicable, a Complete Response action will be taken.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable, a Complete Response action will be taken.

13 Postmarketing Requirements and Commitment

Not applicable, a Complete Response action will be taken.

14 Division Director DPARP (designated signatory authority) Comments

This application is for inhaled dry powder mannitol (DPM) for the proposed indication of the management of cystic fibrosis (CF) in patients 18 years of age and older to improve pulmonary function in conjunction with standard therapies. The proposed dose is 400 mg (10×40 mg capsules) twice daily. The current submission is the Applicant's response to a Complete Response (CR) action taken on the first review cycle due to an unfavorable benefit-risk assement because of the lack of substantial evidence of efficacy as well as safety concerns particularly in pediatric patients. In this complete response to CR, the Applicant has submitted new clinical data to address the deficiencies raised in the March 18, 2013, CR letter. The Applicant submitted the results of a new clinical study and limited the indication to adult patients with CF.

As discussed in the review, the new study 303 provided evidence of a modest treatment effect on FEV_1 in patients with CF, but the secondary endpoints did not support additional benefit of DPM. The primary clinical reviewer and statistical team have recommended a CR action based on the modest effect on FEV_1 through the 26-week treatment period, numerically smaller effect at week 26, and lack of support from other clinically relevant endpoints; coupled with a potential exacerbation related safety concern. Dr. Lim, the CDTL, and I find the benefit-risk for this product favorable and recommend Approval as outlined in the Executive Summary (Section 1) and Benefit-Risk Assessment (Section 1.3). Please refer to those sections for our benefit-risk assessment.

While I find the benefit-risk assessment favorable to support approval, there is an issue with human factors testing that was done to determine if healthcare providers can administer the mannitol tolerance test (MTT), which is necessary to screen patients for bronchospasm prior to treatment with DPM. Per our DMEPA review team, the data from the submitted human factors studies has not demonstrated that HCPs can reliably perform the MTT to identify CF patients who can safely take this medication. This will preclude approval at this time; thus a CR action is planned. Once the human factors issues are resolved, labeling can be completed and the NDA can be approved. The deficiency is as follows:

> The submitted data from the human factors (HF) validation studies do not provide sufficient evidence to demonstrate that healthcare providers can reliably and accurately perform the Mannitol Tolerance Test (MTT) to correctly identify the intended target patient population. HF study results demonstrated several use errors and use difficulties with critical tasks in administering the MTT, which could result in healthcare providers prescribing the medication to patients who cannot tolerate Bronchitol. As inhaled mannitol is known to cause severe bronchospasm in susceptible individuals, this could result in patient harm (e.g. bronchospasm, hypoxia, pulmonary compromise) and is a significant safety concern.

To address this deficiency: (1) revise the product user interface to address the errors and use difficulties seen in your HF validation studies and (2) then conduct a supplemental HF validation study to demonstrate the effectiveness of the additional risk mitigations and to ensure that they address user interface concerns and do not introduce new risks.

15 Appendices

15.1. References

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 114		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Human Factors validation studies deficiencies

Table 1: Identified Issues and Recommendations for Chiesi USA Inc. – based on HF validation studies' results			
	Identified Issue	**Rationale for Concern**	**Recommendation**
HF Validation Study Methodology			
1.	The study environment in your HF validation studies did not include pulse oximeters, spirometry equipment, bronchodilators, or a hand washing device (i.e. sink). We find that the aforementioned study environment is not representative of real-world use and may have influenced user behavior. For example, users may have performed differently on BTT Quick Reference Guide Step A5 (i.e. administer bronchodilator) if the bronchodilator was present in the study environment.	Study environments within your HF validation study should represent the environments that the proposed product will be used.[5]	Ensure that the environments that will be part of the supplemental HF validation study protocol are reflective of real-world use.
2.	In your HF validation study, empty transparent capsules were included in the Training Kit, BTT, and Bronchitol cartons. However, with the intend-to-market product, only the Training Kit carton will contain empty capsules and the BTT and Bronchitol cartons will contain active drug that would be visually identifiable in the transparent capsule. We find	The capsules used within your HF validation study should be representative of real-world use and distinguishable from the empty capsules used in the Training Kit.	Ensure the study materials (e.g. empty Training kit capsules, placebo filled Bronchitol capsules) used in the supplemental HF validation study protocol are reflective of real-world use. In addition, because of the risk of users who may erroneously receive a demonstration kit in error, you may want to consider eliminating the training kit from

[5] Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Medical Devices. 2016. Available from: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

	that the aforementioned use of empty capsules in all the BTT and Bronchitol cartons is not representative of real-world use and may have influenced user behavior. For example, we note that some study participants used the empty Training Kit capsules when simulating performance of the BTT.		your product line as a mitigation. See the Packaging recommendation #1 below.
Bronchitol Tolerance Test (BTT) Quick Reference Guide			
1.	The instruction regarding administration of a beta agonist (Step A5) is not prominent and may be overlooked.	If users do not correctly administer a beta agonist during BTT, there is risk that a patient might receive Bronchitol without opened airways which might result in patient harm (e.g. bronchospasms, hypoxia, pulmonary compromise). The results collected during your second HF validation study indicated that for the critical task "Administer an inhaled beta agonist and wait 5-15 minutes before continuing", 9 study participants (excluding study artifacts) failed this task. Additionally, the subjective feedback indicated that 4 of the 9 participants who failed this task noted that they did not notice the instruction or overlooked the instruction (i.e. Step A5), and 2 of the 9 participants who failed this task were confused regarding when to administer the beta agonist (i.e. they incorrectly indicated to administer the beta agonist before measuring baseline values).	Revise Step A5 to increase the prominence of the instruction to inhale a beta agonist prior to taking Bronchitol.

2.	The instructions regarding waiting 60 seconds and then recording SpO_2 and FEV_1 are not prominent and may be overlooked.	If users do not correctly perform the BTT tasks, there is risk that an unindicated patient could be prescribed Bronchitol which might result in patient harm. The results collected during your second HF validation study indicated that for the critical tasks associated with regarding "Wait 60 seconds, then record SpO_2 (and FEV_1)" (i.e. Steps B2, C2, D2, and E2 of the BTT QRG), 2 study participants (excluding study artifacts) failed the associated tasks. Additionally, the subjective feedback indicated that the 2 participants who failed the associated tasks noted that they did not see the instruction to wait 60 seconds.	Revise Steps B2, C2, D2, and E2 to increase the prominence of the instruction regarding the amount of time to wait (i.e. 60 seconds) prior to measuring and recording SpO_2 and FEV_1. Consider whether formatting and layout changes should be applied to the BTT QRG as a whole.
3.	The instructions regarding administration of more than 1 capsule are not clear.	If users do not administer the correct number of capsules for inhalation during BTT, there is risk that an unindicated patient could be prescribed Bronchitol which might result in patient harm. The results collected during your second HF validation study indicated that for the critical tasks associated with administration of more than 1 capsule (i.e. Steps C1, D1, and E1 of BTT QRG "Instruct patient to inhale contents of xx capsule[s]", 3 study participants (excluding study artifacts) failed the associated tasks. Additionally, the subjective feedback indicated that 1 of 3 study participants who	Consider revising the graphics in Steps C2, D2, and E2 to show the number of capsules per steps (e.g. Step C2 would show graphic displaying 2 capsules vs. 1 capsule).

		failed the associated tasks focused on the capsule images (of 1 capsule) and not the written instructions, which led them to believe that they only needed to administer 1 capsule per step each time.	
4.	In Step E4, users must determine whether to prescribe Bronchitol or continue BTT. However, the step is not prominent and may be overlooked	If users do not perform this BTT task correctly, there is risk that an unindicated patient could be prescribed Bronchitol which might result in patient harm (e.g. in case where patient has not yet qualified for Bronchitol and HCP should proceed to Step F) or there may be confusion regarding the BTT steps (e.g. in case where patient qualifies for Bronchitol at Step E4 but HCP proceeds to Step F). The results collected during your second HF validation study indicated that for the critical tasks associated with administration of more than 1 capsule (i.e. Steps C1, D1, and E1 of BTT QRG "If FEV1 > REF2, – Bronchitol may be prescribed. Otherwise, proceed to F", 2 study participants believed that they should always proceed to Step F; however, Step F is only needed if the patient does not qualify for Bronchitol at Step E4. Additionally, the subjective feedback indicated that 1 of the 2 participants noted they did not see the step and assumed that they should go through all of BTT steps, and the other participant indicated that because the steps appeared repetitive, they did not	Revise Step E4 to increase the prominence of the instruction. Consider whether formatting and layout changes should be applied to the BTT QRG as a whole.

		read all the steps and assumed all the BTT steps should always be completed.	
Bronchitol Quick Reference Guide			
1.	Based on the second HF study results, Step 7 is not prominent and may be overlooked.	If users do not keep the inhaler upright and press and release both inhaler buttons at the same time, there is risk of underdosing (due to capsules not being pierced or pierced multiple times). This could result in intermittent/temporary decrease in clearance or pulmonary function. The results collected during your second HF validation study indicated that 3 HCP participants failed this task. The subjective feedback noted that the 2 of the 3 HCP participants who failed this task overlooked this step or did not see this step (i.e. due to the folding of the QRG) in the Bronchitol QRG.	Revise Step 7 to increase the prominence of the instruction. Consider whether formatting and layout changes should be applied to the Bronchitol QRG as a whole.
2.	Based on the second HF study results, Step 10 is not prominent and may be overlooked.	If users do not open the inhaler and confirm the capsule is empty, there is risk of chronic underdosing and insufficient therapeutic response which can result in reduced/ decreased clearance of secretions, congestion, and decreased pulmonary function (return to baseline/normal state for CF patients). The study results collected during your second HF validation study indicated 5 HCP participants failed	Revise Step 10 to increase the prominence of the instruction. Consider whether formatting and layout changes should be applied to the Bronchitol QRG as a whole.

		this task. The subjective feedback noted that that 3 of the 5 HCP participants who failed this task overlooked this step or did not see this step (i.e. due to the folding of the QRG) in the Bronchitol QRG.	
3.	Based on the first HF study results, Step 1 is not prominent and may be overlooked	If users do not administer an inhaled beta-agonist 5-15 minutes before taking Bronchitol, there is risk of bronchospasms, hypoxia, pulmonary compromise due to receiving Bronchitol without opened airways. The results collected during your first HF validation study indicated that all 15 patient participants failed this task. The subjective feedback indicated that 6 of the 15 patient participants noted that they did not know that an inhaled beta agonist needed to be administered before taking Bronchitol, despite the task being Step 1 of the Bronchitol QRG.	Revise Step 1 and/or other components of the user interface to increase the prominence of this instruction to inhale a beta-agonist prior to taking Bronchitol.
Training Kit Carton Labeling			
1.	The Training Kit carton may be confused for the BTT carton.	Co-packaging the BTT carton and Training Kit carton may lead to user confusion between the two products. If users accidentally use the Training Kit empty capsules for BTT, there is risk that an unindicated patient could be prescribed Bronchitol (i.e. the BTT results would not be accurate because the patient would inhale contents of empty capsule vs. active drug). Additionally, we have received postmarketing reports in	Revise the side panel containing the text (b) (4) to include the statements "CONTAINS NO ACTIVE DRUG. NOT FOR THERAPEUTIC USE." in red capitalized font to provide differentiation and further draw attention to this important information. In addition, because of the risk of

		which patients have received a demonstration product that did not contain active drug. These errors occurred because the users incorrectly thought that the demonstration product contained the active drug. Similarities in appearance of demonstration products to the commercial product have led to confusion and medication errors. When users open the co-packaged carton, the labeling in the line of sight are the side panels of the Training Kit carton and the BTT carton. There are some differing labeling components (e.g. use of different colors on "1st" and "2nd"); however, the side panels may appear similar to some users. We note that unlike the principal display panel (PDP) of the Training Kit carton, the side panel of the Training Kit carton does not alert users that the product does not contain active drug.	users who may erroneously receive a demonstration kit in error, please implement additional risk mitigation, ensure that you address this risk in your updated use-related risk analysis, and evaluate modifications in your subsequent HF validation study.
Packaging			
1.	Co-packaging the BTT carton (with active drug capsules) and Training Kit carton (with empty capsules) may contribute to user confusion between the two cartons.	Co-packaging the BTT carton and Training Kit carton may lead to user confusion between the two products. If users accidentally use the Training Kit empty capsules for BTT, there is risk that an unindicated patient could be prescribed Bronchitol (i.e. the BTT results would not be accurate because the patient would inhale contents of empty capsule vs. active drug). Additionally, we have received postmarketing reports in	Consider revising your packaging presentation to mitigate the risk of confusion between the Training Kit carton and the BTT carton (e.g. supply cartons separately vs. co-packaged). In addition, please implement additional risk mitigation, ensure that you address this risk in your updated use-related risk analysis, and evaluate modifications in your

		which patients have erroneously received a demonstration product that did not contain active drug. These errors occurred because the users incorrectly thought that the demonstration product contained the active drug.[6] Furthermore, we note the results collected during your second HF validation study indicated that for the critical tasks associated with administration of the capsule (i.e. Steps B1, C1, D1, and E1 of BTT QRG "Instruct patient to inhale contents of xx capsule[s]", 2 study participants (excluding study artifacts) repeatedly administered the placebo capsules from Training Kit while simulating performance of BTT. The subjective feedback indicated that 1 of the 2 participants who failed this task believe the Training Kit contained active medication in smaller doses and the other participant did not understand the difference between the Training Kit carton and the BTT carton due to similar appearance.	subsequent human factors validation study.

[6] Institute for Safe Medication Practices. Solid controls needed for demo training devices. ISMP Med Saf Alert Acute Care. 2014;19(8):2-3.

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/s/

ROBERT H LIM
06/14/2019 09:18:03 AM

SALLY M SEYMOUR
06/14/2019 09:21:53 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 5, 2019

TO: File for NDA 202049

FROM: Robert Lim

SUBJECT: Cross-Disciplinary Team Leader (CDTL) Memo for NDA 202049

APPLICATION/DRUG: NDA 202049 inhaled dry powder mannitol (Bronchitol)

Chiesi pharmaceuticals submitted a complete response to a Complete Response (CR) action for NDA 202049 for dry powder mannitol (DPM) for the treatment of patients with cystic fibrosis (CF) 18 years of age and older to improve pulmonary function in conjunction with standard therapies. The proposed dosing regimen is 400 mg inhaled twice daily. The original NDA submission in 2012 was for a similar indication except the age range was broader, ages 6 years and older. A Complete Response (CR) action was taken as there were both efficacy and safety concerns (March 18, 2013). To address the CR deficiencies, the Applicant was asked to perform another phase 3 trial in adults to support efficacy and safety. This complete response to CR was submitted December 18, 2018.

To support this resubmission, Chiesi pharmaceuticals conducted one additional phase 3 randomized, double-blinded, controlled study (study 303) of 26 week duration in cystic fibrosis patients 18 years and older comparing 400mg DPM twice daily to control (50 mg DPM twice daily). In addition, given the change in target population from patients ages 6 years of age and older to 18 years of age and older due to safety concerns from the prior review cycle, *post-hoc* analyses of adults only from two prior phase 3 studies of identical design and duration (studies 301 and 302) were performed and submitted; studies 301 and 302 studied patients age 6 years and older. Results demonstrated a small improvement for the primary endpoint of change from baseline in FEV1 over 26-weeks, with point estimates ranging from approximately 50-80mL, supporting a modest treatment benefit in terms of pulmonary function. However, the clinically relevant secondary endpoints of exacerbation and symptoms offered no additional support for efficacy. With regard to safety, there were some concerns raised for increased CF exacerbations.

The CDTL recommendation is Approval. While the CDTL acknowledges the recommendations of the primary medical reviewer and statistical team have recommended a CR action. and does not dispute the safety and efficacy data, based on several factors, the CDTL has a different recommendation. First, while the FEV_1 benefit is modest, as articulated by PADAC members at the May 8, 2019 PADAC meeting, even a small increase may be clinically meaningful to some patients. This point was also endorsed by patients at the open public hearing. Additionally, responder analyses also suggest that some patients may receive a larger magnitude treatment benefit. As such, the CDTL finds that the FEV_1 data support the efficacy of the product. While the CDTL also concludes that there was no support from clinically relevant secondary endpoints, this does not preclude a recommendation of Approval as the stated indication is somewhat limited in that it specifies "to improve pulmonary function." Additionally, the CDTL recommendation considers the input given at the PADAC from PADAC members, CF patients/family members, and CF care providers. Specifically, that treatment options for inhaled mucolytics are limited, current treatment options require a significant amount of time to administer drug and clean the delivery device, such treatments also require access to a power source, and compliance can be suboptimal with currently available inhaled mucolytics. DPM could address these points. As such, while the treatment effect is modest and limited to FEV_1, DPM does offer a benefit to CF patients. This benefit is not outweighed by the safety findings and this CDTL recommends Approval. That being said, given CF exacerbation safety concerns and input from PADAC members, this CDTL also recommends a post-marketing required study to further investigate safety in terms of CF exacerbation.

The CDTL recommendation is Approval with a PMR study to further investigate CF exacerbation related safety concerns.

The clinical review of safety and efficacy for this resubmission by the CDTL is complete and has been incorporated into the multi-disciplinary review and evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the multi-disciplinary review and evaluation for details.

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/s/

ROBERT H LIM
06/05/2019 08:49:25 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 24, 2019

TO: File for NDA 202049

FROM: Khalid Puthawala

SUBJECT: Clinical review for NDA 202049

APPLICATION/DRUG: NDA 202049 Bronchitol (inhaled mannitol)

Chiesi pharmaceuticals submitted a class 2 resubmission NDA for dry powder mannitol (DPM) for the treatment of patients with cystic fibrosis (CF) 18 years of age and older to improve pulmonary function. The proposed dosing regimen is 400 mg inhaled twice daily. The original submission in 2012 was for a similar indication except the age range was broader, ages 6 years and older. A Complete Response (CR) action was taken as there were both efficacy and safety concerns (March 18, 2013). To address the CR deficiencies, the Applicant was asked to perform another phase 3 trial in adults to support efficacy and safety. This class 2 resubmission was submitted December 18, 2018.

To support this resubmission, Chiesi pharmaceuticals conducted one additional phase 3 randomized, double-blinded, controlled trial (trial 303) of 26 week duration in cystic fibrosis patients 18 years and older comparing 400mg DPM twice daily to control (50 mg DPM twice daily). In addition, given the change in target population from patients ages 6 years of age and older to 18 years of age and older due to safety concerns from the prior review cycle, post-hoc analyses of adults only from two prior phase 3 studies of identical design and duration (trials 301 and 302) were performed and submitted; trials 301 and 302 studied patients age 6 years and older. Results demonstrated a small improvement for the primary endpoint of FEV1, however, there was no secondary endpoint support for efficacy. Given this small improvement, which is of uncertain clinical relevance, and the lack of secondary endpoint support, in the opinion of this reviewer, efficacy has not been demonstrated. With regard to safety, there were some concerns raised for increased CF exacerbations. In the opinion of this medical officer, the benefit-risk assessment for this product is not favorable. This medical officer recommends a Complete Response action.

The clinical review of safety and efficacy for this resubmission is complete and has been added to the multi-disciplinary review and evaluation, which will be uploaded to DARRTS when it is finalized. The primary clinical reviewer does not recommend approval of DPM for the treatment of CF patients ages 18 years and older to improve pulmonary function. Refer to the multi-disciplinary review and evaluation for details.

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/s/

KHALID PUTHAWALA
05/24/2019 12:05:42 PM

ROBERT H LIM
05/24/2019 03:13:44 PM

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 18, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	202049
Applicant Name:	Pharmaxis, Inc
Date of Submission:	May 18, 2012
PDUFA Goal Date:	March 18, 2013
Proprietary Name:	Bronchitol
Established Name:	Mannitol
Dosage form:	Inhalation powder in capsules
Strength:	40 mg
Proposed Indications:	Cystic Fibrosis
Action:	Complete Response

1. Introduction

Pharmaxis submitted this 505(b)(2) new drug application for use of Bronchitol (mannitol inhalation powder) for the management of cystic fibrosis in patients 6 years of age and older to improve pulmonary function. The proposed dose is 400 mg (10 x 40 mg capsules) twice daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan drug population. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 1800 mutations in the CFTR gene, which, when present in both CFTR alleles, results in the clinical constellation that is CF. There is no cure for CF, treatment is limited to alleviation of symptoms and treatment of complications. Current therapies used by patients with CF include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements. In 2012, a drug called ivacaftor, which is classified as a cystic fibrosis transmembrane conductance regulator potentiator, was approved to treat a specific mutation in the CFTR, called the G551D mutation, where the mutated CFTR protein reaches the cell surface, but does not activate normally resulting in a low probability of being open. Ivacaftor acts to treat the underlying defect in the CFTR ion channel, which is the cause of CF, albeit in the small

subpopulation of patients with CF with at least one copy of the G551D mutation in the gene.

Mannitol belongs to a family of sugar alcohols found in most vegetables. Mannitol is used as nutrient and dietary supplement, and is an ingredient in many oral drug products. As a dietary supplement mannitol is generally recognized as safe. As an inhaled product, mannitol was approved in the United States as part of a kit (Aridol) for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. As such, mannitol inhalation powder has the ability to cause severe bronchoconstriction in susceptible subjects.

The rationale of developing mannitol for the management of cystic fibrosis is based on its osmotic property. The genetic defects in CF cause airway liquid hyper-absorption that leads to impaired mucuciliary clearance that results in vulnerability to lung infection, inflammation, and consequent decline in lung function and ultimate respiratory failure. Pharmaxis contends that as an osmotic agent mannitol will improve impaired mucociliary clearance in CF patients irrespective of patient genotype.

Pertinent regulatory history for mannitol relevant to this application is summarized below.

- IND was opened in November 2004, orphan status was granted in July 2005, and fast track development status was granted in November 2006.
- End of Phase 2 meeting was held in February 2006, where suitable endpoints for CF studies were discussed, and need for long-term safety data was discussed.
- Special Protocol Assessment request by Pharmaxis for one of the phase 3 studies (Study 301) in August 2006 and another phase 3 study (study 302) in August 2007 was reviewed by the Agency, but no agreement was reached on the grounds of lack of clear pathway and regulatory precedence for developing a product such as mannitol for CF. The Agency nevertheless agreed with the proposed protocols in concept. The Agency mentioned that 6 months' FEV1 data to support efficacy would be reasonable, but small changes in FEV1 would not be sufficient to support efficacy and will need to be supported by secondary efficacy measures of direct clinically relevant benefit in CF patients, such as exacerbation of CF.
- Pre-NDA meeting was held in December 2010, where Pharmaxis proposed to change statistical analysis plans for both phase 3 studies. (b) (4) The Agency did not agree with either of the changes and noted that protocol specified methods are relied upon on regulatory decision-making and post-hoc analyses are

often considered as hypothesis generating that usually require confirmation in a subsequent program. Pharmaxis did not use these proposed post-hoc changes in the NDA submission as the primary basis to support efficacy, and submitted data using both the protocol-specified analysis and the proposed post-hoc changes.

3. Chemistry, Manufacturing, and Controls

The Bronchitol product contains Bronchitol capsules and a hand held dry powder inhaler for administering mannitol into the lung. Bronchitol capsules are contained in 10 count blister strips and packaged (b) (4) Each capsule contains 40 mg of mannitol and no excipients. The inhaler is similar to other marketed single dose dry powder inhaler devices. The drug substance is manufactured by (b) (4), and the finished product is manufactured by Pharmaxis in Australia. The inhaler device is manufactured by (b) (4). A contract packaging and labeling facility (b) (4) has an unacceptable cGMP recommendation from Office of Compliance. Pharmaxis has submitted adequate stability data to support expiry of (b) (4). All Drug Master Files (DMFs) associated with this application were also found to be acceptable.

Administration of inhaled mannitol requires steps and precautions described below.

To deliver a dose of mannitol, one capsule is placed in the chamber of the inhaler device, buttons on the device are pressed to pierce the capsule on each end, and the patient then breathes in rapidly and deeply through the mouthpiece.

Inhaled mannitol can cause severe bronchospasm in responsive patients. Therefore, the first dose of mannitol is to be administered in a strict monitored setting where patients are first treated with albuterol inhalation aerosol (b) (4), and then given inhaled mannitol in incremental steps of 40 mg (1x40 mg capsule), 80 mg (2x40 mg capsule), 120 mg (3x40 mg capsule), and 160 mg (4x40 mg capsule) mg, with FEV1 monitoring post dosing (the procedure is called the mannitol tolerance test). Patients who are not responsive to the mannitol tolerance test based on predefined criteria (b) (4) reduction in SpO_2 at any time during administration of a dose) are candidates for chronic treatment with mannitol at the proposed dose of 400 mcg twice daily. Patients are also pretreated with albuterol inhalation aerosol (b) (4) prior to every mannitol 400 mg dosing.

4. Nonclinical Pharmacology and Toxicology

The nonclinical program for the application focused on the effect of inhaled mannitol on the respiratory system because the toxicological profile of mannitol for non-inhalation use has been well established. Mannitol is non-carcinogenic, non-genotoxic, and non-

teratogenic; and it is considered to be generally safe when given orally. Pharmaxis submitted reports of up to 3 and 6 months inhalation toxicology studies in rats and dogs, respectively. The studies showed toxicities in the respiratory system, which included increased incidence of alveolitis and macrophages accumulation in the lung in rats, and laryngeal ulceration in dogs. However, these findings in animals had acceptable safety margins to support the proposed human dosage, hence, are not of concern for the intended mannitol use in humans.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology program submitted was limited because mannitol is considered to be generally safe when given orally. This limited program is acceptable. Pharmaxis conducted a study in 18 healthy male subjects to compare the bioavailability of mannitol powder administered by inhalation route to mannitol administered intravenously and orally. The relative bioavailability of inhaled mannitol compared to orally administered mannitol was 96%.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The CF development program for mannitol was relatively small as would be expected for a rare disease with orphan designation. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant cystic fibrosis clinical studies with mannitol inhalation powder

ID [Year*]	**Study Characteristics** **- Patient age, mean (range)** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variables §**	**Countries or Region (% US patients)**
Dose-ranging					
202 [2006-2008]	- 19 (7-68) yrs - Cystic fibrosis - Crossover, open label - 2 weeks, 1 week washout	Mannitol 40 mg Mannitol 120 mg Mannitol 240 mg Mannitol 400 mg	48	1^{o}: ΔFEV_1	Canada, Argentina (0% US)
Pivotal confirmatory					
301 [2007-2009]	- 23 (6-56) yrs - Cystic fibrosis - Parallel arm, blinded - 26 weeks	Mannitol 400 mg Control	176 118	1^{o}: ΔFEV_1 predose from baseline through week 26 2^{o}: ΔFEV_{25-75}, FVC, pulmonary exacerbation, QOL using CFQ-R, rescue	UK, Ireland, New Zealand, Australia, (0% US)

ID [Year*]	**Study Characteristics** **- Patient age, mean (range)** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variables §**	**Countries or Region (% US patients)**
				antibiotic use, hospitalization	
302 **[**2008-2010]	- 20 (6-53) yrs - Cystic fibrosis - Parallel arm, blinded - 26 weeks	Mannitol 400 mg Control	184 121	1^o: ΔFEV_1 predose from baseline through week 26 2^o: $\Delta FEV_{25-75,}$ FVC, pulmonary exacerbation, QOL using CFQ-R, rescue antibiotic use, hospitalization	US, Canada, EU, Argentina (~46% US)

* Study ID, and [year study subject enrollment started-ended]
† Mannitol = mannitol inhalation powder 400 mg twice daily; Comparator = mannitol inhalation powder 40 mg (felt to be sub therapeutic) twice daily
‡ ITT, number randomized and received at least one dose of study medication
§ Primary efficacy variables and selected secondary efficacy variables are shown

b. Design and conduct of studies

Study 202 was crossover in design, conducted in patients with CF with FEV1 of 40-90% predicted. The design of the study was problematic because all patients began their treatment sequence with the highest 400 mg twice-daily dose with subsequent randomization to other treatments.

Studies 301 and 302 were similar in design. These were parallel group studies conducted in patients with CF with FEV1 of 30-90% predicted for study 301 and 40-90% predicted for study 302. Patients with lung transplant or listed for lung transplant, and those with a history of significant hemoptysis (> 60 mL within 3 months of enrollment) were excluded. Patients were allowed to continue their chronic medication regimens, however, the use of inhaled hypertonic saline, a commonly used but not FDA-approved treatment for CF, was not permitted. Patients were initially screened to determine eligibility and randomized to treatment arms once they were determined to be eligible, but start of study drug occurred after 2-5 weeks of the screening period. Screening eligibility included negative mannitol test following procedure described in section 2 above. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. The study had 26 weeks of randomized treatment period where mannitol 400 mg twice daily or control was administered in a blinded way, followed by 26 weeks of open label treatment period where patients completing the randomized treatment period were offered the opportunity to continue mannitol 400 mg twice daily with the aim of gathering safety data for a total of 52 weeks. The randomized treatment period had clinic visits at weeks 0 (baseline, just prior to start of randomized treatment), 6, 14, and 26. The primary efficacy analysis was specified as mixed model for repeated measures (MMRM), and the efficacy population was ITT defined as all subjects randomized who received at least one dose of the study medication. The MMRM method requires at least one post-treatment visit data. One interim efficacy analysis was planned resulting in the two-sided significance level for the final analysis being adjusted to 0.0498. Safety assessments included adverse event recording, and limited clinical laboratory and hematology measures.

c. Efficacy findings and conclusions

The clinical data suggest that there is a possible numerical improvement of FEV1 in patients with CF with treatment of mannitol, but the data do not provide substantial evidence of efficacy of mannitol for the management of patients with cystic fibrosis.

Dose ranging efficacy data was limited and was generated only from study 202, which suggested a dose related increase in FEV1 for the 120 mg, 240 mg, and 400 mg mannitol doses, with a small numerical decrease in FEV1 for the 40 mg dose. With this limited data Pharmaxis decided to study the 400 mg dose in pivotal confirmatory studies 301 and 302, and use 50 mg mannitol as control in these studies. This decision was not unreasonable because conducting large dose ranging study is difficult with a limited pool of available patients with CF. Using mannitol as control was necessary because of sweet taste of mannitol that made blinding difficult without using a sweet tasting agent.

One of the major problems with the pivotal confirmatory studies was that a large number of patients discontinued from the studies and the discontinuations were more common in the mannitol groups than control groups. As shown in Table 2, the discontinuation was seen mainly in study 301, but also occurred in study 302. The discontinuations occurred at all time points, including before receiving study drug, after receiving study drug but prior to any post-baseline efficacy assessment, and also later during the 26 weeks of treatment (Table 2). The large number of discontinuations creates problems as it necessitates exclusion of subjects with no post-baseline data from the analysis because the protocol specified MMRM analysis requires at least one post-treatment visit data and imputation of missing data for other subjects who reported some but not complete post-baseline scores. Exclusion of subjects and/or imputation of missing data can introduce bias, which was particularly a problem in these studies because the discontinuations did not occur at random, and occurred more in mannitol treatment arm and was mostly due to patients not able to tolerate mannitol. Because of these discontinuations, the comparison between mannitol and control treatment arms becomes of questionable validity. Patients completing treatment in these two treatment arms are different because patients in the mannitol treatment arm are "tolerators" of mannitol, whereas patients in the control treatment arm are a mixture of "tolerators" and "non-tolerators" as their status of mannitol tolerance are not known.

Table 2. Discontinuation of patients from the studies 301 and 302

	Study 301		**Study 302**	
	Mannitol	**Control**	**Mannitol**	**Control**
Randomized	192	132	192	126
Withdrew before receiving study drug	15	14	8	5
Withdrawn because missing baseline FEV1	1	0	0	0
ITT, (100%)	176	118	184	121
Discontinuations, no post-baseline assessment	20	6	7	1
MITT, shown as n (%)	156 (89%)	112 (95%)	177 (96%)	120 (99%)
Discontinuations, during study	44	26	24	13
Completed 26 week treatment	112 (64%)	86 (73%)	153 (83%)	107 (89%)
Reasons for discontinuations				

	Study 301		Study 302	
	Mannitol	**Control**	**Mannitol**	**Control**
Withdrew by patient	28	22	13	7
Adverse event	29	10	13	5
Physician decision	6	0	2	1
Sponsor decision	1	0	0	0
Other reasons	1	0	3	1

With the limitation created by missing data discussed above, analyses of the primary efficacy variable of change from baseline in FEV1 from the pivotal confirmatory studies are shown in Table 3. Using the protocol specified mixed model for repeated measures (MMRM) method, statistical significant difference between mannitol and placebo was seen in study 301, but not in study 302 (Table 3). The MMRM requires at least one post-treatment visit data; therefore, the MITT (Table 2), was used in this analysis. Using a baseline observation carry forward (BOCF) method on the ITT populations, statistically significant difference between mannitol and control was seen in study 301, but not in study 302 (Table 3). BOCF is not necessarily an ideal method to impute missing data because it may underestimate the variance, but this method provides a conservative estimate of the treatment effect in the ITT population. Using a cumulative responder plot (Figure 1) and responder analyses at specific thresholds (Table 3), where patients with missing data are classified as non-responders, results were mixed. The cumulative responder plots showed fairly consistent separation between mannitol and control arms across various cutoffs of FEV1 values suggesting an effect of mannitol on FEV1; however, tests of differences between these curves at specific thresholds were not statistically significant in study 301.

Study 301 has major limitation because of missing data noted above. Although study 302 does not have this major limitation of missing data, the study did not reach the usually accepted statistical threshold of significance as discussed above (Table 3). There was also another concern with the study. In this study the FEV1 increased by approximately 60 mL from time of screening and randomization (2-5 weeks before starting randomized treatment) to baseline (week 0 of randomized treatment) in the control group, while FEV1 remained stable over this time period in the treatment group. The reason for this change in FEV1 in the control group is unknown.

Table 3. Efficacy analysis from studies 301 and 302

	Mannitol	**Control**	**Comparison, Mannitol - Control**		
			LS Mean	**95% CI**	**p-value**
MITT *: ΔFEV_1 predose from baseline through week 26, in mL					
Study 301 (m=156, c=112)	118	35	83	(39, 127)	<0.001
Study 302 (m=177, c=120)	107	52	54	(-2, 110)	0.059
ITT †: ΔFEV_1 predose from baseline through week 26, in mL					
Study 301 (m=176, c=118)	81	19	62	(15, 107)	0.010
Study 302 (m=184, c=121)	76	12	65	(-5, 134)	0.070
			Odds Ratio	**95% CI**	**p-value**
ITT responder analysis‡: ΔFEV_1 predose from baseline through week 26, in mL					

	Mannitol	Control	Comparison, Mannitol - Control		
			LS Mean	95% CI	p-value
Study 301 (m=176, c=118)					
FEV increase ≥50 mL	73	42	1.2	(0.8, 2.0)	0.420
FEV increase ≥100 mL	62	33	1.3	(0.8, 2.2)	0.312
Study 302 (m=184, c=121)					
FEV increase ≥50 mL	97	48	2.0	(1.2, 3.3)	0.008
FEV increase ≥100 mL	84	43	1.7	(1.0, 2.8)	0.041

* Analysis using MMRM. MITT group is used and excludes subjects with no post-baseline data, and addresses the patient discontinuations by assuming data is missing at random.
† Analysis using BOCF. ITT group is used and 26-weeek data for patients who discontinued is imputed as having not changed from baseline (i.e., 0 is imputed for the change from baseline in FEV1).
‡ Analysis using entire ITT group, patients with missing data classified as non-responders.

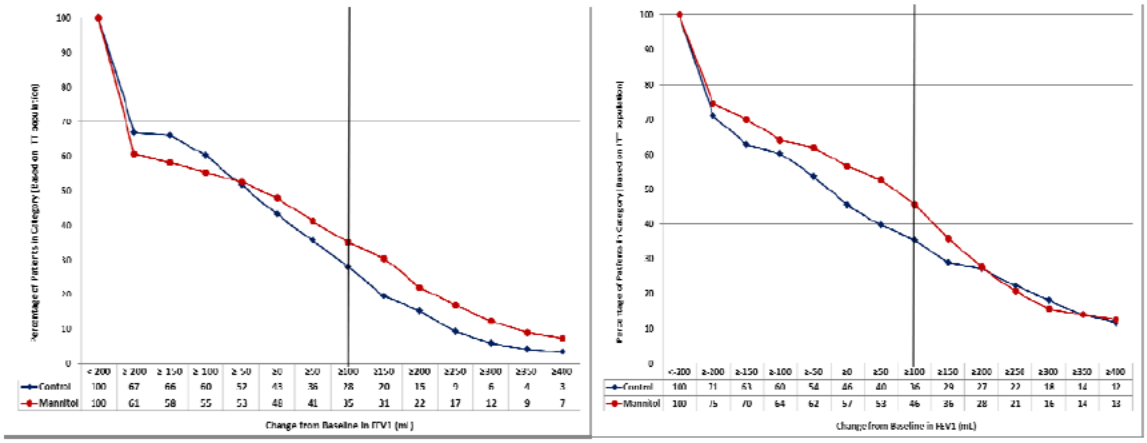

Figure 1. Responder analysis for observed FEV1 change from baseline to week 26 in study 301 (left panel) and study 302 (right panel). Patients with missing data are classified as non-responders.

Efficacy data in pediatric patients ages 6 to 17 years were less impressive, particularly so in study 301. Analysis of the FEV1 data in this subgroup of patients demonstrates minimal to no difference between mannitol and control treatment arms (data not shown in this review).

The FEV1 data analyses presented in Table 3 and Figure 1 and discussed above suggest an effect of mannitol on FEV1. The point estimate of the FEV1 improvement ranged from 54 to 83 mL (2.5% to 4%), but the confidence interval was not able to exclude worsening of FEV1. The FEV1 effect size seen in this program was generally small to modest and not replicated in two studies. The FEV1 efficacy measure in CF is a surrogate, with the expectation that FEV1 improvement with mannitol will result in some direct measure of clinical benefit. None of the secondary efficacy endpoints that directly measure clinical benefit in CF, such as exacerbation, QOL using CFQ-R, rescue antibiotic use, and hospitalization, showed statistically significant difference between mannitol and placebo (data not shown in this review). Given the uncertainties raised by missing data on the FEV1 findings in study 301, lack of statistical significance for FEV1 in study 302, and lack of strong support from secondary efficacy measures of clinical

benefit, the data from the submitted program do not show substantial evidence of efficacy for mannitol for the management of patients with CF to improve lung function.

8. Safety

a. Safety database

The safety assessment of mannitol for CF patients is based primarily on studies 301 and 302 and their long-term extensions (Table 1). A total of 719 patients were administered the mannitol tolerance test of whom 77 failed and the remaining 642 were randomized (Table 2). A total of 600 patients received at least one dose of study treatment and comprise the ITT and the safety population (Table 2). Of the safety population, 361 were exposed to mannitol for at least 6 months and 117 were exposed to mannitol for at least one year. The safety database is reasonable considering that CF is an orphan disease.

b. Safety findings and conclusion

The safety data raises concerns for mannitol related to local lung reactivity leading to many patients discontinuing from the studies, and increased frequency of hemoptysis. This is not unexpected because mannitol is approved (as Aridol) for use for assessment of airway responsiveness and has the ability to cause severe bronchoconstriction in susceptible subjects.

Discontinuations due to tolerability issues are discussed in section 7 above. A large number of patients was not able to tolerate mannitol and discontinued from the study from both treatment arms, but more in the mannitol treatment arm (Table 2).

Hemoptysis was a major safety concern with mannitol. Patients with history of severe hemoptysis (>60 mL) within 3 months prior to the study were excluded from studies 301 and 302. Nevertheless, hemoptysis with varying degree of severity was common during double-blind randomized period, occurring with higher frequencies in mannitol arm compared to control arm (Table 4). Patients who continued to open label treatment had increased frequency of hemoptysis once they switched from control treatment to mannitol treatment (Table 4). Hemoptysis in pediatric patients occurred more in mannitol arm compared to control arm, occurred in higher frequency than in adults, and with frequency increasing with decreasing age (Table 5). Age related increase in hemoptysis may be due to higher lung delivery of mannitol in younger patients, as the dose of mannitol was same across all age groups.

Table 4. Rates of hemoptysis in studies 301 and 302 expressed as number (percentage)

	Double-bling period, 26 wk		**Open-label period, 26 wk**	
	Mannitol N=361	Control N=239	Previous Mannitol N=250	Preveious Control N=180
Any hemoptysis adverse event	34 (9.4)	13 (5.4)	17 (6.8)	13 (7.2)
SAE of hemoptysis	8 (2.2)	2 (0.8)	4 (1.6)	5 (2.8)
Withdrawal due to hemoptysis	6 (1.7)	0	1 (0.4)	2 (1.1)
Severe hemoptysis *	4 (1.1)	1 (0.4)	2 (0.8)	3 (1.7)
* As judged by the investigator				

Table 5. Rates of hemoptysis by age during double-blind period in studies 301 and 302 expressed as number (percentage)

	Adults, ≥ 18 yr		Adolescent, 12-17 yr		Pediatric, 6-11 yr	
	Mannitol N=207	Control N=134	Mannitol N=88	Control N=64	Mannitol N=66	Control N=41
Any hemoptysis adverse event	22 (10.6)	11 (8.2)	8 (9.1)	2 (3.1)	4 (6.1)	0
SAE of hemoptysis	5 (2.4)	1 (0.7)	3 (3.4)	1 (1.6)	0	0
Withdrawal due to hemoptysis	6 (2.5)	0	0	0	0	0
Severe hemoptysis *	2 (1.0)	1 (0.7)	1 (1.1)	0	1 (1.5)	0
* As judged by the investigator						

Some other adverse events that may reflect lung irritation and tolerability also occurred with higher frequency in mannitol treated patients compared to control (cough 26% vs 21%, pharyngolaryngeal pain 12% vs 8%, and bronchospasm 2% vs 0%). CF exacerbation rates did not differ between treatment groups, but this event was difficult to discern because of overlapping pulmonary symptoms from worsening CF and from local lung irritation due to mannitol. The frequency of lung infection with identified respiratory pathogens did not differ between treatment groups.

Given the known profile of mannitol, routine clinical laboratory testing was minimal and included evaluations of hematology and serum chemistries including liver transaminases at baseline and at the end of the double-blind treatment period. There were no significant changes in these parameters through the treatment period. Sputum cultures were also evaluated to determine if mannitol could have an effect on respiratory pathogens observed in CF patients. There was no meaningful difference between the types of pathogens identified in patients treated with mannitol compared to control. Growth of respiratory pathogens in airway is of interest because mannitol can theoretically provide a conducive environment in the lung for growth of pathogens.

There was one death reported in the program. A 15-year old patient with severe CF randomized to control group in study 302 died approximately 5 months into treatment due to worsening lung disease and respiratory failure.

The safety data discussed above raises safety concerns for mannitol. Increased frequency of local lung adverse events and problems with tolerability with mannitol raises the question of whether the mannitol tolerance test (described in section 2 above) used for determining eligibility was too permissive and allowed inclusion of patients who otherwise should have been excluded. As a frame of reference, the FEV1 cut off used to assess bronchial hyperresponsiveness with Aridol is more stringent than what was allowed in studies 301 and 302. Also, it is possible that the mannitol 400 mg twice-daily dose used in the two studies may have been higher than necessary. The observation of increased frequency of hemoptysis seen with decreasing age suggests that at least in pediatric patients the dose was rather high. Comparative efficacy data using the 400 mg twice-daily dose and a lower dose can address this, however; lack of efficacy with the

400 mg twice-daily dose in pediatric patients argues against testing a lower dose, at least in pediatric patients.

c. REMS/RiskMAP

Not relevant in this review cycle as the application will not be approved.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on January 30, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indication, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for mannitol 400 mg twice daily for its proposed indication of management of CF in patients 6 years of age and older to improve pulmonary function. In general, the committee members were concerned with missing data in study 301; lack of demonstrated substantial evidence of efficacy for FEV1 as the finding was not replicated; and lack of support from secondary efficacy measures of clinical benefit. The committee members were concerned with poor tolerability of mannitol, and local lung adverse events, particularly hemoptysis. Committee members were concerned that hemoptysis occurred in a large number of mannitol treated patients where the study protocol screened for hemoptysis and excluded patients with recent history of hemoptysis. The committee members were particularly concerned that pediatric patients 6-17 years of age had very little numerical trends of efficacy, but had higher frequency of hemoptysis compared to adults. Some members of the committee thought that the dose studied in pediatric patients was possibly too high. Committee members thought that some sub group of patients may derive benefit from mannitol, the sub group is not defined in the studies conducted, but the data suggest that the sub group may be adult patients with CF. On voting questions, the Committee voted unfavorably regarding whether there was substantial evidence of efficacy (11 no, 3 yes, and 0 abstain), and also voted unfavorably on the safety of mannitol (11 no, 3 yes, and 0 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were unanimous against approval (14 no, 0 yes, 0 abstain). Overall, panel members felt that Pharmaxis should conduct a rigorous, well-designed program, informed by the two studies to institute design elements that will reduce discontinuation. The panel members felt that the FEV1 threshold for passing mannitol tolerance test used in these studies was high and should be reduced in future studies.

10. Pediatric

CF is an orphan disease and not subject to PREA requirements.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited three US and two ex-US sites recommended by the clinical review team. These sites enrolled slightly larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There was no investigator with significant equity interest in Pharmaxis. No potentially conflicting financial interests were identified.

c. Other

There are no outstanding issues with consults received from OPDP (formerly DDMAC), DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Bronchitol was reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Pharmaxis submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The label was not reviewed in detail because the application will not be approved in this review cycle.

c. Carton and Immediate Container Labels

Not relevant because the application will not be approved in this review cycle.

d. Patient Labeling and Medication Guide

Not relevant because the application will not be approved in this review cycle.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pharmaxis has not submitted adequate data to support approval of mannitol at a dose of 400 mg twice daily for the management of cystic fibrosis in patients 6 years of age and older to improve pulmonary function. The submitted data do not show substantial evidence of efficacy, and raise safety concerns. There is also an unacceptable cGMP recommendation from Office of Compliance for a contract packaging and labeling facility. The regulatory action for this application will be Complete Response.

Below are clinical comments for the Complete Response action letter. Comments from other disciplines will be incorporated from review of other disciplines.

1. The submitted data do not provide a favorable benefit-risk balance to support the use of inhaled mannitol in patients with cystic fibrosis 6 years of age and older. The determination of efficacy based on the two submitted trials are not adequate because of the treatment-related frequent early dropouts in trial 301 for which the primary statistical analyses did not account and the lack of statistical significance in trial 302 for the primary endpoint. Sensitivity analyses conducted on data from study 301 either fail to confirm a treatment effect on the primary efficacy or are problematic in that they attribute a good outcome to some patients who discontinue treatment or they impute a single score without accounting properly for variability. In addition, there was lack of support for efficacy from secondary endpoints in both the studies. Assessment of safety findings show that, compared to control, subjects treated with mannitol 400 mg had a high occurrence of hemoptysis, particularly in pediatric patients, which is concerning and does not balance favorably with the submitted efficacy data, especially in the pediatric population.

   To support approval of inhaled mannitol for the treatment of cystic fibrosis, conduct a clinical program including at least one adequate clinical trial to show substantial evidence of efficacy in patients with cystic fibrosis and balancing safety findings. In order to better balance benefit to risk, consider:1) changing the threshold for passing for the mannitol tolerance test to make it more conservative, 2) including a lower dose of mannitol in addition to the dose that was studied, and 3) testing efficacy and safety initially in adults and later in children informed by data from adults. In the clinical trial include specified criteria that address the specific safety concern of hemoptysis.

b. Risk Benefit Assessment

The overall risk-benefit assessment do not support approval of mannitol for the management of CF in patients 6 years of age and older to improve pulmonary function. The submitted data suggest an effect of mannitol on FEV1, but the effect size was generally small to modest and not replicated in two studies. None of the secondary efficacy measures that measured clinical benefit of CF improved significantly with mannitol. The safety data showed that a large number of patients could not tolerate mannitol due to local lung adverse events and discontinued from the study. Hemoptysis was a major adverse event of concern that occurred with increasing frequency with decreasing age. Pediatric patients 6-17 years of age had very little to no numerical trends in efficacy measures, but had higher frequency of hemoptysis compared to adults.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved in this review cycle.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved in this review cycle.

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/s/

BADRUL A CHOWDHURY
03/18/2013

Cross-Discipline Team Leader Review

Date	February 25, 2013
From	Anthony Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 202049
Applicant	Pharmaxis, Ltd.
Date of Submission	May 18, 2012
PDUFA Goal Date	March 18, 2013
Proprietary Name / Established (USAN) names	Bronchitol/mannitol inhalation powder
Dosage forms / Strength	Oral inhalation/40 mg gelatin capsules
Proposed Indication(s)	For the management of CF in patients 6 years of age or older to improve pulmonary function.
Recommended:	Complete Response

1. Introduction

Pharmaxis Ltd. submitted a 505(b)(2) new drug application (NDA 202049) on May 18, 2012, for the use of mannitol inhalation powder (proposed tradename, Bronchitol) at a proposed dose of 400 mg (contents of 10 capsules) by inhalation twice daily for, "the management of cystic fibrosis (CF) in patients 6 years of age or older to improve pulmonary function. The Applicant is referencing published literature to support the nonclinical pharmacology and toxicology of mannitol. The clinical development program was conducted under IND 70277, which was submitted on November 11, 2004. The PDUFA date for this application is March 18, 2013.

Mannitol inhalation powder is currently marketed as Bronchitol in the EU and Australia in patients with CF ages 18 and 6 years of age, respectively, to improve pulmonary function. A related mannitol inhalation powder product, Aridol, is marketed in the US and elsewhere as part of a single use bronchial challenge test kit, indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma.

This review will provide an overview of the application with a focus on the determination of efficacy and evaluation of safety in patients with CF 6 years of age and older. Note that for consistency with the Applicant's terminology, mannitol inhalation powder will be referred to as "dry powder mannitol" (DPM) in the rest of this review.

2. Background

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan drug population. Lack of properly functioning cystic fibrosis transmembrane conductance regulator (CFTR) ion channel is

responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the presence of tenacious respiratory secretions which are difficult to mobilize, leading to recurrent/chronic pneumonia and lung damage. There is no cure for CF and, until the recent approval of a drug, Kalydeco, indicated for a small subpopulation of CF patients with a G551D mutation in the CFTR, treatment for the majority of CF patients is limited to alleviation of symptoms and treatment of complications. Over the past several decades, with improved care, life expectance has increased significantly, with the current median age of survival to the early-mid thirties. Death is typically due to respiratory failure.

Current therapies, other than antibiotics, used by patients with CF to help manage their disease include mucolytics such as inhaled DNase and hypertonic saline (not approved in US), beta-agonist bronchodilators, pancreatic enzyme supplements, and inhaled corticosteroids (Table 1).

Table 1. Drugs Commonly Used to Treat Cystic Fibrosis (antimicrobials excluded)

Active Ingredient	Trade Name	FDA-approved for CF Indication
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil	Approved as bronchodilators
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilators
Anti-Inflammatory Agents		
Inhaled corticosteroids	Asmacort, Flovent, Pulmicort, Qvar	Approved as asthma controllers
[Source: Approved labeling data from Drugs@FDA..gov]		

Relevant Regulatory History for Dry Powder Mannitol for CF

The IND for DPM (IND# 70,277) was opened in the Division of Pulmonary, Allergy, and Rheumatology Products on November 11, 2004. DPM for the CF indication was given orphan drug status and fast track development status on July 13, 2005, and November 8, 2006, respectively.

- **February 15, 2006: End of Phase 2 meeting:** Issues discussed include Phase 3 study duration, the need for 1-year of safety data to support a chronic use indication, suitable primary and secondary endpoints, clinical pharmacology and nonclinical data needed to support the program, and drug product specifications for both capsules and inhaler device.

- **August 15, 2006: Special Protocol Assessment* (SPA) Request for study 301:** Issues included study duration, endpoints, pooling of control subject data, definition of CF exacerbation, and statistical analyses regarding imputation of missing data. No agreement was reached with the Agency.
  * Concurrence on a SPA creates a binding agreement between a sponsor and the Agency regarding the design, conduct, and analysis of certain types of study protocols, including Phase 3 protocols conducted to support product approval. See: Guidance for Industry: Special Protocol Assessment, May 2002 (*http://www.fda.gov/cder/guidance/index.htm*).

- **August 6, 2007: SPA Request for study 302 and subsequent Type A meeting (telecon):** Issues included study duration to support lung function claim (FEV1) and

exacerbation claims, definition of CF exacerbation, acceptability of the proposed control, and inclusion of children 6 years and older with CF. Specifically, the Agency noted that a study of 6 months duration would not be sufficient to support an exacerbation claim and if labeling claims based on secondary endpoint(s) are desired, pre-specification of these specific endpoints and plans to control type I error for multiplicity would be needed. The Agency also noted that, in general, a clinical program is conducted first in adults before studying children and Pharmaxis will need to justify using the same dose as adults (400 mg twice daily) in the pediatric population. While no agreement was made, the Agency mentioned:

> "that some development programs lend themselves to an SPA agreement, while other programs are not well suited for this type of agreement as certain questions cannot be answered with a "yes" or "no" response, and therefore cannot be part of a binding SPA agreement. These questions will become review issues. However, even though the Agency does not agree with the sponsor on a specific approach, this does not mean that the study cannot be conducted in the manner in which Pharmaxis proposed.

- **December 10, 2010, Pre-NDA meeting:** Pharmaxis and the Agency discussed changes to the statistical analyses that could be used to support registration of DPM. Pharmaxis proposed several post-hoc changes to the statistical analysis plan which it felt would provide a more accurate reflection the efficacy of DPM. These included:
  - After unblinding it was discovered that study 302 had an imbalance between treatment groups in FEV1 at baseline but not at screening. As a result, Pharmaxis proposed characterizing the effect of DPM on the primary efficacy endpoint with post-hoc analyses utilizing change from screening or change from the average of baseline and screening as the response variable instead of the baseline measurement as in the prespecified analysis plan. The Agency mentioned that such post hoc manipulations were generally not acceptable for regulatory purposes and stated that the discrepancy between the screening and baseline FEV1 for control group versus treatment group in study DPM-CF-302 (study 302) creates a significant problem, and raises a question about the study conduct (i.e., problem with blinding). The Agency noted that even though Pharmaxis feels this issue could be addressed by adjusting the baseline measurement, the potential conduct issue creates a large regulatory obstacle to overcome.
  - Pharmaxis also proposed a change to the analysis of the primary efficacy endpoint for study 301. In the original analysis of the primary endpoint for study 301, the response variable in a mixed model for repeated measurements incorporated the change from baseline at baseline (i.e., a zero for all subjects). The sponsor's proposal at the pre-NDA meeting was to re-analyze the primary endpoint utilizing only the post-baseline measurements. The Agency acknowledged the sponsor's intention to reach agreement on proposed types of post-hoc analyses; however, the Agency indicated that it is premature to comment on the adequacy of the proposed methods, stating that this would be

determined as part of the review of the NDA. However, the Agency also stated that:

> "Pre-specified primary analysis methods are generally relied upon heavily in regulatory decision making. Post-hoc analyses are often considered hypothesis generating, and conclusions of such analyses usually require confirmation in a subsequent study."

3. CMC/Device

Dr. Nashed, the CMC reviewer, recommends approval from a CMC perspective, pending an acceptable response to the establishment evaluation request (EER) (see review dated February 11, 2013). All supporting DMFs are adequate. CMC recommends that evaluation of the robustness of the inhaler device should be a post-marketing commitment.

D-Mannitol is a well known, naturally occurring sugar alcohol found in most vegetables. It is used as a nutrient and/or dietary supplement and as an ingredient in numerous drug products. As a dietary supplement, it is generally recognized as safe. As an inhaled product, mannitol inhalation powder is a bronchoprovocation agent approved in the United States as part of a kit (Aridol) for the assessment of bronchial of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. For the treatment of CF, the proposed drug product consists of hard gelatin capsules containing 40 mg of mannitol, without additional excipients, and a breath-actuated hand held dry powder inhaler capable of processing one capsule at a time. The product is package (b) (4) . Each dose consists of inhaling the contents of ten, 40 mg capsules in succession. The proposed dose is 400 mg (10 capsules) inhaled twice daily.

The inhalation device (RS01 Inhaler Model 7 HR), manufactured by Plastiape S.p.A., Italy, is identical to the device used to dose inhaled mannitol in the approved bronchoprovocation test kit, Aridol, except that has a higher resistance to air flow. While the mechanism of action for both inhaler models is the same, the Aridol inhaler was intended for significantly lesser use (maximum 57 capsules) than the use of the inhaler used in the product for CF ((b) (4)). There was some question as to the robustness of the related device during the review of the Aridol NDA, however, because of its limited duration of use (single use test kit with drug administered by a medical professional), it was viewed as acceptable. However, because the proposed duration of use for the CF product (b) (4) , CMC recommends continued evaluation of device robustness and consistency of drug delivery over time as a post-marketing commitment.

There are no outstanding CMC microbiological issues. Stability data support a (b) (4) month expiry.

4. Nonclinical Pharmacology/Toxicology

Dr. Pei, the pharmacology/toxicology reviewer for this NDA, has concluded that the pharmacology and toxicology of mannitol inhalation powder have been adequately studied and that the product is recommended for approval from the pharmacology/toxicology standpoint (see review dated February 5, 3013).

The toxicology of mannitol by non-inhalation use is well understood. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. Because of the extensive clinical and nonclinical data available on mannitol, the toxicology program focused on effects of inhaled mannitol, particularly its effect on the respiratory system. The program included inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol with increased incidences of macrophage aggregation and alveolitis in the 3 month rat study and coughing, laryngeal ulceration and sinus histiocytosis in the 6 month dog study. The no observed adverse effect level (NOAEL) in the 6 month dog study was 43 mg/kg/day.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Agrawal, the clinical pharmacology reviewer, recommends approval from a clinical pharmacology perspective (see review dated February 8, 2013).

While the exact mechanism of its action in the lungs of CF patients is unknown, mannitol, as a hyperosmotic agent, when inhaled into the bronchial tree, may increase hydration of mucus and the periciliary fluid layer thus facilitating clearance of secretions. As a known bronchial irritant, increased cough as a result of its inhalation may also facilitate increased mucus clearance.

The rate and extent of absorption of mannitol after oral inhalation is similar to that observed after oral administration with a 96% relative bioavailability of inhaled mannitol compared to orally administered mannitol. The bioavailability of inhaled mannitol was 59% relative to intravenously administered mannitol. After oral inhalation, the mean time to peak plasma concentration is 1.5 hour. Following oral inhalation, the elimination half-life of mannitol is 4.7 hours regardless of the route of administration (oral, inhalation, and intravenous). It is primarily excreted unchanged via the kidney.

Dose-response is summarized under Section 7 below.

6. Clinical Microbiology

Not applicable as this is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

Overview of the Clinical Program

The overall cystic fibrosis clinical development program for DPM was relatively small as would be expected for a relatively rare disease with orphan designation. Pharmaxis Pharmaceuticals Ltd., has submitted the results from two Phase 3 studies (301 and 302) to

support the regulatory approval of DPM (proposed tradename Bronchitol) at a dose of 400 mg twice daily for the management of CF in patients aged 6 years and older to improve pulmonary function. Support for the dose selected is primarily provided by the findings from a small dose selection study (study 202). The general design of the clinical studies relevant for DPM in patients with CF can be found in Table 2.

Table 2. Relevant Clinical Studies for Inhaled Mannitol for CF

Study/ Years conducted	Study Type	Study Duration	Pt age, (yr)	Disease severity (FEV1)	Treatment groups	N (ITT)	Countries
Dose-ranging and Initial Phase 3 Studies							
Study 202/ 2005-2008	Dose-ranging, open-label, cross-over	Four 2-week Rxment periods	7-68	40-90% predicted	DPM 40 mg DPM 120 mg DPM 240 mg DPM 400 mg	48[a]	Canada, Argentina
Phase 3 Studies							
Study 301/ 2007-2009	Efficacy and safety	26 weeks[b]	6-56	30-90 % predicted	DPM 400 mg Control[c]	177 118	Australia, New Zealand, UK, Ireland
Study 302/ 2008-2010	Efficacy and safety	26 weeks[b]	6-53	40-90 % predicted	DPM 400 mg Control[c]	184 121	United States, Canada, Argentina, Germany, Belgium, France, Netherlands

a. All received 400 mg dose first, then were randomized to receive 40, 120, or 240 mg doses. 4 subjects dropped out after receiving the initial 400 mg dose

b. Pts eligible to enroll in open-label extension of up to 52 and 26 weeks for Studies DPM 301 and 202, respectively

c. Control consisted of 50 mg mannitol inhalation powder, felt to be a subtherapeutic dose

Dose Selection

The dose ranging data for the DPM clinical program primarily comes from study 202 in which the effect of 4 different doses of mannitol inhalation powder (40, 120, 240, and 400 mg administered twice daily) on pulmonary function (FEV1) were assessed. The study was a randomized, open-label, dose response study in 48 patients with CF (ITT population) 7-68 years of age and FEV1 40-90% predicted conducted in Canada and Argentina. While it had a cross-over design (2-week treatment periods separated by a one week wash-out period), its design was problematic in that all patients began their treatment sequence with 2-weeks of treatment with the highest (400 mg) twice daily dose with subsequent randomization to the other 2-week dosing treatment periods. As a result, the value of this open-label, dose-finding study is limited.

The primary endpoints of interest for dose selection were per cent changes in FEV1 and FVC between pre and post-dose measurements. Because of the known capacity of inhaled mannitol to cause acute bronchoconstriction, eligible patients were given a mannitol bronchoprovocation test (mannitol tolerance test, MTT) under medical supervision to screen for airway hyperresponsiveness. Forty-four patients who did not demonstrate airway hyperresponsiveness comprised the ITT population, 44 patients completed the study, and 38 patients were in the PP population (defined as those who completed the study with no missing data).

Given the above-mentioned problematic study design, results from study 202 seem to support the selection of the 400 mg twice daily dose. Improvements in per cent change in FEV1 from baseline were -1.6%, 3.6%, 3.9%, and 8.7% for the 40, 120, 240, and 400 mg twice daily doses, respectively. Results for FVC were similar. Also, based on the lack of response to 40

mg and the need to meet the requirements of matching taste (mannitol has a sweet taste) and appearance, Pharmaxis chose a 50 mg inhaled mannitol twice daily dose (5 mg x10 capsules) as control treatment for phase 3 studies.

Trial Design

The main efficacy and safety studies, 301 and 302, were very similar in design. Both were randomized, double blind, controlled, parallel group trials designed to assess the efficacy and safety of 26 weeks of treatment with DPM 400 mg twice daily in patients ages 6 years and older. The double-blind phase was followed by an open-label phase of up to 52-weeks and 26 weeks duration for trials 301 and 302, respectively. Patients were required to have an FEV1 between 30-90% predicted for trial 301 and between 40-90% predicted for trial 302. Patients with lung transplants or listed for lung transplant, and those with a history of significant hemoptysis (> 60 mL within 3 months of enrollment), were excluded. In general, patients were allowed to continue their chronic medication regimens, however, the use of inhaled hypertonic saline, a commonly used but not FDA-approved mucolytic/expectorant, was excluded.

At the initial screening, eligible patients were screened for airway hyperresponsiveness by receiving a MTT under medical supervision. Patients who were able to complete the MTT successfully were subsequently randomized 3:2 to receive either DPM 400 mg (contents of ten 40 mg capsules) or control (50 mg inhaled mannitol as ten 5 mg capsules) twice daily using a breath-actuated hand held dry powder inhaler. As noted above, a true placebo was not employed primarily due to the need for the control to match the sweet taste of mannitol in the active drug product. Prior to dosing patients were to self-administer a short-acting bronchodilator in order to minimize acute bronchoconstriction. Because patients with CF typically use several inhaled therapies, the following standardized order of treatment was recommended:

1. Short acting bronchodilator
2. Study drug
3. Chest physiotherapy
4. rhDNase (if used)
5. inhaled antibiotics (if used)
6. inhaled corticosteroids (if used)

Evaluations were made at screening to assess for eligibility and, once randomized, at baseline, week 6, week 14, and week 26. For the open-label extension periods, additional evaluations were made at weeks 38, 52, 64, and 78 in study 301 and at weeks 38 and 52 only for study 302.

The primary efficacy endpoint was absolute change from baseline (mL) in FEV1 at week 26. Baseline FEV1 was obtained at week 0 (visit 1).

Other efficacy endpoints included:

- Additional spirometry assessments (FVC, FEF_{25-75})
- Pulmonary exacerbations (PE) based on adverse events entered into the eCRF
- Protocol defined pulmonary exacerbation (PDPE) defined as occurring when patients were treated with IV antibiotics and experienced at least four of the following 12 signs or symptoms: change in sputum production (volume, color, consistency), dyspnea, new or increased hemoptysis, malaise, fatigue or lethargy, fever (> 38°C), anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, FVC or FEV1 decreased by ≥ 10% from previous recorded value, radiographic signs indicative of pulmonary infection, increased cough, changes in physical examination of the chest)
- Quality of life using Cystic Fibrosis Questionnaire-R (CFQ-R) (completed at weeks 0, 14, and 26
- Rescue antibiotic use (recorded in the study diary)
- Days in hospital due to pulmonary exacerbation

Efficacy Statistical Analyses Issues

In this application there are several data analysis issues that are concerning from a statistical perspective. The most significant is the treatment-related early discontinuations that occurred disproportionally more often in the DPM-treated groups than the control groups, albeit much worse in study 301. These early discontinuations, because they occurred before the first post-baseline assessment at 6-weeks, were not captured by Pharmaxis' statistical analysis method (mixed model repeated measures analysis, MMRM). This "modified" intent to treat population (MITT) therefore included only ITT patients who attended the week 6 study visit. As a result, patients who dropped out before week 6 of either study were entirely excluded from efficacy analyses. The effect of early drop-outs is more pronounced for study 301 and results in only 88% (156 of 177) DPM patients being included in the MITT analysis compared to 95% (112 of 118) of control patients. For study 302, 96% (174 of 184) of DPM patients and 99% (120 of 121) of control patients were included in the MITT population.

Compounding the early discontinuation differential missing data problem is the fact that throughout the conduct of the studies there was additional missing data as a result of differential drop-out at weeks 14 and 26 when efficacy assessments (FEV1 determinations) were made. For example, in study 301, at week 26, 66% (116 of 177) of DPM patients compared to 77% (89 of 116) of control patients have observed data while in study 302, 85% (157 of 184) of DPM patients and 92% (111 of 121) of control patients have observed data. While the analyses using the MITT population do not exclude these patients as the MITT population does with the early dropouts prior to week 6, because the pre-specified analysis plan used a mixed model for repeated measurements (MMRM), missing data were not to be imputed. This method is valid only if any missing data occurs at random which was not the case for DPM, a product with known side effects making it difficult to tolerate for many patients.

As a result of the differential drop-out, from a statistical perspective, any MMRM estimate of the treatment effect using the continuous change from baseline in FEV1 outcome would not be reliable. Therefore, sensitivity analyses assessing the impact of the missing data on the treatment effect were necessary. However, these analyses are also problematic in that they do

not include the entire ITT population. Further, regardless of the analysis method, the substantial differential patient drop-out (especially in study 301) ultimately creates two, unequal patient populations; those that can tolerate the active treatment and those that may or may not be able to tolerate the treatment. Any comparison between such unequal study populations for the basis of making a regulatory decision is suspect.

Another analysis issue was that for study 302 the control group's screening FEV1 value was higher by 60 mL (2016 mL vs 1956 mL) than the baseline value. This issue was discussed at the pre-NDA meeting, at which time Pharmaxis proposed to adjust the baseline value for FEV1 by averaging the screening and baseline FEV1 values to arrive at a new "adjusted" baseline. As the screening and baseline values for all other groups for both trials 301 and 302 were very similar, the functional effect of this proposal would be that the difference between treatment groups in the change from baseline in FEV1 would be larger if the baseline was "adjusted" to try to account for the difference between the baseline and screening values. The Agency mentioned that such post hoc manipulations were generally not acceptable and stated that the discrepancy between the screening and baseline FEV1 for control group versus treatment group in DPM-CF-302 (study 302) creates a significant problem, and raises a question about the study conduct (i.e., problem with blinding). The Agency noted that even though Pharmaxis feels this issue could be addressed by adjusting the baseline values, the potential conduct issue creates a large regulatory obstacle to overcome.

One interim efficacy analysis was conducted for each study; therefore, the alpha level for declaring significance of the primary efficacy analysis has been adjusted downwards to 0.0498.

Efficacy Findings

About 66% of enrolled patients completed the 26-week double-blind portion study 301 and 85% in study 302. Early discontinuation occurred more frequently in the DPM group (37% in study 301 and 17% in study 302) than in the control group (28% in study 301 and 12% in study 302) in each study. The primary reasons for premature discontinuation were adverse events (including CF exacerbations) and withdrawal by patient.

The pattern of withdrawal illustrating the greater and more rapid withdrawal in the DPM groups is shown in Table 3.

Table 3. Pattern of Withdrawal (Missing FEV1 Data) by Treatment Group, N (%) ITT Population

	Study CF301 (N=295)			*Study CF302 (N=305)*		
	Number	**Number Missing**	**Percent Missing**	**Number**	**Number Missing**	**Percent Missing**
DPM						
Week 0	176	0	0	184	0	0
Week 6	156	20	11.4	174	10	5.4
Week 14	132	44	25.0	167	17	9.2
Week 26	116	60	34.1	157	27	14.7
Control						
Week 0	118	0	0	121	0	0
Week 6	112	6	5.1	119	2	1.7
Week 14	103	15	12.7	116	5	4.1
Week 26	89	29	24.6	111	10	8.3

[Source: Modified from FDA's Biostatistical review, Table 5, p. 17]

An estimation of treatment compliance was made by counting used and unused blister packs that patients were to return at each assessment visit for compliance checks. However, given the large number of study drop-outs who may not have returned blister packs and the length of time (up to 12 weeks) between assessments that patients would need to collect the packs, the determination of treatment compliance is not felt to be reliable. Nevertheless, median compliance for studies 301 and 302 was reported as between 89-95%.

- *Primary Endpoint: Absolute Change in FEV1*

The primary efficacy endpoint for both phase 3 studies was absolute change in FEV1 from baseline across the 26 week of double-blinded study period.

Following are the efficacy results using Pharmaxis' MMRM analyses for the MITT population. These analyses are problematic in that they do not include the entire ITT population and the MRMM model does not appropriately account for the differential rates of patient drop-out that is higher in the DPM groups. Sensitivity analyses were undertaken by the Applicant and the FDA statistical team with the goal of understanding the impact the missing data had on the pre-specified primary efficacy analyses. Most of the Applicant's sensitivity analyses were inadequate in that they continued to rely heavily on the missing at random assumption (as was the case with the MMRM analysis). These methods therefore impute missing data by preserving the treatment effect that was observed prior to discontinuation, even though DPM patients who have dropped out are no longer taking the drug and would not derive any benefit. Because the single imputation baseline-observation-carried-forward or BOCF approach does not have the above-mentioned faults, it is included as an additional sensitivity analysis in this review.

Using the analysis for the MITT population, for study 301, the adjusted mean value for absolute improvement in FEV1 (mL) from baseline in the DPM group was 118.0 mL versus 34.9 mL in the control group with the overall treatment effect averaged across the 26-week treatment period statistically significantly favored DPM at 83.1 mL; 95% CI (39.5, 126.8) (Table 4).

For study 302, the adjusted mean value for absolute improvement in FEV1 (mL) from baseline in the DPM group was 106.5 mL versus 53.4 mL in the control group (Table 4). While the overall mean treatment effect numerically favored DPM at 54.1 mL; 95%CI (-2.0, 110.3), the treatment difference did not meet the interim-analysis-adjusted α of 0.0498 (p=0.059).

Table 4. Primary Analysis-Absolute Change from Baseline FEV1 (MITT Population)

	DPM 400mg	Control*	Treatment-Comparison DPM 400mg - Control		
			LS mean (SE)	95% CI	p-value
Average effect from week 6 to week 26 [LS mean (SE)]					
Study 301 (m=157, c=112)	118.0 (15.3)	34.9 (17.4)	83.1 (22.2)	(39.5, 126.8)	<.001
Study 302 (m=177, c=120)	106.5 (22.4)	52.4 (25.6)	54.1 (28.5)	(-2.0, 110.3)	0.059

* Control consisted of 50 mg inhaled mannitol which, based on the results of study 202, was felt to be an ineffective dose
SE=standard error.
For Study 301, the p-value, LS mean, and LSMD obtained from an MMRM repeated model with change from baseline in trough FEV1 as response, and the following predictors: treatment, visit, age, rhDNase use, baseline FEV1, disease severity (baseline FEV1 % predicted), gender, region, and subject (as a random effect). This is the model pre-specified in the SAP for study 301.
For Study 302, the p-value, LS mean, and LSMD obtained from a similar MMRM repeated model as was specified in the SAP for Study 301; only differences are replacing region with country and adding the visit by treatment interaction term.
[Source: Modified from FDA's Biostatistical review, Table 7, p. 20]

As mentioned above, the BOCF approach as a sensitivity analysis, while conservative, does not, as the MRMM analyses do, presume that any benefit received by a patient before he/she drops out would be maintained over the rest of the course of the study. Historically, this approach has often been used by the FDA and sponsors to evaluate efficacy in the presence of missing data such as is displayed in these studies. However, as noted in the FDA statistical review, the BOCF also has limitations because variance in data may be underestimated and, as such, any confidence intervals may be overly narrow. Using the BOCF analysis, for Study 301, the difference in primary endpoint between DPM and control is estimated at 62 mL, with 95% confidence intervals from 15mL to 108mL. This supports the primary analysis, but suggests the treatment effect is less than the 83 mL observed in the MMRM analysis. Study 302's difference is consistent with the pre-specified analysis and the result remains not statistically significant (Table 5).

Table 5. Sensitivity Analysis for Primary Endpoint, BOCF, Absolute change from Baseline in FEV1 (mL) (ITT)

	DPM	Control	Treatment Comparison DPM--Control		
			LS Mean (SE)	95% CI	p-value
Baseline Observation Carried Forward (BOCF)					
STUDY 301 (DPM=176, Control=118)	80.6 (14.9)	19.0 (18.2)	61.6 (23.6)	(15.2, 108.0)	0.009
STUDY 302 (DPM=184, Control=121)	76.4 (22.4)	11.7 (27.6)	64.6 (35.5)	(-5.2, 134.5)	0.070

SE=standard error.
The p-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline to week 26 in trough FEV1 as response with treatment as a predictor
[Source: Modified from FDA's Biostatistical Review, Table 8, p. 21]

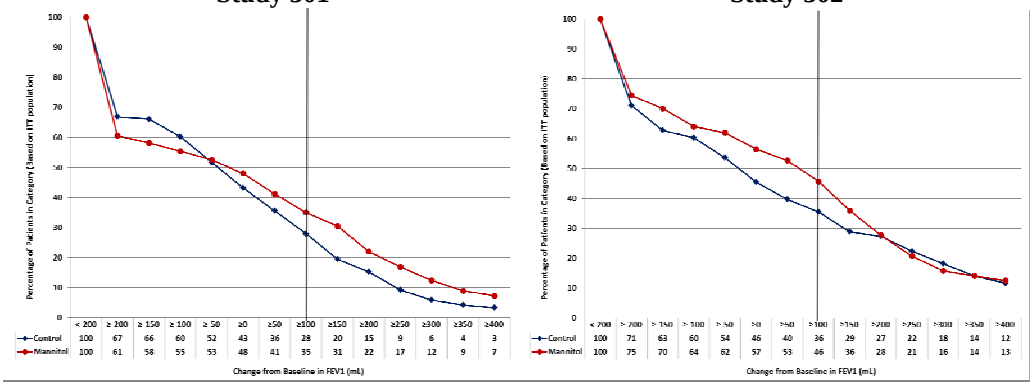
- *Responder Analyses (dichotomized analyses)in the ITT Population*

Responder analyses of the primary endpoint were constructed to provide a presentation of the efficacy data that incorporates the entire ITT population. For this analysis, it was assumed that missing data at weeks 6, 14, or 26 represented a failure of DPM treatment. These data may be viewed as more representative of the entire CF population since those who could not tolerate treatment with DPM would not be expected to receive any benefit.

For each analysis, a patient is classified as having been successfully or unsuccessfully treated according a specific threshold for the change from baseline in FEV1 at week 26, in this case from -200 to +400 mL. The x-axis displays the thresholds required to classify a subject as a successfully treated subject while the y-axis represents the proportion of ITT subjects who achieved the corresponding threshold. The proportion of DPM treated patients achieving each threshold is represented by the red line and proportion of control subjects by the blue (Figure 1).

For both graphs, there is an initial dramatic drop from 100% to approximately 60% in the y-axis, corresponding to the proportion of subjects who dropped out. Dropouts were more frequent in the DPM group compared to control in both studies but particularly so in study 301. However, it is also evident that there is some separation between the treatment groups. After overcoming the initial lower rates of efficacy due to the imputation of failure for patients who dropped out, for each study, the DPM group has a numerically higher proportion of subjects who achieve the increasing change from baseline in FEV1 thresholds than does the control group [red line (DPM) generally lies above the blue line (control)]. With regard to the statistical significance of these findings, using the Van der Waerden test to determine the significance of the difference between treatment groups across a range of thresholds, the changes are not statistically different between treatment groups for either study (p=0.7 for study 301 and p=0.6 for study 302).

Figure 1. Responder Analysis for Observed FEV1 Change from Baseline to Week 26



Source: FDA's Biostatistical Review, Figures 5 and 6, p. 23]

Because statistical hypothesis testing of the treatment effect over the entire range of thresholds, such as with the Van der Waerden test, is not standardized, generally accepted, straight forward statistical analyses were conducted to test for differences at different thresholds for efficacy. Table 6 provides a comparison of treatment groups using several such thresholds in the change from baseline in FEV1: (1) a change of at least 50 mL, (2) a change of at least 75 mL, and (3) a change of at least100 mL. All patients who dropped out before week 26 are considered unsuccessfully treated for this analysis.

For study 301, while numerically the results favored patients treated with DPM, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV1 change from baseline at any of the thresholds examined (p values 0.259-0.420. However, for study 302, differences between treatment groups in the proportion of

patients who achieved a 50 mL, 75 mL, or 100 mL threshold in the change from baseline in FEV1 were associated with p-values generally felt to represent statistical significance (p values 0.007-0.041).

Table 6. Responder Analysis Results for the Primary Endpoint at Week 26 (ITT Population)

Response Definition	DPM 400mg	Control*	Odds Ratio (95%CI)[1] (DPM vs. Control)	p-value
Study 301				
ITT[2]	176	118		
FEV1 absolute increase≥50mL	73 (41%)	42 (36%)	1.23 (0.75, 2.02)	0.420
FEV1 absolute increase≥75mL	66(37%)	35 (30%)	1.34 (0.80, 2.24)	0.259
FEV1 absolute increase≥100mL	62 (35%)	33 (28%)	1.31 (0.78, 2.21)	0.312
Study 302				
ITT[2]	184	121		
FEV1 absolute increase≥50mL	97 (53%)	48 (40%)	1.99 (1.20, 3.31)	0.008
FEV1 absolute increase≥75mL	92 (50%)	44 (36%)	2.01 (1.21, 3.35)	0.007
FEV1 absolute increase≥100mL	84 (46%)	43 (36%)	1.69 (1.02, 2.80)	0.041

* Control consisted of 50 mg inhaled mannitol which, based on the results of study 202, was felt to be an ineffective dose
1. Logistic regression with treatment, rhDNAse use, region (or country for Study 302), baseline FEV1, gender, age, and FEV1 severity at screening (SAP pre-specified model)
2. Included the patients who dropped out before week 6.
[Source: Modified from FDA's Biostatistical Review, Table 9, p. 24]

In summary, given the difference in results when data for missing patients are included in the analyses along with the patients with observed data, from a statistical perspective, a replicated statistically significant effect of DPM on the primary efficacy endpoint has not been demonstrated and, as such, the overall effect of DPM in CF patients in terms of the change from baseline in FEV1 in the ITT population cannot be confirmed.

- *Secondary Efficacy Endpoints*

It is notable that for study 301, no secondary endpoints were distinguished as being part of a pre-specified multiplicity plan to control type I error. For study 302, the protocol did not designate any key secondary endpoints or provide a multiplicity plan for the secondary endpoints; however, the SAP specified a multiplicity correction (using Holmes procedure) for the following secondary endpoints.

  - Change in absolute FVC from baseline across the 26 weeks of blinded treatment overall and by RhDNase use
  - Change from baseline in percent predicted FEV1 over the blinded treatment period
  - Sputum weight post-treatment at baseline
  - Change from baseline in absolute FEV1 across the 26 weeks of blinded treatment in RhDNase use group
  - Change in absolute FEF25-75 from baseline across the 26 weeks of blinded treatment overall and by rhDNase use

- *Secondary Spirometry Endpoints*

Spirometric endpoints other than FEV1 (FVC, FEF_{25-75}) and were included as secondary endpoints in the 2 studies. However, as described above, the analysis of other spirometric endpoints in a continuous form is also problematic due to the treatment-related early discontinuations. When responder analyses in the ITT population using a relative change of 5% were employed, the results are consistent with those for the primary efficacy endpoint,

FEV1, in the ITT population; no difference between treatment groups is observed for study 301 while some marginal differences between treatment groups favoring DPM over control were observed for study 302. Nevertheless, as these endpoints are spirometry-based pulmonary function tests as is the primary endpoint, they would be expected to trend with FEV1 and therefore add little independent support to the primary endpoint.

- *Pulmonary Exacerbations*

As noted above, the protocols outlined a specific definition of pulmonary exacerbations (PDPE) to assess as an efficacy parameter. In addition, the treatment-related early discontinuations previously described may have also impacted these results as patients who discontinued study participation early were not available to report the occurrence of these events. For study 301, the annual rate of PDPE was numerically lower in the DPM group than in the control group (0.78 and 1.05 events per patient per year, respectively) while for study 302 the annual rate of PDPE was very similar between groups (0.52 vs. 0.50 for mannitol and control, respectively). The results for either study were not statistically significant. The determination of PDPE was also problematic in that exacerbations were only assessed for a 26-week period, which is felt to be too short to generate reliable exacerbation data. This was communicated to Pharmaxis at an August 6, 2007, meeting when it was communicated that a study of 6 months duration would not be sufficient to support an exacerbation claim.

The time to first PDPE was also analyzed and there were no statistically significant differences between DPM and control treatment groups. In study 301, the hazard ratio for DPM compared with control was 0.77 (95%CI: 0.47, 1.26, p=0.295) while in study 302, the hazard ratio for DPM compared with control was 0.74 (95%CI: 0.42, 1.32, p=0.308).

- *Other Endpoints*

Sputum weight post treatment at week 14 for study 302 was not specified in the protocol but was added as a key secondary endpoint in the SAP. Sputum weight was not specified as a key secondary endpoint in either the SAP or protocol for study 301. For study 302 there was a 1.4 gram increase in expectorated sputum weight in the DPM group at week 14 study visit compared to control and a 4 gram difference in study 301. From a statistical standpoint, despite the designation of sputum weight as a key secondary endpoint for study 302, it was not part of the multiplicity-corrected set of endpoints so that interpretation of the p-values are difficult in that the appropriate significance level for comparison is unknown. Nevertheless, the clinical benefit of any difference in expectorated sputum weight at a single study visit cannot be determined.

There were no significant differences in hospitalizations, rescue antibiotic use, or quality of life as determined by the CFQ-R between the DPM and control treatment groups when analyzed in the MITT population without correction for multiplicity.

In summary, substantial demonstration of efficacy for DPM indicated for the management of CF in patients 6 years of age or older to improve pulmonary function has not been demonstrated. While Study 301 appeared to demonstrate a statistically significant increase in absolute FEV1 across the 26-week treatment period when the MMRM analysis was utilized, the results were confounded by substantial missing data and differential withdrawal of patients

in the active treatment group which the MMRM statistical analysis method could not account for, thus relying on multiple sensitivity and responder analyses to determine a range of possible FEV1 treatment effect. These additional analyses, conducted by both the Applicant and FDA statistical team fail to confirm a substantial demonstration of a treatment effect on the primary efficacy endpoint for either study 301 or 302. There was no significant support for efficacy from secondary endpoint analyses (analysis of which suffered from the same statistical issues as those for the primary analysis).

In addition, the differential withdrawal of patients in the active treatment group ultimately created different unequal treatment and control patient subpopulations which make any comparison between them for the purpose of determining efficacy suspect. Further, any potential increase in FEV1 suggested in Study 301 was not supported by non-spirometric secondary endpoints or the results of Study 302, in which the change in FEV1 between mannitol and control treatment groups failed to reach statistical significance.

8. Safety

- *Overview of the Safety Database*

The safety database for DPM 400 mg twice daily is comprised primarily of the two efficacy and safety trials and their two open-label extension periods. The study designs for the main trials are described in the preceding section. Safety assessments conducted throughout the Phase 3 program included assessments of pulmonary function during the MTT to determine the presence and extent of bronchial hyperreactivity that would preclude randomization and further dosing and the occurrence of adverse events throughout the studies. Given the known safety profile and metabolism of mannitol, laboratory assessments such as blood chemistry and hematology were minimal.

CF is regarded as an orphan disease with approximately 30,000 persons with the disease in the US. For the DPM 400 mg twice daily program, the safety population includes 361 patients exposed for at least 6 months and 117 patients exposed for at least one year.

For the study 301 and 302 combined safety population, a total of 719 patients were administered the MTT to assess for airway hyperreactivity to determine eligibility for randomization. A total of 77 patients either failed the test outright as a result of decreased FEV1, could not tolerate the dose as demonstrated by the inability to complete inhalation of the 10 mannitol capsules that comprised the 400 mg dose, or otherwise withdrew prior to randomization. As a result 642 patients were randomized. An additional 42 patients withdrew in the 2-5 week period between randomization and the start of study drug administration. This left 600 randomized patients who received at least one dose of study drug and comprised the main safety population.

Approximately 23% per cent of the study population was from the United States with the rest from the European Union or Australia/New Zealand. As would be expected for CF, the demographics of the overall patient populations are notable for a study population that was almost exclusively Caucasian (97% for the combined studies). Males and females were generally evenly matched except for a modest preponderance of males (60%) in the DPM treatment group in study 301. Mean age for the study populations was similar, approximately 23 years for study 301 and 20 years for study 302. Across both studies, more than 50% of the

patients were adults (≥18 years), with 25% and 18% of patients being adolescents (12-17 years of age) and children (6-11 years of age), respectively. As you would expect from the greater mean age, there were more adults in study 301 (64%) than in study 302 (50%). Baseline FEV1, both as absolute volume and as per cent predicted, were generally well matched across both studies with mean values of approximately 2 L and 63% predicted, respectively. Weight, height, body mass index were also well matched across treatment groups for both studies. However, more patients in study 302 reported use of DNase at screening (≈75%) compared to trial 301 (≈55%).

- *Deaths*

There was one death reported during the conduct of the DPM program. A 15 year old adolescent with severe CF lung disease in the control group for study 302 received treatment for approximately 5 months; his illness progressed and study drug was halted after hospitalization and pneumothorax. He continued to deteriorate and died of respiratory failure despite mechanical ventilation and a trial of extracorporeal membrane oxygenation.

- *Serious Adverse Events and Discontinuations due to Adverse Events*

In the placebo-controlled trials, overall more patients in the control group experienced SAEs than in the DPM group, 27% vs 21%, respectively. A wide range of events were reported and most events occurred in just 1 or 2 patients. CF exacerbations (described by the term, "condition aggravated") was the most frequent SAE and occurred in 19% and 17% of control and DPM patients, respectively. Hemoptysis was reported more frequently as an SAE in the DPM group compared to control with 8 patients (2%) with hemoptysis compared to 2 patients (1%) of control patients. Other SAEs were infrequent and primarily related to other systemic manifestations of CF such as diabetes, respiratory infections, and intestinal obstruction.

During the several weeks between screening and randomization, several SAEs were reported in patients who had received the MTT as an assessment of airway hyperreactivity. These SAEs, typically CF exacerbations, generally occurred at least several days after the MTT and felt not related.

For the 430 patients who continued into the open-label extension periods, except for hemoptysis, the types and numbers of patients who reported SAEs in the open-label extension were similar as in the 26-week double-blinded period (Table 22, below). While it did not appear as if the incidence of hemoptysis increased over time in patients who received DPM in the double-blind phase and continued receiving it in the open-label periods, for control patients, the number of cases of hemoptysis increased from less than 1% in the double-blind period to about 3% in the open-label extension period.

A total of 41 (11.4%) patients from the DPM group and 15 (6.3%) from the control group withdrew from studies 301 and 302 due to adverse events. Most of the increased number of discontinuations in the DPM group was from respiratory system AEs likely to be associated with inhaled mannitol, including cough, hemoptysis, bronchospasm, chest discomfort, and pharyngolaryngeal pain.

Following are brief discussions regarding adverse events of interest observed in patients treated with DPM 400 mg twice daily.

- *Hemoptysis*

Patients with a previous history of significant hemoptysis episode (>60mL) within the 3 months prior to study enrollment were excluded from phase 3 studies. Nevertheless, during the double-blind, controlled phase of the studies, the occurrence of hemoptysis was 2 to 4 times higher for serious adverse events, adverse events leading to withdrawal, severe AEs, and AEs in patients receiving DPM compared to control (Table 7). For patients who continued into open-label treatment, those who received control in the double-blind phase note an increased reporting of hemoptysis events once beginning DPM that is similar to those patients who received double-blinded DPM treatment.

Table 7. Rates of Reported Hemoptysis Events for Phase 3 Program

	Phase 3 Controlled Studies Double-Blinded Phase		Phase 3 Controlled Studies[a] Uncontrolled Open-Label Phase	
Category	**DPM 400mg N=361 (%)**	**Control* N=239 (%)**	**Prev. DPM 400 N=250 (%)**	**Prev. Control N=180 (%)**
Withdrawal due to AE-Hemoptysis	6 (1.7)	0	1 (0.4)	2 (1.1)
SAE Hemoptysis	8 (2.2)	2 (0.8)	4 (1.6)	5 (2.8)
AE Hemoptysis	34 (9.4)	13 (5.4)	17 (6.8)	13 (7.2)
Severe AE Hemoptysis	4 (1.1)	1 (0.4)	2 (0.8)	3 (1.7)

* Control consisted of 50 mg of mannitol, the active drug product
a= All patients who continued into OL extension received DPM 400mg BID
[Source: Module 5.3.5.3. ISS, Modified from Applicant's Tables 24, 27, 28, 29, 38, 40, 41, 42; ISS Appendix table ist20sum1_101]

The occurrence of hemoptysis was also increased in children who received DPM compared to control (Table 8). In the safety (ITT) population, 4 patients (6.1%) in the DPM 400mg group aged 6 to 11 years reported an AE of hemoptysis, versus none in the control group. In addition, 8 patients (9.1%) of the patients in the DPM 400mg group versus 2 (3.1%) control, aged 12 to 17 years of age, reported hemoptysis. The values between adult groups were similar, at 10.6 vs. 8.2%, respectively.

Table 8. Hemoptysis Events by Age

Phase 3 Controlled Studies Double-Blinded Phase			
Category	**DPM 400mg N (%)**	**Control* N (%)**	**Total N (%)**
Pediatric (6-11 yr)	**N= 66**	**N= 41**	**N= 107 (18%)**
Any Hemoptysis	4 (6.1)	0	4 (6.1)
Severe AE	1 (1.5)	0	1 (1.5)
SAE	0	0	0
WD due to AE	0	0	0
Adolescent (12-17 yr)	**N= 88**	**N=64**	**N= 152 (25%)**
Any Hemoptysis	8 (9.1)	2 (3.1)	10 (6.6)
Severe AE	1 (1.1)	0	1 (0.7)
SAE	3 (3.4)	1 (1.6)	4 (2.6)
WD due to AE	0	0	0
Adult (≥ 18 yr)	**N= 207**	**N= 134**	**N= 341 (57%)**
Any Hemoptysis	22 (10.6)	11 (8.2)	33 (9.7)
Severe AE	2 (1)	1 (0.7)	3 (0.9)
SAE	5 (2.4)	1 (0.7)	6 (1.8)
WD due to AE	6 (2.9)	0	6 (1.8)

* Control consisted of 50 mg of mannitol, the active drug product
[Source: Module 5.3.5.3. ISS, Section 7.3.3, Modified from Applicant's Table 33]

- *Exacerbations (Condition Aggravated)*

Exacerbations were evaluated both as efficacy and safety parameters in the Phase 3 studies. For study 301 but not 302, the annual rate of PDPE was numerically lower in the DPM group than in the control group (full results for PDPE are provided under efficacy secondary endpoints above). With regard to investigator reported exacerbations (reported as "condition aggravated"), a greater percentage of patients (20%) in the DPM group reported SAEs of exacerbations compared to 18% in the control group.

- *Other Adverse Events of Interest*

Cough, pharyngolaryngeal pain, bronchospasm, and pulmonary infections were noted as other adverse events of interest. Cough is ubiquitous in patients with CF but, as would be expected based on the known effects of DPM when inhaled, was reported more frequently as an AE in DPM patients and likely contributed to the poor tolerability of DPM in some patients. Pharyngolaryngeal pain, also reported more commonly in DPM treated patients also contributed to the lack of tolerability in patients. On the other hand, there did not appear to be a significant increase in the overall incidence of bronchospasm or a change in pulmonary respiratory pathogens detected in CF patients who received DPM.

- *Common Adverse Events*

With regard to common adverse events, the overall rate was similar across the treatment arms of the two controlled trials (88-90%; Table 9). Cough was the most common AE reported. Overall, the types of events are to be expected in the CF population, however, AEs likely related to the bronchial irritation as a result of inhaled mannitol powder such as cough,

hemoptysis, pharyngolaryngeal pain, and vomiting were seen more in patients who received DPM.

Table 9. Common Adverse Events in >4% of Patients and Occurring at a Frequency Greater than in Control (Studies 301 and 302)

Event by Preferred Term	DPM 400mg N=361 (%)	Control* N= 239 (%)
Patients with any AE	319 (88)	215 (90)
Cough[a]	93 (26)	49 (21)
Pharyngolaryngeal Pain	44 (12)	18 (8)
Nasopharyngitis	37 (10.2)	23 (9.6)
Hemoptysis	34 (9)	13 (5)
Vomiting[b]	30 (8)	8 (3)
Pyrexia	24 (7)	15 (6)
Diarrhea	17 (5)	6 (3)
Arthralgia	14 (4)	7 (3)

* Control consisted of 50 mg of mannitol, the active drug product
a= Includes the terms "cough," and "productive cough"
b= Includes the terms "vomiting," and "post-tussive vomiting"
[Source: Module 5.3.5.3.28, ISS Appendix Table ist20sum1 101]

Subgroup analysis of AEs by age, gender, and CF severity were evaluated. With regard to children, the pediatric population (< 18 years old) accounted for 43% of the safety data base (259 of 600). In general, the number of patients with any AE (95% vs. 92%) and with any SAE (28% vs. 20%) are both higher for the control group over DPM. Consistent with the overall population, the number of pediatric patients with an AE leading to discontinuation was higher in the DPM 400mg group (6% vs. 3%). Reasons for discontinuation were likely due to inability to tolerate chronic DPM therapy and included: condition aggravated (2), cough (2), chest discomfort (1), hyperventilation (1), pharyngolaryngeal pain (1), asthma (1), and throat irritation (1). The increase in hemoptysis in pediatric patients receiving DPM, especially in the 6-11 year age group, was more notable than in adults (Table 6).

Notable findings also include an almost 2X increase in hemoptysis in CF patients with severe lung disease (defined as an FEV1 < 40%predicted) at 19% vs 10% for the DPM and control groups, respectively.

- *Other Safety Parameters*

Given the known safety profile of mannitol, routine clinical testing for this safety program was minimal but included evaluations of hematology and serum chemistries including liver transaminases at baseline and at the end of the double-blind treatment period. Overall, there were no significant differences in the occurrence of post-baseline laboratory abnormalities throughout the 26-week treatment period between treatment groups. Sputum cultures were also evaluated to determine if DPM could have an effect on respiratory pathogens observed in CF patients. There was no meaningful difference between the types of pathogens identified in patients treated with DPM compared to control.

In summary, from a safety perspective, the safety database also reflected the issues related to dropouts, with higher rates of treatment-related discontinuation for DPM-treated patients throughout the double-blinded treatment periods, at a rate of 2:1 for those on DPM over control. For those patients who were able to tolerate DPM and continue treatment, cough and hemoptysis occurred at consistently higher rates than in controls across all adverse event reporting categories. In the total safety population, hemoptysis was noted in twice as many

DPM 400mg-treated patients than those receiving controls. This small but clear signal for hemoptysis occurred even in the youngest age group of 6 to 11 year-olds, raising issues of safety specifically for pediatric patients. While no patients died from hemoptysis events in the safety population during the conduct of these studies, the long-term effect of the 2-to-4-fold increases in hemoptysis seen in this program, when projected to chronic use over the course of a CF patient's lifetime, is unknown. There were not many additional concerns, with overall numbers, in terms of SAE and AEs, slightly favoring DPM treatment.

9. Advisory Committee Meeting

On January 30, 2013, the Division and Pharmaxis discussed the findings from the inhaled mannitol NDA at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting.

There were 6 points for discussion and voting:

1. (DISCUSSION) Discuss the evidence to support the efficacy of dry powder mannitol (DPM) at a dose of 400 mg twice daily in improving pulmonary function in patients 6 years and older with cystic fibrosis.

2. (DISCUSSION) Discuss the overall safety profile of DPM.

3. (DISCUSSION) Discuss the support for efficacy and the safety profile of DPM in children and adolescents 6-17 years of age.

4. (VOTE) Considering the totality of the data, is there substantial evidence of efficacy for DPM at a dose of 400 mg twice daily for improvement of pulmonary function in patients 6 years and older with cystic fibrosis? If not, what further efficacy data should be obtained?

VOTE: YES: 3 NO: 11

5. (VOTE) Is the safety profile for DPM for the maintenance treatment of patients with cystic fibrosis sufficient to support approval? If not, what further safety data should be obtained?

VOTE: YES: 3 NO: 11

6. (VOTE) Do the efficacy and safety data provide substantial evidence to support approval of DPM at a dose of 400 mg twice daily for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function? If not, what further data should be obtained?

VOTE: YES: 0 NO: 14

With regard to efficacy, the committee noted concern over the relatively small effect size, and the difficulty knowing the true treatment effect, given the differences in comparator groups due to the large number of differential drop-outs especially in study 301. There were some comments that DPM did not show strong statistical evidence that would meet the regulatory definition of substantial evidence. Two members also commented that there did seem to be evidence of efficacy, at least in adults. Another member noted that the first study which met

statistical significance was "plagued with missing data," had no US patients, and saw no differences in children, while the second study which was free of these issues did not demonstrate statistical significance.

With regard to safety, members expressed concern for the high occurrence of hemoptysis in patients receiving DPM, especially children. One member noted that the number of hemoptysis cases in the trials can not be underestimated, as hemoptysis is relatively uncommon in pediatrics and is of concern as the lungs of children are still growing and repeated insult may lead to chronic injury to the airways.

With regard to the overall discussion of risk-benefit, one member commented that there is no benefit in the population <18 years of age. Another member noted that if the sponsor is using FEV1 as a surrogate for efficacy, then it is a poor surrogate and that there was no evidence that the quality of patients' lives were improved on the basis of the improvement in FEV1 observed.

Another member expressed that in the face of a small benefit, the importance of the safety of the drug becomes more prominent, especially for patients that are desperate for a solution, and we should not provide a drug just to give patients something.

10. Pediatrics

The safety and efficacy of DPM in patients 6 to 17 years of age with CF was assessed in both studies 301 and 302. Subgroup analyses suggest that there may be less of a treatment effect in children compared to adults and that the relatively high incidence of hemoptysis compared to control patients was concerning from a safety standpoint (see sections 7 and 8 for a more detailed review).

Patients with CF are an orphan drug population and not subject to PREA, so a PeRC meeting was not scheduled. However, in light of the oral inhalation delivery of DPM through a high resistance inhaler device, it is unlikely that children with CF much less than 6 years of age would be able to generate enough force to adequately administer/deliver the drug to the lungs.

11. Other Relevant Regulatory Issues

- Financial Disclosure: For the trials designated as pivotal (studies 301 and 302), the Applicant acknowledged that no investigators were identified as having a significant financial interest as defined in 21 CFR 54.2(b).

- DSI audits information: At the request of DPARP, the Division of Scientific Investigations (DSI) audited clinical sites that participated in Studies 301 and 302:

    - Study 301: Site #44103, Dr. Upton, Norwich, UK and Site # 44111, Dr. Walshaw, Liverpool, UK
    - Study 302: Site #10131, Dr. Brown, Boise, ID; Site #10116, Dr. Fornos, San Antonio, TX; Site #10125, Dr. Schaeffer, Jacksonville, FL

While inspection of Dr. Brown's site revealed a number of protocol violations related to how spirometry was conducted and data recorded, overall, there were no irregularities identified that would alter the results or interpretation of the data for either study.

- The Division of Medication Error Prevention and Analysis reviewed the proposed proprietary name "Bronchitol" from a safety and promotional perspective and judged it "tentatively" acceptable.

12. Labeling

Based on the Complete Response recommendation from the clinical and statistical teams and the 14 to 0 vote against approval from the PADAC, a substantial label review was not conducted.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is a Complete Response.

- Risk Benefit Assessment

Substantial demonstration of efficacy for DPM indicated for the management of CF in patients 6 years of age or older to improve pulmonary function has not been demonstrated. The determination of efficacy based on the 2 phase 3 studies was complicated by the extent of differential missing data due to patient drop-out higher in the active treatment groups (especially for study 301) which Pharmaxis' statistical analyses did not account for. Using these analyses in a modified ITT population, a modest but statistically significant increase for the primary endpoint of change from baseline in FEV1 across the 26-week treatment period was observed in study 301 while the results of study 302 (p value=0.059) did not meet the usual standard for statistical significance. Subsequent sensitivity analyses and responder curves analyses conducted by the company and the FDA statistical team fail to confirm a substantial demonstration of a treatment effect on the primary efficacy endpoint for either study 301 or 302. There was no significant support for efficacy from secondary endpoint analyses (analysis of which suffered from the same statistical issues as those for the primary analysis).

Regarding the safety of DPM, while inhaled mannitol may cause severe bronchospasm in persons with airway hyperreactivity and its adverse event profile suggests it is a respiratory system irritant, there did not seem to be a significant increase in either bronchospasm in patients treated with DPM or most other adverse events, with the exception of hemoptysis. However, while hemoptysis is known to occur in patients with CF, both adults and children treated with DPM had increased numbers of AEs for hemoptysis, including SAEs and severe AEs. This was especially notable in the pediatric population, a population which, typically, would be less likely to have hemoptysis. The lack of additional dose exploration in children (6 year old children received the same 400 mg twice daily dose as adults) may have contributed to the increase in hemoptysis observed. In addition, it is possible that lower doses of DPM may be able to demonstrate some level of efficacy without resulting in the significant tolerability problem that resulted in differential drop-out. In this light, it is also possible that the threshold

for "passing" the initial mannitol "tolerance test" is too low, resulting in patients passing the test and continuing therapy who will ultimately drop out due to the inability to tolerate the drug with chronic use. As a result of this issue, if development is continued, justification for the "passing" threshold for the initial mannitol tolerance test (which currently is lower than the discontinuation of dosing threshold for the related bronchoprovocation test, Aridol) should be required and additional doses should be evaluated, at least in the pediatric population.

- Recommendation for Postmarketing Risk Management Activities

As DPM will not be approved during this cycle, no post-marketing risk management activities are recommended.

- Recommendation for other Postmarketing Study Commitments

As DPM will not be approved during this cycle, no post-marketing risk studies are recommended.

- Recommended Comments to Applicant

Clinical Efficacy
The submitted data do not provide substantial evidence of efficacy for mannitol inhalation powder for the treatment of cystic fibrosis. The determination of efficacy based on the 2 phase 3 studies was complicated by the extent of differential missing data due to patient drop-out higher in the active treatment groups (especially for study 301) which your statistical analyses did not account for. Subsequent sensitivity analyses and responder curves analyses conducted by both you and the FDA statistical team fail to confirm a substantial demonstration of a treatment effect on the primary efficacy endpoint for either study 301 or 302. In addition, there was little support for efficacy from secondary endpoint analyses (analyses of which suffered from the same statistical issues as those for the primary analysis).

To support approval of inhaled mannitol for the treatment of patients with CF, conduct a clinical program including at least one adequate and well-controlled clinical trial demonstrating substantial evidence of efficacy in patients with CF. All trial(s) must have an appropriate pre-specified statistical analysis plan and adjustments for multiplicity. We recommend that because of the major issue of differential drop-out in patients receiving inhaled mannitol that, in order to ensure study treatment populations are comparable, that additional trial(s) incorporate a run-in phase during which patients unable to tolerate inhaled mannitol may be identified and excluded from randomization such that the true treatment effect of inhaled mannitol could be quantified.

Safety
With regard to safety, we have concern for the high occurrence of hemoptysis in adults and especially children treated with inhaled mannitol in which hemoptysis was noted in twice as many DPM 400mg-treated patients than those receiving controls. This small but clear signal for hemoptysis occurred even in the youngest age group of 6 to 11 year-olds, raising issues of safety specifically for pediatric patients. While no patients died from hemoptysis events in the safety population during the conduct of these studies, the long-term effect of repeated episodes

of hemoptysis that would likely be seen with chronic use over the course of a CF patient's lifetime, is unknown. In addition, the clinical program had significant issues related to treatment-related dropouts, with higher rates of discontinuation for DPM-treated patients throughout the double-blinded treatment periods, at a rate of 2:1 for those on receiving inhaled mannitol over control. This issue may, in part, be related to a too lenient threshold for "passing" the initial mannitol tolerance test resulting in patients passing the test and continuing therapy who will ultimately drop out due to adverse reactions with continued use.

In order to support the safety of chronic use of inhaled mannitol to improve lung function in CF patients, you will need to demonstrate acceptable safety as it pertains to the increased occurrence of hemoptysis as well as overall tolerability in the indicated population. To accomplish this, both a justification for the threshold to establish the initial tolerance of inhaled mannitol should be provided as well additional dose exploration, especially in children, which may result in a dose(s) of inhaled mannitol which may prove to be efficacious while providing an improved risk-benefit profile.

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/s/

ANTHONY G DURMOWICZ
02/25/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 202-049 (Cross references: IND 70,277)
Supplement #:	S000
Drug Name:	Bronchitol (Mannitol inhalation powder capsules 400mg, DPM)
Indication(s):	Management of cystic fibrosis patients to improve pulmonary function
Applicant:	Pharmaxis Ltd
Date(s):	Received 5/17/2012; PDUFA due date 3/17/2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Ruthanna C. Davi, Ph.D., Secondary Reviewer
	Joan Buenconsejo, Ph.D., Team Leader
	Thomas Permutt, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Kimberly Witzmann, M.D., Medical Reviewer
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Project Manager:	Angela Ramsey

Keywords: Clinical studies, NDA review, dropouts, missing data

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1 EXECUTIVE SUMMARY

The applicant has submitted the results of two phase 3 studies (DPM-CF-301 and DPM-CF-302, hereafter referred to as CF301 and CF302, respectively) in support of the efficacy of DPM for management of cystic fibrosis in patients age 6 years and older to improve pulmonary function. Studies CF301 and CF302 were similar in design. They were double blind, randomized (stratified according to presence or absence of rhDNase use and for study CF301 Australia or Europe and for study CF302 Argentina, Canada, Germany, Belgium, France, Netherlands, or US), parallel group (DPM, 40mg mannitol x 10 capsules, BID, or control, 5 mg mannitol x 10 capsules, BID), controlled, clinical trials with the primary measure of efficacy being the absolute change in FEV_1 from baseline across the 26 week double blind period.

The overriding statistical concern in the analyses of the efficacy data in studies CF301 and CF302 is the treatment-related frequent early dropouts. Analyses of the primary efficacy endpoint using the pre-specified statistical methods are problematic because they cannot incorporate the entire ITT group and because they require inappropriate assumptions about missing data. Patients who dropped out before week 6 are necessarily entirely excluded from these analyses so that only 156 of 177 (88%) DPM patients and 112 of 118 (95%) control patients are included in the MITT group in study CF301. In study CF302, 177 of 184 (96%) DPM patients and 120 of 121 (99%) control patients are included in the MITT group. Additional missing data at weeks 14 and 26 also occurred differentially by treatment group. In study CF301, at week 26, 116 of 177 (66%) DPM patients and 89 of 118 (75%) control patients have observed data. In study CF302, at week 26, 157 of 184 (85%) DPM patients and 111 of 121 (92%) control patients have observed data. The pre-specified primary statistical analysis method, a mixed model for repeated measures (MMRM), requires an assumption that missing data occurred at random, unrelated to treatment. Since this assumption is violated in these studies, the MMRM analysis estimating the treatment effect is flawed and the MMRM estimates of the treatment effect in the change from baseline in FEV_1 outcome may be systematically larger than the true treatment effect. Therefore, sensitivity analyses assessing the impact of the missing data on the treatment effect were necessary.

Many sensitivity analyses were undertaken by the applicant and by the division with the goal of understanding the impact the missing data had on the pre-specified primary efficacy analyses. Some analyses are better than others but none of them are perfect. While description of these sensitivity analyses may at first make them seem conservative, even punitive, closer examination of the assumptions underlying several of these methods reveal that these methods rely heavily on the missing at random assumption. These methods therefore more or less impute missing data by preserving the treatment effect that was observed prior to discontinuation, even though DPM patients who have dropped out are no longer taking the drug. A sensitivity analysis that does not have these faults is the baseline-observation-carried-forward or BOCF approach. However, BOCF also is not perfect. A single value is imputed for each patient with missing data and is assumed to be the true value that would have been observed if follow-up had been continued. As a result, the statistical precision in the estimate of the treatment effect in all randomized participants is overstated (e.g., the width of the confidence interval for the mean difference between treatment groups is artificially narrow). In summary, none of the sensitivity analyses

provided by the applicant or conducted by the FDA simultaneously imputes a conservative value in terms of estimating the treatment effect while also appropriately representing the statistical uncertainty in the imputed values. It is theoretically conceivable that statistical methods that would achieve both of these goals could be created but such methods are not currently available. In conclusion, while we agree with critics of the method that the BOCF analysis may overstate the statistical significance of results, we also believe BOCF provides a conservative point estimate of the treatment effect in the setting of missing data such as is observed in these studies and for that reason the BOCF results are described here. In study CF301, the difference between DPM and control in the change from baseline in FEV_1 at week 26 is estimated to be 62 mL. This is consistent with the conclusion from the pre-specified primary efficacy analysis that DPM is having a better outcome than control but suggests that the difference between treatment groups is smaller than the treatment effect of 83 mL estimated in the pre-specified analysis. In study CF302, this difference is estimated to be 65 mL and is fairly consistent with the pre-specified analysis. But as previously described, the statistical significance associated with the BOCF analyses is not reliable. As a result, we conclude that while numerical trends indicate there may be a beneficial treatment effect, clear-cut substantial demonstration of a treatment effect on the primary efficacy endpoint has not been achieved in either study.

Continuous responder curves (i.e., empirical distribution functions) illustrating the proportion of DPM and control patients achieving a certain threshold in the primary endpoint by dichotomizing the primary endpoint over a range of possible thresholds allow inclusion of the entire ITT group and account for the treatment-related missing data by considering subjects with missing data nonresponders. In both studies, the DPM group had numerically (but not always statistically significantly) higher proportions of patients who achieved the change from baseline FEV_1 thresholds than did the control group. These numerical trends are consistent with the numerical trends in the MMRM analyses and BOCF approach.

To summarize the conclusions regarding the secondary efficacy endpoints, no statistically significant differences between treatment groups were demonstrated for any non-spirometric endpoint.

Post-hoc exploratory analyses of the frequency of hemoptysis revealed no statistically significant differences between treatment groups in the proportion of patients experiencing hemoptysis and no statistically significant difference in the treatment effect across age groups.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Pharmaxis Ltd., the applicant, proposes Bronchitol (Inhaled Dry Powder Mannitol 400mg capsules twice daily BID, hereafter referred to as DPM), an orally inhaled osmotic agent, for the

management of cystic fibrosis (CF) in patients age 6 years and older to improve pulmonary function. The applicant described the rationale for the product as follows:

> Cystic fibrosis is a progressive, life-threatening, genetic disease. The genetic defect in CF causes airway liquid hyper-absorption that leads to the impairment of mucociliary clearance (MCC), resulting in vulnerability to pulmonary infection, inflammation and consequent permanent loss of lung function. The major cause of morbidity and eventual death among individuals with CF is linked to pulmonary disease and associated declining lung function, resulting in respiratory failure. The primary aim in the treatment of CF lung disease is to slow the decline in lung function that ultimately leads to death.
>
> RhDNase (Pulmozyme®) is an approved mucolytic agent specifically developed to treat CF pulmonary symptoms by improving lung function and reducing pulmonary exacerbations in patients with CF. The applicant stated that mechanistically, rhDNase alters sputum properties but has not been shown to increase MCC. Since Bronchitol functions by increasing MCC, it addresses a medical need common to all CF patients and can provide additional benefit when used in combination with other CF therapies, including inhaled antibiotics and rhDNase.

2.1.2 History of Drug Development

The clinical development program for DPM was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products on November 11, 2004 under IND 70,277 and was granted orphan drug status and fast track development status on July 13, 2005 and November 8, 2006, respectively.

The DPM clinical development program consists of two Phase 1 studies (DPM-PK-101 and DPM-PK-102), three Phase 2 studies (DPM-CF-201, DPM-CF-202 and DPM-CF-203) and two Phase 3 clinical studies (DPM-CF-301 and DPM-CF-302). The applicant requested a Special Protocol Assessment (SPA) for both phase 3 studies, but no agreement was reached between the applicant and the division.

An End of Phase 2 meeting was held on February 15, 2006, SPA request for study CF301 was made August 15, 2006, SPA request for study CF302 was made August 6, 2007 and a subsequent Type A meeting (telecom) was held on November 7, 2007, and a pre-NDA meeting was held on December 10, 2010. Discussion and/or agreements between the applicant and the division resulting from these meetings, that are pertinent to the statistical review of this application, are summarized below.

- Pre-meeting comments and Type A meeting to discuss a SPA request for study CF302 (November 7 , 2007)
    - The sponsor proposed that the primary measure of efficacy would be improvement in FEV_1 and secondary measures would be improvement in other measures of pulmonary function (FVC, FEF_{25-75}), reductions in pulmonary exacerbations, reduction of antibiotic use, reduction of days of hospitalization, and improvement in quality of life. The division advised the Sponsor that "if labeling claims based on any of the secondary endpoint(s) are desired, pre-

specification of these specific endpoints and plans to control type I error for multiplicity in the secondary endpoints are needed."

- The division agreed with the sponsor that the exacerbation definition based on Fuchs JH et al (1994) criteria is an acceptable definition for regulatory purposes while disagreeing with an additional proposal by the sponsor for "early exacerbation" since it was a more subjective definition for exacerbations. The sponsor was also advised that information derived from the clinical trials with regard to exacerbations may, subject to review, be described in the clinical trials section of the label (b) (4)
- The division advised the Sponsor that at least two adequate and well-controlled studies would be needed to establish efficacy in this setting.

- Review of Statistical Analysis Plan for study CF302 (May 2010)
  - The SAP defined the intent-to-treat (ITT) population as all subjects who are randomized and have receive at least one dose of study medication. In response to the sponsor's inquiry regarding the acceptability of this definition the division indicated that to ensure the integrity of the random treatment assignment, the number of subjects randomized but not receiving study drug is expected to be very small, if not zero.
  - In response to an inquiry from the sponsor, the division agreed that analyzing the absolute (i.e., not percent) change from baseline in FEV_1 over the treatment period using a restricted maximum likelihood based repeated measures approach was acceptable. The division also indicated that while the procedures for handling missing data appeared acceptable these may be further evaluated as part of the review of the study report.
- Pre-NDA meeting (December 10, 2010)
  - The sponsor's stated objective for this meeting was, in part, "to discuss the types of analyses … of the clinical data to support registration of Bronchitol [referred to as DPM in this review]". The sponsor proposed several post-hoc changes to the statistical analysis plan which according to the sponsor would provide a more accurate reflection the efficacy of DPM. First, the sponsor proposed characterizing the effect of DPM on the primary efficacy endpoint with post-hoc analyses utilizing change from screening or change from the average of baseline and screening as the response variable since after unblinding it was discovered that study CF302 has an imbalance between treatment groups in FEV_1 at baseline (but not screening). The sponsor also proposed a change to the analysis of the primary efficacy endpoint for study CF301. In the original analysis of the primary endpoint for study CF301, the response variable in a mixed model for repeated measurements incorporated the change from baseline at baseline (i.e., a zero for all subjects). The sponsor's proposal at the pre-NDA meeting was to re-analyze the primary endpoint utilizing only the post-baseline measurements. The division acknowledged the sponsor's intention to reach agreement with the division on proposed types of post-hoc analyses; however, the division indicated that it was premature for the division to comment on the adequacy of the proposed

methods, stating that this would be determined as part of the review of the NDA. The division also stated the following.

- "Pre-specified primary analysis methods are generally relied upon heavily in regulatory decision making. Post-hoc analyses are often considered hypothesis generating, and conclusions of such analyses usually require confirmation in a subsequent study."
- "[since the sponsor proposes] differing statistical approaches in the study reports and/or in portions or all of the Integrated Summary of Efficacy, clear documentation of the statistical approach used in each case is needed to explain why two sources may provide differing results." The sponsor agreed to provide this documentation.

- In pre-meeting correspondence the sponsor claimed that the division had entered into a Special Protocol Agreement (SPA) with the company for study CF302. Although study CF302 was submitted for review by the division as a SPA, the division did not enter into any agreement regarding the conduct or analysis of the study under a SPA.

- Pulmonary-Allergy Drug Advisory Committee Meeting (January 2013)
  - The Committee convened to discuss the new drug application that is the subject of this review.
  - In discussing the efficacy of DPM, the following issues were raised by the Committee: small effect size, statistical issues associated with missing data, occurrence of hemoptysis especially in children, FEV_1 as a surrogate for clinical benefit, and risk benefit arguments when the benefit may be very small.

2.1.3 Specific Studies Reviewed

This original NDA submission describes two Phase 3 efficacy studies in a total of 642 randomized patients (DPM-CF-301 and DPM-CF-302) and three Phase 2 studies in a total of 113 randomized patients (DPM-CF-201, DPM-CF-202, and DPM-CF-203). Among the phase 2 studies, Trial DP-CF-202 is the only dose-ranging study. The focus of this review will be on the one dose-range study DPM-CD-202 (hereafter referred to as study CF202) and on the two efficacy studies DPM-CF-301 and DPM-CF-302 (hereafter referred to as studies CF301 and CF302) in CF patients (Table 1).

Table 1: List of All Studies Included in Analysis

Study ID (Period)	location	Design	Treatment and follow-up period	# of Patients per Arm	Study population
CF202 (DPM-CF-202) (Nov. 2005 – Jun. 2008)	12 centers in Canada 7 and Argentina 5	Cross-over Partial-randomized, Open-label, Multi-doses	2 weeks treatment with 1 week washout	36 patients in mannitol 400mg BID, 240mg BID, 120mg BID, 40mg BID	Cystic fibrosis, aged >7 years, baseline FEV_1 >40% - 80% predicted or a decline in FEV_1 of ≥20% in the last 12 months for those >80% predicted. Patients concurrently using RhDNase or other mucolytic agents were not eligible to join the study.
CF301 (DPM-CF-301) (Apr. 2010 – Aug. 2010)	40 centers in Australia 10, New Zealand 2, United Kingdom 24, and Ireland 4	Randomized Double-blind, Parallel-arm, Placebo-controlled Open-label extension	26 weeks DB treatment followed by 52 weeks of OL treatment	DPM (mannitol 400mg) BID, 177 Control BID (5mg mannitol), 118	Cystic fibrosis, aged >6 years, baseline FEV_1 >30% - 90% predicted, not be pregnant or breast feeding, no intolerance to mannitol or beta agonists, no concurrent use of hypertonic saline or beta blockers for the study duration.
CF302 (DPM-CF-302) (Sep. 2008 – Apr., 2010)	53 centers in 7 countries (USA 28; Canada 3; Argentina 8; Germany 3; Belgium 4; France 6; Netherlands 1)	Randomized Double-blind, Parallel-arm, Placebo-controlled Open-label extension	26 weeks DB treatment followed by 26 weeks of OL treatment	DPM (mannitol 400mg) BID, 184 Control BID (5mg mannitol), 121	Cystic fibrosis; > 6 years of age; FEV_1 >40% and <90% predicted; no concomitant hypertonic saline use; negative (failed) mannitol tolerance test.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location \\...\202049.enx. The information utilized in this review was contained in submission S-0000 modules 1, 2.7, and 5.3.5, and submissions S-0003 to S-0012 module 5 for datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During the course of review, Information Request (IR) letters were sent to the applicant regarding the need for additional documents and/or to address possible errors in the electronic datasets and programs. The applicant's responses to these IR's are described below.

- Replacement datasets for Study CF301 were submitted to correct the protocol population flag in S-003.
- Programs which were used to create the analysis datasets and main efficacy tables were provided in S-004, S-005, and S-006.
- Missing interim report, charter, DSMB meeting minutes, and associated documents for Studies CF301 and CF302 were submitted in S-007 and S-012.
- The datasets related to three interim analyses for Study CF301 (Jan-2008, Aug-2008, and Dec-2008) and three interim analyses for Study CF302 (Jun-2009, Mar-2010, and Sep-2010) were submitted in S-008.
- The corrected ISE exacerbation analysis dataset (adpx.xpt) was submitted in S-011.

3.2 Evaluation of Efficacy

3.2.1 Dose Finding Study

Study CF202 was a phase 2 randomized, open-label, dose response study conducted in 12 centers in Canada and Argentina. The randomization was not stratified by center. The objective of this study was to determine the optimum dose of mannitol required for obtaining clinical improvement in FEV_1 in patients with Cystic Fibrosis (CF).

As shown in Table 2, at the run-in period eligible patients were to be given a Bronchial provocation test using inhaled mannitol (Aridol™) to screen for airway hyperresponsiveness. Those with a negative Aridol™ test result at Visit 1 and a minimum baseline FEV_1 volume of between 40% and 90% of the predicted normal value were eligible for the study. Eligible patients were randomly assigned to receive the following treatment sequences (with one week washout periods between each active treatment period).

400 mg → 240 mg → 120 mg → 40 mg
400 mg → 40 mg → 240 mg → 120 mg
400 mg → 120 mg → 40 mg → 240 mg
400 mg → 120 mg → 240 mg → 40 mg
400 mg → 40 mg → 120 mg → 240 mg
400 mg → 240 mg → 40 mg → 120 mg

Note that this is not a typical cross-over design in that all treatment sequences begin with two weeks of treatment with mannitol 400mg BID.

Table 2: Study flow plan

V1	V2	V3	V4	V5	V6	V7	V8	V9
Day 1	Week 2 & 3	Week 4	Week 5 & 6	Week 7	Week 8 & 9	Week 10	Week 11 & 12	Week 13
Aridol Challenge Randomise	400mg BD	Wash Out	40 or 120 or 240mg BD	Wash out	40 or 120 or 240mg BD	Wash out	40 or 120 or 240mg BD	Follow-up assessment

[Module 5.3.5.1 Study Report Body DPM-CF-202, page 24]

The Statistical Analysis Plan (SAP) was finalized on June 21, 2007. Based on SAP, the primary endpoint was the percentage changes in FEV_1 and FVC between the post-dose and pre-dose measurements for each dose.

Percent change in FEV_1= (post-dose FEV_1 – pre-dose FEV_1)/pre-dose FEV_1
Percent change in FVC= (post-dose FVC – pre-dose FVC)/pre-dose FVC

The secondary endpoints included 1) mean change in FEV_1/FVC, FEF_{25-75}, and PEF before and after treatment periods; 2) presence of acquired bacteria in sputum; 3) frequency and type of

adverse events; 4) quality of life scores; 5) change in treatment effect scores; 6) change in respiratory symptoms scores; 7) change in expectorated sputum volume post treatment.

A linear mixed-effects model with orthogonal contrasts was used to compare mean percent difference in FEV_1 or FVC improvements at doses of mannitol of 40, 120, 240mg relative to the reference dose of 400mg of mannitol. The primary analysis was based on the per-protocol population (PP population) which defined as all patients who completed treatment period with valid spirometry recordings and had 80% compliance or higher. Missing data were not imputed. Patients with missing data were not included in the analyses. Based on the nature of study design (i.e. all patients received mannitol 400mg first), the value of this open-label, dose-finding study is limited. Only descriptive results of this study are provided in this review.

Based on the applicant's sample size calculation, 42 patients were needed. Eighty five patients were enrolled in order to ensure 42 patients not receiving rhDNase would be randomized. Overall 85 patients were included in the safety population. Thirty-seven patients excluded from safety population due to the ineligibility (8), failed Aridol challenge (27), or withdrew prior to study treatment (2). Out of 48 patients in the ITT population, 44 patients (92%) completed the study and 38 patients (79%) were in PP population.

Of the 48 patients included in ITT population 26 (54%) were male and 22 (46%) were female. The majority of these patients were Caucasian (40 (83%) or Hispanic (7 (15%)) with mean age of 19.2 years. Nineteen (40%) patients were aged 18 years and older.

The baseline, change from baseline, and percent change from baseline in FEV_1 and FVC are reported in Table 3, Figure 1, and Figure 2.

Although open to criticism because of the non-random order of treatments, there appears to be a dose response with a 400mg BID mannitol dose providing the greatest FEV_1 change (mean 8.7%), while minimal change to FEV_1 was observed in the 40mg BID dose (mean -1.6%) and the similar results observed for FVC (Table 3). As shown in Figure 1 and Figure 2, the p-values for the comparisons with the 400mg treatment arm were $p<0.001$ for the 40mg in FEV_1 and FVC. Based on this study, the applicant indicated that choosing 50mg mannitol BID (5mg x10 capsules) as control treatment in phase 3 study would be reasonable in order to meet the requirements of matching taste and appearance and sub-therapeutic. Thus 400mg and 40mg doses were utilized in the phase 3 studies.

Table 3: Baseline and Change from Baseline in FEV_1/FVC (ITT, Observed)

	Baseline		Absolute Change		Percent Change	
Treatment	Mean(STD)	Median (Min, Max)	Mean (STD)	Median (min, max)	Mean (STD)	Median (min, max)
FEV_1(mL)						
40mg (n=43)	1876 (713)	1760 (720, 3820)	-34.2 (168)	0 (-510, 240)	-1.6 (9.0)	0 (-19.6, 17.1)
120mg (n=43)	1840 (711)	1800 (760, 3700)	37.9 (150)	40 (-250, 340)	3.6 (10.8)	2.5 (-11.5, 44.7)
240mg (n=43)	1891 (689)	1760 (800, 3580)	76.3 (209)	50 (-320, 580)	3.9 (12.8)	2.7 (-20.5, 33.6)
400mg (n=47)	1872 (659)	1790 (760, 3610)	150.2 (191)	140 (-210, 570)	8.7 (12.4)	6.3 (-12.1, 45.8)
FVC						
40mg (n=43)	2589 (1071)	2240 (1160, 5180)	-37.2 (206)	10 (-660, 360)	-0.9 (7.9)	0.8 (-15.6, 17.7)
120mg (n=43)	2536 (1056)	2260 (103, 4950)	20.0 (206)	40 (-680, 460)	1.7 (9.2)	1.8 (-18.8, 36.2)
240mg (n=43)	2582 (1061)	2230 (1140, 5010)	71.6 (274)	30 (-960, 660)	3.1 (11.7)	1.4 (-26.8, 32.9)
400mg (n=47)	2582 (1059)	2360 (770, 4810)	182.8 (247)	180 (-610, 690)	8.1 (10.9)	6.3 (-16.6, 38.5)

Figure 1: Percent Change from Baseline in FEV_1 for Each Treatment Arm (ITT)

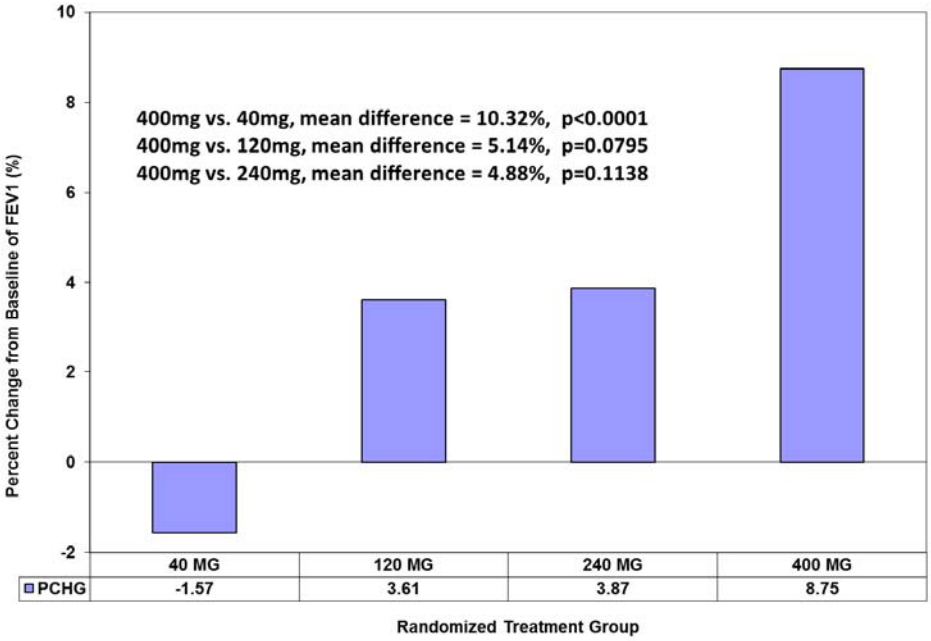
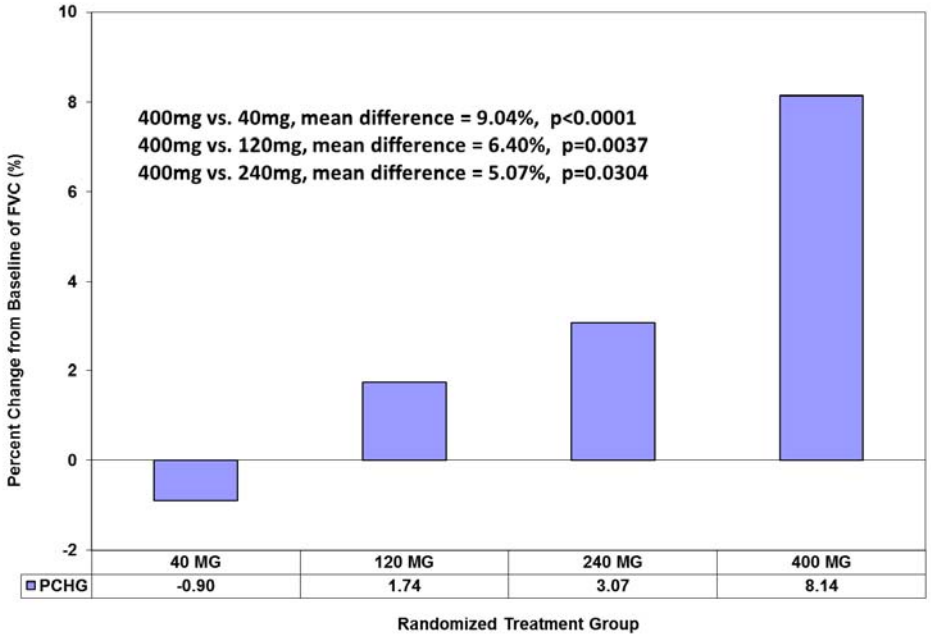


Figure 2: Percent Change from Baseline in FVC for Each Treatment Arm (ITT)



3.2.2 Phase 3 Studies

3.2.2.1 Study Design, Endpoints, and Statistical Methodologies

Studies CF301 and CF302 were similar in design. They were double blind, parallel group, multi-center, randomized studies. Randomization was stratified by rhDNase use (yes/no) and region (Australia and Europe) for study CF301 or country (Argentina, Canada, Germany, Belgium, France, Netherlands, and US) for study CF302. As shown in Figure 3, both studies required a negative outcome to a mannitol tolerance test at 2 to 5 weeks before randomization. The patients who passed the mannitol tolerance test (MTT) during screening were randomized (3:2) to treatment with either DPM (mannitol 40mg x 10 capsules, BID) or control (mannitol 5mg x 10 capsules, BID) for the entire duration of the double blind period. In the open label period (OLP), all patients who continued participation in the trial were treated with DPM for 26 to 52 weeks. Studies CF301 and CF302 were not conducted concurrently, so that study CF302 was designed with experiences obtained during study CF301 known. The applicant has indicated that patients in study CF302 were given more realistic expectations regarding the likelihood of cough following DPM administration than were the patients in study CF301. The differences in design between studies CF301 and CF302 include, in part, the following.

(1.) For study CF301, screening FEV_1 was required to be greater than 30% predicted. For study CF302, the requirement was for FEV_1 to be greater than 40% predicted.

(2.) The open label phase in CF302 was 26 weeks in duration, compared to 52 weeks in CF301.

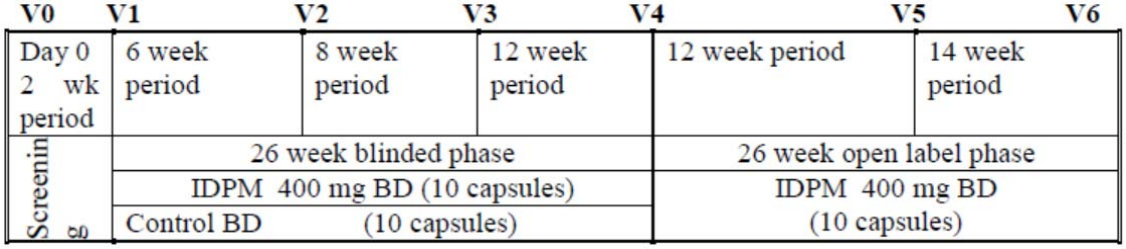
(3.) There were differences in the a priori specified methods for statistical analysis between studies CF301 and CF302 which are described further below.

(4.) There were small differences in doses administered for MTT test:

a) CF301: 5mg, 10mg, 20mg, and 40mg until total dose of 395mg;

b) CF301: 40mg until total dose of 400mg.

Figure 3: Study Design for Phase 3 Study Design (CF301 and CF302)



[Module 5.3.5.1.4.16.1.1, DPM-CF-301 Protocol V5, pg. 439; DPM-CF-302 Protocol V2, pg. 107.]

The primary efficacy endpoint was the absolute change from baseline in FEV_1 across the 26 weeks of the double-blinded treatment period. Screening FEV_1 was obtained at week -5 to -2 (visit 0). Baseline FEV_1 was obtained at week 0 (visit 1). On-treatment FEV_1 measurements were obtained throughout the double blind period (at weeks 6, 14, and 26 after baseline). All pulmonary function testing was done in the clinic.

While numerous discrepancies in the statistical methods proposed for quantifying the primary and secondary efficacy data exist between the protocol and statistical analysis plan for each of the studies, the applicant has indicated that finalization of the SAPs occurred before unblinding. Within this review, we are accepting the methods described in the SAP as the pre-specified methods.

In each study, the SAP-specified analysis method for the primary efficacy endpoint was a mixed model for repeated measurements or MMRM with the following predictors: treatment as a main effect and visit, rhDNasae use, age, gender, baseline FEV_1, disease severity, and region as covariates. There was treatment-by-visit interaction as an additional predictor and country replaced region for study CF302. For both studies, the estimate of the treatment effect is that associated with the main effect of treatment, i.e., the average effect across visits. Both SAPs defined the intent-to-treat (ITT) population as all patients randomized who received at least one dose of study drug and the ITT population was to be used in the primary efficacy analyses. Importantly, missing data were not to be imputed since MMRM was to be employed and MMRM methods can incorporate partly-missing cases. This approach to the missing data requires an assumption that missing data occurred at random; that is the patients who discontinued treatment nevertheless had outcomes like those who continued. If this assumption is violated, MMRM analyses estimating the treatment effect may not be reliable. The SAP-specified sensitivity analyses for the primary efficacy endpoint included analysis of covariance (ANCOVA) at 26 weeks post-baseline based on the last-observation-carried-forward (LOCF) and baseline-observation-carried-forward (BOCF) imputation methods.

One interim efficacy analysis was conducted in each study at which the Data Safety Monitoring Board (DSMB) was to make recommendations regarding continuing or stopping the study, so that to maintain an overall type 1 error rate of 0.05, the final two-sided significance level for reference in the primary efficacy analysis is 0.0498.

For study CF301, no secondary endpoints were distinguished as being part of a pre-specified multiplicity plan to control type I error. For study CF302, the protocol did not designate any key secondary endpoints or provide a multiplicity plan for the secondary endpoints; however, the SAP specified a multiplicity correction (using Holm's method) for the following secondary endpoints.

- Change in absolute FVC from baseline across the 26 weeks of blinded treatment overall and by rhDNase use
- Change from baseline in percent predicted FEV_1 over the blinded treatment period
- Sputum weight post-treatment at baseline
- Change from baseline in absolute FEV_1 across the 26 weeks of blinded treatment in rhDNase use group
- Change in absolute FEF_{25-75} from baseline across the 26 weeks of blinded treatment overall and by rhDNase use

Other efficacy endpoints included the following.

- Absolute change from baseline in FEV_1 over the DB treatment period for rhDNase non-users at screening
- Proportion of subjects achieving an absolute increase of at least 100mL from baseline in FEV_1 at week 26.
- Proportion of subjects achieving a relative increase of at least 5% from baseline in FEV_1 at week 26.
- Proportion of subjects achieving an absolute increase of 5% percent predicted FEV_1 at week 26.
- Pulmonary exacerbations (PE) (AE entered into the eCRF)
- Protocol defined pulmonary exacerbation (PDPE) (defined as occurring when patients were treated with IV antibiotics and experienced at least four of the following 12 signs or symptoms: change in sputum production (volume, color, consistency), dyspnea, new or increased haemoptysis, malaise, fatigue or lethargy, fever (> 38^oC), 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)
- QoL scores using Cystic Fibrosis Questionnaire-R (CFQ-R) (completed at visits 1, 3, 4)
- Rescue antibiotic use (recorded in the study diary)
- Days in hospital due to pulmonary exacerbation

PDPE, rescue antibiotic use or hospitalization due to PDPE, and quality of life (QOL) are endpoints that have been highlighted by the FDA clinical team as being of particular importance as they assess the effect of DPM outside that of spirometric endpoints which are naturally expected to follow patterns similar to FEV_1. So although not corrected for multiplicity, these endpoints will be examined further in this review. The number of PDPE events was analyzed using a Poisson regression model with terms for treatment, age, gender, rhDNase use, disease severity at baseline which is defined as the percent predicted FEV_1, and region/country. For study CF302, a history of pulmonary exacerbations term was added to the model by the applicant. The length of the observation period during the double blind period was included in the model as an offset adjusting for differential lengths of exposure on study for different patients. In the case of overdispersion in the Poisson regression analysis, a similar model using the negative binomial distribution was to be used. In addition, time to first PDPE was analyzed using a Cox proportional hazards model with treatment group, age, gender, rhDNase use, disease severity at baseline, and region as factors. For study CF302, a history of pulmonary exacerbations term was added to the model by the applicant. Rescue antibiotic use due to PDPE and hospitalization due to PDPE were also analyzed with a Poisson regression model as described for PDPE. QOL was measured using the Quality of Life Respiratory Domain from the Cystic Fibrosis Questionnaire and differences between treatment groups were summarized with ANCOVA with the following predictors: treatment, visit, rhDNasae use, age, gender, baseline FEV_1, disease severity, and country.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Three hundred twenty four and 318 patients who satisfied the mannitol tolerance tests were randomized in studies CF301 and CF302, respectively. During the approximately 2 to 5 weeks between randomization and start of study drug administration, there were unusual post-randomization but pre-study drug administration withdrawals in both studies. The reasons for these withdrawals included adverse event, protocol violation, and withdrawal of consent. Although we do not believe these withdrawals were treatment related since study treatment had not yet begun, the occurrence of these withdrawals may bring into question the rigor with which the studies were being conducted. These patients are not included in any efficacy or safety analyses. In study CF301, 20 DPM and 6 control patients withdrew after receiving study drug but without providing any post-baseline data. In study CF302, 7 DPM and 1 control patients withdrew after receiving study drug but without providing any post-baseline data. These withdrawals are likely treatment-related; however, because these patients have not reported any post-baseline measurements, these patients are completely excluded from many of the efficacy analyses. These early discontinuations occurred more frequently in the DPM groups than the control groups in both studies. The remaining patients form the modified ITT, or MITT population. Analyses utilizing the MITT population will provide differences between treatment groups that are impacted by these exclusions. Differences between treatment groups in the efficacy variables could be due to a treatment effect but also could be due to the differential exclusion of patients. Differential early discontinuation continued throughout the treatment period so that 64% of DPM and 73% of control patients in study CF301 and 83% of DPM and 88% of control patients in study CF302 completed the intended 26 week treatment period. These completion rates illustrate the net discontinuation that occurred during studies CF301 and CF302. The discontinuation rates were differential by treatment group in both studies but more prominently so in study CF301 (Table 4).

Overall, the most common reasons for early study discontinuation were “withdrew by patient” and “adverse event”. In order to carryout statistical analyses utilizing either the MITT or ITT population, assumptions regarding these differentially missing data will need to be made. If these assumptions are not reflective of the true nature of these data if it had been observed, the treatment effect estimates resulting from these analyses may be inaccurate.

Table 4: Patient Disposition of Two Efficacy Studies, N (%) ITT Population

	Study CF301 (N=295)			Study CF302 (N=305)		
	DPM	Control	Total	DPM	Control	Total
Population						
Randomized	192	132	324	192	126	318
Withdrew prior to receiving drug	15	14	29	8	5	13
Safety [a]	177 (100)	118 (100)	295 (100)	184 (100)	121 (100)	305 (100)
ITT [b]	177* (100)	118 (100)	295 (100)	184 (100)	121 (100)	305 (100)
MITT [c]	156 (88)	112 (95)	268 (91)	177 (96)	120 (99)	297 (97)
Per-protocol [d]	111 (63)	89 (75)	200 (68)	152 (83)	109 (90)	261 (86)
Completed the blinded phase	112 (63)	86 (73)	198 (67)	153 (83)	107 (88)	260 (85)
Patients continued into the OLP	170 (58)	--	170 (58)	260 (85)	--	260 (85)
Discontinued study treatment	65 (37)	33** (28)	98 (33)	31 (17)	14 (12)	45 (15)
Reason of early discontinuation of study treatment						
AE	29 (16)	11 (9)	40 (14)	13 (7)	5 (4)	18 (6)
Physician decision	6 (3)	0	6 (2)	2 (1)	1 (<1)	3 (1)
Withdrew by patient	28 (16)	22 (19)	50 (17)	13 (7)	7 (6)	20 (7)
Applicant decision	1 (<1)	0	1 (<1)	0	0	0
Other reasons	1 (<1)	0	1 (<1)	3 (2)	1 (<1)	4 (1)

Percentages are based on the ITT population.

a The safety population includes all patients who received at least one dose of study medication.

b The ITT population includes all patients who were randomized and who received at least one dose of study medication.

c Excludes subjects who discontinued prior to week 6, the first post-treatment measurement time.

d The per protocol population includes all patients who were randomized, with no major protocol violations, a minimum of 60% compliance with study treatment and at least two assessments of FEV_1 after commencing study treatment.

*Patient number (b) (6) had missing baseline FEV_1 so was omitted from many efficacy analyses.

**One patient in the control group attended visit 1, reported an AE and did not receive study drug. This patient was not counted in the ITT population.

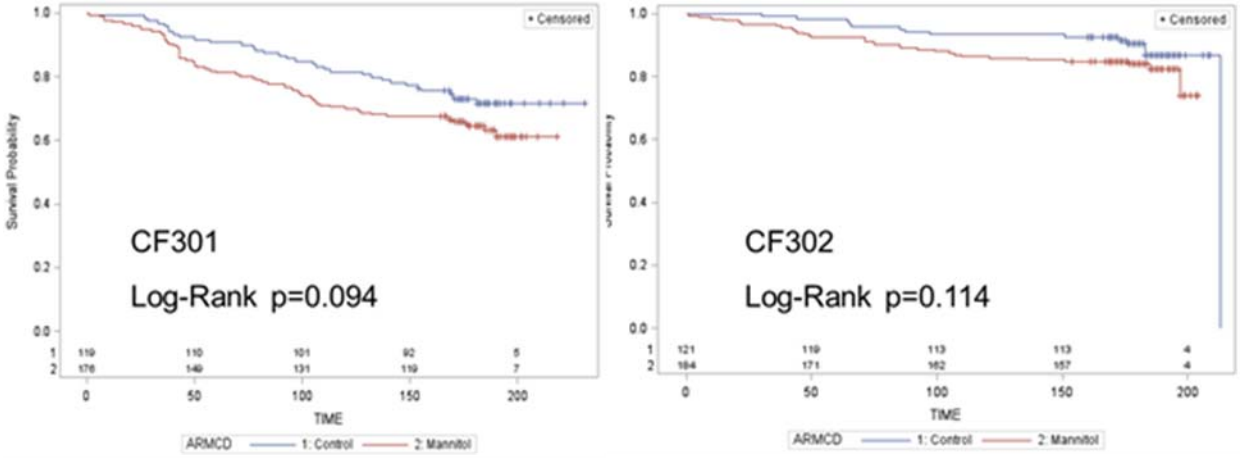
The pattern of withdrawal is shown numerically in Table 5 and graphically with Kaplan- Meier plots of the time to discontinuation for each study in Figure 4. These illustrate the faster withdrawal in the DPM group than the control group.

Table 5: Pattern of Missing FEV_1 Data by Treatment Group, N (%) ITT Population

	Study CF301 (N=295)			Study CF302 (N=305)		
	N	**N Miss**	**Percent missing**	**N**	**N Miss**	**Percent missing**
DPM						
Week 0	176*	0	0	184	0	0
Week 6	156	20	11.4	174	10	5.4
Week 14	132	44	25.0	167	17	9.2
Week 26	116	60	34.1	157	27	14.7
Control						
Week 0	118	0	0	121	0	0
Week 6	112	6	5.1	119	2	1.7
Week 14	103	15	12.7	116	5	4.1
Week 26	89	29	24.6	111	10	8.3

* There was one patient ((b) (6)) missing covariate data (missing baseline FEV_1) and omitted from the analysis.

Figure 4: Kaplan-Meier Plots on Time to the Discontinuation



The frequent and disproportionate early subject-discontinuation rates in these studies, particularly in study CF301, raise concerns regarding the appropriateness of the pre-specified primary efficacy analyses (MMRM). The balance in covariates normally afforded by random treatment assignment in the ITT group in a randomized clinical study is compromised in the MITT groups for these studies because there is a substantial portion of subjects with missing data, the early discontinuation rates are differential by treatment group, and the reasons for early discontinuation are different between treatment groups. The early discontinuations in these studies are commonly due to AE or withdrawal by patient and thus represent a failure of the treatment in that a patient who cannot tolerate the product will not receive efficacy from the product. In addition, missing data after week 6 (at weeks 14 or 26) are more frequent in the DPM groups. Assuming that these patients are simply missing at random, unrelated to treatment (as is assumed in the SAP-specified primary efficacy analyses, the MMRM analysis of the change from baseline in FEV_1) is not appropriate. Therefore, sensitivity analyses designed to assess the impact the missing data is having on the primary efficacy analysis will be necessary and are further described and discussed in section 3.2.2.3.

Demographic and Baseline Characteristics

The vast majority of patients in the two Phase 3 studies were Caucasian (>97%). More than 50% of the patients were adults (≥18), with 25% and 18% of patients being adolescents (12-17 years of age) and children (6-11 years of age), respectively. In study CF301, there were more adults than in study CF302. Use of rhDNase was well balanced between the treatment groups; however, fewer patients used rhDNase in study CF301 than in study CF302. Patients in both studies represented a broad range of disease severity with FEV_1 percent predicted of normal values ranging from 26% to 96% (Table 6).

Table 6: Demographic and Baseline Characteristics of ITT Patients, N (%)

	Study CF301 (N=295)		Study CF302 (N=305)	
Demographic Parameter	DPM (N=177)	Control (N=118)	DPM (N=184)	Control (N=121)
Age at Randomization (yrs)				
Mean (SD)	23.1 (11.7)	22.8 (10.8)	19.6 (9.3)	20.4 (10.2)
Median (Range)	21.0 (6 – 56)	22.0 (6 – 48)	6 – 48	6 – 53
6 – 11	31 (18)	17 (35)	35 (19)	24 (20)
12 – 17	32 (18)	25 (44)	56 (30)	39 (32)
≥18	114 (64)	76 (40)	93 (51)	58 (48)
Sex				
Male	106 (60)	57 (48)	94 (51)	63 (52)
Female	71 (40)	61 (52)	90 (49)	58 (48)
Race				
Caucasian	169 (95)	115 (97)	182 (99)	119 (98)
Asian	3 (2)	2 (2)	0	0
African	1 (<1)	0	2 (1)	2 (2)
Indigenous	1 (<1)	0	0	0
Other	4 (2)	1 (<1)	0	0
Geographic Region				
Australia/New Zealand	61 (59)	43 (41)	--	--
United Kingdom/Ireland	116 (61)	75 (39)	--	--
Non-US	--	--	99 (54)	67 (55)
US	--	--	85 (46)	54 (45)
BMI at baseline (kg/m^2)				
Mean (SD)	21.1 (4.0)	20.4 (3.6)	20.0 (4.1)	19.8 (3.7)
Median (Range)	20.9 (13, 37)	20.0 (14, 31)	19.8 (13, 45)	19.1 (11, 33)
RhDNase Use at Screening, n (%)				
User	96 (54)	67 (57)	137 (74)	92 (76)
Non-Use	81 (46)	51 (43)	47 (26)	29 (24)
Screen FEV_1 (L)				
Mean (SD)	2.08 (0.82)	1.95 (0.71)	2.06 (0.71)	2.02 (0.72)
Median (Range)	1.97 (0.58 – 4.73)	1.84 (0.87 – 3.72)	1.97 (0.69 – 3.85)	1.93 (0.80 – 3.85)
Screen FEV_1 (% predicted) (age at screening used)				
Mean (SD)	62.8 (15.8)	61.3 (15.8)	65.2 (13.9)	64.3 (15.3)
Range	65.8 (29 – 92)	62.5 (31 – 88)	66.0 (34 – 96)	64.4 (36 - 95)
Baseline FEV_1 (L)				
Mean (SD)	2.07 (0.82)	1.95 (0.69)	2.06 (0.77)	1.96 (0.74)
Median (Range)	1.95 (0.71 – 4.92)	1.82 (0.78 – 3.75)	1.95 (0.61 – 4.09)	1.79 (0.75 – 4.12)
Baseline FEV_1 (% predicted) (age at screening used)				
Mean (SD)	62.4 (16.4)	61.4 (16.1)	64.7 (15.7)	62.3 (16.0)
Median (Range)	62.6 (26 – 93)	63.1 (30 – 94)	65.7 (25 – 104)	60.1 (32 - 99)

Note: Results from study report and dataset of ADSL.xpt.

3.2.2.3 Results and Conclusions

Review of Primary Efficacy Endpoint (SAP-specified MMRM and Sensitivity Analyses)

Table 7 shows the results from the SAP pre-specified MMRM model for each study. The average difference between treatment groups in the change from baseline in FEV_1 was 83mL in study CF301 and 54mL in study CF302. In study CF301, this difference is statistically significant with the lower limit of the 95% confidence interval demonstrating that the average results with DPM should be expected to be at least 39mL greater than that of the control group. In study CF302, in a strict sense, the difference between treatment groups of 54 mL is not statistically significant; however, the results may be suggestive of a treatment effect. Considering the lower limit of the 95% confidence interval for the difference between treatment

groups, it is plausible that the mean difference between treatment groups could be less than zero at -2 mL but we acknowledge that almost all of the confidence interval does lie above zero.

Table 7: Primary Analysis - Absolute Change from Baseline in FEV_1 (mL) (MITT)

	DPM	Control	Treatment Comparison DPM – Control		
			LS Mean (SE)	95%CI	P-value
Average effect from week 6 to week 26 (LS mean (SE))					
Study CF301 (m=157, c=112)	118.0 (15.3)	34.9 (17.4)	83.1 (22.2)	(39.4, 126.8)	<.001
Study CF302 (m=177, c=120)	106.5 (22.4)	52.4 (25.6)	54.1 (28.5)	(-2.0, 110.3)	0.059

SE=standard error.
For Study CF301, the p-value, LS mean, and LSMD obtained from an MMRM repeated model with change from baseline in trough FEV_1 as response, and the following predictors: treatment, visit, age, rhDNase use, baseline FEV_1, disease severity (baseline FEV_1 % predicted), gender, region, and subject (as a random effect) with unstructured covariance structure. This is the model pre-specified in the SAP for study CF301. This analysis includes the response at weeks 6, 14, and 26 only. It does not include the change from baseline at baseline in the response variable.
For Study CF302, the p-value, LS mean, and LSMD obtained from a similar MMRM repeated model as was specified in the SAP for Study CF301; only differences are replacing region with country and adding the visit by treatment interaction term.

However, these results may be being influenced by the differentially missing data previously described in section 3.2.2.2. First, these analyses utilize the MITT population, not the ITT population, and therefore are impacted by the exclusion of subjects without post-baseline data allowing for the possibility that the estimates of the treatment effect being shown here are exaggerated. Secondly, subjects with some but not complete post-baseline FEV_1 data are included in the MMRM analyses by requiring an assumption that the missing data be missing at random. Given that the early discontinuation rates are not the same in both treatment groups for either study and the nature of the reasons for withdrawal suggests that early study withdrawal is associated with coughing, the missing data likely did not occur at random and rather are directly linked to the tolerability of the treatment assignment. Because of the assumption in the MMRM analyses that missing data would be similar to observed data if it could have been observed, the estimates of treatment effect from the MMRM analyses represent a treatment effect that could be expected if all patients were able to tolerate DPM. These estimates do not represent a treatment effect in a patient group that is tolerant to DPM. In summary, the statistical assumption associated with the MMRM analyses requiring that the missing data be missing at random is not justified.

Many sensitivity analyses were undertaken by the applicant and by the division with the goal of understanding the impact the missing data had on the pre-specified primary efficacy analyses. These included several multiple imputation methods, pattern mixture models, and tipping point analyses. Some of these analyses are better than others but none of them are perfect. While description of these sensitivity analyses may at first make them seem conservative, even punitive, closer examination of the assumptions underlying several of these methods reveal that these methods rely heavily on the missing at random assumption. These methods therefore more or less impute missing data by preserving the treatment effect that was observed prior to discontinuation, even though DPM patients who have dropped out are no longer taking the drug. Advice received from the statistical members of the Pulmonary-Allergy Drug Advisory Committee in discussing this application echoed these concerns. For these reasons, these types of sensitivity analyses are not presented here. A sensitivity analysis that does not have these faults is the single imputation baseline-observation-carried-forward or BOCF approach.

Historically, this approach has often been used by the Center and sponsors to evaluate efficacy in the presence of missing data such as is displayed in these studies. This approach is generally considered a conservative approach in terms of estimating the treatment effect size and an accurate representation of the efficacy of a product in that subjects who discontinue treatment are considered as having had no change in their baseline status. In addition, this approach was pre-specified as a sensitivity analysis for these studies. However, BOCF also is not a perfect method for dealing with missing data. A single value is imputed for each patient with missing data and is assumed to be the true value that would have been observed if follow-up had been continued. As a result, the statistical precision in the estimate of the treatment effect in all randomized participants is overstated (e.g., the width of the confidence interval for the mean difference between treatment groups is artificially narrow). This concern of an inadequate representation of the statistical uncertainty associated with a single imputation approach was also expressed by the statistical members of the Pulmonary-Allergy Drug Advisory Committee. In summary, none of the sensitivity analyses provided by the applicant or conducted by the FDA simultaneously impute a conservative value in terms of estimating the treatment effect while also appropriately representing the statistical uncertainty in the imputed values. It is theoretically conceivable that statistical methods that would achieve both of these goals could be created but such methods are not currently available.

In conclusion, while we agree with critics of the method that the BOCF analysis may overstate the statistical significance of results, we also believe BOCF provides a conservative estimate of the point estimate of the treatment effect in the setting of missing data such as is observed in these studies and for that reason it is presented here. In study CF301, the difference between DPM and control in the change from baseline in FEV_1 at week 26 is estimated to be 62 mL. This is consistent with the conclusion from the pre-specified primary efficacy analysis that DPM is having more of an effect than control but suggests that the difference between treatment groups is smaller than the point estimate of 83 mL observed in the pre-specified analysis. In study CF302, this difference is estimated to be 65 mL and is fairly consistent with the pre-specified analysis (Table 8). But as described in the preceding paragraph the statistical significance associated with the BOCF analyses is not reliable. As a result, we conclude that while numerical trends indicate that there may be a beneficial treatment effect, clear-cut substantial demonstration of a treatment effect on the primary efficacy endpoint has not been achieved in either study.

Table 8: Sensitivity Analysis for Primary Endpoint (Baseline Observation Carried Forward) - Absolute Change from Baseline in FEV_1 (mL) (ITT)

	DPM	Control	Treatment Comparison DPM – Control		
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	95%CI	p-value
BOCF					
Study CF301 (m=176, c=118)	80.6 (14.9)	19.0 (18.2)	61.6 (23.6)	(15.2, 108.0)	0.009
Study CF302 (m=184, c=121)	76.4 (22.4)	11.7 (27.6)	64.6 (35.5)	(-5.2, 134.5)	0.070

SE=standard error.
The p-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline to week 26 in trough FEV_1 as response with treatment as a predictor

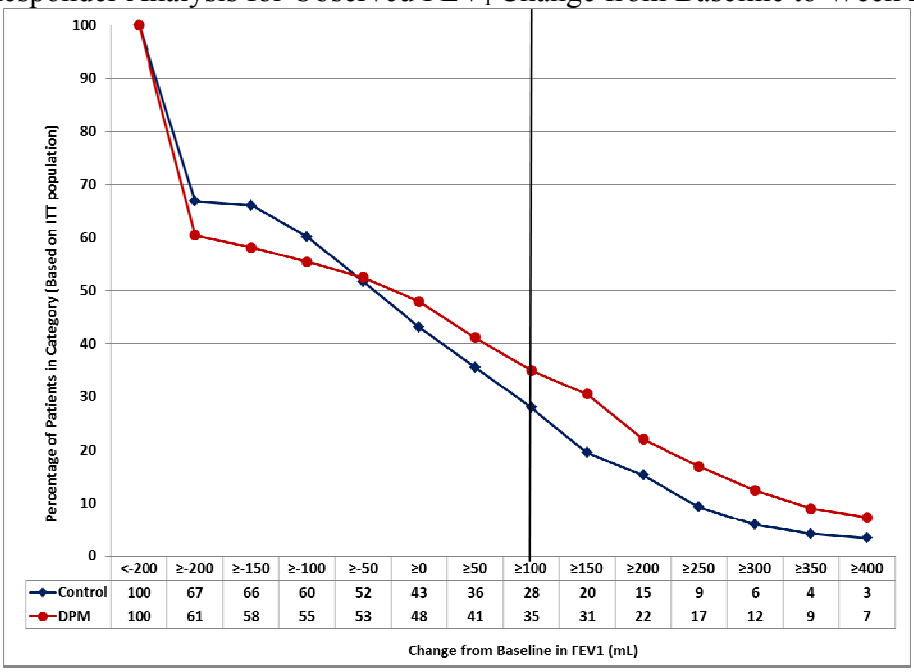
As an additional sensitivity analysis and to supplement the pre-specified and BOCF analyses, we provide a post-hoc presentation of the primary efficacy endpoint which incorporates the entire

ITT population by assuming that patients with missing data are non-responders to treatment. This is likely an appropriate assumption since patients who cannot tolerate the treatment should not be expected to receive any efficacy from the treatment.

Figure 5 and Figure 6 provide continuous responder curves (i.e., empirical distribution functions) for studies CF301 and CF302, respectively. These presentations are developed as follows. Each patient is classified as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the change from baseline in FEV_1 at week 26. This dichotomization of the change from baseline in FEV_1 is repeated across a range of possible thresholds, in this case from -200 to +400 mL. Patients with missing FEV_1 data at week 26 are classified as unsuccessfully treated for all thresholds. In the continuous responder curve, the x-axis displays the thresholds required to classify a patient as a successfully treated patient. The y-axis represents the proportion of ITT patients who achieved the corresponding threshold. The proportion of DPM patients achieving each threshold is represented by the red line and proportion of control patients by the blue. For example, using study CF301, at the vertical reference line of a change from baseline in FEV_1 of 100 mL, the continuous responder plot illustrates that 35% of DPM patients had FEV_1 improved by at least 100 mL while only 28% of control patients experienced such a change.

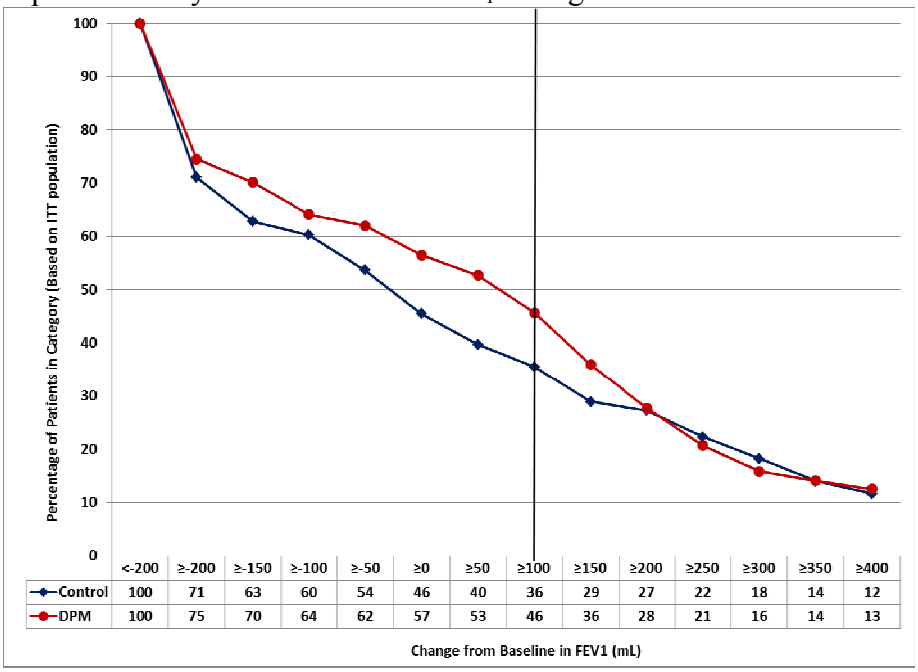
As shown in both figures, there is an initial dramatic drop from 100% to approximately 60% in the y-axis, corresponding to the proportion of patients who dropped out since patients with missing data were classified as unsuccessfully treated for all thresholds. Dropouts were more frequent in the DPM group compared to control in both studies but particularly so in study CF301. Also evident from Figure 5 and Figure 6 is that there is some separation between the treatment groups. After overcoming the initial lower rates of efficacy due to the imputation of failure for patients who dropped out, in each study, the DPM group had a numerically (but not statistically significantly) higher proportion of patients who achieved the change from baseline FEV_1 thresholds than did the control group. This is evidenced by the fact that the red line (DMP) generally lies slightly above the blue line (control) in both figures.

Figure 5: Responder Analysis for Observed FEV_1 Change from Baseline to Week 26 (CF301)



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	67	66	60	52	43	36	28	20	15	9	6	4	3
DPM	100	61	58	55	53	48	41	35	31	22	17	12	9	7

Figure 6: Responder Analysis for Observed FEV_1 Change from Baseline to Week 26 (CF302)



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	71	63	60	54	46	40	36	29	27	22	18	14	12
DPM	100	75	70	64	62	57	53	46	36	28	21	16	14	13

In supplement to the continuous responder plot, Table 9 provides a comparison of treatment groups using several thresholds in the change from baseline in FEV_1: (1) a change of at least 50 mL, (2) a change of at least 75 mL, and (3) a change of at least 100 mL. All patients who dropped out before week 26 are considered nonresponders for these analyses. For study CF301, there were no statistically significant differences between treatment groups in the proportion of DPM responders compared to that of the control patients; however, numerical trends that favored DPM over control were present at each threshold examined. For study CF302, the proportion of subjects who achieved each of the thresholds examined were higher in the DPM group than the control group.

Table 9: Responder Analysis Results for the Primary Endpoints at Week 26

Response Definition	*DPM*	*Control*	*Odds Ratio (95%CI)*[1] *(DPM vs. Control)*	*p-value*[1]
Study CF301				
ITT[2]	176	118		
FEV_1 absolute increase≥50mL	73 (41%)	42 (36%)	1.23 (0.75, 2.02)	0.420
FEV_1 absolute increase≥75mL	66 (37%)	35 (30%)	1.34 (0.80, 2.24)	0.259
FEV_1 absolute increase≥100mL	62 (35%)	33 (28%)	1.31 (0.78, 2.21)	0.312
Study CF302				
ITT[2]	184	121		
FEV_1 absolute increase≥50mL	97 (53%)	48 (40%)	1.99 (1.20, 3.31)	0.008
FEV_1 absolute increase≥75mL	92 (50%)	44 (36%)	2.01 (1.21, 3.35)	0.007
FEV_1 absolute increase≥100mL	84 (46%)	43 (36%)	1.69 (1.02, 2.80)	0.041

1. Logistic regression with treatment, rhDNase use, region (or country for study CF302), baseline FEV_1, gender, age, and FEV_1 severity at screening (model terms chosen based on similarity to terms pre-specified in the primary efficacy analysis model in the SAP)
2. Included the patients who dropped out before week 6.

The continuous responder curves at each visit prior to week 26 were also considered. The patterns in these data are similar to those presented in this report for week 26.

Other Spirometry Endpoints

As for the primary efficacy endpoint, analyses of the other spirometric endpoints are complicated by the treatment-related early discontinuations previously described. For this reason and because the treatment effect on spirometric endpoints generally are expected to be similar to that of the primary efficacy endpoint, cumulative responder plots are provided to summarize these data in a descriptive way (Figure 7 through Figure 9). Dichotomized responder analyses are also provided (Table 10). These results provide conclusions regarding the treatment effect that are generally consistent with that of the primary efficacy endpoint.

Figure 7: Responder Analysis for FVC (mL) Change from Baseline to Week 26 (ITT)

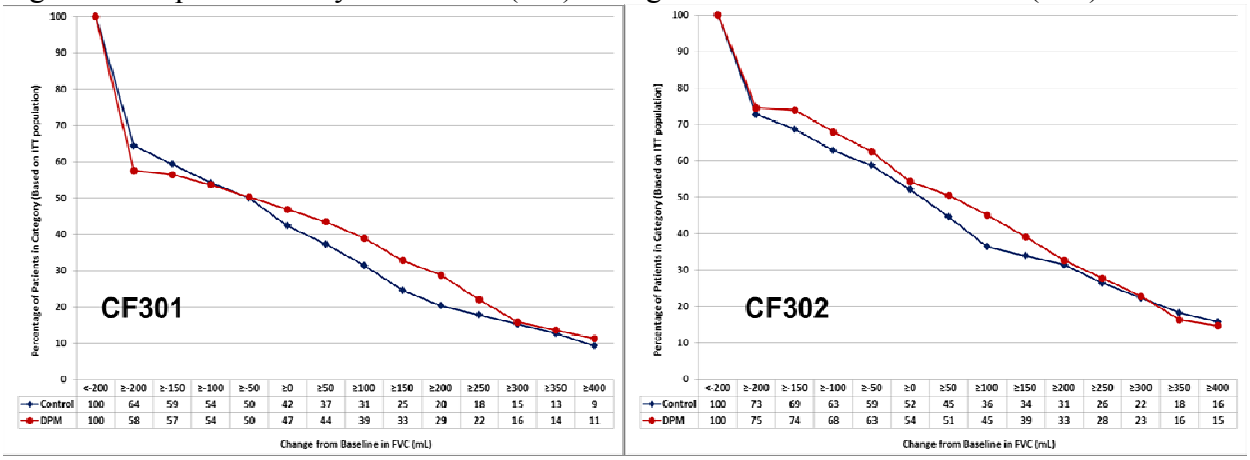


Figure 8: Responder Analysis for Percent Predicted FEV_1 Change from Baseline to Week 26 (ITT)

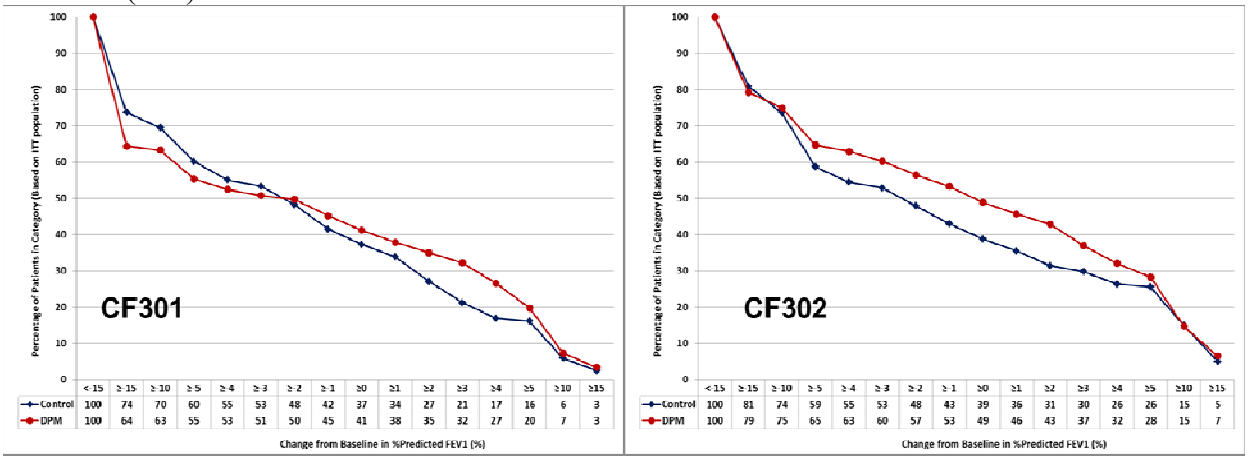


Figure 9: Responder Analysis for FEF_{25-75} (mL) Change from Baseline to Week 26 (ITT)

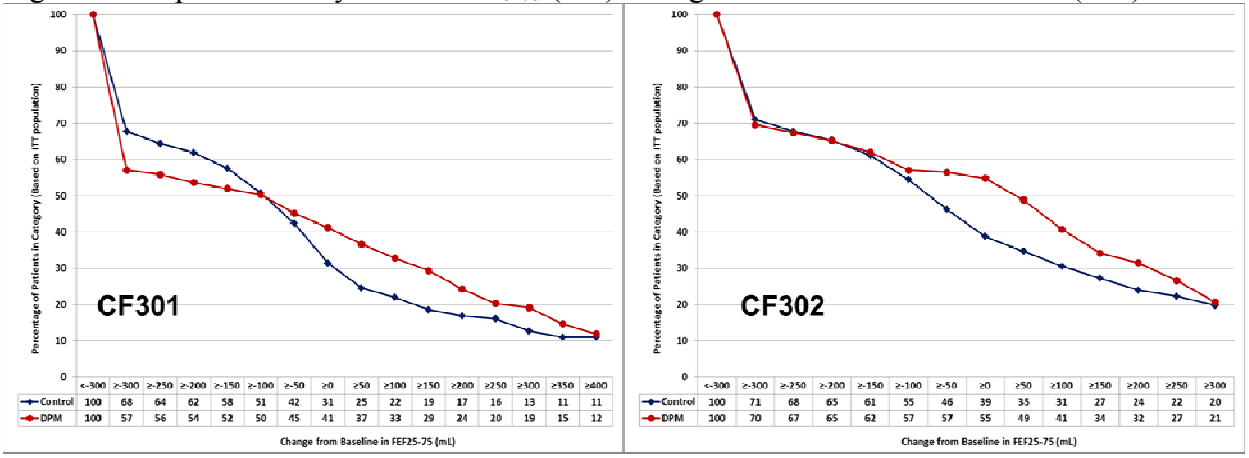


Table 10: Responder Analysis Results for the Secondary Endpoints at Week 26 (ITT)

Response Definition	DPM	Control	Odds Ratio (95%CI)[1] (DPM vs. Control)	p-value[1]
Study CF301				
ITT[2]	176	118		
FEV_1 percent increase ≥5%	64 (36%)	36 (31%)	1.24 (0.74, 2.09)	0.406
Percent predicted FEV_1 increase ≥5%	35 (20%)	19 (16%)	1.26 (0.67, 2.40)	0.470
Study CF302				
ITT[2]	184	121		
FEV_1 percent increase ≥5%	86 (47%)	44 (36%)	1.85 (1.09, 3.13)	0.023
Percent predicted FEV_1 increase ≥5%[3]	52 (28%)	31 (26%)	1.20 (0.69, 2.10)	0.510

1. Logistic regression with treatment, rhDNase use, region (or country for study CF302), baseline FEV_1, gender, age, and FEV_1 severity at screening (model terms chosen based on similarity to terms pre-specified in the primary efficacy analysis model in the SAP)
2. Included the patients who dropped out before week 6.
3. Percent predicted FEV_1 was derived using measured height.

Selected Non-Spriometric-Related Endpoints

To examine the effects of DPM outside that of spriometric-related endpoints and in the absence of any pre-specified multiplicity correction for secondary endpoints in study CF301, the following endpoints were selected by the FDA clinical team for review here: PDPE, rescue antibiotic use for PDPE, occurrence of hospitalization for PDPE, and QOL.

Results for the PDPE endpoint are provided in Table 11. The treatment-related early discontinuations previously described may have also impacted these results. Patients who discontinued study participation early were not available to report the occurrence of these events. While these analyses do adjust for differential exposure time, they also assume missing data would have been similar to the observed data, if it had been observed. In study CF301, the PDPE mean annual event rate was numerically lower in the DPM group than in the control group (0.78 and 1.05 events per patient per year respectively); however this numeric difference could be a result of the differential early discontinuation rates. Regardless, this numeric difference was not statistically significant. For study CF302, the PDPE mean annual event rate was similar between the treatment groups (0.52 vs. 0.50 for DPM and control, respectively) with no statistically significant difference.

Table 11: Annual Rate of Exacerbation over 26 Weeks of Treatment (ITT)

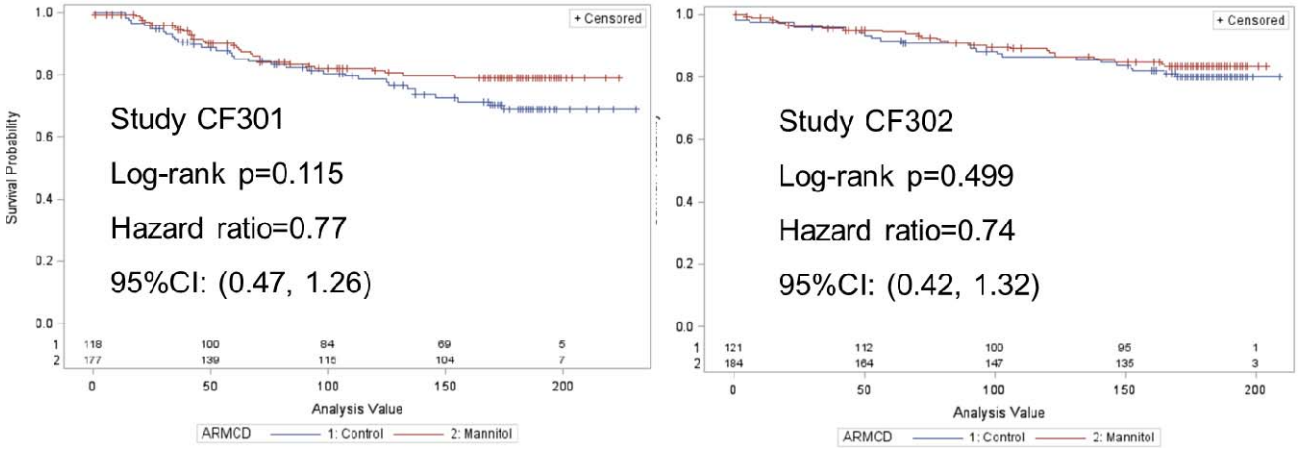
			Poisson		Negative Binomial	
Response Definition	DPM[1] Mean (SD)	Control[1] Mean (SD)	Rate Ratio (95%CI)[2] (DPM. vs. Control)	p-value[2]	Rate Ratio (95%CI)[3] (DPM. vs. Control)	p-value[3]
Study CF301						
N	177	118				
PDPE	0.78 (1.98)	1.05 (2.15)	0.78 (0.51, 1.19)	0.251	0.74 (0.47, 1.18)	0.205
Study CF302						
N	184	121				
PDPE	0.52 (1.70)	0.50 (1.14)	0.85 (0.51, 1.41)	0.520	0.95 (0.57, 1.58)	0.839

1: For each subject, the rate of PDPE events is estimated as 365.25 x (the number of PDPE / the number of days of drug exposure).
2:The Poisson regression model fitted is # of PDPE = treatment group + age at visit 1 + RhDNase use + country/region + FEV_1 percent predicted at visit 1 + error with the natural logarithm of the extent of exposure to study medication (in days) used as an offset term in the model
3:The negative binomial regression model fitted is # of PDPE = treatment group + age at visit 1 + RhDNase use + country/region + FEV_1 percent predicted at visit 1 + error with the natural logarithm of the extent of exposure to study medication (in days) used as an offset term in the model. Study CF302's model also included historical rates of exacerbation which were not collected in study CF301.

The time to first PDPE was analyzed using a Cox proportional hazards model. No statistically significant differences between treatment groups for this endpoint were found. In study CF301,

the hazard ratio for DPM compared with control was 0.77 (95%CI: 0.47, 1.26, p=0.295). In study CF302, the hazard ratio for DPM compared with control was 0.74 (95%CI: 0.42, 1.32, p=0.308). Kaplan-Meier estimates for the time to first PDPE are provided in Figure 10.

Figure 10: Kaplan- Meier Curve of Time to First PDPE (ITT)



Similar results were observed for the rate of episodes of rescue antibiotic use for PDPE and the rate of hospitalization due to PDPE. No statistically significant differences between treatment groups for either endpoint were observed in either study (Table 12).

Table 12: Annual Rate of Rescue Antibiotic Use or Hospitalization due to PDPE (ITT)

Secondary Endpoints		***Study CF301***	***Study CF302***
Episodes of Rescue Antibiotic Use due to PDPE		RR=0.76	RR=0.89
	95%CI	(0.50, 1.16)	(0.69, 1.15)
	p-value	0.197	0.368
Hospitalization due to PDPE		RR=1.00	RR=0.75
	95%CI	(0.59, 1.68)	(0.42, 1.33)
	p-value	0.992	0.328

1:The Poisson regression model fitted is # of event = treatment group + age at visit 1 + RhDNase use + country/region + FEV_1 percent predicted at visit 1 + error with the natural logarithm of the extent of exposure to study medication (in days) used as an offset term in the model. Study CF302's model also included historical rates of exacerbation which were not collected in study CF301.

Quality of life was measured using the Quality of Life Respiratory Domain from the Cystic Fibrosis Questionnaire. Comparisons between treatment groups are provided in Table 13. No statistically significant differences between treatment groups in the QOL were observed in either study. In study CF302, there were no statistically significant differences between treatment groups but the results numerically favored the control.

Table 13: QoL-CFQ-R-Respiratory Domains Score (Subset of MITT)

Secondary Endpoints		Study CF301	Study CF302
N		DPM=114, Ctrl=87	DPM=156, Ctrl=110
QoL – CFQ-R-Respiratory domains			
	95%CI	TRT Diff=0.0	TRT Diff=-3.88
	p-value	(-2.0, 2.0)	(-8, 0.22)
		0.996	0.063

[Module 5.3.5.1 Study Report Tables DPM-CF-301: table 14.2.9.2; Study Report Tables PDM-CF302: table14.2.19.14]

Efficacy Conclusion

The overriding statistical concern in the analyses of the efficacy data in studies CF301 and CF302 is the treatment-related frequent early study discontinuations. This is more problematic in study CF301 than study CF302. In study CF301, 64% of DPM and 73% of control patients completed the 26 week treatment period. In study CF302, 83% of DPM and 88% of control patients completed the 26 week treatment period. The pre-specified MMRM provides estimates of the treatment effect for the change from baseline in FEV_1 that may be systematically larger than the true treatment effect because of the differential effect these early study withdrawals may have had. BOCF analyses are numerically consistent with a positive treatment effect for DPM relative to control but are not reliable for demonstration of statistical significance. For study CF301, the BOCF analyses suggest that the magnitude of the treatment effect size (if a treatment effect exists) may be smaller than the 83 mL estimated by the pre-specified analyses. We conclude that clear-cut substantial demonstration of a treatment effect on the primary efficacy endpoint has not been achieved in either study.

To summarize the conclusions regarding the secondary efficacy endpoints, no statistically significant differences between treatment groups were demonstrated for any non-spirometric endpoint.

3.3 Evaluation of Safety

As part of the review of this application, the FDA clinical team identified the occurrence of hemoptysis as an important endpoint for evaluation of the safety of DPM. Therefore post-hoc exploratory analyses of the frequency of hemoptysis are included in this section. The MITT group is utilized in these analyses since in the setting of these studies with differential early discontinuation by treatment group, including patients who did not return for at least one post-baseline follow-up visit (i.e., the ITT group) could dilute the between treatment group difference.

The proportion of patients experiencing hemoptysis is provided in Table 14. There are no statistically significant differences between treatment groups in the proportion of patients experiencing hemoptysis and no statistically significant difference in the treatment effect across age groups (test for homogeneity of odds ratio p-value=0.6 for each study); however, numerical trends indicate that the risk of hemoptysis may be increased with DPM use and possibly suggest that the difference between treatment groups in hemoptysis may be more pronounced in patients less than 18 years of age as opposed to patients older than 18 years of age. The sponsor attributes the numeric differences in the treatment effect for different age groups to the fact that the patients in the younger age groups had lower percent predicted FEV_1 at baseline than those older than 18 years of age. From a statistical perspective, this rationalization is not plausible in the setting of a randomized study. Lower percent predicted FEV_1 at baseline in the younger age groups may be an explanation for why younger patients (in either treatment group) experience hemoptysis more frequently; however, it is not a reasonable explanation for why the difference between treatment groups in the younger subjects should be larger than that of older patients.

Table 14: Frequency of Hemoptysis (MITT Population)

	Study CF301			Study CF302		
	DPM	Control	p-value	DPM	control	p-value
MITT	21/157 (13%)	10/112 (9%)	0.26	13/177 (7%)	3/120 (3%)	0.07
Ages 6 to 11 years	1/28 (4%)	0/17 (0%)	0.43	3/35 (9%)	0/24 (0%)	0.14
Ages 12 to 17 years	4/30 (13%)	1/24 (4%)	0.25	4/55 (7%)	1/39 (3%)	0.32
Ages ≥18 years	16/99 (16%)	9/71 (13%)	0.53	6/87 (7%)	2/57 (4%)	0.39

p-value associated with test for difference between treatment groups in proportion of patients experiencing hemoptysis

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since studies CF301 and CF302 differed in terms of the early discontinuation rate and pattern subgroup analyses are presented separately for each study. The subgroup analyses of the primary efficacy variable using a BOCF approach and by age, gender, region, RhDNase use, and baseline percent predicted FEV_1 are provided in Table 15. We acknowledge that the BOCF analysis may overstate the statistical significance of results slightly because of an artificial reduction in the variance; however, we believe BOCF provides a conservative point estimate of the treatment effect in the setting of missing data such as is observed in these studies and therefore is useful in interpreting these results in that regard.

While some numerical trends in the magnitude of the effect on the primary efficacy endpoint were observed by age group in study CF301, these differences were not statistically significant. In fact, no statistically significant differences in the treatment effect was observed by age, gender, region, RhDNase use, and baseline percent predicted FEV_1 in either study (as evidenced by insignificant p-values associated with the test of treatment-by-subgroup interaction terms in the ANCOVA model in all cases).

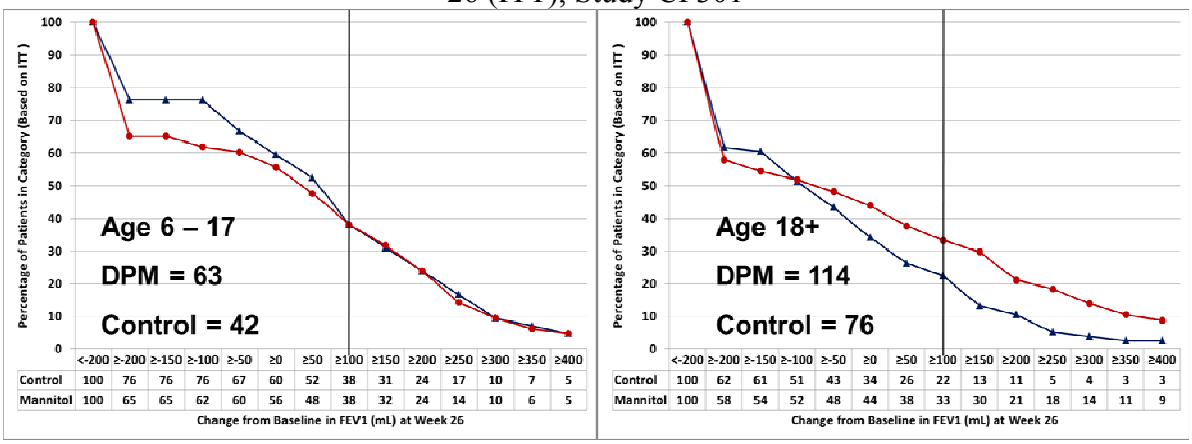
Table 15: Subgroup Analysis of Absolute Change from Baseline in FEV_1 (mL) at Week 26 using Baseline Observation Carried Forward Imputation Method (ITT)

	DPM LS Mean (SD)	*Control LS Mean (SD)*	**Treatment Comparison DPM – Control** *LS Mean (SE)*	*95%CI*
Study CF301				
Aged 6 – 11 year (m=30, c=17)	102.7 (26.3)	80.0 (35.0)	22.7 (43.8)	(-65.5, 110.8)
Aged 12 – 17 years (m=32, c=25)	88.1 (43.8)	54.8 (49.5)	33.3 (66.1)	(-99.1, 165.8)
Aged <18 years (m=62, c=42)	95.2 (26.1)	65.0 (31.7)	30.2 (41.1)	(-51.4, 111.7)
Aged ≥18 years (m=114, c=76)	72.6 (18.0)	-6.4 (22.1)	79.1 (28.5)	(22.8, 135.4)
Female (m=70, c=61)	59.4 (22.8)	2.6 (24.4)	56.8 (33.4)	(-9.4, 123.0)
Male (m=106, c=57)	94.5 (19.8)	36.5 (26.9)	58.0 (33.4)	(-8.0, 124.0)
AU/NZ (m=61, c=43)	53.9 (23.2)	35.6 (27.6)	18.4 (36.0)	(-53.1, 89.8)
UK/IR (m=115, c=75)	94.7 (19.3)	9.5 (23.9)	85.2 (30.7)	(24.7, 145.7)
RhDNase Non-User (m=81, c=51)	102.6 (24.0)	63.7 (30.3)	38.9 (38.7)	(-37.7, 115.4)
RhDNase User (m=95, c=67)	61.8 (18.3)	-15.1 (21.8)	76.9 (28.5)	(20.6, 133.2)
BaseFEV_1<50%Pred (m=41, c=32)	38.5 (21.9)	12.5 (24.8)	26.0 (33.1)	(-40.0, 92.0)
BaseFEV_1≥50%Pred (m=135, c=86)	93.3 (18.4)	21.4 (23.0)	71.9 (29.4)	(14.0, 129.9)
Study CF302				
Aged 6 – 11 year (m=35, c=24)	104.3 (38.6)	53.3 (46.6)	87.0 (60.5)	(-34.1, 208.0)
Aged 12 – 17 years (m=56, c=39)	87.9 (48.4)	91.5 (58.1)	-3.7 (75.6)	(-153.8, 146.5)
Aged <18 years (m=91, c=63)	108.0 (33.2)	77.0 (40.0)	31.0 (51.9)	(-71.6, 133.7)
Aged ≥18 years (m=93, c=58)	45.4 (29.3)	-59.1 (37.0)	104.5 (47.2)	(11.2, 197.8)
Female (m=90, c=58)	72.3 (28.9)	22.8 (36.0)	49.6 (46.2)	(-41.7, 140.9)
Male (m=94, c=63)	80.2 (34.0)	1.6 (41.6)	78.6 (53.7)	(-27.5, 184.7)
Non-US (m=99, c=67)	105.1 (33.0)	76.4 (40.1)	28.6 (51.9)	(-73.9, 131.2)
US (m=85, c=54)	42.9 (28.4)	-68.5 (35.6)	111.5 (45.6)	(21.3, 201.6)
RhDNase Non-User (m=47, c=29)	123.4 (41.8)	73.4 (53.3)	50.0 (67.7)	(-85, 184.9)
RhDNase User (m=137, c=92)	60.2 (26.3)	-7.7 (32.1)	67.9 (41.5))	(-13.8, 149.7)
BaseFEV_1<50%Pred (m=34, c=34	150.9 (50.1)	21.2 (50.1)	129.7 (70.8)	(-11.7, 271.2)
BaseFEV_1≥50%Pred (m=150, c=87)	59.5 (25.0)	8.0 (32.8)	51.4 (41.2)	(-29.8, 132.7)

SE=standard error.
The p-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline to week 26 in trough FEV_1 as response with treatment as a predictor

To further describe the numeric differences in the treatment effect within age groups, the cumulative responder plots for each subgroup are provided. Figure 11 shows the result for study CF301. On the left is the cumulative responder plot for the 6 to 17 year old age group. On the right is the same for the 18 and older group. Results for study CF302 are shown in Figure 12.

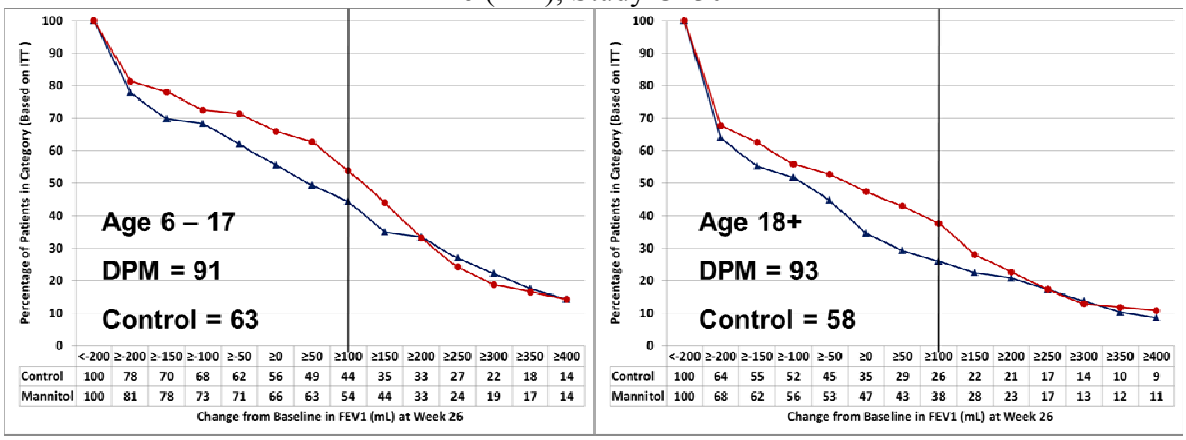
Figure 11: Responder Analysis: Change from Baseline in Change from Baseline in FEV_1 at week 26 (ITT), Study CF301



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	76	76	76	67	60	52	38	31	24	17	10	7	5
Mannitol	100	65	65	62	60	56	48	38	32	24	14	10	6	5

	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	62	61	51	43	34	26	22	13	11	5	4	3	3
Mannitol	100	58	54	52	48	44	38	33	30	21	18	14	11	9

Figure 12: Responder Analysis: Change from Baseline in Change from Baseline in FEV_1 at week 26 (ITT), Study CF302



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	78	70	68	62	56	49	44	35	33	27	22	18	14
Mannitol	100	81	78	73	71	66	63	54	44	33	24	19	17	14

	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	64	55	52	45	35	29	26	22	21	17	14	10	9
Mannitol	100	68	62	56	53	47	43	38	28	23	17	13	12	11

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The following statistical issues have been described and commented upon throughout the review.

- The overriding statistical concern in the analyses of the efficacy data in studies CF301 and CF302 is the treatment-related frequent early dropouts. Analyses of the primary efficacy endpoint using the SAP-specified MMRM methods may systematically overestimate the treatment effect of DPM. Sensitivity analyses (including but not limited to BOCF and cumulative responder plots) were undertaken to assess the impact the missing data had on the primary efficacy analysis.
- Sensitivity analyses for the primary efficacy that simultaneously impute a conservative value in terms of estimating the treatment effect (such as that of BOCF) while also

appropriately representing the statistical uncertainty in the imputed values (by employing a multiple imputation approach) are not available.

- Numerous inconsistencies or inaccuracies in the documentation of the SAP and protocol for study CF301 were identified including, among others, variations in the selection of covariates for inclusion in the MMRM model; however the practical impact of these inconsistencies are expected to be relatively little next to that of the treatment-related frequent early dropouts.

5.2 Collective Evidence

The overriding statistical concern in the analyses of the efficacy data in studies CF301 and CF302 is the treatment-related frequent early dropouts. Analyses of the primary efficacy endpoint using the pre-specified statistical methods are problematic because they cannot incorporate the entire ITT group and because they require inappropriate assumptions about missing data. Patients who dropped out before week 6 are necessarily entirely excluded from these analyses so that only 156 of 177 (88%) DPM patients and 112 of 118 (95%) control patients are included in the MITT group in study CF301. In study CF302, 177 of 184 (96%) DPM patients and 120 of 121 (99%) control patients are included in the MITT group. Additional missing data at weeks 14 and 26 also occurred differentially by treatment group. In study CF301, at week 26, 116 of 177 (66%) DPM patients and 89 of 118 (75%) control patients have observed data. In study CF302, at week 26, 157 of 184 (85%) DPM patients and 111 of 121 (92%) control patients have observed data. The pre-specified primary statistical analysis method, a mixed model for repeated measures (MMRM), requires an assumption that missing data occurred at random, unrelated to treatment. Since this assumption is violated in these studies, the MMRM analysis estimating the treatment effect is flawed and the MMRM estimates of the treatment effect in the change from baseline in FEV_1 outcome may be systematically larger than the true treatment effect. Therefore, sensitivity analyses assessing the impact of the missing data on the treatment effect were necessary.

Many sensitivity analyses were undertaken by the applicant and by the division with the goal of understanding the impact the missing data had on the pre-specified primary efficacy analyses. Some analyses are better than others but none of them are perfect. While description of these sensitivity analyses may at first make them seem conservative, even punitive, closer examination of the assumptions underlying several of these methods reveal that these methods rely heavily on the missing at random assumption. These methods therefore more or less impute missing data by preserving the treatment effect that was observed prior to discontinuation, even though DPM patients who have dropped out are no longer taking the drug. A sensitivity analysis that does not have these faults is the baseline-observation-carried-forward or BOCF approach. However, BOCF also is not perfect. A single value is imputed for each patient with missing data and is assumed to be the true value that would have been observed if follow-up had been continued. As a result, the statistical precision in the estimate of the treatment effect in all randomized participants is overstated (e.g., the width of the confidence interval for the mean difference between treatment groups is artificially narrow). In summary, none of the sensitivity analyses provided by the applicant or conducted by the FDA simultaneously imputes a conservative value in terms of estimating the treatment effect while also appropriately representing the statistical uncertainty in the imputed values. It is theoretically conceivable that statistical methods that

would achieve both of these goals could be created but such methods are not currently available. In conclusion, while we agree with critics of the method that the BOCF analysis may overstate the statistical significance of results, we also believe BOCF provides a conservative point estimate of the treatment effect in the setting of missing data such as is observed in these studies and for that reason the BOCF results are described here. In study CF301, the difference between DPM and control in the change from baseline in FEV_1 at week 26 is estimated to be 62 mL. This is consistent with the conclusion from the pre-specified primary efficacy analysis that DPM is having a better outcome than control but suggests that the difference between treatment groups is smaller than the treatment effect of 83 mL estimated in the pre-specified analysis. In study CF302, this difference is estimated to be 65 mL and is fairly consistent with the pre-specified analysis. But as previously described, the statistical significance associated with the BOCF analyses is not reliable. As a result, we conclude that while numerical trends indicate there may be a beneficial treatment effect, clear-cut substantial demonstration of a treatment effect on the primary efficacy endpoint has not been achieved in either study.

Continuous responder curves (i.e., empirical distribution functions) illustrating the proportion of DPM and control patients achieving a certain threshold in the primary endpoint by dichotomizing the primary endpoint over a range of possible thresholds allow inclusion of the entire ITT group and account for the treatment-related missing data by considering subjects with missing data nonresponders. In both studies, the DPM group had numerically (but not always statistically significantly) higher proportions of patients who achieved the change from baseline FEV_1 thresholds than did the control group. These numerical trends are consistent with the numerical trends in the MMRM analyses and BOCF approach.

To summarize the conclusions regarding the secondary efficacy endpoints, no statistically significant differences between treatment groups were demonstrated for any non-spirometric endpoint.

Post-hoc exploratory analyses of the frequency of hemoptysis revealed no statistically significant differences between treatment groups in the proportion of patients experiencing hemoptysis and no statistically significant difference in the treatment effect across age groups.

5.3 Conclusions and Recommendations

The analysis of efficacy data from studies CF301 and CF302 are complicated by the frequent and treatment-related early discontinuations resulting in systematically missing FEV_1 measurements. The pre-specified primary statistical analysis method, a mixed model for repeated measures (MMRM), requires an assumption that missing data occurred at random, unrelated to treatment. Since this assumption is violated in these studies, the MMRM analyses estimating the treatment effect is flawed and the MMRM estimates of the treatment effect in the change from baseline in FEV_1 outcome may be systematically larger than the true treatment effect. BOCF analyses provide a conservative point estimate of the treatment effect in the setting of missing data such as is observed in these studies. In study CF301, the difference between DPM and control in the change from baseline in FEV_1 at week 26 is estimated to be 62 mL. This is consistent with the conclusion from the pre-specified primary efficacy analysis that DPM is having a better outcome

than control but suggests that the difference between treatment groups is smaller than the treatment effect of 83 mL estimated in the pre-specified analysis. In study CF302, this difference is estimated to be 65 mL and is fairly consistent with the pre-specified analysis. But the statistical significance associated with the BOCF analyses is not reliable. As a result, we conclude that while numerical trends indicate there may be a beneficial treatment effect, clear-cut substantial demonstration of a treatment effect on the primary efficacy endpoint has not been achieved in either study.

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/s/

FENG ZHOU
02/19/2013

RUTHANNA C DAVI
02/19/2013

JOAN K BUENCONSEJO
02/19/2013
I concur.

THOMAS J PERMUTT
02/19/2013
concur

Secondary Pharmacology and Toxicology Review for NDA 202-049

TO: NDA 202-049 (Pharmaxis Ltd.)

FROM: Marcie Wood, Ph.D.
Pharmacology and Toxicology Acting Supervisor
Division of Pulmonary, Allergy, and Rheumatology Drug Products

DATE: February 14, 2013

Overview: I concur with the recommendation of Dr. Luqi Pei (detailed in a nonclinical review dated February 5, 2013) that the pharmacology and toxicology of Bronchitol (D-mannitol inhalation powder) have been adequately studied and the drug product should be approved from a nonclinical perspective.

No new nonclinical data were submitted to the current NDA. Instead, the current NDA referenced Aridol NDA 22-368 (approved on October 5, 2010 as a diagnostic agent for assessing airway hypersensitivity in asthmatics at an inhaled dose of 635 mg) for nonclinical support. (Note: Pharmaxis is the owner of both NDA 22-368 and 202-049). The Division had previously determined that a 6-month inhalation toxicity study of mannitol in an appropriate species would support registration of both Aridol and Bronchitol, as the toxicological profile of mannitol by non-inhalation routes is well-known. Therefore, inhalation toxicity studies (described below) were conducted and submitted to IND 70,277.

Inhalation toxicity studies up to 3 and 6 months in duration in rats and dogs, respectively, identified the respiratory system as the target organ of inhaled mannitol. Briefly, increased incidences of macrophage aggregation and alveolitis were observed in a 3-month study in rats. Cough, laryngeal ulceration, and sinus histiocytosis were observed in a 6-month study in dogs. There were no neoplastic or pre-neoplastic findings in the respiratory tract. In addition, mannitol was not carcinogenic in 2-year National Toxicology Program (NTP) dietary carcinogenicity studies conducted in rats and mice. Mannitol was also non-genotoxic in a battery of studies conducted by NTP. Finally, available nonclinical data in the literature showed that mannitol was not teratogenic in studies in mice or rats.

Labeling: A labeling review will be completed at a later time.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/

MARCIE L WOOD
02/14/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202,049
Priority or Standard	Standard
Submit Date(s)	May 18, 2012
Received Date(s)	May 18, 2012
PDUFA Goal Date	March 18, 2013
Division / Office	DPARP, ODE II, OND
Reviewer Name(s)	Kimberly A. Witzmann, MD
Review Completion Date	
Established Name	Mannitol Inhalation Powder
(Proposed) Trade Name	Bronchitol
Therapeutic Class	Mucolytic
Applicant	Pharmaxis
Formulation(s)	40mg capsules
Dosing Regimen	400mg (10 capsules) by inhalation twice daily
Indication(s)	For the management of CF in patients 6 years of age or older to improve pulmonary function
Intended Population(s)	Patients ≥6yo with CF

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this submission for New Drug Application (NDA) 202,049, mannitol inhalation powder for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function, is **complete response**. This recommendation is based on inadequate evidence of efficacy and safety for the indicated population.

The primary basis for support for the efficacy and safety of dry powder mannitol were two Phase 3 controlled trials (Studies 301 and 302) that used the dose of dry powder mannitol (DPM) proposed for approval, at 400mg twice daily. In the Phase 3 studies, 719 patients received the first test dose of DPM under direct physician observation, given that DPM is approved as a test for bronchial hyperresponsiveness. Of that number, 600 patients (361 DPM, and 239 control) were included in the Intent-to-Treat (ITT) population.

From an efficacy perspective, Studies 301 and 302 failed to provide sufficient data to support a finding of substantial evidence of efficacy of DPM in CF. Both studies demonstrated frequent and treatment-related early discontinuations, which could not be accounted for in the Applicant's pre-specified mixed effects model for repeated measurements (MMRM), because an assumption of this method is that missing data will be few, and at random. In addition, MMRM analysis includes only patients with post-baseline measurements (the modified ITT, or MITT, population), and therefore excludes patients who were randomized and received study drug but who dropped out before the week 6 time point. Using the Applicant's MMRM analyses in a modified ITT population (MITT), there was a statistically significant treatment effect for the primary endpoint, absolute change in FEV1 through week 26 in Study 301 (an 83mL difference favoring DPM 400mg, $p<0.001$), with the 54mL difference observed in Study 302 ($p=0.059$) not meeting the usual standard for statistical significance. Because the proposed MMRM analysis does not account for the differential dropout of patients, numerous sensitivity analyses were conducted to determine the impact of missing data on the primary endpoint. Most of these retained statistical significance for Study 301, with an estimated treatment effect of 60 to 80mL. However, this does not consider a second issue caused by the missing data, which is that, because of unequal dropout, the comparison is no longer in two similar groups. The DPM group is of "tolerators," and control may or may not chronically tolerate DPM. Therefore, because the differential dropout created two different populations, and comparison of these two dissimilar groups is problematic. Last, the proposed indication extends to children a young as 6 years of age, but the efficacy data in pediatric patients 6 to 17 years of age is mixed, offering less surety of effect than that for the entire study population.

From a safety perspective, the database reflected the issues of dropouts, with higher rates of discontinuation for DPM-treated patients throughout the double-blinded treatment periods, at a rate of 2:1 for those on DPM over control. For those patients who were able to tolerate DPM and continue treatment, cough and hemoptysis occurred at consistently higher rates than in controls across all adverse event reporting categories. In the total safety population, hemoptysis was noted in twice as many DPM 400mg-treated patients than those receiving controls. This small but clear signal for hemoptysis occurred even in the youngest age group of 6 to 11 year-olds, raising issues of safety specifically for pediatric patients. While no patients died from hemoptysis events in the safety population during the conduct of these studies, the long-term effect of the 2-to-4-fold increases in hemoptysis seen in this program, when projected to chronic use over the course of a CF patient's lifetime, is unknown. There were not many additional concerns, with overall numbers, in terms of SAE and AEs, slightly favoring DPM treatment.

Efficacy and safety of DPM was discussed at a Pulmonary-Allergy Drugs Advisory Committee meeting, held on January 30, 2013. The issues regarding efficacy and safety were presented by FDA and Pharmaxis, and the advisory committee was asked to discuss and vote upon issues of efficacy, safety, and risk-benefit for the indicated population.
Considering if there was substantial evidence of efficacy for patients aged 6 years and older, the committee voted 3 yes, 11 no. Those who voted "yes" noted the first trial reaching statistical significance with a small treatment effect, and a trend in the second study. Those who voted "no" felt the standard of evidence has not been met, and future studies would be required. Most members felt that pediatric efficacy was not demonstrated, and two members who voted "no" stated they would have voted "yes," if the indication had been for adults only.

Safety was viewed as a major concern, as the committee voted (3 yes, 11 no) that the safety data were adequate for CF patients 6 and older. Members voting "yes" felt that the hemoptysis described was not life-threatening, and could be managed by discontinuing the treatment. Those voting "no" felt that the safety profile, especially in pediatrics, had not been fully evaluated, and that long-term studies would be needed. Concerns for the amount of tolerability issues and dropout rates were also described.

Regarding if the overall efficacy and safety provided substantial evidence for approval, the results were against approval (0 yes, 14 no), commenting there is no substantial evidence of efficacy, with concern for the risk-benefit ratio in children. Several members noted more confidence in efficacy and safety in the adult population over the pediatric population.

1.2 Risk Benefit Assessment

The benefit-to-risk analysis for DPM is complex, given that CF is a serious, life-threatening disease with high morbidity and early mortality, and the majority of

treatments available being supportive. One trial of two demonstrated a statistically-significant benefit in FEV1 of DPM over control, but differential dropout formed two different comparator groups at the end of 26 weeks, such that the overall treatment effect for the intended population has not been adequately characterized. In addition, the small changes in FEV1 measured were not supported by any statistically significant secondary endpoints that would be expected to carry clinical impact, such as rate of hospitalizations, rate of antibiotic use, rate of pulmonary exacerbations, or improvements in quality of life measurements over the treatment period. Add to this a greater variability between results from each study for patients 6 to 17 years of age, raising even more the question of treatment benefit in the pediatric population. Considering the safety data, there are increased signals for tolerability issues and hemoptysis in the adult population, but given the severity of the disease, these could be considered acceptable if the treatment benefit were more clear. However, specifically for pediatrics, questionable efficacy and a clear safety signal for hemoptysis negatively impact my assessment of benefit-to risk assessment.

In order to address the deficiencies presented in the current application, this reviewer feels another clinical trial is necessary to assess the efficacy of DPM in the adult CF population. The trial would need to clearly identify DPM "tolerators," so that the true treatment effect of DPM could be quantitated. This study design could include a run-in period to identify those patients who could tolerate DPM on a chronic basis, then randomize to DPM or control. In addition, the parameters used to determine a positive MTT test should be reassessed, similar to those of the approved Aridol label for demonstration of bronchial hyperresponsiveness, namely any decrease of $\geq$ 15% predicted FEV1 should be considered a failed test, and the patient should be excluded from further study.

Another deficiency within the package is regarding the dose of DPM chosen. The 400mg dose is the highest dose studied, and the only one that demonstrated a statistically-significant difference between the 40mg negative dose from the small dose-ranging Study 202. It is not clear if a higher dose might be more beneficial for adults, since one was not studied, limited by technique and number of capsules required. However in pediatrics, additional dose exploration is challenging, because of the safety signal seen at the 400mg dose, with marginal determination of benefit in pediatric patients.

The concerns for both efficacy and safety identified in this review were mirrored in the discussion and voting of the Pulmonary-Allergy Drugs Advisory Committee, which ultimately voted 0 to 14 against approval for DPM.

In this reviewer's opinion, if the Applicant were able to demonstrate substantial evidence of efficacy in a population of DPM tolerant adult patients, the risk-benefit assessment would be more favorable. The support for the pediatric population would require a demonstration of substantial benefit with a demonstration of acceptable safety, especially with regard to the long-term effects of recurrent hemoptysis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In light of the complete response recommendation, there are no post-market requirement risk-evaluation and mitigation strategy comments at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

In light of the complete response recommendation, there are no post-market requirement comments at this time.

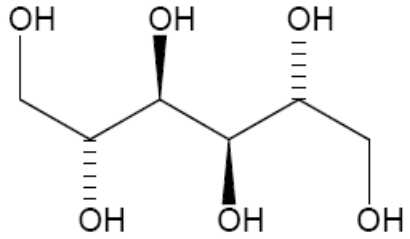
2 Introduction and Regulatory Background

2.1 Product Information

Information

Mannitol is the drug substance and is used neat in the drug product. It is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. There are (b) (4) morphic forms of mannitol denoted as (b) (4). The structural formula is depicted in Figure 1 below:

Figure 1: Mannitol Molecular Structure



The drug product consists of 40 mg of hard gelatin capsules containing mannitol sealed in blister packs and a hand held dry powder inhaler device. No excipients are included in the contents of the capsules. Presumably, because of the large number of capsules (10) whose contents are required to be inhaled for each dose, (b) (4) (b) (4).

A review of the safety of impurities, extractables and leachables in the mannitol powder capsules did not reveal any concerns.

Brief Clinical Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[1], and approximately 36,000 children and adults in Europe[2]. Approximately one in 3,500 children in the United States is born with CF each year, and CF affects all ethnic and racial groups, although is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-30's[1].

In 1989, researchers discovered the gene that caused CF[3], which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is an epithelial chloride ion channel, which aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. While CF affects most organ systems in the body, the majority of morbidity and mortality from cystic fibrosis results from its effects in the lungs[4]. The lack of normally functioning CFTR causes abnormal chloride secretion and water reabsorption, leading to dehydration of the airway surface liquid and impaired mucociliary clearance. Over time, the CF lung is exposed to a vicious cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure[5, 6].

Pharmaxis proposes that their inhaled dry powder mannitol product will improve mucus clearance in patients with CF due to the osmotic properties of mannitol remaining in the extracellular compartment to cause an outflow of water into surrounding tissues, and thus reduce the thickness and stickiness of CF mucus secretions.

2.2 Tables of Currently Available Treatments for Proposed Indications

Other than Kalydeco, approved in January 2012 to treat a small subpopulation of patients with CF who have a *G551D-mutation* in *CFTR*, all drugs available to treat cystic fibrosis treat the symptoms and sequelae of the disease. Listed below in the table are drugs commonly used for the treatment of cystic fibrosis and its complications, including those with both FDA-approved indications and those with common off-label usage. This list is not exhaustive, but is rather meant to address the most common categories of medications typically utilized by patients with CF.

Table 1: Drugs Commonly Used for the Treatment of Cystic Fibrosis

Active Ingredient	Trade Name	FDA-approved for CF Indication?
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol™, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-Inflammatory Agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
[Source: Approved labeling data from Drugs@FDA,.gov]		

2.3 Availability of Proposed Active Ingredient in the United States

Mannitol inhalation powder (Aridol) is marketed in the United States as part of a bronchial challenge test kit, indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. Mannitol administered either intravenously or orally is currently marketed for multiple medical indications, including as a diuretic and laxative. It is also used as an excipient in many products and is available as a dietary supplement.

2.4 Important Safety Issues with Consideration to Related Drugs

The principle safety issues for the related mannitol inhalation powder bronchoprovocation agent (Aridol) and the unapproved but commonly used inhaled expectorant/mucolytic agent, hypertonic saline (7%) are the potential for bronchoconstriction in patients with underlying bronchial hyperreactivity, and severe cough. The Aridol label contains a boxed warning instructing that the test should be performed only under the supervision of a physician trained in and thoroughly familiar with management of acute bronchospasm.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to submission of this NDA, Dry Powder Mannitol Inhalation Powder (henceforth referred to as DPM), IND # 70,277 was opened in the Division of Pulmonary, Allergy, and Rheumatology Products on November 22, 2004. It was granted orphan drug status in 2005, and fast track development status in 2006.

The following includes a list of meetings and interactions with the Applicant during the development program.

February 15, 2006: End of Phase 2 meeting:
Key discussion topics with the Applicant included the following:

- that Phase 3 study duration would differ depending on primary outcome measure chosen. For example, a 6-month study duration would be reasonable for an FEV1 outcome, but that a 1-year duration would be needed for an exacerbation endpoint.
- that one-year safety data was necessary for registration because of proposed chronic use of the product,
- and that a variety of proposed endpoints may or may not be suitable. Specifically, the choice of an FEV1 variable would be reasonable, but, "because Bronchitol is not expected to act as a bronchodilator, small changes in FEV1 over short periods of time would not, by themselves, be sufficient to support approval, and additional co-primary or secondary outcomes would be required."

August 15, 2006: Special Protocol Assessment* (SPA) Request for study 301:
Issues addressed included study duration, endpoints, pooling of control subject data, definition of CF exacerbation, and statistical analyses regarding imputation of missing data. No agreement was reached with the Agency.
* Concurrence on a SPA creates a binding agreement between a sponsor and the Agency regarding the design, conduct, and analysis of certain types of study protocols, including Phase 3 protocols conducted to support product approval. See: Guidance for Industry: Special Protocol Assessment, May 2002 (*http://www.fda.gov/cder/guidance/index.htm*).

August 6, 2007: SPA Request for study 302 and subsequent Type A meeting (teleconference): Issues discussed included study duration to support lung function claim (FEV1) and exacerbation claims, definition of CF exacerbation, acceptability of the proposed control, and inclusion of children 6 years and older with CF. Specifically, the Agency noted that a study of 6 months duration would not be sufficient to support an exacerbation claim and if labeling claims based on secondary endpoint(s) are desired, pre-specification of these specific endpoints and plans to control type I error for multiplicity would be needed. The Agency also noted that, in general, a clinical program is conducted first in adults before studying children and Pharmaxis will need to justify

using the same dose as adults (400 mg twice daily) in the pediatric population. While no agreement was made, the Agency mentioned:

> "that some development programs lend themselves to an SPA agreement, while other programs are not well suited for this type of agreement as certain questions cannot be answered with a "yes" or "no" response, and therefore cannot be part of a binding SPA agreement. These questions will become review issues. However, even though the Agency does not agree with the sponsor on a specific approach, this does not mean that the study cannot be conducted in the manner in which Pharmaxis proposed."

December 10, 2010: Pre-NDA meeting:
Pharmaxis and the Agency discussed changes to the statistical analyses that could be used to support registration of DPM. Pharmaxis proposed several post-hoc changes to the statistical analysis plan which it felt would provide a more accurate reflection the efficacy of DPM. These included:

- After unblinding it was discovered that study 302 had an imbalance between treatment groups in FEV1 at baseline but not at screening. As a result, Pharmaxis proposed characterizing the effect of DPM on the primary efficacy endpoint with post-hoc analyses utilizing change from screening or change from the average of baseline and screening as the response variable instead of the baseline measurement as in the prespecified analysis plan. The Agency mentioned that such post hoc manipulations were generally not acceptable for regulatory purposes and stated that the discrepancy between the screening and baseline FEV1 for control group versus treatment group in study DPM-CF-302 (study 302) creates a significant problem, and raises a question about the study conduct (i.e., problem with blinding). The Agency noted that even though Pharmaxis feels this issue could be addressed by adjusting the baseline measurement, the potential conduct issue creates a large regulatory obstacle to overcome.

- Pharmaxis also proposed a change to the analysis of the primary efficacy endpoint for study 301. In the original analysis of the primary endpoint for study 301, the response variable in a mixed model for repeated measurements incorporated the change from baseline at baseline (i.e., a zero for all subjects). The sponsor's proposal at the pre-NDA meeting was to re-analyze the primary endpoint utilizing only the post-baseline measurements. The Agency acknowledged the sponsor's intention to reach agreement on proposed types of post-hoc analyses; however, the Agency indicated that it is premature to comment on the adequacy of the proposed methods, stating that this would be determined as part of the review of the NDA. However, the Agency also stated that:

  > "Pre-specified primary analysis methods are generally relied upon heavily in regulatory decision making. Post-hoc analyses are often considered

hypothesis generating, and conclusions of such analyses usually require confirmation in a subsequent study."

2.6 Other Relevant Background Information

Inhaled dry powder mannitol (DPM), used on a chronic basis, is currently approved for marketing in Australia (patients > 6 years of age) and the European Union (patients >18 years) for the treatment of patients with CF. (b) (4) Inhaled mannitol (Aridol) is also currently marketed in the United States, European Union, Australia, and other countries worldwide as a bronchial challenge test for the assessment of bronchial hyperresponsiveness.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The original NDA dated May 18, 2012, was submitted in electronic common technical document (eCTD) format. Its organization was acceptable and the document was navigable. With respect to submission quality, both the Clinical and Biostatistical reviewers sent information requests to the Applicant to clarify or resubmit data, including multiple information requests from the Biostatistical reviewer requesting re-submission and clarification of the data sets. There were no issues with respect to submission integrity.

The Division has requested an audit by the Office of Scientific Investigation (OSI) for this NDA, since there were divergent outcomes between Phase 3 trial primary efficacy endpoints; the study which demonstrated statistically positive effect was conducted outside of the US, and the second trial which included US study sites did not demonstrate statistically-positive outcome. Due to the rarity of this orphan disease, there were a large number of US and international clinical trial sites, with few subjects enrolled at each site. Three US sites (all from Study 302) were recommended for audit based on relatively high enrollment, and demonstration of outcomes that were in favor of DPM.

- Site #10131, Dr. Brown, Boise, ID [N=10, 229mL treatment effect]
- Site #10116, Dr. Fornos, San Antonio, TX [N=7, 311mL treatment effect]
- Site #10125, Dr. Schaeffer, Jacksonville, FL [N=7, 318mL treatment effect]

Preliminary report of the DSI inspections notes that there were no major deficiencies and only minor protocol violations found at the clinical sites operated by Drs. Fornos and Schaeffer , and that both were in compliance with Good Clinical Practices (GCP),

and required no action. The clinical inspection for Dr. Brown's site in Boise, Idaho, demonstrated a number of protocol violations with respect to spirometry (wrong reference values used, spirometry performed on different devices, no flow-volume loops printed for some visits, 3 maneuvers not recorded for each value, etc). While these events are considered poor reporting and sloppy, from a practical standpoint, it did not alter the outcome for Study 302, because each site contributed a relatively small number of patients. When the FDA biostatistical reviewer performed calculations of the primary efficacy endpoint (using the pre-specified model) for Study 302 completely excluding data from site 10131, the results demonstrated an overall treatment effect (LSmean) of 49.1mL (with 95%CI -8.1, 106.3), which provides a p-value of 0.0921 for the trial. So when the data from this site was excluded, the outcome of Study 302 remained the same.

In addition, because the ex-US study had the statistically significant result, two of the highest-enrolling centers in the UK were also inspected.

- Site #44103, Dr. Upton, Norwich, UK [N=11, 154mL treatment effect]
- Site # 44111, Dr. Walshaw, Liverpool, UK [N=14, 123mL treatment effect]

Dr. Walshaw's site demonstrated only minor protocol deviations. Dr. Upton's site had some spirometry issues similar to those seen at Dr. Brown's site, described above. When FDA Biostatistical reviewers removed the data from Dr. Upton's site, data for Study 301 was still able to demonstrate a treatment effect of 80.4mL (95% CI 25.6, 125.3) with a p-value of 0.0005. Again, even if data from this site was removed, Study 301's outcome remained unchanged.

Overall, the OSI inspections concluded that no major regulatory violations were noted, and based on inspectional findings, the study data collected appear generally reliable in support of the requested indication. Please refer to Dr. Anthony Orencia's Clinical Inspection Summaries for further details.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report, within the electronic submission.

3.3 Financial Disclosures

The Applicant has submitted a Debarment statement to Module 1.3.3 of this NDA submission, certifying that no debarred individuals were used in the conduct of the trials included in this NDA.

No financial disclosures are provided within the package, indicating the Applicant's acknowledgement that no financial interests of any investigators were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product, BRONCHITOL (mannitol) Inhalation Powder, 40 mg, is proposed for treatment of cystic fibrosis. The same formulation (neat mannitol) was approved in a diagnostic kit for assessment of bronchial hyperresponsiveness in patients 6 yrs of age and older with symptoms of asthma (NDA 22-368, Aridol Inhalation Powder).
The drug product is a non-sterile dry powder inhaler with formulation (neat mannitol) pre-metered in hard-gelatin capsules, each containing 40 mg of spray-dried mannitol. The capsules are packaged into aluminum foil blisters and co-packaged with the inhalation device RS01 Inhaler Model 7 HR, a high-resistance inhaler manufactured by Plastiape S.p.A. (Italy). Upon the insertion of the capsule into the inhaler and piercing it from both sides, inhalation from the mouthpiece results in spinning of the capsule and releasing the powder by entraining it into the air-stream. The in-vitro emitted dose, at 60 L/min for 2 L aspiration volume, is 32 mg (target delivery). Two package configurations are proposed for marketing. (b) (4)

The drug substance is a sugar alcohol. It is a white, crystalline powder or free flowing granules. It is freely soluble in water (22 g/100 mL) and very slightly soluble in alcohol. (b) (4) (b) (4). There are (b) (4) morphic forms of mannitol denoted as (b) (4) The drug substance consists of (b) (4) and has a melting range of 164-169°C, with a pKa of 13.5 at 18°C. It is not hygroscopic and known to resist moisture sorption at high relative humidity. The drug substance is synthesized, tested and packaged by (b) (4) (DMF (b) (4)). The retest period of the drug substance is (b) (4) (b) (4) and is supported by the stability data. The specification controls for the drug substance include appearance, appearance of solution, assay, related substances, (b) (4) (b) (4) melting range, conductivity, specific rotation, endotoxins, microbial limits, (b) (4) and residue on ignition.

For the drug product manufacture, the mannitol is (b) (4) (b) (4) (b) (4) The critical steps in the process are identified (b) (4). The regulatory specification controls for the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4), appearance (of capsules, capsule contents, blisters and packs), bacterial endotoxins, microbial limits, aerodynamic particle size distribution and uniformity of delivered dose. As amended, all

methods and acceptance criteria for the drug substance and drug product were found acceptable and all supporting DMFs have adequate status.

The proposed dosage is inhalation of the contents of 10 x 40 mg capsules, twice daily with a total daily dose of 800 mg (2 x 400 mg). The treatment kit should be stored (b) (4) It should not be frozen or refrigerated. The currently supported expiry period is (b) (4) months for storage at the described above conditions.

A review of the safety of impurities, extractables and leachables in the mannitol powder capsules did not reveal any concerns.

At the time of this review, the CMC opinion is that the NDA is considered approvable, pending acceptable recommendation from the Office of Compliance for the manufacturing and testing facilities and pending satisfactory responses to the major remaining issues, summarized below:

- Revise the manufacturing to include (b) (4) (b) (4) tighten the processing and holding times (b) (4) (b) (4).
- Submit improved and validated method for the foreign particulate matter, based on the statement provided in amendment dated Nov 29, 2012.
- Perform through life device ruggedness study for the to-be-marketed device. Critically evaluate the number of inhalers supplied for the delivery of (b) (4) in view of the intermittent occurrence of high drug delivery due to powder accumulation in the device occurring more often for doses #15-28 and in view of the results of the requested ruggedness study. Support conclusions with data and revise labeling accordingly.
- Expiry period of (b) (4) months should not be extended *via* annual report due to changes in fine particles observed during processing and storage. Post-approval stability protocol needs to be revised to include 3 months testing point for the assay and the (b) (4).

4.2 Clinical Microbiology

Clinical microbiology review of the NDA package concluded that all findings are satisfactory, and the NDA is recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

Mannitol is used as a nutrient and/or dietary supplement and as an ingredient in numerous drug products. As a dietary supplement, mannitol is considered generally recognized as safe [GRAS, 21CFR§582.5470].

The mannitol toxicology by non-inhalation use is well understood. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. The National Toxicology Program evaluated carcinogenicity and mutagenicity of D-mannitol. It concluded that F344/N rats and B6C3F1 mice fed with up to 5% D-mannitol in diet for 103 weeks did not reveal any evidence of tumorigenicity. Mannitol was non-genotoxic in a bacterial mutation assay, an in vitro mouse lymphoma cell assay, an in vivo mouse micronucleus assay and other assays. The Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol considered D-mannitol non-teratogenic.

The application has adequately evaluated the toxicity profile of inhaled mannitol. Because of the extensive clinical and nonclinical data available on mannitol, the toxicology program focused on effects of inhaled mannitol, particularly its effect on the respiratory system. The program included inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol with increased incidences of macrophage aggregation and alveolitis in the 3 month rat study and coughing, laryngeal ulceration and sinus histiocytosis in the 6 month dog study. The no observed adverse effect level (NOAEL) in the 6 month dog study was 43 mg/kg/day.

4.4 Clinical Pharmacology

Clinical pharmacology review of the NDA package concluded that all findings are satisfactory, and the NDA is acceptable for approval from the viewpoint of the Office of Clinical Pharmacology, with no Phase 4 commitments required.

4.4.1 Mechanism of Action

Inhaled mannitol is an inhaled non-ionic hyperosmotic product used to promote airway clearance. The precise pharmacological mechanism whereby mannitol increases the clearance of mucus remains unclear. Osmotic agents have the potential to increase the amount of water in the airway lumen which might alter the surface properties of the mucus and increase both cilia and cough clearance of the mucus. Mannitol may benefit patients by reducing the mucus load acutely, or it may have a prolonged effect on mucociliary clearance. Inducement of cough can also contribute to airway clearance.

4.4.2 Pharmacodynamics

No pharmacodynamic data was presented in this NDA application.

4.4.3 Pharmacokinetics

Because the safety profiles of large intravenous (IV) and oral doses of mannitol have been well established, the Agency did not require an extensive formal clinical pharmacology program. However, because of the lack of data on the fate of the drug in the lungs after inhalation, a PK and BA study (study DPM-PK-101) was conducted to

determine: 1) the absolute BA of mannitol powder for inhalation compared to mannitol administered intravenously; 2) the relative bioavailability of mannitol powder for inhalation compared to mannitol administered orally; 3) the pharmacokinetic parameters of systemically available mannitol after inhalation. The study was originally conducted to support a related inhaled mannitol product, Aridol mannitol inhalation powder, which the sponsor markets as a bronchial challenge test.

The study was an open-label, randomized, three-way cross over study design in 18 healthy male subjects aged 18-65 years old. Each subject received three treatments: 635 mg mannitol powder for inhalation using a dry powder inhaler, 500 mg mannitol powder administered orally (5 ml of mannitol 10% solution), and mannitol 500 mg (5 ml of mannitol intravenous infusion 10%) in a commercial formulation for intravenous use. The results indicate that the absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 0.59. The relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 0.96. The time to reach the mannitol peak plasma concentration (Cmax) was similar; 1.5 hour for inhaled and 1.4 hour for oral administration, and the mean terminal half-life of mannitol was 5 hours, regardless of route of administration.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant's Clinical Development program for DPM was comprised of 7 clinical studies, which include two Phase 1, three Phase 2, and two Phase 3 clinical trials. This includes one Phase 1 trial of 18 healthy volunteers to assess initial clinical pharmacology parameters, with the remainder of data collected in patients with cystic fibrosis; five Phase 2/3 studies form the primary basis for evaluation of the clinical efficacy and safety DPM in patients with cystic fibrosis. These studies are briefly described in the table below.

In addition, the Applicant has submitted clinical study reports for two Phase 2 and two Phase 3 studies performed in patients with non-CF bronchiectasis, in order to support the safety program.

Table 2: Relevant Clinical Trials

Study #/ Year	Study Type/ Design	Duration	Population	Pt Age	FEV1	n	Treatment Arms	Countries
Dose-Ranging and Proof of Concept								
DPM-PK-101[a] 2006	R, open-label, cross-over *PK and bioavailability*	3 single-doses separated by 1 week	Healthy volunteer males	19-48 years	normal	18	DPM inhaled 635mg Mannitol oral sol'n 500mg Mannitol IV sol'n 500mg	Australia
DPM-PK-102 2009	Open-label, parallel group by age *PK by age*	1 week	CF	6-32 years	>30%[b] 30<90%	18	DPM inhaled 400mg once on Days 1 and 7, and 400mg BID Days 2-6	Australia, UK
DPM-CF-201[a] 2004-2005	R, DB, cross-over *Proof of concept*	Two 2-week treatments, two week washout	CF	8- 48 years	40- 80% or decrease of ≥20% last 6-12 m	38 36[c]	DPM inhaled 420mg BID Crystalline mannitol 420mg BID	Australia, New Zealand
DPM-CF-202 2005-2008	Open-label, cross-over, partial R *Dose-ranging*	Four 2-week treatments, one week washout each	CF	7- 68 years	40-90% predicted	48[d] 44	DPM 400mg BID DPM 40mg BID DPM 120mg BID DPM 240mg BID	Canada, Argentina
DPM-CF-203 2005-2007	R, open-label, cross-over	Three 12-wk treatments, 2-week washout each	CF	9-17 years	<70%	26[e] 23 23 21	DPM 400mg BID DPM 400mg BID+rhDNase 2.5mg QD rhDNase 2.5mg QD only	UK
Phase 3 Trials								
DPM-CF-301 2007-2009	*Efficacy* *Safety* R, DB, AC, PG	26 weeks + up to 52 weeks OL	CF	6-56 years	30- 90% predicted	177 118	DPM 400mg BID DPM 50mg (Control) BID	Australia, New Zealand, UK, Ireland
DPM-CF-302 2008-2010	*Efficacy* *Safety* R, DB, AC, PG	26 weeks + up to 26 weeks OL	CF	6- 53 years	40- 90% predicted	184 121	DPM 400mg BID DPM 50mg (Control) BID	USA, Canada, Argentina,Germany, Belgium,France, Netherlands

a= Initially submitted under NDA 22,368, for Aridol
b= >30% predicted for 6 to 11yo, and 30 to <90% predicted for 12yo and over
c= two dropped out after DPM and before crystalline mannitol (non-respirable control)
d= four dropped out after 400mg dose period; all received 400mg dosing, then randomized to receive 40, 120, or 240mg periods in random order
e= 23 subjects completed the 400mg DPM and DPM+ rhDNase arms, 21 completed rhDNase only arm
[Source: Module 5.3.5.3, ISS, Table 1, pg 25/274, and Section 3.1, pages 28- 30]

5.2 Review Strategy

The clinical development program for Dry Powdered Mannitol was relatively small, as would be expected for a program designed for an orphan patient population. Dose ranging exploration was limited to Study 202, and this study will be reviewed in more detail below in section 5.3. The final dose of 400mg was chosen by the Applicant since "the use of more than 10 mannitol capsules for each dose may compromise compliance" and because "the 400mg dose BID appears to be the most reasonable balance between acceptability and efficacy." [M 2.5, Clinical Overview, section 2.5.3.3, Clinical Pharmacodynamics]. The rationale for the twice-daily dosing regimen was not described by the Applicant in their package; the first multiple-dose study of DPM was initiated at twice daily dosing, and no other dosing intervals were explored. The initial proof-of-concept data was collected in Study 201, and study 203 was an open-label cross-over comparison of use of rhDNase, a commonly-used, approved CF drug in the same class. Studies 301 and 302 are the Phase 3 clinical trials in the intended CF patient population, for the intended indication; each has a double-blind period of 26 weeks. Study 301 had two 26-week open label extension periods (a total of 52 weeks OL), and Study 302 had an open-label extension of 26 weeks; these provide additional unblinded long-term safety data for the indicated population.

As studies 301 and 302 are each important for assessing the safety and efficacy of DPM in patients with cystic fibrosis, both will be reviewed individually below. Reviews are based primarily on the original protocols and statistical analysis plans. All summary data tables submitted by the Applicant as well as relevant Case Report Forms (CRFs) were also reviewed. Meetings with the biostatistical team were held to review the analyses performed by the Applicant, as well as the confirmatory and additional analyses performed by the biostatistical review team. Open-label data from the two trials will be very briefly described, since it adds additional unblinded safety data to support the program, and will be addressed further in Section 7 Review of Safety.

To orient the reader, the review has been organized in the following manner. The protocols for trials 202, 301, and 302 are discussed in detail in section 5.3, "Discussion of Individual Studies/ Clinical Trials." Dose selection based on the results of Study 202, and efficacy results for each trial (patient disposition, demographics, primary and secondary outcomes) are presented in section 6, "Review of Efficacy." Safety results from Studies 301 and 302, and the open-label long-term safety data from these same studies, including extent of exposure, deaths, serious adverse events, and adverse events, are presented in Section 7, "Review of Safety."

5.3 Discussion of Individual Studies/Clinical Trials

STUDY DPM-CF-202

Study Title

A Phase IIa Randomized, Open-label, Dose Response Study to Determine the Optimum Dose of Dry Powder Mannitol Required to Generate Clinical Improvement in Patients with Cystic Fibrosis.

Study Dates

November 7, 2005, through June 29, 2008

Study Sites

There were a total of 12 sites in two countries; 7 in Canada and 5 in Argentina.

Description of Study

This was a Phase 2a, randomized, open-label dose-response study, to determine the dose of dry powder mannitol required to achieve clinical improvement in FEV1 in patients with CF. Eligible patients were given a 475mg of inhaled mannitol, and those with a negative result (the intent being to exclude patients with potentially severe bronchospasm to inhaled mannitol) were randomized to receive 4 two-week treatment periods with DPM via inhalation. At Visit 2, all subjects began a two-week treatment arm with mannitol 400mg BID. At Visits 4, 6, and 8, subjects were then randomized to treatment with 40, 120, or 240mg DPM, in random order. Each treatment period was followed by a 1-week washout period.

Study Schedule

The schedule of treatments for Study 202 is listed below, Figure 1: Schematic for Study 202. All patients began with Visit 1, which included eligibility assessment, history and physical exam, vital signs, sputum collection, baseline spirometry, and pregnancy testing if applicable. They received pre-medication with albuterol, and then underwent bronchoprovocation testing with inhaled mannitol. If they were without significant bronchospasm or intolerance, patients were enrolled to the first 2-week treatment period, beginning 2-14 days after Visit 1. Visit 2 began the first 2-week treatment block, during which all subjects received open-label, unblinded treatment with DPM 400mg BID (10 capsules twice daily). Patients completed two questionnaires (the CFQ-R and “Treatment Effects Questionnaire”), followed by history, physical, pre-dose spirometry,

pre-treatment with albuterol, and first DPM dose in clinic. A 1-hour post-dose sputum weight was collected, and patients were discharged home with a two-week supply of 400mg DPM BID, a diary card, and home spirometer. Visit 3 was the last day of 400mg DPM treatment, which repeated the above assessments, and included collection of the study diary card and download of home spirometry data. This was the first day of the 7-day washout period. After the washout, the following pattern of assessments was repeated three more times, for visits 4/5, 6/7, and 8/9, except that patients received treatments with one of three additional doses of DPM, in randomized order: 40mg, 120mg, or 240mg.

Figure 1: Schematic for Study 202

V1	V2	V3	V4	V5	V6	V7	V8	V9
Day 1	Week 2 & 3	Week 4	Week 5 & 6	Week 7	Week 8 & 9	Week 10	Week 11 & 12	Week 13
Aridol™ Challenge Randomise	400 mg BD	Assessment Start Wash Out	40 or 120 or 240 mg BD	Assessment Start Wash Out	40 or 120 or 240 mg BD	Assessment Start Wash Out	40 or 120 or 240 mg BD	Assessment

[Source: Module 5.3.5.1.2 Study Report Body DPM-CF-202, V 3.0, page 22]

Schedule of assessments for Study 202 is listed below:

Figure 2: Schedule of Assessments, Study 202

Visit	1	2	3	4	5	6	7	8	9
Informed Consent Obtained	X								
Review Eligibility Criteria	X								
Pregnancy Test	X								
Medical History and Demographics	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Clinical exam and Vital Signs	X	X	X	X	X	X	X	X	X
Respiratory Symptoms		X	X		X		X		X
Aridol™ Challenge	X								
Randomisation	X								
Administer 1st treatment in clinic and dispense treatment and salbutamol		400 mg Mannitol		Dose X Mannitol		Dose X Mannitol		Dose X Mannitol	
Administer final treatment in clinic and commence washout			400 mg Mannitol		Dose X Mannitol		Dose X Mannitol		Dose X Mannitol
Study drug compliance			X		X		X		X
Sputum sample	X	X	X	X	X	X	X	X	X
Spirometry	X	X	X	X	X	X	X	X	X
Distribute Diary and Pikometer	X								
Download Piko and copy diary			X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X
CFQ-r		X	X		X		X		X
Treatment Effects Questionnaire.		X	X		X		X		X

[Source: Module 5.3.5.1.2, Study Report Body DPM-CF-202, Version 3.0, page 37]

Reviewer's Comments:
The Applicant notes that their first dose of 400mg was chosen to "replicate previous improvements and outcome measures from earlier studies" [DPM-CF-202 Final Study Report page 30]. No higher doses were used, and all subjects received the highest dose in the first treatment period, making the first part of this study not randomized.

Population

For Study 202, 36 cystic fibrosis patients were required based on power calculations. Patients were aged ≥ 7 years, with FEV1≥ 40% and <90% predicted, with no intolerance to mannitol or beta-agonists, and with no concurrent use of hypertonic saline or beta-blockers for the study duration. The final actual numbers were 85 patients recruited and enrolled, 48 randomized, and 38 analyzed as the per protocol population.

Summary of Notable Inclusion Criteria

- Male or female patient aged ≥ 7 years, with confirmed diagnosis of cystic fibrosis
- FEV1 ≥ 40% and < 90% predicted
- No additional antibiotics or oral steroids for 14 days prior to study entry
- Able to perform all lung function measurement techniques

Reviewer's Comment:
"Confirmed diagnosis of CF" is defined as an abnormal sweat chloride test or known CF genotype.

Summary of Notable Exclusion Criteria

- Patients with currently active asthma
- Chronic infection with *Burkholderia cepacia* or MRSA
- Mannitol intolerance
- Hypertonic saline use
- Use of beta-blockers
- Use of mucolytics other than DNase
- Use of home oxygen or assisted ventilation
- Lung transplant recipient
- "terminally ill" or listed for lung transplant
- History of significant hemoptysis (>60mL) within 3 months before enrollment
- Myocardial infarction, cerebrovascular accident, or major surgery within 3 months before enrollment, or other illness which constitutes increased risk

Reviewer's Comment:
Asthma diagnosis, infection status, and use of oxygen or assisted ventilation are exclusion criteria for this study, therefore selecting a more healthy CF population for this first trial. These are not listed for the two Phase 3 studies, which appropriately studied a wider patient population.

Treatments

Study Treatments
Test kits were used at Visit 1 to determine if patients had bronchoprovocation with DPM, which would preclude them from randomization. Incremental doses of inhaled mannitol were administered up to a maximum of 475mg. Patients who had less than or equal to 15% decline in FEV1 were considered to lack significant bronchoconstriction and were eligible for entry into the study. All patients received the first period dose of 400mg BID x2 weeks (10 capsules BID). They subsequently were randomized to receive doses of 40mg (1 capsule), 120mg (3 capsules), or 240mg (6 capsules) BID x 2 weeks for each treatment arm thereafter. All study drug was instructed to be given after using a short-acting beta-agonist (SABA).

Reviewer's Comments:
The Integrated Summary of Safety notes that, due to country-specific requirements, some patients in Study 202 from Canada did not receive pre-treatment with a bronchodilator.

No placebo or control was given.

Dose Modification
No dose modifications were specified in the protocol.

Permitted Medications and Concomitant Therapies
All standard medications used to treat patients with CF were allowed, with the exception of inhaled hypertonic saline. All concurrent treatments given one month before and up to the end of the observation period were recorded; alternative or homeopathic therapies were not recorded.

In addition, beta-agonists were withheld for at least 4 hours prior to study visits, and patients were asked to perform their chest physiotherapy or exercise no closer than 4 hours prior to their scheduled visit.

Reviewer's Comments:
No adjustments were made for LABA or combination inhaler use for this Phase 2 trial.

Prohibited Medications
The use of inhaled hypertonic saline and beta-blockers was prohibited.

Patient Discontinuation / Withdrawal Criteria

Patients were free to withdraw at any time; the Investigator could withdraw subjects for reasons pertaining to their health or well-being, or for lack of cooperation.
Patients were discontinued for the following:

- Withdrawal of consent
- Investigator decision
- Primary attending physician requested patient be removed from study
- Investigator or Sponsor stops study
- Erroneously enrolled patients
- Pregnancy
- Pulmonary exacerbation requiring discontinuation of medication
- Positive Aridol challenge
- Fall in oxygen saturation by ≥10% from baseline, or fall in FEV1 by ≥ 15%, not reversible by positive airway pressure, during Aridol Challenge

Follow-up after Premature Discontinuation
The study design planned that efforts should be made to complete all observations made up until the time of withdrawal, and that if withdrawal was due to an AE or abnormal laboratory value, monitoring should continue until resolution. There was no early termination visit specified.

Replacement Plans
Withdrawn patients were replaced with a new subject.

Study Endpoints

The primary objective of this study was to determine a dose of DPM to obtain clinical improvement in lung function as measured by FEV1 and FVC. Changes in FEV1 and FVC from baseline for each dose level were calculated using a mixed models approach.

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the protocol, and performed according to the American Thoracic Society Guidelines, utilizing Crapo (≥18yo) and Polgar (<18yo) reference standards. No alterations were made on the basis of race. All spirometry was to be collected pre-bronchodilator.

Secondary endpoints included other mean changes from baseline in evaluations of lung function, sputum microbiology, AEs, QOL, sputum weights, clearance, and cough, and respiratory symptoms.

Summary statistics were used for most data. For all statistical tests, a two-sided p-value below 5% was pre-specified as significant. No correction was made for multiplicity, but since this was a Phase 2 study, the risk of falsely identifying significance was considered acceptable. Missing data was not imputed.

Protocol Amendments/ Conduct

Study 202 had two protocol amendments before data lock, noted below in Table 3: Conduct of Study 202. In addition, there were two changes from the planned SAP.

Reviewer's Comments:
The subgroup analysis of rhDNase users was not performed, since only 2 patients out of 85 reported using rhDNase, and both of these subjects failed the Aridol challenge. This raises a question as to the applicability of the Phase 2 data to a US CF population, for which the majority use rhDNase on a daily basis. Per the CFF Patient Registry for 2007 (during study conduct), 74% and 34% of US patients were using rhDNase and hypertonic saline respectively. These numbers have increased to 78% and 50% for the most recent year of available data, 2010. Benefits seen in this study which were used to craft the Phase 3 program may not carry over to those patients for whom daily mucolytic is already a standard of care.

Table 3: Conduct of Study 202

Conduct	Date	Major Changes Made
Version 1	04-16-2005	• N/A
Version 2 Amendment 1	06-08-2006	• Exclusion criterion removed for rhDNase use • Definition of Aridol positive challenge modified • Only one FEV1 maneuver required after each dose step of Aridol challenge • Total dose changed from 635mg to 475mg • Pre-medicate with SABA 15 min. before challenge
Version 3 Amendment 2	09-06-2006	• Added Argentina sites • Argentina sites not permitted to use other mucolytics • Inclusion criterion increased upper end of FEV1 to 90% predicted • Exclusion criterion of drop in FEV1 over prior year was removed • Total number randomized changed to accommodate rhDNase use; max 42 subjects using rhDNase • Use of low-resistance osmohalers removed from CF trials • Added Adverse Event assessment category "probably not related"
Other changes from SAP		• Planned subgroup analysis of rhDNase not done • Primary efficacy analysis changed from end arm post-dose to end arm pre-dose
[Source: Module 5.3.5.1.2, Clinical Study Report DPM-CF-202, Section 9.8, page 50]		

STUDY DPM-CF-301

Study Title

"Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis-A Safety and Efficacy Study"

Study Dates

April 5, 2007, through April 24, 2009

Study Sites

There were a total of 40 centers in 4 countries: Australia (10), New Zealand (2), United Kingdom (24), Ireland (4).

Description of Study

This was a double-blinded, randomized, parallel-group, controlled, interventional 26 week clinical trial, followed by a 26-week open label phase during which all subjects received active treatment. Eligible patients were randomized at the screening visit in a 3:2 fashion to receive either treatment with inhaled Dry Powder Mannitol (DPM) 400mg BID, or matched control, for 26 weeks. At the end of the treatment phase, a 26-week open-label phase was offered to patients, during which all patients received active study drug. A later protocol amendment added a second 26-week open-label period to the trial, with a total potential open-label period of 52 weeks.

Study Schedule

The study schedule for Study CF-301 is presented below; Study CF-302, discussed next in this section of the review, was of similar design. All patients began with a Visit 0 screening period, scheduled two weeks before Visit 1. At the screening, patients were administered the initial dose of DPM , called the Mannitol Tolerance Test (MTT), under supervision to assess for airway hyperresponsiveness and tolerance of the medication. If they were without significant bronchospasm or intolerance (see below), patients were randomized at Visit 1 to double-blinded treatment with either DPM 400mg BID (10 capsules twice daily) or control treatment of inhaled dry powder mannitol 50mg BID (10 capsules twice daily). The treatment period was defined as Day 0 to week 26 (Visit 4). If eligible, patients were continued into a 26-week open-label phase, during which all patients received active DPM. There were two additional study visits (5 and 6). After this 54-week study period, there was a second open-label phase for an additional 26 weeks, during which eligible patients could continue on treatment DPM out to a total of 80 weeks.

Reviewer's Comments:

(b) (4)

The lower 50mg dose of DPM was proposed by the Applicant as a sub-therapeutic dose (based on Study CF-202 data), which would still allow for blinding without having differing safety risks for the control group.

The Applicant has labeled the second 26 week block of treatment with open-label therapy as the "Open label phase," and the subsequent 26-week block of open-label treatment as the "Second Open Label Phase." The second open-label period was added late in the trial, after a number of patients had already completed the first open-label period, and exited the trial. This terminology is somewhat confusing, so to mitigate reader confusion, this review will describe the entire open-label period from Visit 4 through Visit 8 as the 52 week open-label phase, unless otherwise specified.

The schematic for Study CF-301 (and subsequent CF-302) is shown below.

Figure 3: Schematic for Studies DPM-CF-301 and -302

Diagram 1. Study Schema

V0	V1	V2	V3	V4	V5	V6
Day 0 2 wk period	6 week period	8 week period	12 week period	12 week period	14 week period	
Screening	26 week blinded phase			26 week open label phase		
	IDPM 400 mg BD (10 capsules)			IDPM 400 mg BD (10 capsules)		
	Control BD (10 capsules)					

[Source: Module 5.3.5.1.4.16.1.1, DPM-CF-301 Protocol V5, pg. 439; DPM-CF-302 V2, pg. 107.]

Figure 4: Schematic for Second Open-Label Phase, Study 301

Diagram 2. Study Schema: Second Open Label Phase

V6	V7	V8
12 week period	14 week period	
26 week open label phase IDPM 400 mg BD (10 capsules)		

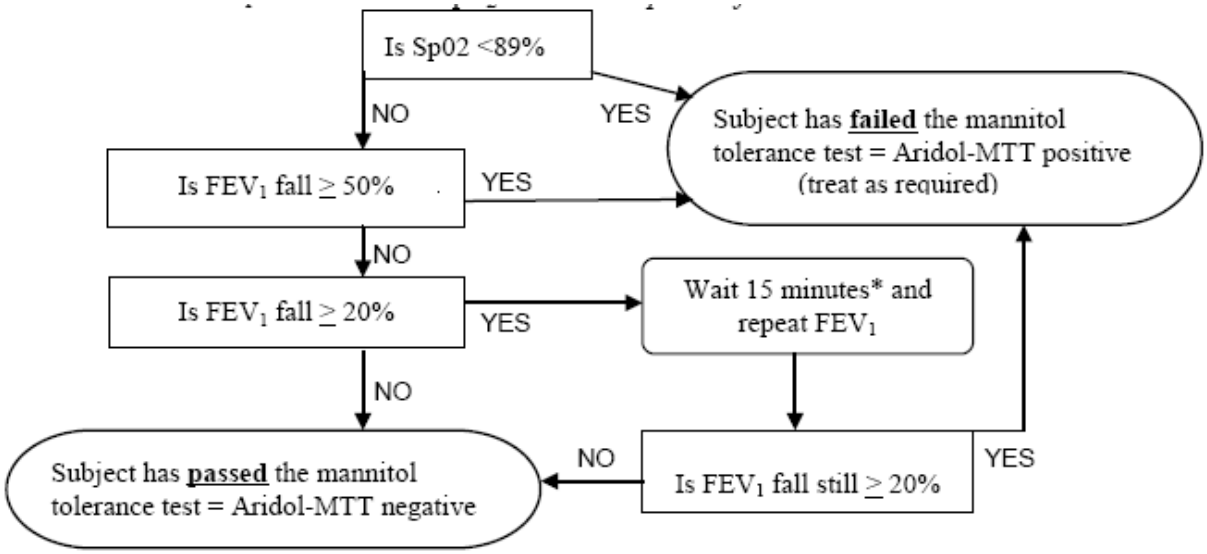
[Source: Module 5.3.5.1.4.16.1.1, Study DPM-CF-301 Protocol Version 5, page 440]

Screening assessments included comprehensive history, demographics, CF sputum microbiology, review of prior and concomitant medications/ treatments, physical exam, vital signs, pulse oximetry, spirometry, report of adverse events, and clinical laboratories. Patients who met all the eligibility criteria and none of the exclusion criteria and for whom there was documented informed consent/assent as applicable, received the initial dose of DPM while being closely monitored in the clinic. If subjects had a less than 20% decrease in FEV1 (or a 20-50% decrease, and noted to improve within 20% of baseline within 15 minutes), they were continued on to Visit 1.

Reviewer's Comment:
The Applicant refers to this initial dose procedure as the "Aridol-Mannitol Tolerance Test (MTT)." However, since the study was conducted prior to approval of the Aridol product in the US, it was not conducted in the exact same manner as outlined in the approved product label. The procedure for Aridol is to use gradually increasing doses of drug from 0mg to a total of 635mg (by 5 to 40mg increments), with a dose given every 60 seconds followed by spirometry, until the maximal dose is reached, the subject's FEV1 declines by 15% or more, or oxygen saturations fall below 89% on room air.

For this Phase 3 protocol, CF patients were all pre-treated with short-acting bronchodilator after baseline spirometry was obtained. Then they were given doses of 35, 80, 120, and 160mg of DPM, with spirometry performed after the 120mg and 160mg doses. If oxygen saturation fell below 89%, or if FEV1 fell >50%, it was considered a failed test. If FEV1 dropped less than 20%, or if FEV1 fell 20-50%, but recovered at repeat FEV1 15 minutes later to less than 20% fall from baseline, subject was considered to have passed the testing; see Figure 5 *below.*

Figure 5: Schematic for First DPM Dose at Screen, Studies 301 and 302



[Source: Module 5.3.5,1.4.16.1.1, Study DPM-CF-301 Protocol Version 5, page 452]

The double-blinded treatment period began at randomization at Visit 1 (day 0), and continued through week 26. Patients were randomized in a 3:2 fashion to either DPM 400mg BID, or control 50mg BID. Patients were stratified based on rhDNase use; age and baseline lung function were not used to stratify patients, based on results from prior Phase 2 studies showing no evidence of treatment differences [Module 5.3.5.1, Clinical Study Report DPM-CF-301, section 9.7.1.2.2, page 48]. Patients continued their blinded study drug, with regularly scheduled evaluations at Visit 2 (week 6), Visit 3 (week 14), and Visit 4 at week 26 [see Figure 6: Schedule of Assessments below].

The protocol utilizes the patient-reported outcome (PRO) tool, the Cystic Fibrosis Questionnaire-Revised (CFQ-R), to assess the patient's/parent's perception of the physical, emotional, and social impact of disease on the patient and their families. This was collected at Visits 1, 3, and 4. It was not collected in the open-label periods.

Sputum microbiology was collected at each visit, and induced sputum samples for sputum weight were collected at Visits 1 and 3. Pregnancy testing as applicable, and bloodwork for safety were performed at Screening and Visit 4, as well as Visits 6 and 8 if the patient continued into open-label periods. A symptom diary was given to patients at Visit 1, and collected at the end of the 26-week treatment period. Second and third diaries were issued for subjects continuing into each open-label period, as needed.

Figure 6: Schedule of Assessments, Studies 301 and 302

Appendix 1: Time and Events Schedule

Event	Screening Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit due at week	Day -14	0	6	14	26	38	52
		26 weeks IDPM/control Blinded phase				26 weeks Open label phase	
Informed Consent [1]	X[1]				X[4]		X[7]
Inclusion/exclusion criteria	X						
Medical History /Demographics	X						
Concomitant medications	X	X	X	X	X	X	X
Physical examination/ vital signs	X	X	X	X	X	X	X
Pulmonary function tests [2]	X	X	X	X	X	X	X
FOT**		X	X	X	X		
Bronchodilator response test		X			X		
Pregnancy Test[3]	X				X[4]		X[7]
Cystic Fibrosis Questionnaire		X		X	X		
Pulmonary exacerbations review			X	X	X	X	X
Medical resource use review			X	X	X	X	X
Blood tests	X				X		X
Randomise subject	X						
Administer treatment dose in clinic		X		X	X[4*]		
Phone call to subject					X[6]		
Aridol-MTT procedure	X						
Dispense study medication & beta agonist		X	X	X	X[4]	X	X[7]
Weigh treatment induced sputum sample		X		X			
Sputum qualitative micro	X	X	X	X	X	X	X
Issue study diary / Collect diary		X			X[4] / X[5]		X
Adverse event assessment		X	X	X	X	X	X
Drug compliance and accountability			X	X	X	X	X
Discharge subject from study					X[5]		X[5*]

[Source: Module 5.3.5.1.4.16.1.1, Study DPM-CF-301 Protocol V5, pg. 493; DPM-CF-302 V2, pg. 161]

All patients who completed through week 26 either continued into the open-label extension, or they completed a discharge visit (study diary collected).

There was no formal "termination visit" for patients who prematurely discontinued from the double-blind portion of the study. Patients withdrawing would be asked for a blood

sample for safety follow-up (hematology and biochemistry) if they had received more than 2 months' treatment. If the withdrawal occurred at a visit, the study visit was to be completed "as much as practical," and if between visits, the next study visit procedures were to be conducted "as practical"; drug collection and accountability were stressed.

Population

For Study 301, a minimum of 340 cystic fibrosis patients were planned to be randomized. Patients were aged ≥ 6 years, with FEV1≥ 30% and <90% predicted, with no intolerance to mannitol or beta-agonists, and with no concurrent use of hypertonic saline or beta-blockers for the study duration. They were to be randomized to 400mg DPM versus control (50mg) BID of inhaled study drug treatment. The final actual numbers were 389 patients enrolled, 324 randomized, and 295 analyzed as the ITT population.

Reviewer's Comment:
Version 1 of the protocol initially proposed a minimum of 300 patients, randomized 2:1 to either 400 or 200mg BID, versus control (50mh) BID. Version 2 was changed to 250 patients randomized 3:2 to 400mg DPM versus control (50mg) BID. This was amended to a minimum of 340 subjects in Version 4, which was continued to the final protocol Version 5.

Summary of Notable Inclusion Criteria

- Male or female patient aged ≥ 6 years, with confirmed diagnosis of cystic fibrosis
- FEV1 ≥ 30% and < 90% predicted
- No intolerance to mannitol or beta-agonists
- Able to perform all lung function measurement techniques

Reviewer's Comment:
There was no formal definition provided for "confirmed diagnosis of CF."

Summary of Notable Exclusion Criteria

- "Aridol-MTT test positive" (as evaluated by first dose)
- Hypertonic saline use
- Lung transplant recipient
- "terminally ill" or listed for lung transplant
- Use of beta-blockers
- History of significant hemoptysis (>60mL) within 3 months before enrollment
- Myocardial infarction, cerebrovascular accident, or major surgery within 3 months before enrollment
- Have a known cerebral, aortic, or abdominal aneurism
- Be pregnant, breastfeeding, or plan to become pregnant while in study
- Using unreliable birth control method (females only)

- Have uncontrolled hypertension
- Have a condition that, per Investigator, would put patient at risk or confound study results

Reviewer's Comment:
The inclusion and exclusion criteria are broad, and would include a large percentage of patients with CF.

Treatments

Study Treatments
Subjects were randomized to inhaled treatments of either DPM 400mg BID, or control (DPM 50mg) BID. The 50mg DPM dose was chosen as the control based on results from Study 202, which showed no efficacy of a 40mg BID dose.

Treatments were given as 10 capsules inhaled, twice per day (20 capsules daily), because CMC issues for DPM restricted the largest dose of DPM per capsule to 40mg. Therefore, in order to meet 400mg dosing, ten capsules were required for each administration. To keep the study blinded, the control group also needed to use 10 capsules, and the Applicant already formulated a 5mg capsule as part of the Aridol test kit, so a 50mg dose was chosen. All treatments were administered using the Osmohaler HR (high resistance) device.

All study drug was instructed to be given after using a short-acting beta-agonist (SABA).

Reviewer's Comments:
Initially, the first version of the protocol included a 200mg dose as well as the 400mg dose. This was removed in version 2, because analysis from Study 202 became available, which noted that the improvement with the 400mg dose was significant, but that there was no statistically significant difference between the 200mg dose and control.

The protocol required that all patients use a SABA prior to study drug dosing to prevent severe bronchospasm. If approved, product labeling will need to include pre-treatment with SABA such as albuterol.

Dose Modification
No dose modifications were specified in the protocol.

Permitted Medications and Concomitant Treatments
All standard medications used to treat patients with CF were allowed, with the exception of inhaled hypertonic saline. The protocol provides a recommended order of treatment for the inhaled medications, as follows:

1. bronchodilator
2. DPM/control study drug

3. physiotherapy
4. rhDNase
5. inhaled antibiotic
6. inhaled corticosteroid

In addition, the protocol specifically notes that beta-agonist and combination medications should be held for 6 to 12 hours prior to study visits, but that if patients develop chest tightness or shortness of breath, that they should use their rescue SABA medication, and re-schedule their visit.

Prohibited Medications
Inhaled hypertonic saline, while not FDA-approved as a treatment for CF, is commonly used by CF patients as a mucolytic/expectorant, and was the only CF-specific treatment excluded from this trial. Patients were allowed to wash out from inhaled saline therapy (for 4 weeks) in order to enroll in the trial. Any other investigational study drugs were not permissible within 4 weeks of study entry.

Beta-blockers were also prohibited.

Patient Discontinuation / Withdrawal Criteria

The protocol states that each patient has the right to withdraw from the study at any time, without prejudice, and that the Investigator has the right to withdraw patients in the event of intercurrent illness, AEs, or other reasons concerning the patient's health or well-being, or due to lack of compliance.

Reviewer's Comment:
No specific patient stopping criteria were provided, other than "failure" of the initial dose, with decrease in FEV1 of more than 20% which does not recover quickly. The Applicant noted that all efforts should be made to collect data from patients who withdraw, but a specific early termination visit was not described. No plans to minimize dropouts, or to correct statistical analyses in the event of frequent dropout, were included within the protocol. This is of concern, because higher dropout in the treatment group could potentially select for "responders," and enhance the overall treatment effect seen in favor of treatment over control (so patients who do well continue, and patients who do not do well or have increased adverse events drop out, thus making the patients who complete look better than what the true overall average of the group would otherwise be). In addition, reason for withdrawal included 'patient withdraws consent,' which can miss capturing the actual reason- was it too hard to use the 10 capsules BID (administration), or did they have too much cough (Adverse event), or did it not work as well as their previously used hypertonic saline (efficacy issue)? Patient dropouts for this program will be discussed further in Sections 6 and 7, Efficacy and Safety.

Follow-up after Premature Discontinuation

The protocol notes that efforts should be made to complete all observations made up until the time of withdrawal, and that if withdrawal was due to an AE or abnormal laboratory value, monitoring should continue until resolution. There was no early termination visit specified in the protocol; only subjects who completed the 26-week, double-blinded period but chose not to continue into the open-label phase, had a "Discharge Visit."

Replacement Plans
There was no description of patient replacement in the study, and patients who demonstrated significant bronchospasm at the screening visit with the first dose of study drug were discontinued.

Study Endpoints

The primary efficacy endpoint for Study 301 was change in absolute FEV1. The primary efficacy analysis utilized a mixed effects model for repeated measurements (MMRM). The model used age, disease severity, and baseline FEV1 as covariates. With a mixed effects model as the primary analysis model, no imputation of missing data was done. However, sensitivity analyses assessing the impact of missing data on efficacy evaluations were performed [Module 5.3.5.1, Clinical Study Report DPM-CF-301, section 9.7.1.2.2, page 48]. The issues of missing data and the statistical analysis methods for Study 301 are significant issues, and are discussed in detail in the FDA statistical review, and summarized in Section 6 Review of Efficacy. One interim analysis was planned, using a significance rate of 0.001 for testing the primary endpoint at the interim analysis, and a significance level of 0.0498 at the end of the study.

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the protocol, and performed according to the American Thoracic Society/ European Respiratory Society Guidelines, utilizing NHANES III (Hankinson) and Wang reference standards. All spirometry was to be collected pre-bronchodilator, if possible, defined as no SABA within 6 hours and no LABA within 12 hours. If patient forgot to hold his SABA or LABA at the screening visit, then visit was re-scheduled.

No pre-specified key secondary endpoints were identified and for this protocol. All secondary endpoints were listed and evaluated as below; there was no pre-specified correction for multiplicity.

- Change in absolute FEV1 in the rhDNase group- analysis is the same as for the primary efficacy endpoint

- Pulmonary exacerbations- descriptive statistics will identify the number and percentage of patients experiencing at least one exacerbation, by treatment group. In addition, exacerbation rates will be compared using Poisson regression analyses, with age and baseline disease severity as covariates in the model.

o Definition of Pulmonary Exacerbation

This protocol used the definition for pulmonary exacerbation published by Fuchs and colleagues, which occurs when patients are treated with IV antibiotics in the presence of four or more of the following signs or symptoms:

-change in sputum
-dyspnea
-new or increased hemoptysis
-malaise, fatigue, or lethargy
-fever ≥ 38°C
-anorexia or weight loss
-sinus pain or tenderness
-change in sinus discharge
-FVC or FEV1 decreased by ≥10% from previous value
-radiographic signs of pulmonary infection
-increased cough
-changes in chest physical examination

- Quality of Life scores using the Cystic Fibrosis Questionnaire- component questions from the questionnaire were transformed, and the total was the sum of the responses. Descriptive statistics and change from baseline scores at weeks 14 and 26 were to be used, with inferential analysis performed in a similar manner to the primary endpoint.

- Rescue antibiotic use- displayed for each patient, number and percentage of patients with rescue events. Data was to be analyzed using Poisson regression.

- Change in FVC, and FEF25-75 from baseline- to be analyzed in similar fashion as was the primary endpoint

- Days in the hospital due to pulmonary exacerbations- descriptive statistics will be used for each patient, by study treatment, and by events. Overall rate of hospitalizations will also be calculated.

Protocol Amendments/ Conduct

Study 301 had four protocol revisions at the time of database lock. Two protocol amendments were made prior to patient enrollment, so Version 3 was the protocol in place at study start. A brief summary of significant changes is included in the table below. The potential impact of these amendments will be discussed further in Section 6 Review of Efficacy.

Table 4: Conduct of Study 301

Conduct	Date	Major Changes Made
Version 1 (Before enrollment)	08-08-2006	• First Protocol submitted to FDA as a Special Protocol Assessment (SPA), subsequently withdrawn from the IND
Version 2 Amendment 1 (Before enrollment)	12-22-2006	• Study design amended based on advice from FDA, EMA, and potential Investigators • Addition of the "MTT" dose at Screening to check for airway hyperresponsiveness • Removal of 200mg dose cohort and its control • Stratification based on rhDNase use added • Exacerbation definition according to Fuchs' criteria • CRP and chest X-ray removed from assessments
Version 3 Amendment 2 (105 patients enrolled under this version)	03-12-2007	• Telephone call added to the open-label phase • Objectives were re-worded slightly • Addendum 04-25-2007- typographical error corrected • Addendum 05-16-2007- QOL questionnaire CFQ-R changed to CFQ-UK V1 for UK sites, and QOL analysis clarified
Version 4 Amendment 3 (180 patients enrolled under this version)	08-16-2007	• Number of subjects increased from 250 up to 340, based on ICH-E1A chronic safety exposure recommendations of 100 subjects to receive treatment for 12 months, and 300 for 6 months • Study sites in Germany and New Zealand added • Enrollment increased to 18 months • Added pharyngeal swab if sputum could not be collected • Interim safety analysis in DSMB charter added • German QOLQ and drug names added
Version 5 Amendment 4 (no subjects enrolled)	11-16-2008	• Second 26-week OL extension added to ensure a minimum of 100 patients would receive 12 months of active treatment
SAP vs. protocol differences	04-24-2009 SAP Date	• Changed analysis of all secondary variables to be based on ITT population • Added geographic region as a covariate to models • Added rhDNase use as a covariate to models • Added responder analyses based on FEV1 and QOL • **New endpoint** of % patients who respond on the basis of FEV1, stratified by rhDNase use • **New endpoint** of % patients who respond on the basis of QOL, stratified by rhDNase use • **New Exploratory endpoints** added (prolonged response in FEV1, response in QOL, relation between QOL and FEV1)

		• **New analysis** of Time-to-first-Exacerbation added

[Source: Module 5.3.5.1.3, Clinical Study Report DPM-CF-301, Section 9.8, page 55]

STUDY DPM-CF-302

Study Title

"Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis-A Safety and Efficacy Study"

Study Dates

September 3, 2008, through April 12, 2010

Study Sites

There were a total of 53 centers in 7 countries: USA (28), Canada (3), Argentina (8), Germany (3), Belgium (4), France (6), and Netherlands (1).

Description of Study

This was a double-blinded, randomized, parallel-group, controlled, interventional 26 week clinical trial, followed by a 26-week open label phase during which all subjects received active treatment. Eligible patients were randomized at the screening visit in a 3:2 fashion to receive either treatment with inhaled Dry Powder Mannitol (DPM) 400mg BID, or matched control, for 26 weeks. At the end of the treatment phase, a 26-week open-label phase was offered to patients, during which all patients received active study drug.

The clinical design for Study 302 is very similar to that of Study 301, with the following exceptions:

- The FEV1 inclusion criterion was increased to $\geq$ 40% predicted (from $\geq$ 30%)
- The "MTT" initial dose at screening was changed slightly; the first dose given was a single 40mg capsule (rather than a 5+ 10+ 20mg =35mg)
- Quantitative microbiology was incorporated into the 302 protocol
- Bronchodilator response test at Visit 1 was not included in study 302
- CF genotype and presence of bronchiectasis data were collected in study 302
- There was a single 26-week open-label phase in study 302

Study Schedule

The study schedules for Study 301 and 302 are almost the same, except that Study 301 had a second open-label 26-week period for which some patients were eligible. Refer to Figure 3: Schematic for Studies DPM-CF-301 and -302, in the previous section.

The Screening visit assessments collected were the same as those from Study 301, but moved the first collection of the PRO tool, the Cystic-Fibrosis Questionnaire-Revised (CFQ-R) from Visit 1 to Visit 0. A Health Utilities Index (HUI) was completed at this time, to measure health status. Bloodwork, pregnancy testing, and sputum collection schedules were the same as for study 301. Patients who met all the eligibility criteria and none of the exclusion criteria and for whom there was documented informed consent/assent as applicable, received the initial dose of DPM while being closely monitored in the clinic. If subjects had a less than 20% decrease in FEV1 (or a 20-50% decrease, and noted to improve within 20% of baseline within 15 minutes), they were continued on to Visit 1. The process is the same as that for Study 301, captured in Figure 5: Schematic for First DPM Dose at Screen.

The double-blinded treatment period began at randomization at Visit 1 (day 0), and continued through week 26. Patients were stratified based on rhDNase use. Patients continued their blinded study drug, with regularly scheduled evaluations at Visit 2 (week 6), Visit 3 (week 14), and Visit 4 at week 26. The timing and event schedule for Study 302 is the same as that for study 301, with the exceptions noted above. Refer to Figure 6: Schedule of Assessments, in the previous section above.

All patients who completed through week 26 either continued into the open-label extension, or they completed a discharge visit (study diary collected).

A formal “termination visit” was added to Study 302 for patients who prematurely discontinued from the double-blind portion of the study. Patients withdrawing at any time before completing all study visits completed the termination visit, which consisted of all assessments for Visit 4, and were to be completed no later than 14 days after withdrawal. Two attempts to contact the patient by phone, and two more in writing, were planned before the subject would be considered lost to follow-up.

Reviewer’s Comment:
The protocol only notes using CFQ-R US/English version (also used in study 301), which might not be appropriate for all countries who enrolled patients into Study 302, including 22 centers in Argentina, Germany, France, Belgium, and the Netherlands. The HUI was not collected in study 301, but was added to Study 302 to gather cost effectiveness information.

Population

For Study 302, a minimum of 300 cystic fibrosis patients were planned to be recruited for study. Patients were aged ≥ 6 years, with FEV1≥ 40% and <90% predicted, with no intolerance to mannitol or beta-agonists, and with no concurrent use of hypertonic saline or beta-blockers for the study duration. The final actual numbers were 342 patients enrolled, 318 randomized, and 305 analyzed as the ITT population.

Summary of Notable Inclusion/Exclusion Criteria
The inclusion and exclusion criteria for Study 302 are the same as that for Study 301 [refer to Population for Study DPM-CF-301 section above], with the notable exception of change in FEV1 parameters. For Study 302, baseline FEV1 was ≥ 40% and <90% predicted, (using the same NHANES III or Wang reference standards as were utilized in Study 301).

Treatments

Study Treatments, Dose Modifications, Permitted and Prohibited Medications are almost identical to those of Study 301. The exception is that for Study 302, the medications that should be held prior to study visits and spirometry include inhaled short- and long-acting anticholinergics, and oral theophylline, in addition to SABA, LABA, and combination medications.

Reviewer's Comment:
It is not clear if the additional withholding medications were added due to difficulties that arose during Study 301, or if this was an effort to further tighten study parameters for 302.

Patient Discontinuation / Withdrawal Criteria

Patient withdrawal criteria and monitoring plans were more comprehensive for Study 302 than they were for 301. In addition to noting that patients have the right to withdraw at any time for any reason, the Applicant added a listing of specific events that would warrant withdrawal, and include the following:

- Pregnancy
- Cepacia Syndrome
- Cor Pulmonale
- Pancreatitis
- Pneumothorax or hemothorax requiring chest tube insertion
- Admission to the intensive care unit
- Organ transplant
- Major abdominal, thoracic, or neurosurgery
- Drop in FEV1 ≥20% after inhaled DPM that lasts >30 minutes

- Reduction in FEV1 ≥50% immediately after inhaled DPM
- Oxygen desaturation to <89% immediately following inhaled DPM

Follow-up after discontinuation was captured in a termination visit, as described above. There was no replacement of patients who discontinued.

Reviewer's Comment:
It is unclear why the Applicant chose to use ≥20% when describing declines in FEV1 for the CF patient population, since the labeled Aridol product uses a cut off of ≥15% to determine bronchial hyperresponsiveness.

Study Endpoints

The primary efficacy endpoint for Study 302 was change in absolute FEV1. The Applicant described that descriptive statistics would be used to identify the mean change, the standard deviation, median change, and minimum and maximum changes at each post-baseline FEV1 assessment (at weeks 6 ,14, and 26). The primary efficacy analysis differed from that for Study 301, in that Study 302 utilized a mixed effects model for repeated measurements, which identified age and baseline FEV1 as covariates. Disease severity was included as a covariate for Study 301, but not for Study 302 in the protocol, but this was added in the SAP prior to database lock. One interim analysis was planned, using a significance rate of 0.001 for testing the primary endpoint at the interim analysis, and a significance level of 0.0498 at the end of the study.

Reviewer's Comment:
The SAP for Study 302 was somewhat different than that for Study 301. In addition, Study 302 had a number of additional post-hoc analyses performed after the study was completed. (Please refer to the Biostatistical Review for specific details).

Spirometry measurements were conducted in a similar fashion as for Study 301.

No pre-specified key secondary endpoints were identified in this protocol, nor was there a pre-specified ranking of secondary endpoints in the protocol. All secondary endpoints listed here were evaluated, and were the same as those in Study 301 unless noted; there was no pre-specified correction for multiplicity. The statistical analysis plan for Study 302 did specify 5 key secondary endpoints, however, 2 of these were not identified as endpoints in the protocol.

- Change in absolute FEV1 in the rhDNase group
- Pulmonary exacerbations- the definition of Exacerbation was the same as that used in Study 301, as was the plan for endpoint analysis
- Quality of Life scores using the Cystic Fibrosis Questionnaire

- Rescue antibiotic use
- Change in FVC, and FEF25-75 from baseline
- Days in the hospital due to pulmonary exacerbations

Cost-effectiveness including total costs of hospital and community care was added to Study 302 as a secondary analysis. This was to be evaluated by recording data collected in medical records, discharge summaries, subject diaries, and Health Utility Index Quality Adjusted Life Years (QALY) scores, to compare the cost-effectiveness of using mannitol vs. control.

Protocol Amendments/ Conduct

There was one protocol amendment for Study 302 in the US version, and there were two for the EU version. A number of changes were made to the Statistical Analysis Plan for Study 302, which included adding covariates to the analysis models for primary and secondary endpoints, changing the model used for the CFQ-R endpoint, and changing the defining parameter of the "Per Protocol" population, to drop the lower border of compliance from "≥80%," to "≥60%." The significance of these changes will be discussed in Section 6, Efficacy, and in the FDA's Biostatistical Review. A brief summary of changes can be found in the table below.

Table 5: Conduct of Study 302

Conduct	Date	Major Changes Made
Version 1 (pre enrollment)	12-18-2007	• Original Version
Version 2 Amendment 1 (Before enrollment)	04-04-2008	• Subject number increased from 250 to 300 • "MTT" dose at Screening modified to 400mg • Expected attrition rate changed from 20 to 30% • Randomization process changed prior to study commencement • Interim safety analysis procedure clarified
Version 2- EU Amendment 2	05-20-2008	• European Version only • Drug names changed for Europe • Regulatory reporting requirements added according to local legislation • CFQ-R translations added to be country-specific
SAP vs. protocol differences	05-29-2010 SAP Date	• For change in absolute FEV1- **Added** additional covariates of disease severity at baseline, rhDNase use, gender, and geographic region • For Change in Abs FEV1 rhDNase, Change in FVC, FEF25-75- **Added** additional covariates of disease severity at baseline, rhDNase use, gender, and region

		• For Pulmonary exacerbation, Rescue antibiotic use, and Days in hospital - **Added** additional covariates of historical rate of exacerbations, rhDNase use, gender, and geographic region • For CFQ-R- **Model changed** to ANCOVA and **Added** additional covariates of disease severity at baseline, rhDNase use, gender, and region • Health economics not addressed in this report • Definition of Per-Protocol Analysis Set **differs** from the protocol with compliance change from ≥80% to ≥60% to be consistent with Study 301
[Source: Module 5.3.5.1.3, Clinical Study Report DPM-CF-302, Section 9.8, page 60]		

6 Review of Efficacy

Efficacy Summary

The efficacy of the 400mg BID dose of DPM for the treatment of CF in patients aged 6 and older was evaluated in Studies 301 and 302. Both trials were randomized, controlled, double-blinded 26-week period studies in patients with CF. Study 301 was performed entirely outside the US, whereas Study 302 included US patients.

Both studies evaluated an appropriate patient population which was fairly well-balanced at baseline between control and DPM 400mg-treated groups. The choices of patient population, control groups, and the primary pulmonary function (FEV1) endpoint were relevant and clinically meaningful to this patient population. Using the Applicant's MMRM analyses in a modified ITT population (MITT), there was a statistically significant treatment effect for the primary endpoint, absolute change in FEV1 through week 26 in Study 301 (an 83mL difference favoring DPM 400mg, $p<0.001$), while the 54mL difference observed in Study 302 ($p=0.059$) did not meet the usual standard for statistical significance ($p<0.050$). However, as discussed in detail in the FDA's Biostatistical review, because the above analyses do not account for the frequent, differential early discontinuations in the active treatment (DPM) group, especially in Study 301, the Applicant's pre-specified primary efficacy analyses alone cannot be relied upon to reflect an accurate estimation of the treatment effect of DPM in the entire ITT population. As a result, both the Sponsor and the Agency conducted a number of sensitivity analyses to determine the impact the missing data might have had on the primary endpoint. Ultimately, Study 301 retains statistical significance, with sensitivity analyses providing evidence that the effect seen is not due to chance alone, and the smaller treatment effect for Study 302, which had much less missing data, still does not achieve statistical significance. However, this does not consider the second issue caused by the missing data, which is that, because of unequal dropout, the comparison is no longer in two similar groups. The DPM group, due to dropout, is a group of

patients who can chronically tolerate treatment with DPM over 26 weeks, whereas the control group is made up of patients who may or may not tolerate DPM chronically.

The size of the treatment effect of the primary endpoint in Study 301 is another issue of clinical relevance. While the pre-specified MMRM analysis of the MITT population was 83mL, the treatment effect varies widely depending on the sensitivity analysis method used to consider the missing data. This leaves us to consider a range of treatment effect, (for example, with 95% confidence intervals from as little as 15mL, up to 107mL when a Baseline Observation Carried Forward approach is used as a sensitivity analysis). Most of the sensitivity analyses identify a treatment effect of roughly 60mL. In addition, because of the "apples to oranges" comparison between DPM and control populations, we lose the ability to assess the magnitude of change in FEV1 across the treatment versus control groups of the CF population originally selected for randomization. For regulatory purposes on which to base drug approval, we typically need a comparison in the same population, in this case DPM chronic tolerators, to determine treatment effect.

Because of a small change in FEV1, and statistical significance being achieved in only one study, it is important to look to other clinically-meaningful secondary outcomes to support FEV1, as we told the Applicant in the End-of-Phase-2 meeting held on February 15, 2006, when we stated that because "bronchitol" is not expected to act as a bronchodilator, the changes in FEV1 over short periods of time would not, by themselves, be sufficient to support approval, and additional co-primary or secondary outcomes would be required. In this case, we see that these secondary endpoints are either not supportive of any meaningful FEV1 treatment effect or simply favor in trend of DPM. Secondary spirometric endpoints are all parameters of lung function and would be expected to track with change in FEV1 and therefore add little independent support to the primary endpoint. As such, the secondary endpoints provide limited support to reassure us that the small change in FEV1 is representative of any other clinically-meaningful pulmonary improvement.

Last, when we examine the pediatric efficacy data from subgroup analysis, there appears to be variability between results from each study for patients 6 to 17 years of age. Responder curves from Study 301 suggest a lack of benefit, while data from 302 suggests benefit in FEV1 similar to the overall study population for that study. Data from the Applicant's analyses, however, suggest a subgroup of patients aged 12-17 years in Study 302 worsening over the 26-week treatment period. When taken into context of the risk profile of DPM, the uncertainty of efficacy in pediatric patients is problematic.

Despite the beneficial effect of DPM 400mg on FEV1 as a whole being relatively small, because cystic fibrosis is a chronic progressive disease in which the majority of early deaths are due to respiratory failure, it could be argued that any benefit, no matter how small, can be considered "clinically-meaningful" for this patient population. However, given the fact that the statistical significance achieved in Study 301 was not replicated in

302, that there were was little support from any clinically-meaningful secondary outcomes, and an additional suggestion of decreased efficacy in the pediatric population, the totality of the efficacy data for this application fails to demonstrate substantial evidence of efficacy for DPM in the treatment of patients with CF to improve pulmonary function.

6.1 Indication

The Applicant's proposed indication for DPM (proposed trade name, Bronchitol) is for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function.

6.1.1 Methods

This is a relatively small program of two Phase 3 multi-center, controlled clinical trials (Studies 301 and 302) which form the basis for efficacy determination in patients with cystic fibrosis. The Applicant submitted both of these Phase 3 protocols for Special Protocol Assessments (SPA), but no agreement was reached between the Applicant and the Division for either protocol (study 301's SPA-no agreement letter dated 9/28/2006, and that for Study 302 dated 9/14/2007). Specifically, no agreement was reached regarding choice of endpoints, duration of study, or analysis methods. Study 302's efficacy endpoints were chosen after evaluating the final results of Study 301, and some of these endpoints were not identified in the final protocol, but only in the final Statistical Analysis Plan (SAP). In addition, efficacy and safety results had been reported for Study 301 before the SAP for Study 302 was finalized.

Concerns identified in the development program include the large, unequal dropout rate in study 301 between randomization and the first visit, that for Study 302 the control group's screening FEV1 value was higher by 60 mL than the baseline value, and post-hoc analyses methods for interpretation of data for which agreement with the Division was not reached (see FDA's Biostatistical Review of Efficacy for details).

Applicant's Pre-Specified Analysis Methods

The statistical analysis plan (SAP) for the blinded phase of Study 301 was finalized and signed on April 24, 2009 (version 2) and was developed using protocol version 4 dated August 16, 2007. Statistical Analysis Plan for Study 302 was finalized on May 29, 2010. The Applicant stated that both SAPs were written after the blind review and before un-blinding the study data. Of note, the double blind phase of Study CF301 was completed, with efficacy and safety results reported, before Study 302 SAP was finalized.

At the pre-NDA meeting (held on December 10, 2010), the applicant proposed and attempted to reach agreement with the Division on the following:

- *That the post-hoc analysis to correct for bias at baseline to the primary endpoint should be applied to the other spirometric variables in the study report and Integrated Summary of Efficacy (ISE) for the NDA.*
- *To use the Study 302 MMRM model, which excludes Visit 1 (a change from baseline of 0 for all patients) from the model, for the presentation of all efficacy endpoints in both phase 3 studies and the integrated data.*
- *To use of the "adjusted baseline" for the presentation of efficacy endpoints in the ISE for study Study 302 and for the integrated phase 3 studies.*

The Division's response at the pre-NDA meeting was the following:

> *• We acknowledge your intention to reach agreement with the Division on proposed types of post-hoc analyses that will be presented in the NDA to support mannitol for use in the treatment and management of cystic fibrosis lung disease. Many of your questions are specific with regard to the acceptability of post-hoc statistical approaches and observed data. It is premature for the Division to comment on the adequacy of your proposed methods or data at this time. These issues will evaluated as part the NDA review.*

The Applicant submitted their data as they planned, above. Therefore, FDA has analyzed the data with multiple models, including the pre-specified models in each SAP, as well as the post-hoc methods later proposed by the Applicant and by the FDA (see FDA's Biostatistical Review of Efficacy for details).

6.1.2 Demographics

For the two Phase 3 studies (301 and 302) a total of 731 patients were evaluated, with 719 patients, (378 and 341 from studies 301 and 302, respectively), screened who received the initial challenge dose of mannitol to assess for drug tolerability. 642 patients were randomized, but 42 patients withdrew from the study after randomization and prior to any study drug administration, leaving 600 patients in the Intent-to-Treat (ITT) population (Refer to 6.1.3 Subject Disposition below for more information). The ITT population will be described for the demographic data, because this population who received at least one dose of randomized study drug is the most pertinent for comparison. For the ITT population, there were 295 patients in Study 301, and 305 in Study 302.

Table 6: Demographics Phase 3 Trials (ITT)

	Study 301 N=295		Study 302 N=305		
Demographic Parameter	DPM N=177	Control N=118	DPM N=184	Control N=121	Overall N=600
Geographic region					
USA			139		23%
Canada			20		3%
Argentina			80		13%
Europe[a]			66		11%
UK	191				32%
Australia/ New Zealand	104				17%
Age (years)					
Mean (SD)	23.1(11.7)	22.8(10.8)	19.6(9.3)	20.4(10.2)	
Median	21	22	18	17	
Min, max	6, 56	6, 48	6, 48	6, 53	
Age group (years), n (%)					
Age 6-11 years	31 (18)	17 (14)	35 (19)	24 (20)	
Age 12 -17 years	32 (18.)	25 (21)	56 (30)	39 (32)	
Age ≥18 years	114(64)	76 (64)	93 (51)	58 (48)	
Sex, n (%)					
M	106 (60)	57 (48)	94 (51)	63 (52)	
F	71 (40)	61 (52)	90 (49)	58 (48)	
Race					
Caucasian	169 (95)	115 (97)	182 (98)	119 (98)	
African descent	0	0	2 (2)	2 (2)	
East Asian	0	1 (1)	0	0	
West Asian (middle east)	3 (2)	1 (1)	0	0	
Other	5 (3)	1 (1)	0	0	

a= Study 302 included Belgium (16), France (23), Germany (23), Netherlands (4)

[Source: Module 5.3.1.5.3, CSR 301, Table 11-1, CSR 302, Table 10.1.6.1, Table 11.2.1, FDA's Biostatistical review, Table 6]

Overall, Study 302 had a median age slightly lower than study 301 (22 vs. 18 years), and Study 302 was divided evenly with half of patients 6-17 years old, and half 18 years and older. Study 301, by contrast, noted almost 65% of patients 18 or older, with 35% of patients in the younger group. The median age in the young-adult range is not unexpected for the life-shortening disease being studied, and the age range of patients (6 to 56) represents a reasonable cross section of patients with CF. The vast majority of patients were Caucasian, which, again, is not unexpected for a disease most common in Caucasians. Patients from the USA made up 23% of the ITT population (all from Study 302). The ratio of male to female subjects is fairly even, except that 60% of the DPM group in Study 301 was male; this is not very likely to skew results, since the control group was evenly distributed, as were both groups from Study 302.

Baseline characteristics for all patients who received at least one dose of the randomized study drug are listed below, in Table 7. When examining baseline lung function, all groups were fairly equal in both absolute FEV1 and FEV1 percent

predicted. Body mass index was similar across treatment and control groups for both studies as well.

Table 7: Baseline Characteristics, ITT

	Study 301		Study 302	
Baseline Characteristic	DPM N=177	Control N=118	DPM N=184	Control N=121
FEV1, n (%)				
Mean FEV1 (L), (SD)	2.07 (0.82)	1.95 (0.69)	2.06 (0.77)	1.96 (0.74)
Median	1.95	1.82	1.95	1.79
(min, max)	(0.71, 4.92)	(0.78, 3.75)	(0.61, 4.09)	(0.75, 4.12)
Mean % Predicted FEV1 (SD)	62.4% (16.4)	61.4% (16.1)	64.7% (15.7)	62.3% (16.0)
Median	62.6%	63.1%	65.7%	60.1%
(min, max)	(26, 93)	(30, 94)	(25, 104)	(32, 99)
BMI (kg/m^2)				
Mean (SD)	21.1 (4.0)	20.4 (3.6)	20.0 (4.1)	19.8 (3.7)
Median	20.9	20.0	19.8	19.1
Min, Max	(13, 37)	(14, 31)	(13, 45)	(11, 33)
Genotype[a]				
ΔF508/ ΔF508	---	---	77 (42)	45 (37)
ΔF508/ other	---	---	57 (31)	52 (43)
Unknown/ unknown	---	---	35 (19)	19 (16)
Prior Medical History				
Bronchiectasis	34 (19)	21 (18)	128 (70)	86 (71)
Pancreatic Insufficiency	107 (61)	74 (63)	160 (87)	106 (88)
Sinusitis	24 (14)	14 (12)	44 (24)	26 (22)
Gastroesophageal Reflux	49 (28)	33 (28)	57 (31)	38 (31)
Asthma	61 (35)	23 (20)	39 (21)	20 (17)
ABPA	28 (16)	15 (13)	21 (11)	6 (5)
CF-Related Diabetes	42 (24)	20 (17)	34 (19)	16 (13)
Hemoptysis	20 (11)	16 (14)	29 (16)	20 (17)
Hepatobiliary Disorder	33 (19)	26 (22)	27 (15)	31 (26)
Baseline Sputum Mcrobiology				
P. aeruginosa (mucoid)	58 (33)	48 (41)	49 (27)	39 (33)
P. aeruginosa (non-muc.)	42 (24)	32 (27)	51 (28)	32 (27)
Staph aureus	32 (18)	25 (21)	87 (48)	49 (41)
Aspergillus species	28 (16)	11 (9)	23 (13)	13 (11)
Candida species	14 (8)	8 (7)	19 (10)	14 (12)
Burkholderia cepacia	9 (5)	6 (5)	6 (3)	6 (5)

a= Data was not collected for Study 301; For Study 302, genotype data for only 169 of 184 in the DPM group, and 116 of 121 in the control, were reported, so the totals do not add to 100%

[Sources: Module 5.3.5.1, CSR 301, Tables 11-1, 11.2,11-3, 11-4 ; CSR 302, Tables 11.2.1, 11.2.2.1, 11.2.3.1, 14.1.8.1; FDA's Biostatistical Review, Table 6]

Baseline medical history is strikingly different between studies for the rate of bronchiectasis; 19% of patients in Study 301 reported the diagnosis, as compared to 70% of patients in Study 302. This reported rate of 19% seems exceedingly low for a patient population in which 65% were over the age of 18 years; this could reflect differences in genotype across populations, regional differences in use of the designation "bronchiectasis," or differences in standard of care and treatment, or perhaps is due to poor data capture. Rates for hemoptysis, which is associated with bronchiectasis, are similar, however.

Incidence of pancreatic insufficiency is also different between studies, with Study 301 noting 61% PI, but 302 having 87%. Sinusitis was 10% more common in patients in Study 302, but CF Related Diabetes (CFRD) and Acute Bronchopulmonary Aspergillosis (ABPA) were more often seen in Study 301 patients. Asthma was noted in 35% of the DPM group of Study 301, but its control group, and both arms of Study 302, noted only a 20% incidence. Baseline rates of gastroesophageal reflux and prior hemoptysis were well-matched across all groups.

Genotype data was not collected for Study 301, so it is not clear if this patient population was similar to that of Study 302 with regard to genotype, or to that of the US CF population, of whom approximately 85% carry at least one copy of the *F508del* gene.

Baseline microbiology also demonstrates some differences between the two study populations. For study 301, only 19% of patients grew *Staphylococcus aureus*, and 36% were identified with mucoid *Pseudomonas aeruginosa* species. This makes sense for an older population of patients (65% over 18 years), since *Staph* species tend to present earlier in the course of respiratory infecting agents, replaced by mucoid *Pseudomonal* species over time. This is in contrast to Study 302, which noted 45% of patients with *Staph. aureus*, and only 29% with mucoid *Pseudomonas*.

The Applicant has listed medications used in >10% of patients; this reviewer has identified the pertinent medications commonly used within the standard of care for patients with cystic fibrosis, listed below in Table 8: Pertinent Baseline Medications.

Table 8: Pertinent Baseline Medications

	Study 301		Study 302	
Prior Medications	DPM N=177	Control N=118	DPM N=184	Control N=121
Any prior medication	177 (100)	117 (99)	184(100)	121 (100)
Pancrelipase	157 (88)	110 (93)	163 (89)	112 (93)
Albuterol	113 (64)	78 (66)	154 (84)	98 (81)
Inhaled corticosteroid[a]	103 (58)	73 (62)	91 (50)	58 (48)
Dornase alpha (DNase)	97 (55)	65 (55)	136 (74)	93 (77)
Other mucolytics[b]	23 (13)	13 (11)	21 (11)	14 (12)
Systemic corticosteroid	23 (13)	13 (11)	4 (2)	2 (2)
Azithromycin[c]	98 (55)	59 (50)	80 (44)	53 (44)
Tobramycin[c]	68 (38)	50 (42)	88 (48)	44 (36)
Colistin	83 (47)	47 (40)	33 (18)	24 (20)
Acid treatment	65 (37)	53 (45)	91 (50)	55 (46)
Bile and liver therapy	34 (19)	19 (16)	38 (21)	27 (22)

a= Study 301 listed ICS use; Study 302 line items included combination LABA+ICS separate from ICS, calculated by reviewer
b= Includes listings of "mucolytics," "carbocisteine," and "acetylcysteine"
c=chronic use is standard of care for subjects with chronic pseudomonal infection

[Sources: Module 5.3.5.1, CSR 301, Tables 11-5 and 14.1.10, and CSR 302, Tables 11.2.4.1 and 14.1.9.1]

Although history of pancreatic insufficiency differed between groups, the rates of pancreatic enzymes are fairly consistent. Other differences in the baseline medications to note are that in Study 301, rates for use of albuterol and DNase (dornase alpha) were approximately 20% lower than for Study 302, but use of corticosteroids was higher for Study 301. Chronic oral azithromycin and cycled inhaled antibiotics are standard of care for patients chronically infected with *Pseudomonas aeruginosa*, so the slightly higher values for Study 301 of azithromycin may reflect this difference in bacterial sputum cultures at baseline discussed earlier. Inhaled tobramycin was used equally in both studies. Inhaled Colistin use varies between the two studies, with 44% of patients in Study 301 versus 19% of patients in Study 302 using the drug; this is likely due to inhaled Colistin not having FDA approval in the US, but having widespread use in other countries. Use of acid blockers and hepatobiliary medications were both slightly more common in Study 302.

6.1.3 Subject Disposition

A total of 731 patients were screened for eligibility for inclusion in the two Phase 3 trials of DPM. Because of the known bronchoconstrictive potential for inhaled mannitol, the criteria for screening included receiving a test dose of inhaled mannitol (Mannitol Tolerance Test, MTT) under medical supervision with subsequent exclusion if the patient could not tolerate dosing (decrease in FEV1 or inability to complete administration). As a result, a relatively large number of patients (n=89, 12% of screened population) were excluded. Six percent of patients had a positive (ie,

bronchospastic) response to the first dose of DPM when given as the MTT, and therefore were not randomized. An additional 27 patients (4%) did not complete the testing, and ten subjects (1%) had a test dose considered negative, but they were not randomized. 642 patients were randomized at the end of the screening visit, but 42 patients did not receive their study drug at Visit 1 (which could occur as much as 2 to 5 weeks after screening) for various reasons (AE, protocol violation, withdrawal of consent, etc.). Thus, 600 patients from both studies comprised the Intent-to-Treat (ITT) Population, including 295 patients in Study 301, and 305 in Study 302. Table 9, below, details the disposition of patients, as well as their reasons for withdrawal. Overall, 82% of patients enrolled were considered in the ITT/safety population, of which 76% completed the 26-week double-blind treatment period. Table 9, below, also provides the reasons for not completing Visit 1. The Intent-to-Treat (ITT) and Safety Populations were identical.

Table 9: Disposition, Studies 301 and 302

Disposition Category	Study 301		Study 302		Overall
	DPM n (%)	Control n (%)	DPM n (%)	Control n (%)	n (%)
All Enrolled	389 (100)		342 (100)		731 (100)
Ineligible at enrollment	11 (3)		1 (0.3)		12 (2)
All Screened/given test-dose	378 (97)		341 (99.7)		719 (98)
Subjects test-dose positive	27 (7)		14 (4)		41 (6)
Subjects test incomplete	19 (5)		8 (2)		27 (4)
Subjects test neg but not R	8 (2)		2[d] (1)		10 (1)
All Subjects Randomized	324 (83)		318 (93)		642 (88)
Did not get drug Visit 1[a]	29 (7)		13 (4)		42 (6)
Reasons:					
Adverse Event	4 (14)		2 (16)		
Protocol violation	3 (10)		5[e] (38)		
Withdrew consent	12 (41)		5 (38)		
Sponsor/MD decision	9 (31)		0		
Other[b]	1 (4)		1 (8)		
Safety/ ITT Total	295		305		600 (82)
Safety Population	177	118	184	121	600
Intent-to-Treat Population	177	118	184	121	600
Week 26 Completers	112 (63)	86 (73)	153 (83)	107 (88)	458 (76)
Did not complete to Wk 26	65 (37)	32 (27)	31 (17)	14 (12)	142 (24)
Reasons:					
Adverse Event	29 (45)	10 (33)	13 (42)	5 (36)	57 (40)
Protocol violation	0	0	1 (4)	0	1 (1)
Withdrew Consent	28 (43)	22 (67)	13 (42)	7 (50)	70 (50)
Sponsor/MD decision	7(11)	0	2 (6)	1 (7)	10 (7)
Other[c]	1 (1)	0	2 (6)	1 (7)	4 (2)

a= For Study 301, 28 patients were withdrawn before Visit 1, and 1 attended but did not receive study drug; Study 302, 13 patients were withdrawn before Visit 1
b= For Study 301,one subject attended Visit 1, but had unstable lung function (AE); Study 302, one patient "lost to follow-up" before Visit 1
c= For Study 302, one DPM patient "lost to follow-up"
d= For study 302, 1 patient test negative but not randomized, one ineligible due to FEV1
e= For Study 302, 4 DPM and 1 control "randomized in error"

[Sources: Module 5.3.5.1, Clinical Study Report 301, Section 10.1, Table 10-1, Table 10-2, Fig. 10-1; Module 5.3.5.1, Clinical Study Report 302, Section 10.1.2, Table 10.1.1.1, Fig. 10.1.1.1,].

Patient Withdrawal

Out of the 600 patients in the ITT population (who received at least one dose of randomized study drug), 142 (24%) did not complete the double-blinded 26-week treatment period. Of those, 32% of Study 301 did not complete, versus 15% for Study 302. In both studies, dropouts were higher in the DPM groups than the control groups: 36% DPM versus 27% control for Study 301, and 17% DPM versus 12% control for Study 302. Withdrawal due to adverse events was higher in the DPM groups, with 45% DPM vs. 33% control, and 42% DPM vs. 36% control, of those patients withdrawn for studies 301 and 302, respectively. Ten patients were withdrawn due to Sponsor or

Physician decision. For Study 301, this included physician withdrawal for hemoptysis (1), developing cystic fibrosis-related diabetes (CFRD) (1), poor recovery from SAE (1), and poor compliance (3). There was one Sponsor withdrawal for poor compliance. Study 302 had 3 patients withdrawn for physician decision, not further described in the study report.

"Withdrawal of consent" was listed as an option to document withdrawal from the study. Unfortunately, this does not easily allow for a detailed assessment of the underlying reasons for withdrawal; subjects could have experienced lack of efficacy, drug intolerance, adverse events not otherwise clarified, or could have had difficulty with the time and technique required to use the study drug, or a reason unrelated to study drug. Half of all patients who did not complete the double-blinded treatment period used "withdrawal of consent" as the reason. The Applicant describes that for Study 301, of the 50 patients who withdrew consent, 15 cited the extra time required to administer the study treatment, 8 stated "failure to comply with medication," 5 noted lack of effect, 3 had difficulty taking medication, and two withdrew for adverse effects (it is not clear if these were captured as adverse events or not). The 12 remaining patients did not provide additional explanation. For Study 302, the Applicant notes that of the 20 withdrawn consents, 7 noted extra time requirement as a factor; there was no additional reason given for the remaining 13 patients.

Protocol Violations

For both studies, protocol deviations leading to exclusion from the Applicant's Per Protocol analysis population include poor treatment compliance (<60%), missing pulmonary tests, and use of precluded medications at one or more study visits. Study 302 also noted violation of eligibility criteria, irrespective of medical exceptions granted.

The Applicant identified 200 patients (111 DPM/ 86 control) as per protocol in Study 301, excluding 64 DPM and 32 control patients from the ITT population, and 261 (152 DPM/ 109 control) in Study 302, excluding 32 DPM and 12 control subjects from the ITT population. [Source: Module 5.3.5.1 CSR 301 sections 10.1, 10.3, and 11.1, Table 10-1 and Figure 10-1, CSR 302, Section 10.1,10.1.2, 10.2.1, and 11.1.2, Table 10.1.1.1 and Figure 10.1.1.1] For both studies, the number of patients is numerically higher for DPM than control, but patients were randomized 3:2, so for Study 302, the difference is not large, with 83% of DPM versus 90% of control patients meeting the PP definition. Study 301 was more discrepant, both for the large number of patients who did not meet the PP definition, as well as the difference between DPM (63%) and control (73%) groups. The remainder of this review will focus only on the ITT population for these reasons, unless otherwise specified.

Compliance and Exposure Rates

Exposure to study drug for the 26-week double blind treatment period (182 days) and percent of patients meeting the definition of treatment compliance as >60% use, is shown below in Table 10. Patients were prescribed enough medication to last until their next visit, plus an additional 2-week supply in the event of delayed visit. Patients were to return any unused medication as well as all used blister packs at visits 2, 3, and 4, and numbers returned were reconciled with those dispensed. Accurate compliance was dependent upon patients taking the medication as prescribed, returning all empty blister packets and unused study medication at the proper visit, and attending the subsequent visit as scheduled. Failure to return unused medication gave >100% compliance, and returning medication at a later-than-designated visit was interpreted as under-compliance. In addition, withdrawals between visits and failure to return medication also affected compliance rates. The majority of patients in both studies met the criteria for compliance, with no significant differences noted between groups, except that the mean for the DPM group in Study 301 was skewed by 3 patients who did not return any study medication. Median compliance rates were consistent across all groups. [Source: Module 5.3.5.1.3 CSR 301, section 11.3, CSR 302, sections 9.5.1 and 11.3]

Table 10: Study Drug Exposure and Estimated Compliance, Studies 301 and 302

	Study 301		Study 302	
Category or statistic	**DPM N=177**	**Control N=118**	**DPM N=184**	**Control N=121**
Exposure to Study Drug (Days)				
N	177	118	184[a]	121[a]
Mean (SD)	136 (70)	151 (57)	156 (53)	168 (36)
Median	176	175	177	180
Min, max	1, 218	4, 231	0, 201	6, 207
Estimated Compliance (%)[b]				
N	175	118	184	121
Mean (SD)	180 (720)	86 (37)	85 (24)	89 (18)
Median	89%	91%	94%	95%
Min, max	9, 5600[c]	1, 350	8, 124	11, 133

a= Study 302 table 14.1.2.1 was reported in months; converted to days by reviewer
b=Compliance= 100 x (# dispensed-# returned)/ (20 x days between 1st & last drug use)
c= For study 301, 3 patients withdrew day 1 and did not return any study drug, therefore 100 x (1120-0)/(20 x 1)= 5600%

[Sources: M5.3.5.3.1, CSR 301, section 11.3 and tables 11-6 and 14.3.1.15; CSR 302, section 11.3, tables 11.3.1, 14.1.12.1 and 14.1.13.1]

6.1.4 Analysis of Primary Endpoint(s)

Basis for Choice of Endpoints

The primary efficacy parameter for these studies was the "change in absolute FEV1" through week 26. The Applicant's choice of FEV1 as the primary efficacy endpoint was

appropriate for a disease in which the major cause of early death is respiratory failure. Pulmonary function is monitored very closely in patients with cystic fibrosis, and progressively declines over the lifetime, at a rate as high as 1-4% of total function per year, so improvement in FEV1 would be considered clinically meaningful. In addition, cystic fibrosis lung disease as measured by FEV1 is correlated with pulmonary outcomes and morbidity and mortality[1, 2]. In the case of DPM, FEV1 is not being used to measure an acute change (as would be done with a bronchodilator), but rather the drug purports to facilitate airway clearance. Therefore, the change we would expect with chronic use should result in improved pulmonary outcomes. In this case, FEV1 is being used as a measure for overall improvement in pulmonary function.

In the context of cystic fibrosis, the majority of death is due to pulmonary causes[1], so improvement in FEV1 is a useful and clinically-meaningful endpoint, which we would expect should carry over to other endpoints that better reflect overall pulmonary function, such as fewer infections, hospitalizations, and exacerbations, and better quality of life. So if DPM were having a significant impact upon overall pulmonary function, we would expect to see support from clinically meaningful secondary endpoints chosen in these studies, as well as FEV1.

Change in FEV1 has been used as the primary basis for demonstration of clinical benefit and subsequent regulatory approval for a wide variety of respiratory products. Spirometry testing has standardized methods, and physicians and CF clinicians utilize spirometric assessments to determine overall lung health chronically, as well as acute worsening (pulmonary exacerbation), to guide overall patient management decisions, such as when to give antibiotics, when to hospitalize, when to place a patient on a lung transplant list. When performed according to accepted standard practices[3], individual patient data can be evaluated by the clinician for repeatability among values, and reproducibility over time.

Choice of Control Population

The Applicant chose to conduct Phase 3 controlled studies, in addition to regularly prescribed medications/ standard-of-care management. The Applicant's choice of a control group is appropriate, since blinding would not have been possible with a true placebo, given that DPM 400mg has a notable sweet taste, and the technique of using dry powder inhaler with 10 capsules twice a day required matching as well. The Applicant used data from study 202 that demonstrated no measurable improvement in FEV1 with 40mg DPM, and therefore chose 50mg as the best way to maintain the blind (10 capsules of 5mg each). Studies were stratified to include DNase use, which is also reasonable, given that DNase is a mucolytic product commonly used as standard-of-care in most patients with CF. Inhaled hypertonic saline was not allowed for either study (it works on a similar mechanism as inhaled mannitol).

Summary of Primary Efficacy Endpoint

Studies 301 and 302 utilized absolute change in FEV1 from baseline across 26 weeks of double-blinded study as the primary efficacy endpoint. Following are the efficacy results using the Applicant's MMRM analyses for the MITT population. This analysis removes the number of patients who discontinued prior to week 6, for whom there are no post-baseline spirometry values. It includes 156 of 177 (88%) of DPM 400mg patients, and 112 of 116 (97%) of controls at week 6. By week 26, 66% of the DPM 400mg patients and 77% of control-treated patients are included in this number, due to additional missing data. The pattern of withdrawal illustrating the greater and more rapid withdrawal in the DPM groups is shown in Table 11, below.

Table 11: Pattern of Missing FEV1 Data by Treatment Group, N(%) ITT Population

	Study 301 (N=295)			Study 302 (N=305)		
	N	N Missing	Percent missing	N	N Missing	Percent missing
DPM 400mg						
Week 0	176*	0	0	184	0	0
Week 6	156	20	11.4	174	10	5.4
Week 14	132	44	25.0	167	17	9.2
Week 26	116	60	34.1	157	27	14.7
Control						
Week 0	118	0	0	121	0	0
Week 6	112	6	5.1	119	2	1.7
Week 14	103	15	12.7	116	5	4.1
Week 26	89	29	24.6	111	10	8.3

*: There was one patient ((b) (6)) missing covariate data (missing baseline FEV1) and omitted from the analysis.
[Source: Modified from FDA's Biostatistical review, Table 5]

These analyses are problematic in that they do not include the entire ITT population, and the MRMM model does not appropriately account for the differential rates of patient drop-out that is higher in the DPM groups. Because of this missing data, both the Applicant and the FDA used multiple sensitivity analyses to assure that the difference in treatment was not due to chance alone, or due to the lost data. The Agency believes analyses that incorporate the true ITT population that are able to account for the missing data as a result of the differential drop-outs are an important representation of the primary efficacy endpoint; responder analyses are presented following the Applicant's analyses.

Applicant's Analyses

The Applicant utilized multiple models to analyze their data, which have been evaluated in depth in the FDA's Biostatistical Review. Both studies demonstrated frequent and treatment-related early discontinuations, which could not be accounted for in the

Applicant's pre-specified mixed effects model for repeated measurements (MMRM), because an assumption of this method is that missing data will be few, and at random. In addition, MMRM analysis includes only patients with post-baseline measurements (the modified ITT, or MITT, population), and therefore excludes patients who were randomized and received study drug but who dropped out before the week 6 time point. Interim efficacy analyses were accounted for by adjusting the primary efficacy endpoint to be tested at a 4.98% significance level.

Results for the primary efficacy endpoint for these two studies using the SAP-specified MMRM models in the Applicant's proposed MITT population are presented in Table 12, below.

Table 12: Primary Analysis-Absolute Change from Baseline FEV1 (mL) (MITT)

	DPM	Control	Treatment Comparison DPM--Control		
			LS Mean (SE)	95% CI	p-value
Average effect from week 6 to week 26 (LS mean (SE))					
STUDY 301 (DPM=157, Control=112)	118.0 (15.3)	34.9 (17.4)	83.1 (22.2)	(39.4, 126.8)	<0.001
STUDY 302 (DPM=177, Control=120)	106.5 (22.4)	52.4 (25.6)	54.1 (28.5)	(-2.0, 110.3)	0.059

SE=standard error.
For Study CF301, the p-value, LS mean, and LSMD obtained from an MMRM repeated model with change from baseline in trough FEV1 as response, and the following predictors: treatment, visit, age, rhDNase use, baseline FEV1, disease severity (baseline FEV1 % predicted), gender, region, and subject (as a random effect) with unstructured covariance structure. This is the model pre-specified in the SAP for study CF301. This analysis includes the response at weeks 6, 14, and 26 only. It does not include the change from baseline at baseline in the response variable.
For Study CF302, the p-value, LS mean, and LSMD obtained from a similar MMRM repeated model as was specified in the SAP for Study CF301; only differences are replacing region with country and adding the visit by treatment interaction term.
[Source: Modified from FDA's Biostatistical Review, Table 7]

However, significant issues impacted this efficacy analysis:

1. There was high dropout in Study 301, with more DPM 400mg patients dropping out than controls as previously described
2. This analysis excluded data from the 38 patients who dropped out before week 6 in the two studies (30 mannitol vs. 8 control)
3. The Applicant's pre-specified analysis model, the MMRM, requires the assumption that missing data are missing at random; however, withdrawal data suggests a large number of patients withdrew due to adverse events, or difficulty tolerating chronic DPM treatment.
4. Unequal dropouts greater in the DPM-treated group created two unequal populations for comparison, those of DPM tolerators versus control (tolerators plus non-tolerators), which makes any comparison between groups suspect

Sensitivity Analyses

Many sensitivity analyses were therefore undertaken by both the Applicant and the FDA, with the goal of understanding the impact missing data had on the pre-specified primary analyses. Many of these analyses have limitations, with some also having the underlying assumption of data missing at random.

The single imputation baseline-observation-carried-forward, or BOCF, approach as a sensitivity analysis, while conservative, does not, as the MMRM analyses do, presume that any benefit received by patients before he/she drops out would be meaningful over the rest of the course of the study. Historically, this approach has often been used by the FDA and sponsors to evaluate efficacy in the presence of missing data such as is displayed in these studies. This approach is generally considered a conservative approach in terms of estimating the treatment effect size, and an accurate representation of the efficacy of a product, in that subjects who discontinue treatment are considered as having had no change in their baseline status. In addition, this approach was pre-specified as a sensitivity analysis for these studies. BOCF also has limitations because variance in data may be underestimated, but overall, FDA felt that BOCF provides a conservative estimate of the point estimate of the treatment effect in the setting of missing data. (See FDA's Biostatistical Review for full details). In Study 301, the difference in primary endpoint between DPM and control is estimated at 62mL, with 95% confidence intervals from 15mL to 108mL. This supports the primary analysis, but suggests the treatment effect is less than the 83mL observed there. Study 302's difference is consistent with the pre-specified analysis and the result remains not statistically significant; see Table 13, below.

Table 13: Sensitivity Analysis for Primary Endpoint, BOCF, Absolute change from Baseline in FEV1 (mL) (ITT)

	DPM	Control	Treatment Comparison DPM--Control		
			LS Mean (SE)	95% CI	p-value
Baseline Observation Carried Forward (BOCF)					
STUDY 301 (DPM=176, Control=118)	80.6 (14.9)	19.0 (18.2)	61.6 (23.6)	(15.2, 108.0)	0.009
STUDY 302 (DPM=184, Control=121)	76.4 (22.4)	11.7 (27.6)	64.6 (35.5)	(-5.2, 134.5)	0.070

SE=standard error.
The p-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline to week 26 in trough FEV1 as response with treatment as a predictor
[Source: Modified from FDA's Biostatistical Review, Table 8]

Because of the significant, unequal dropout rates across the two studies between DPM and control groups, responder analyses were conducted by the Agency in order to present an alternate interpretation of the efficacy endpoint, which takes into account the entire ITT population. The responder analyses do this by assuming that missing data at

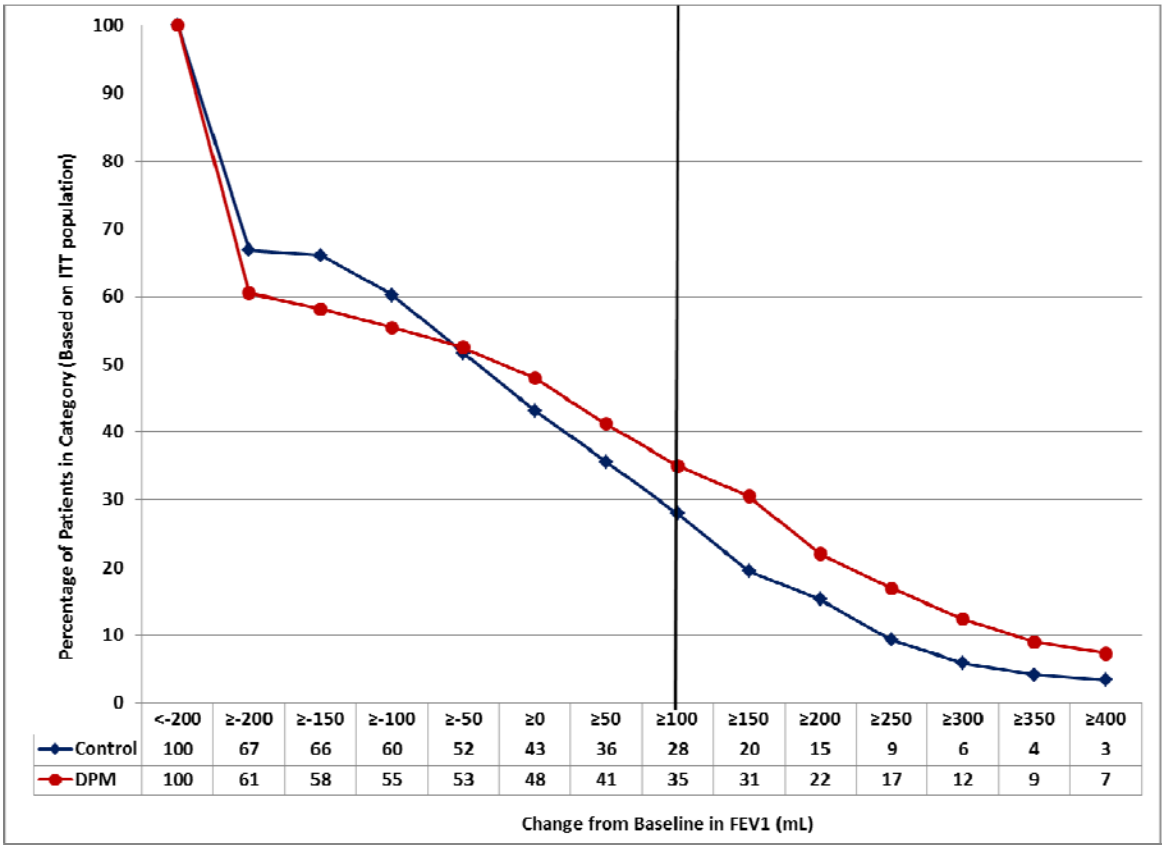
weeks 6, 14, or 26 represent a failure in treatment. Given the fact that those who dropped out for tolerability issues cannot be expected to benefit from treatment, this was felt to be a reasonable assumption.

The FDA provided continuous responder analyses for Studies 301 and 302, which capture the entire ITT population by describing patients as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the change from baseline in FEV1 at week 26. This is reported across a range of thresholds; patients with missing data are classified as being unsuccessfully treated for all thresholds. (See FDA Biostatistical Review for further details).

In the continuous responder curves, the x-axis displays the thresholds required to classify a patient as a successfully treated patient. The y-axis represents the proportion of ITT patients who achieved the corresponding threshold. The proportion of DPM patients achieving each threshold is represented by the red line and proportion of control patients by the blue. For example, using study CF301, at the vertical reference line of a change from baseline in FEV1 of 100 mL, the continuous responder plot illustrates that 35% of DPM patients had FEV1 improved by at least 100 mL while only 28% of control patients experienced such a change.

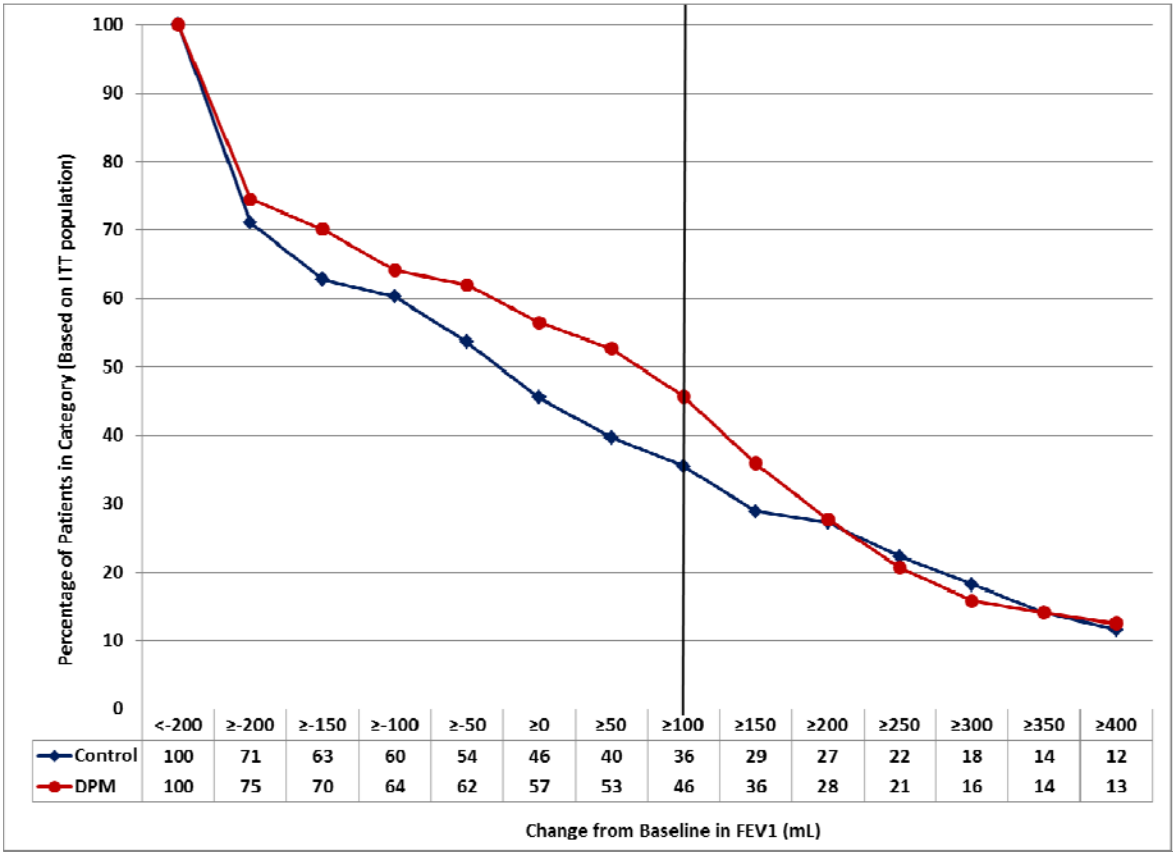
As one can see in Figure 7 and Figure 8, below, there is an initial dramatic drop from 100% to roughly 60%, which corresponds to the proportion of patients who dropped out, since those with missing data were categorized as unsuccessfully treated for all thresholds. One can also see that there is some separation between the treatment groups. After overcoming the initial lower rates of efficacy due to the failures for patients who dropped out, the DPM group has a numerically higher proportion of patients who achieve the increasing change from baseline in FEV1 thresholds than does the control group. This is evidenced by the fact that the red line (DMP) generally lies slightly above the blue line (control) in both figures.

Figure 7: Continuous Responder Analysis for Observed FEV1 Change from Baseline to Week 26-Study 301



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	67	66	60	52	43	36	28	20	15	9	6	4	3
DPM	100	61	58	55	53	48	41	35	31	22	17	12	9	7

Figure 8: Continuous Responder Analysis for Observed FEV1 Change from Baseline to Week 26-Study 302



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	71	63	60	54	46	40	36	29	27	22	18	14	12
DPM	100	75	70	64	62	57	53	46	36	28	21	16	14	13

The continuous responder curves at each visit prior to week 26 were also considered. The patterns in these data are similar to those present in this report for week 26.

Table 14, below, provides an additional FDA post hoc responder analysis in support of the continuous responder plots, which examines the data in terms of meeting specific efficacy thresholds, in this case, patients who achieved a 50, 75, or 100mL or greater increase from baseline in FEV1. For study 301, there were no statistically significant differences between treatment groups in the proportion of DPM responders compared to that of the control patients; however, numerical trends that favored DPM over control were present at each threshold examined. For study 302, the differences between treatment groups in the proportion of subjects who achieved each of the thresholds examined were higher in the DPM group than the control group, but given that Study 302 failed to meet statistical significance for its primary efficacy endpoint, this data is presented for completeness only.

Table 14: Responder Analysis for Primary Endpoint at Week 26, ITT Population

Response Definition	DPM 400mg	Control	Odds Ratio (95%CI)[1] (DPM vs. Control)	p-value*
Study 301				
ITT[2]	176	118		
FEV1 absolute increase≥50mL	73 (41%)	42 (36%)	1.23 (0.75, 2.02)	0.420
FEV1 absolute increase≥75mL	66(37%)	35 (30%)	1.34 (0.80, 2.24)	0.259
FEV1 absolute increase≥100mL	62 (35%)	33 (28%)	1.31 (0.78, 2.21)	0.312
Study 302				
ITT[2]	184	121		
FEV1 absolute increase≥50mL	97 (53%)	48 (40%)	1.99 (1.20, 3.31)	0.008
FEV1 absolute increase≥75mL	92 (50%)	44 (36%)	2.01 (1.21, 3.35)	0.007
FEV1 absolute increase≥100mL	84 (46%)	43 (36%)	1.69 (1.02, 2.80)	0.041

1. Logistic regression with treatment, rhDNAse use, region (or country for Study 302), baseline FEV1, gender, age, and FEV1 severity at screening (SAP pre-specified model)
2. Included the patients who dropped out before week 6.
[Source: Modified from FDA's Biostatistical Review, Table 9]

Primary endpoint summary

To summarize, the Applicant's pre-specified analysis cannot account for the missing data before week 6, but demonstrated a statistically significant treatment effect of DPM over control over 26 weeks for study 301. Study 302 had less missing data, but did not achieve statistical significance. Multiple sensitivity analyses were performed by the Applicant and the FDA to determine the level of confidence in the data, especially that from study 301. These analyses supported the effect seen in study 301 as real, but the treatment effect size varied, depending upon the model and population used (averaging around 60mL), and the lower bound for the 95% confidence interval was as low as 15mL (for BOCF). So there is a small but significant treatment effect for Study 301, with no statistically-significant result for 302, but a trend toward improvement for some patients which favors DPM. The FDA sensitivity analyses demonstrate that the percentage of patients with improvement at week 26 was higher in DPM group compared to control group for Study 301.

However, the statistical analyses are not able to overcome the fact that, due to unequal dropouts throughout the trials, the comparison groups at week 26 are no longer similar, as identified with initial inclusion/exclusion criteria. The DPM group, due to dropout, is a group of patients who can chronically tolerate treatment with DPM over 26 weeks, whereas the control group is made up of patients who may or may not tolerate DPM chronically. Because of this "apples to oranges" comparison, we lose the ability to assess the magnitude of change in FEV1 across the treatment versus control groups of the CF population originally selected for randomization. For regulatory purposes on which to base drug approval, we typically need a comparison in the same population, in this case DPM chronic "tolerators," to determine treatment effect. So even though statistically, sensitivity analyses are able to estimate a treatment effect for Study 301 in the range of 60-80mL, the treatment effect between two dissimilar groups is

problematic. Higher dropout in the treatment group could have selected for "responders," and enhanced the overall treatment effect seen in favor of treatment over control (so patients who do well continue, and patients who do not do well or have increased adverse events drop out, thus making the patients who complete look better than what the true overall average of the group would otherwise be).

6.1.5 Analysis of Secondary Endpoints(s)

Both protocols 301 and 302 included a list of secondary endpoints. Neither protocol identified pre-specified key secondary endpoints, nor pre-specified ranking of secondary endpoints. The Statistical analysis plan for Study 302 did specify 5 key secondary endpoints, however, two of these were not identified as endpoints in the protocol.

At the End of Phase 2 meeting, it was discussed with the Applicant that small changes in FEV1 over short periods of time would not, by themselves, be sufficient to support approval, and additional co-primary or secondary outcomes would be required. Despite the advice given by the Division, the Applicant did not pre-specify additional outcomes other than the primary.

Spirometric Endpoints

Secondary spirometry endpoints included change from baseline to week 26 percent predicted FEV1, FVC,FEF25-75, and PEF. These endpoint analyses were subject to the same difficulties seen for the primary analysis. For this reason, FDA biostatisticians performed cumulative responder plots and dichotomized responder analyses for these spirometric endpoints (please see FDA Biostatistical Review for results). As would be expected, percent predicted FEV1, FVC, and PEF, supported the absolute FEV1 primary endpoint. The parameter of FEF25-75 did not support the primary endpoint, which is concerning, since it is typically felt to be a measurement of small airways obstruction.

Non-Spirometric Endpoints

The non-spirometric endpoints thought to be clinically meaningful include pulmonary exacerbations, rescue antibiotic use and hospitalizations for exacerbations, and quality of life measures.

Sputum weight post treatment at week 14 was added as a key secondary endpoint for Study 302 in the SAP, but was neither specified in the Study 302 protocol, nor in the SAP or protocol for Study 301. Patients in the DPM group demonstrated increased sputum weight at baseline and Week 14 over controls, but the , the clinical relevance is not clear, given that the DPM group had higher sputum weights at baseline over controls for both studies. The inequity at baseline makes it difficult to ascribe a

difference as treatment-related, and in addition, the clinical significance of a one-time increase in sputum production in a subset of patients at a single visit cannot be determined.

Analysis of protocol-defined pulmonary exacerbation (PDPE) was also included as a secondary endpoint. These analyses suffer from the same issue as the Applicant's primary analyses; since they were done using the MRMM model in the MITT population, they do not account for the unequal differential dropout of patients seen in both studies. For Study 301, the PDPE mean annual event rate was numerically lower in the DPM 400mg group than in the control group, (0.78 and 1.05 events per patient per year respectively); however, this reduction was not statistically significant. For Study 302, the PDPE mean annual event rate was similar between two groups (0.52 vs. 0.50 for DPM and control, respectively), with no statistically significant difference. Results are presented in Table 15 below. In addition, the time to first exacerbation was also analyzed, and no statistically significant difference between treatment groups was found [data not shown, Source: FDA's Biostatistical review, Figure 10].

Table 15: Annual Rate of Exacerbation Over 26 Weeks of Treatment, MITT

Response Definition	DPM 400[1] Mean (SD)	Control[1] Mean (SD)	*Poisson*		*Negative Binomial*	
			Rate Ratio (95%CI)[2] (Mann. vs. Contr.)	p-value[2]	Rate Ratio (95%CI)[3] (Mann. vs. Contr.)	p-value[3]
Study 301						
N	177	118				
PDPE	0.78 (1.98)	1.05 (2.15)	0.78 (0.51, 1.19)	0.251	0.74 (0.47, 1.18)	0.205
Study 302						
N	184	121				
PDPE	0.52 (1.70)	0.50 (1.14)	0.85 (0.51, 1.41)	0.520	0.95 (0.57, 1.58)	0.839

1: For each subject, the rate of PDPE events is estimated as 365.25 x (the number of PDPE / the number of days of drug exposure).
2:The Poisson regression model fitted is # of PDPE = treatment group + age at visit 1 + RhDNase use + country/region + FEV1 percent predicted at visit 1 + error with the natural logarithm of the extent of exposure to study medication (in days) used as an offset term in the model
3:The negative binomial regression model fitted is # of PDPE = treatment group + age at visit 1 + RhDNase use + country/region + FEV1 percent predicted at visit 1 + error with the natural logarithm of the extent of exposure to study medication (in days) used as an offset term in the model. Study CF302's model also included historical rates of exacerbation which were not collected in study CF301.
[Source: Modified from FDA's Biostatistical Review of Efficacy, Table 11]

Other secondary endpoints that could be considered clinically relevant in support of a small change in FEV1 were also examined. Similar results were observed for the rate of episodes of rescue antibiotic use for PDPE and the rate of hospitalization due to PDPE (see Table 16 below). Quality of life was measured using the Respiratory Domain from the Cystic Fibrosis Questionnaire (revised). Comparisons between treatment groups are provided in Table 16. No statistically significant differences between treatment groups in QOL scores were observed in either study; of note, however, the difference in respiratory domain scores for Study 302 was close to

significant in favor of control over DPM, reinforcing the lack of support of secondary endpoints.

Table 16: Other Secondary Endpoints, Studies 301 and 302

Secondary Endpoint	Study 301		Study 302	
	Mean/ RR	(95%CI) p-value	Mean/ RR	(95%CI) p-value
Hospitalizations due to PDPE†	1.00	(0.59, 1.68), p=0.992	0.75	(0.42, 1.33), p=0.328
Episodes of Rescue Antibiotic Use due to PDPE†	0.76	(0.50, 1.16), p=0.197	0.89	(0.69, 1.15), p=0.368
QoL – Respiratory domain scores‡	0.00	(-2.0, 2.0) p=0.996	3.88	(-8.0, 0.22), p=0.063

PDPE: Protocol defined pulmonary exacerbation; PE: pulmonary exacerbation reported as an AE
†=ITT group
‡=Subset of the MITT group
[Source: Modified from FDA's Biostatistical Review, Tables 12 and 13]

In summary, with regard to secondary findings from the two Phase 3 studies, there appears to be little supportive evidence of treatment effect from the other endpoints. The non-spirometry endpoints that would be considered clinically-meaningful, such as rate of exacerbations, rate of hospitalizations, need for antibiotics, and quality of life parameters, were unable to demonstrate a significant supportive effect.

6.1.6 Other Endpoints

All other endpoints are discussed in 6.1.5 Analysis of Secondary Endpoints(s) above.

6.1.7 Subpopulations

The Applicant performed their subgroup analysis based on pooled data using the primary analysis model from Study 302. Because there were differences in rates and patterns of dropout between the two studies, FDA performed subgroup analyses of the primary efficacy variable using responder analyses by age, gender, region, rhDNase use and baseline percent predicted FEV1. Results are provided in Table 17

Table 17: Responder Analysis for FEV1 Absolute Increase≥100mL at Week 26 (ITT)

Response Definition	DPM	Control	Odds Ratio (95%CI)* (DPM vs. Control)	p-value*
Study 301				
Aged 6 – 11 year (m=31, c=17)	13 (42%)	6 (35%)	1.09 (0.26, 4.48)	0.908
Aged 12 – 17 years (m=32, c=25)	11 (34%)	10 (40%)	0.86 (0.27, 2.73)	0.803
Aged <18 years (m=63, c=42)	24 (38%)	16 (38%)	0.97 (0.42, 2.20)	0.933
Aged ≥18 years (m=114, c=76)	38 (33%)	17 (22%)	1.58 (0.78, 3.23)	0.207
Female (m=71, c=61)	22 (31%)	12 (20%)	1.81 (0.79, 4.16)	0.163
Male (m=106, c=57)	40 (38%)	21 (37%)	1.00 (0.50, 2.01)	0.991
AU/NZ (m=61, c=43)	18 (30%)	13 (30%)	1.00 (0.42, 2.41)	0.998
UK/IR (m=116, c=75)	44 (38%)	20 (27%)	1.44 (0.74, 2.82)	0.281
RhDNase Non-User (m=81, c=51)	32 (40%)	21 (41%)	0.90 (0.43, 1.85)	0.766
RhDNase User (m=96, c=67)	30 (31%)	12 (18%)	1.88 (0.86, 4.14)	0.114
BaseFEV1<50%Pred (m=42, c=32)	7 (17%)	8 (25%)	0.53 (0.15, 1.84)	0.319
BaseFEV1≥50%Pred (m=135, c=86)	55 (41%)	25 (29%)	1.60 (0.88, 2.90)	0.121
Study 302				
Aged 6 – 11 year (m=35, c=24)	24 (69%)	12 (50%)	2.25 (0.66, 7.72)	0.196
Aged 12 – 17 years (m=56, c=39)	25 (45%)	16 (41%)	1.25 (0.48, 3.30)	0.639
Aged <18 years (m=91, c=63)	49 (54%)	28 (44%)	1.62 (0.78, 3.35)	0.196
Aged ≥18 years (m=93, c=58)	35 (38%)	15 (26%)	1.73 (0.81, 3.72)	0.158
Female (m=90, c=58)	42 (47%)	19 (33%)	1.80 (0.86, 3.74)	0.117
Male (m=94, c=63)	42 (45%)	24 (38%)	1.52 (0.73, 3.13)	0.261
Non-US (m=99, c=67)	52 (53%)	32 (48%)	1.19 (0.62, 2.30)	0.599
US (m=85, c=54)	32 (38%)	11 (20%)	3.09 (1.31, 7.31)	0.010
RhDNase Non-User (m=47, c=29)	22 (47%)	14 (48%)	1.03 (0.37, 2.86)	0.956
RhDNase User (m=137, c=92)	62 (45%)	29 (32%)	2.15 (1.18, 3.93)	0.013
BaseFEV1<50%Pred (m=34, c=34)	19 (56%)	11 (32%)	3.09 (0.90, 10.63)	0.072
BaseFEV1≥50%Pred (m=150, c=87)	65 (43%)	32 (37%)	1.46 (0.82, 2.62)	0.199

* Logistic regression with treatment, rhDNAse use, region (country for study CF302), gender, age, baseline FEV_1, and disease severity.
[Source: Modified from FDA's Biostatistical PADAC Briefing document and presentation, January 30, 2013]

Because 43% of the ITT population for these Phase 3 studies consisted of patients 6-17 years old, and the proposed indication is for patients 6 years and older, efficacy data was examined specifically in terms of the pediatric subgroup as well.

Figure 9 and Figure 10, below are cumulative responder plots only for the pediatric patients 6 to 17 years of age, based on the ITT population for both studies 301 and 302, respectively.

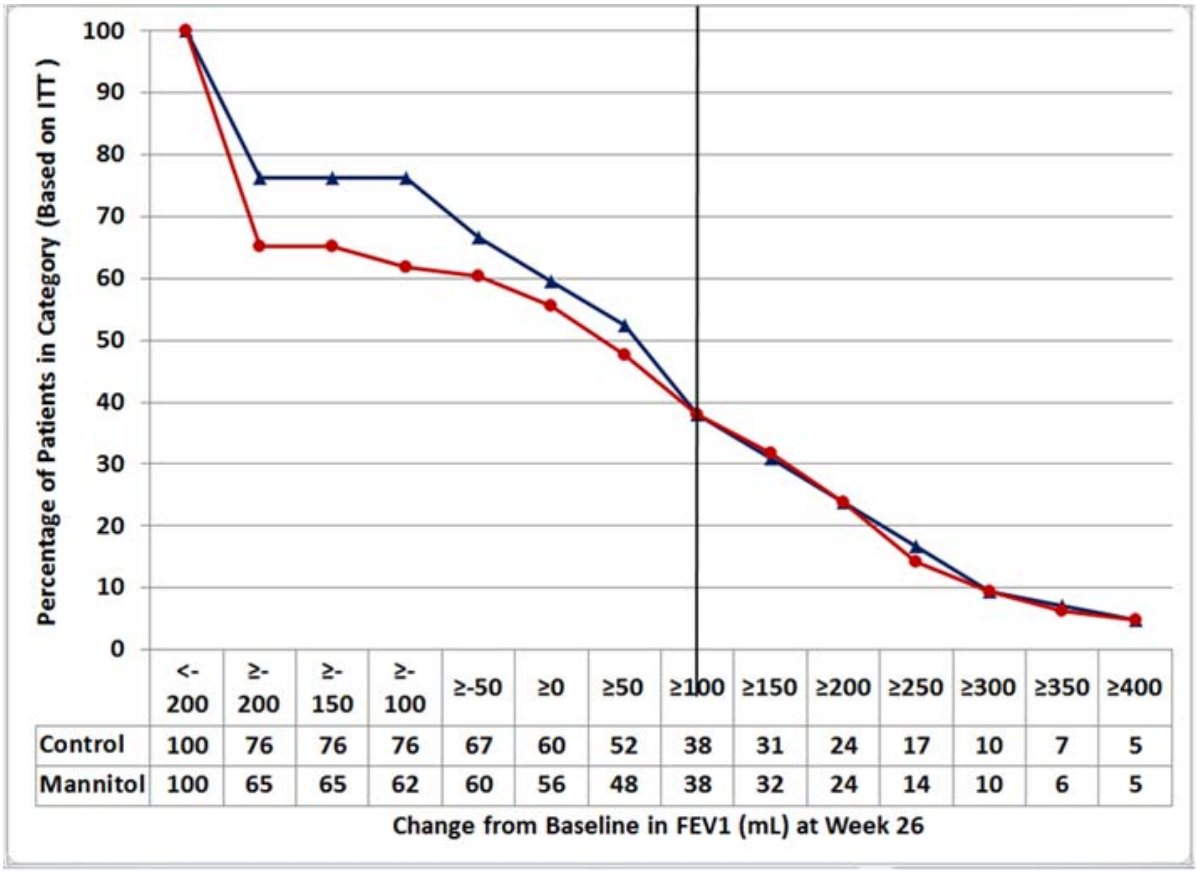
The x-axis shows the specific thresholds for change from baseline FEV1, with the greater than or equal to 100milliliter vertical demarcation as reference. The y-axis is the percentage of patients who met each cutoff, with the DPM line in red, and control line in blue.

For Study 301, the numerical difference between the proportion of DPM subjects achieving the various thresholds in the primary efficacy endpoint, as demonstrated by

the red line, and that of control subjects, in blue, shows little separation of the curves suggesting a lack of effect for pediatric patients in this study. Study 302 suggests a different conclusion regarding the effect of DPM in pediatrics, with results similar to that seen both in adults and in the ITT population as a whole.

So study 301, which demonstrates statistical significance overall, does not show separation between treatment groups for the 6 to 17 year old population, raising the question of the degree to which we can clinically feel comfortable that the benefit seen overall in Study 301 extends to the pediatric group.

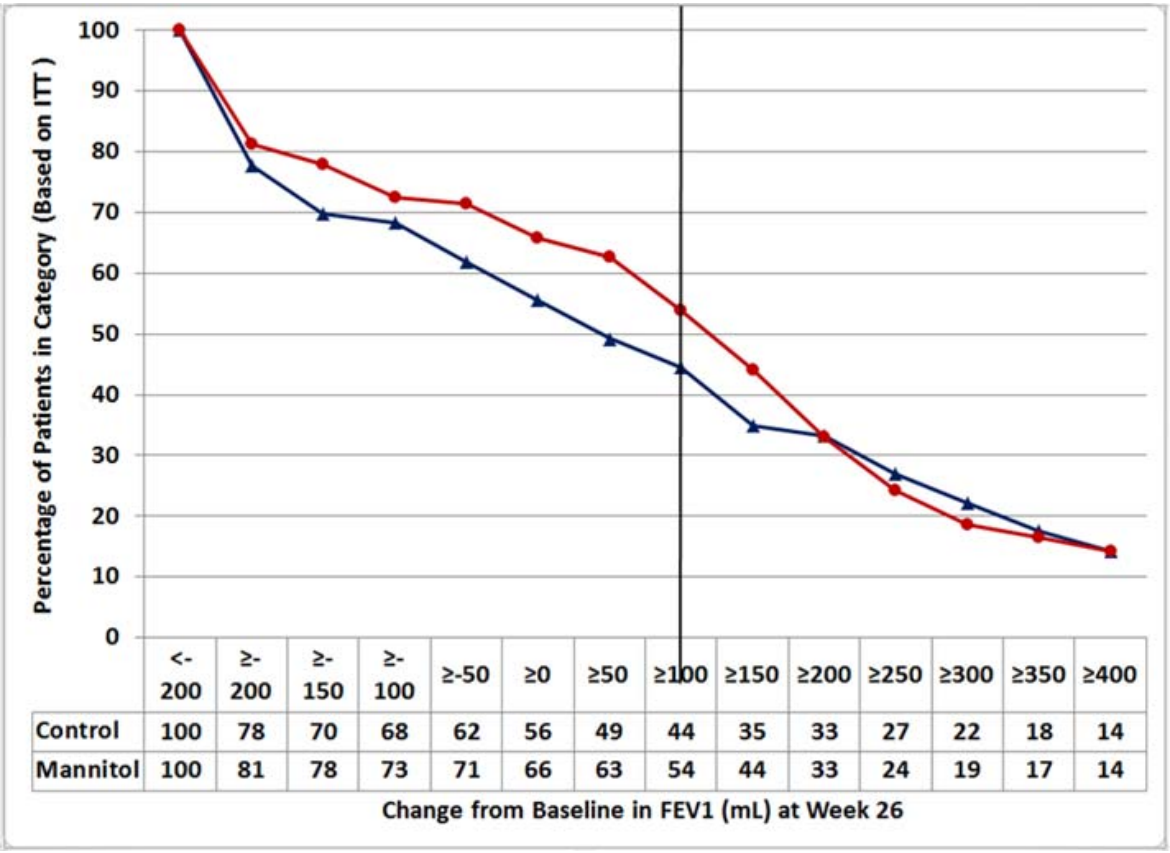
Figure 9: Continuous Responder Analysis, Pediatrics age 6-17 (ITT), Study 301



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	76	76	76	67	60	52	38	31	24	17	10	7	5
Mannitol	100	65	65	62	60	56	48	38	32	24	14	10	6	5

[Source: Modified from FDA's Biostatistical PADAC Briefing document and presentation, January 30, 2013]

Figure 10: Continuous Responder Analysis, Pediatrics age 6-17 (ITT), Study 302



	<-200	≥-200	≥-150	≥-100	≥-50	≥0	≥50	≥100	≥150	≥200	≥250	≥300	≥350	≥400
Control	100	78	70	68	62	56	49	44	35	33	27	22	18	14
Mannitol	100	81	78	73	71	66	63	54	44	33	24	19	17	14

[Source: Modified from FDA's Biostatistical PADAC Briefing document and presentation, January 30, 2013]

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose ranging data for the DPM clinical program primarily comes from study 202, in which the effect of 4 different doses of mannitol inhalation powder (40, 120, 240, and 400 mg administered twice daily) on pulmonary function (FEV1) were assessed (refer to Section 5.3, under STUDY DPM-CF-202 for a complete description of the study design). Briefly, the study was a randomized, open-label, dose response study in 48 patients with CF (ITT population), 7-68 years of age and FEV1 40-90% predicted, conducted in Canada and Argentina. While it had a cross-over design (2-week treatment periods separated by a one week wash-out period), its design was problematic in that all patients began their treatment sequence with 2-weeks of treatment with the highest (400 mg) twice daily dose, followed by randomization to the other 2-week dosing treatment periods. As a result, the value of this open-label, dose-finding study is limited.

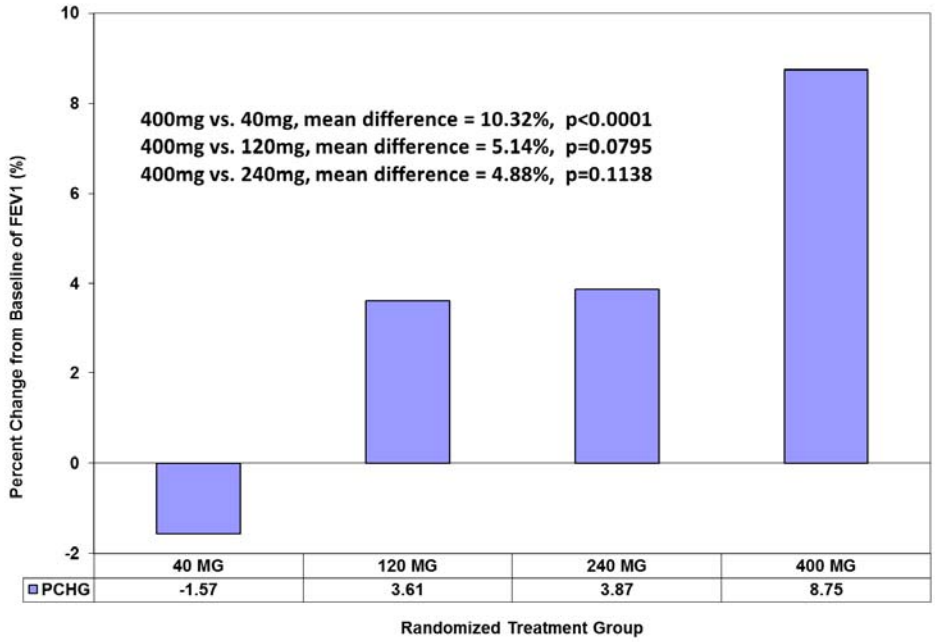
The primary endpoints of interest for dose selection were percent changes in FEV1 and FVC between pre- and post-dose measurements. Because of the known capacity of inhaled mannitol to cause acute bronchoconstriction, eligible patients were given a mannitol bronchoprovocation test (mannitol tolerance test, MTT) under medical

supervision to screen for airway hyperresponsiveness. Forty-eight patients who did not demonstrate airway hyperresponsiveness comprised the ITT population, 44 patients completed the study, and 38 patients were in the per protocol population (defined as those who completed the study with no missing data).

A dose-response was observed in Study 202 with the 400mg dose of DPM providing the greatest change in FEV1, and no significant change seen with the 40mg dose of DPM. FDA's analysis of percent change from baseline in FEV1 at the end of each treatment period is presented below, in Figure 11.

The Applicant notes in their Clinical Overview that, while the highest possible dose has not been established, the 400mg dose (10 capsules) likely represents a balance between compliance and efficacy. Dosing interval of 12 hours was likely chosen based on the terminal half-life of DPM. Although prior studies used a placebo of non-respirable mannitol, it was felt that the increased irritant nature of that product would not make a good comparator for Phase 3 studies. Therefore, based on a lack of response with the 40mg dose and the need to account for the sweet taste of mannitol, a 50mg dose was selected as a control for Phase 3 studies.

Figure 11: Study 202-Percent Change from Baseline in FEV1, ITT



[Source: FDA's Biostatistical Review, Figure 1]

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Data from the Phase 3 program for DPM 400mg includes double blinded data to 26 weeks, as described above. There was additional open-label data collected for 26 to 52 additional weeks across the Phase 3 Studies. The Applicant suggests in their Integrated Summary of Efficacy that the "open-label phase efficacy data confirms sustainability of effect," and that data from the control groups supports this with demonstration of improvement from baseline FEV1 after change to open-label DPM treatment [Source: Module 5.3.5.3, ISE, Section 2.3.6.1, p 122]. FDA does not agree with these assessments, however. Persistence of efficacy is not easily assessed from this open-label data, as it is biased by the significant, unequal dropouts which occurred throughout the double-blinded treatment period, and again more bias is introduced at the time of decision whether to continue into open-label phase. More importantly, there is no comparator for this data. The design of these open-label periods were not rigorous, and do not demonstrate adequate controlled data necessary for regulatory conclusions. FDA has therefore used this open-label data primarily to support the safety database, which will be discussed in Section 7 Review of Safety.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues identified, other than those described above.

7 Review of Safety

Safety Summary

The safety information for DPM 400mg is derived primarily from Studies 301 and 302. As the studies were randomized, controlled, of similar design, and conducted in patients with CF with similar demographics, the data from these studies were pooled in order to assess the safety of DPM 400mg. Safety assessments were adequate, and included adverse events, physical examinations, vital signs, clinical laboratory testing, including sputum culture testing. There were a total of 361 patients treated with DPM 400mg twice daily, and 239 patients treated with control (a sub-therapeutic dose of 50mg DPM). Overall, the size of the safety database is reasonable for an orphan disease, and the 26-week duration of Studies 301 and 302 are supported by additional open-label data, providing information from 541 patients exposed to DPM 400mg in the double-blind and/or open label periods, and 117 who received DPM 400mg for over 52 weeks.

Tolerability of DPM 400mg was identified as an issue for the Phase 3 studies, both for tolerability of the drug on first use, and also throughout the study. Discontinuations (DC) for any reason and AE leading to DC were higher in the DPM 400mg group over control. For those patients who were able to tolerate DPM and continue treatment, cough and hemoptysis occurred at consistently higher rates than in controls across all

adverse event reporting categories. One reason for this might have been that the threshold for a positive mannitol tolerance test (MTT) was higher than that used in labeling of the Aridol product which tests for bronchoprovocation; Aridol uses a ≥15% drop in FEV1 as evidence of reactivity, but the MTT used cutoffs of FEV1 decline≥20% to <50% drop at 400mg dose which does not return to <20% of baseline within 15 minutes. There were not many additional concerns, with overall numbers, in terms of SAE and AEs, slightly favoring DPM treatment. Specific safety issues evaluated included bronchospasm, hemoptysis, exacerbations, and overall tolerability. Cough and local throat effects occurred more commonly in DPM 400mg patients, as might be expected for this drug and method of delivery. The incidence of bronchospasm was fairly similar between treatment groups. Exacerbations were seen less frequently in patients who received DPM 400mg. In the total safety population, hemoptysis was noted in twice as many DPM 400mg-treated patients than those receiving controls.

Common adverse reactions in the safety population which occur more frequently for DPM 400mg-treated patients than in controls include cough, pharyngolaryngeal pain, hemoptysis, vomiting, diarrhea, pyrexia, and arthralgia.

When adverse events were evaluated in the 6 to 17 year-old pediatric population (259 patients out of 600, or 43%), there was a small but clear signal for hemoptysis in the DPM 400mg-treated patients over controls, even in the youngest age group of 6 to 11 year-olds. Additional adverse drug reactions in pediatric patients included cough, pharyngolaryngeal pain, vomiting, diarrhea, and epistaxis.

Overall, the primary safety risks for DPM 400mg include those related to tolerability, which led to early discontinuation for a significant proportion of the safety population. For those patients who continued treatment, AE including cough and pharyngolaryngeal pain occurred more often in the treatment group over controls. In addition, hemoptysis led to more SAEs, discontinuations due to AEs, and adverse events overall for those on DPM 400mg over control. While no patients died from hemoptysis events in the safety population during the conduct of these studies, the long-term effect of the 2-to-4-fold increases in hemoptysis seen in this program, when projected to chronic use over the course of a CF patient's lifetime, is unknown. The full discussion of safety follows.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical development program for Dry Powdered Mannitol for cystic fibrosis consisted of 7 clinical trials; please refer to Table 2: Relevant Clinical Trials. A total of 18 healthy volunteers, and 918 patients with CF, were exposed to dry powder mannitol during the screening period (see 7.1.4 Unique Safety Issue for the Phase 3 Program, below). Of these seven clinical trials, one was the initial PK study in healthy males, and

a second PK study was performed in patients with CF. There were three Phase 2 trials, one of which was Study 202, the open-label crossover study which evaluated dose-ranging. Study 201 was a double-blind, crossover study of DPM versus non-respirable mannitol, with two weeks of exposure for each arm. Study 203 was an open label crossover of 26 patients, with three 12-week treatment arms, assessing DPM 400mg twice daily, rhDNase 2.5mg daily, and a combined DPM 400mg twice daily plus rhDNase 2.5mg daily. Given the different objectives and relative short-term exposures to DPM, the data from these studies will be considered supportive, and discussed only where pertinent.

The double-blind periods of the two Phase 3 trials, Studies 301 and 302, are the primary source for the pooled safety database, and provide the basis for the determination of safety in the CF population. Study 301 had two 26-week open-label follow-up periods, and Study 302 had one open label follow-up; these open-label periods contribute to the long-term safety database, and will be discussed briefly throughout the review as uncontrolled safety data.

For the purposes of this review, the pooled safety set includes 600 patients with CF who received DPM 400mg BID or control (DPM 50mg BID) in one of the two Phase 3 trials. Of the 600 subjects, 361 received DPM 400mg twice daily, and 239 received control treatment. The initial focus of the safety discussion will be on the analysis of the data from the two double-blind periods of the phase 3 trials (600 patients), to include evaluation of deaths and major safety events, as well as supportive safety information including common adverse events.

The Applicant also supplied summary data from ongoing clinical trials of inhaled mannitol (320mg twice daily) in patients with non-CF bronchiectasis. This information was briefly reviewed, and did not uncover any new safety signals; as the patient population is significantly different, and the inhaled mannitol dose is lower than for CF trials, it is not considered as relevant.

7.1.2 Categorization of Adverse Events

An adverse event was defined as any untoward/unfavorable or unintended medical occurrence or change in the structure, function, or chemistry of the body of a subject administered a pharmaceutical product, without regard to the possibility of a causal relationship. AEs were collected from the screening visit up through 12 hours after the last study visit, or for those who discontinued prematurely, for a period of 7 days after the last dose of study drug.

Adverse event verbatim terms were classified using MedDRA to assign preferred terms (PT) and primary system organ classes (SOC) to each event. While MedDRA classification was used for all studies, the versions used in Studies 301 and 302 were different (Versions 9.1 and 11.0, respectively). Of note, an important difference

between the two is that CF exacerbations under version 9.1 (Study 301) were coded as "condition aggravated," but in version 11.0 (Study 302), exacerbations were initially coded to genetic disease. The Applicant changed coding for Study 302 so that exacerbations were coded to "condition aggravated," for consistency with Study 301.

Individual narratives for serious adverse events (SAEs) and discontinuations from treatment, and verbatim terms from narratives agreed with the Applicant's coding of preferred terms. In general, there was little evidence of splitting or lumping in the individual coding terms noted for the Safety set data, and it appears appropriate. There was some splitting of terms seen in the coding of reported events leading to withdrawal for patients after the challenge dose of DPM but before randomization; see Discontinuations Due to AE, Prior to Randomization, below, under Section 7.3.3. In general, SAEs and discontinuations appeared within the scope of what might be expected for patients with cystic fibrosis, and were not significantly different across studies. Because this database is small, it is difficult to identify the appropriate weight to ascribe events that occurred only in the DPM-treated group; a single event might represent coincidence, or might be a suggestion of a potential safety signal. Since there is no way to determine this at this at this time, brief synopses of single events that fall outside the expected norm for patients with cystic fibrosis are included where appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Since the patient population demographics, study design, and treatments were similar between Studies 301 and 302, adverse event data were examined as pooled data.

7.1.4 Unique Safety Issue for the Phase 3 Program

Because dry-powder mannitol is used for bronchoprovocation testing (under NDA # 22,368, Aridol), each of the studies included what the Applicant described as a "mannitol tolerance test" preceded by administration of a short-acting beta agonist. The two Phase 3 clinical trials used either 395 mg (Study 301) or 400 mg (Study 302) for the maximal test dose given. In addition, the definition of a positive test for the Phase 3 trials was any of the criteria below:

- a decrease in FEV1 of greater than or equal to 20% of baseline at the 120- or 240mg doses,
- ≥20% to <50% drop at 400mg dose which does not return to <20% of baseline within 15 minutes,
- A >50% drop from baseline,
- Decreased oxygen saturation of ≥10%from baseline
- SpO2 below 88 or 89%
- Occurrence of acute bronchospasm

For Study 301, 41 patients required a Re-test (i.e., 20-49% drop in FEV1), but 34 were later concluded to have a "negative MTT." For Study 302, 7 of 8 patients re-tested were considered to have met criteria for a "negative MTT." [Sources: M5.3.5.1.3, CSR 301, Table 14.1.8, p 206 and M5.3.5.1.3, CSR 302, Appendix 16.2.4, p 306.]

There were 719 patients screened for the Phase 3 trials of DPM; 41 patients met criteria for a "positive" test, 27 did not complete the testing (presumably to increased symptoms or intolerance), 10 completed testing but did not randomize, and 42 presented at Visit 1, but did not receive a dose of study drug. These subjects account for 120 patients, or 17% of the total number screened, most of whom did not tolerate DPM. So while the Safety Population is defined as any patient who received one or more doses of randomized study drug, for the purpose of determining the population of patients with CF who would be able to tolerate treatment, it is important not to discount that there was a substantial proportion of patients who could not tolerate the first test dose of drug, when challenged at screening. The total number of subjects for the entire DPM program who failed first dose challenge with DPM is provided below, in Table 18.

Table 18: Failed Challenge Dose of DPM, Clinical Development Program

Study	# Screened	# with "Positive MTT"[a]	# who were not randomized		Randomized, but WD before study drug given		# ITT Population
			#	reason	#	reason	
101[db]	25	2	2 3	WD due to AE Study Alternate	0	---	18
102[c]	18	0	---	---	---	---	18
201[d]	49	10	---	---	2	WD due to AE[e]	39
202[f]	85	27	8 2	Met exclusion WD prior to study	0	---	48
203[g]	40	12	---	---	2	No reason given	26
301[h]	378	46	8	[See Sec. 6.1.3]	29	[See Sec. 6.1.3]	295
302[i]	342	22	2	[See Sec. 6.1.3]	13	[See Sec. 6.1.3]	305
Totals	936	119	25		46		749

a= First test dose called "MTT," although maximal dose and dosing schedule varied across studies; Positive MTT = Failed challenge
Sources:
b= M5.3.1.1, CSR 101, Sec. 10.1, p 37.
c= M5.3.3.2.1, Legacy Rpt 102, sec 10.1, p30, and Listing 16.2.2.5, p643
d= M5.3.5.1.3, CSR 201, Sec. 10.1, p 38, and Table 10.1.2, p 39
e= These 2 subjects were counted in ITT, even though no dose given
f= M5.3.5.1.1, Legacy Rpt 202, Sec. 10.1, p 52, and Appendix 16.2.1
g= M5.3.5.1.1, Legacy Rpt 203, Sec. 10.1, p 46, and Appendix 16.2.1.1.
h= M5.3.5.1, CSR 301, Sec. 10.1, Table 10-1, Table 10-2, Fig. 10-1
i= M5.3.5.1, CSR 302, Sec. 10.1.2, Table 10.1.1.1, Fig. 10.1.1.1

In addition to those patients who failed the challenge dose (had a "positive MTT"), there were a number of other patients in the development program who were withdrawn due to adverse events prior to randomization, and some who were withdrawn due to adverse events after randomization but before the first dose of study drug was given at Visit 1. Also, a number of patients listed "withdrew consent" as their reason for study withdrawal, which might underestimate the number of discontinuations due to adverse

event after first challenge dose of inhaled mannitol. For example, the Applicant notes that in Study 203, six of the 26 subjects were withdrawn from the study, and included one withdrawal due to AE, and 5 for "patient decision," but 4 of those 5 had an adverse event identified before withdrawal. [Source: M5.3.5.1.1, Legacy Rpt 203, Sec. 10.1, p 46.] So while the total number of failed inhaled mannitol challenges from the development program is 119 of 936, or 13%, this number might be greater, based on the Applicant's classification of withdrawals before study drug was given at Visit 1. Adverse events collected between the challenge dose but before first randomized study dose of DPM will be described under separate heading in Section 7.4 Supportive Safety Results.

A possible reason for some of these discontinuations could be that the threshold for a positive mannitol tolerance test (MTT) for Studies 301 and 302 was higher than that used in labeling of the Aridol product which tests for bronchoprovocation. Aridol uses a ≥15% drop in FEV1 as evidence of reactivity (or positive test), but the MTT fro CF patients used cutoffs of FEV1 decline≥20% to <50% drop at 400mg dose which does not return to <20% of baseline within 15 minutes. In addition, Study 301 included the possibility of a re-test for patients who failed the first MTT to be tested again and possibly pass to randomization.

Reviewer's Comment:
If the number of patients withdrawn before the fist dose of randomized study drug (who withdrew for AE before or after randomization, who withdrew consent, and who were withdrawn by the physician) are added to those classified as a "positive MTT," the number of subjects who could not tolerate the challenge dose might increase to 155, or 17% of the total screened patient population.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequacy of Overall Clinical Experience

The Applicant's safety submission provides information from double-blinded study periods of 26 weeks each, which is a reasonable length of time for the identified primary efficacy endpoint of change in FEV1 over 26 weeks. While no firm agreement was met regarding duration of study, this was in line with discussions between the Applicant and the Division, as noted in the End-of Phase 2 meeting minutes from February 15, 2006 (dated April 4, 2006). This is reasonable for a drug planned to be used chronically, as outlined in Guidance ICH E1A. While this Guidance is not directly applicable because

those numbers it specifies are designed for more common conditions, and CF is an orphan population, the Applicant has collected data in 361 patients with CF treated with DPM 400mg every 12 hours for 26+ weeks, with open-label data from the 2 studies adding safety information for an additional 26 to 52 weeks. When the duration of treatment includes those patients, there have been 117 patients who have received greater than 52 weeks' exposure to DPM 400mg overall, which falls within the Guidance's recommended 100+ patients for one year. Given that these patients will likely remain on the drug throughout their lifetime, information regarding safety and durability of treatment of at least one year is reassuring from a clinical safety perspective.

The studies in this clinical program were designed to assess safety of DPM in a general population of CF patients, which covers a reasonable spectrum of disease. This safety population excluded CF patients with severe or end-stage lung disease, but the Applicant's rationale that changes in this group might be difficult to measure, given the severity and irreversibility of their disease processes, is reasonable, as is excluding this sickest population with little pulmonary reserve from challenge with an agent known to cause bronchospasm.

Extent of Exposure

In the Phase 3 program for DPM, 719 patients were eligible for enrollment, and therefore exposed to a challenge dose of DPM under monitored conditions (referred to as the "MTT" by the Applicant), to assess for the ability of individual patients to tolerate an agent known to cause acute bronchoconstriction. Subsequently, 541 patients were exposed to DPM 400mg in the double-blind and/or open label periods, 180 of whom were patients who received control study drug for the 26-week double-blinded period and transitioned to open-label treatment with DPM 400mg during the extension. The duration of exposure to study drug is listed below in Table 19: DPM Exposure, Safety Set. The grey bars at 0 to 26 weeks represent the double blind phase of study, with the subsequent weeks of open-label treatment unshaded. (Of note, the "control" column to the right for weeks 26 and beyond, include the first 26 weeks of control treatment, so weeks 26-39 actually represent 24 patients who rolled over to open-label treatment with DPM 400mg for up to thirteen weeks).

Table 19: DPM Exposure, Safety Set

		Phase 3 Controlled Studies	
Duration of Exposure	**Statistic**	**DPM 400mg N= 361**	**Control[a] N=239**
Exposed	N	361	180
	Mean (months)	9.4	6.0
	SD	(5.5)	2.9
	Median (max/min)	11.7 (0, 23.8)	6.0 (0, 15.5)
Exposure in Weeks, Double Blind plus Open Label (after 26 weeks)			
0-12 weeks	N	77	27
12-26 weeks	N	30	30
26-39 weeks[b]	N	24	24
39-52 weeks	N	113	94
>52 weeks	N	117	64

a= Control group includes 239 subjects who were randomized to receive control treatment, and 180 of these subjects continued into OL periods to receive DPM 400mg
b= Patients in "Control" group rolled over to active open-label treatment with DPM 400mg BID at week 26

[Source: Modified from the Applicant's, M 5.3.5.3, ISS, Section 4, Tables 5 and 6.]

Demographics of Safety Set

Overall, of the 600 patients who received at least one dose of blinded study drug, 458 (76%) completed the double-blinded, 26-week treatment phase. A total of 73% of patients receiving DPM completed, in comparison to 81% of the control group. There were 142 patients who did not complete the double-blinded treatment phase, including 70 for withdrawn consent, 57 for adverse events, 10 for Sponsor or Physician decision, 1 for protocol violation, and 4 for other reasons. (See Sections 6.1.2 Demographics, and 6.1.3 Subject Disposition, for further discussion of this study population). Demographics of the pooled safety set are listed below, in Table 20.

Table 20: Demographics, Pooled Safety Set

Baseline Characteristic	DPM 400mg BID N=361	Control N=239
Sex, n (%)		
Female	161 (45)	119 (50)
Male	200 (55)	120 (50)
Age in years		
Mean	21.3	21.6
(SD)	10.7	10.5
Range	6 to 56	6 to 53
Age 6-11years, n (%)	66 (18)	41 (17)
Age 12-17 years, n (%)	88 (24)	64 (27)
Age ≥18 years, n (%)	207 (58)	134 (56)
Race, n (%)		
African descent	2 (0.6)	2 (0.8)
Caucasian	351 (97)	234 (98)
West Asian	3 (1)	1 (0.4)
Other	5 (1.4)	2 (0.8)
Baseline FEV1		
Mean FEV1 (L)	2.06	1.95
(SD)	0.8	0.7
Mean % Predicted FEV1	64	62
(SD)	16	16
BMI (kg/m^2)		
Mean	20.6	20.1
(SD)	4.1	3.6
rhDNase use, n (%)		
Treatment with rhDNase	233 (65)	159 (67)

[Source: Module 5.3.5.3.2, ISS, Section 6.1.1, Table 11].

Demographics between the two treatment groups were similar, including average patient age of 21 years, baseline mean FEV1 of approximately 2 liters, body mass index of approximately $20kg/m^2$, and use of rhDNase at 65-67% of patients for both studies.

7.2.2 Explorations for Dose Response

A single dose was explored in the Phase 3 program. Dose response to 40, 120, 240, and 400mg inhaled DPM was explored in a small Phase 2 crossover study (Study 202, described in Section 5.3 Discussion of Individual Studies/Clinical Trials, above), and while the conduct of the study was suboptimal (see FDA's Biostatistical Review and Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations), the data collected generally support further evaluation of the safety and efficacy of the 400mg dose.

7.2.3 Special Animal and/or In Vitro Testing

Two-year carcinogenicity studies in rats and mice did not show evidence of carcinogenicity for mannitol given orally at doses that were as high as 55 times the MRHDID on a mg/m^2 basis. Mannitol tested negative in gene mutation assays. The effect of inhaled mannitol on fertility has not been studied, but mannitol did not cause any embryofetal malformations when given to pregnant mice and rats at oral doses approximately 10-20 times the MRHDID in adults on a mg/m^2 basis.

7.2.4 Routine Clinical Testing

Given that mannitol is generally considered safe when administered by the oral route and the large majority is eliminated unchanged, the use of routine clinical testing was minimal. Liver function tests, serum electrolytes, and urea were assessed as screening at the end of the 26-week double-blind treatment period and at the end of any open-label extensions, if the patient continued into the extension period. There were no meaningful differences in clinical laboratory tests between the DPM 400 mg and control treatment groups during the 26-week double-blind treatment period

7.2.5 Metabolic, Clearance, and Interaction Workup

The data for inhaled mannitol was originally submitted under the NDA for Aridol, and is included in the Aridol labeling, as below. This same data is supportive for the current DPM program in CF, and will also be included in the label.

Absorption: The rate and extent of absorption of mannitol after oral inhalation was generally similar to that observed after oral administration. In a study of 18 healthy adult male subjects the absolute bioavailability of mannitol powder following oral inhalation was 59% while the relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. Following oral inhalation of 635 mg, the mean mannitol peak plasma concentration (Cmax) was 13.71 mcg/mL while the mean extent of systemic exposure (AUC) was 73.15 mcg•hr/mL. The mean time to peak plasma concentration (Tmax) after oral inhalation was 1.5 hour.
Distribution: Based on intravenous administration, the volume of distribution of mannitol was 34.3 L.
Metabolism: The extent of metabolism of mannitol appears to be small. This is evident from a urinary excretion of about 87% of unchanged drug after an intravenous dose to healthy subjects.
Elimination: Following oral inhalation, the elimination half-life of mannitol was 4.7 hours. The mean terminal elimination half-life for mannitol in plasma remained unchanged regardless of the route of administration (oral, inhalation, and intravenous). The urinary excretion rate versus time profile for mannitol was consistent for all routes of administration. The total clearance after intravenous administration was 5.1 L/hr while the renal clearance was 4.4 L/hr. Therefore, the clearance of mannitol was

predominately via the kidney. Following inhalation of 635 mg of mannitol in 18 healthy subjects, about 55% of the total dose was excreted in the urine as unchanged mannitol. Following oral or intravenous administration of a 500 mg dose, the corresponding values were 54% and 87% of the dose, respectively.
Hepatic and Renal Impairment: Formal pharmacokinetic studies using ARIDOL have not been conducted in patients with hepatic or renal impairment. Since the drug is eliminated primarily via the kidney, an increase in systemic exposure can be expected in renally-impaired patients.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Inhaled mannitol is also approved as a single use bronchial challenge test kit (Aridol) and, as such, inhaled mannitol has the known capacity to induce cough and severe bronchial constriction in sensitive subjects. The Aridol Prescribing Information includes a boxed warning of the risk of severe bronchospasm.

The use of inhaled hypertonic sodium chloride (7%), while not approved for use as a means to improve pulmonary function in the United States, is commonly used by the CF population and has become part of the standard of care for CF patients. As a hypertonic solution, it may have a similar mechanism of action and its use may also prompt adverse events suggestive of significant bronchoconstriction (cough, chest tightness).

Reviewer's Comments:
DPM is the same drug product as the 40mg capsule from the Aridol test kit, only it is packaged as 10 capsules to be used twice daily on a chronic basis for the CF indication. Many of the same contraindications, warnings and precautions, and adverse reactions will apply to this product as well.

7.3 Major Safety Results

Major safety results for the DPM program are described in detail in the sections below. Table 21 gives a high-level overview of each of the major categories to be discussed further in this section.

Table 21: Overview of Safety, Safety Set

	Phase 3 Controlled Studies[a] Double-Blinded Period	
Subject group	**DPM 400mg N= 361 N (%)**	**Control N= 239 N (%)**
Deaths	0	0
Subjects with at least one SAE	77 (21)	65 (27)
Subjects who Discontinued from Study for Any Reason	96 (27)	46 (19)
Subjects with any AE Leading to Study Discontinuation	41 (11)	15 (6)
Subjects with a TRAE[b] leading to Study Discontinuation	36 (10)	8 (3)
Subjects with at least one Adverse Event Reported	319 (88)	215 (90)

a= Studies 301 and 302, 26-weeks
b= TRAE= Treatment-related Adverse Event

[Source: Module 5.3.5.3.28, ISS Tables 9, 23, and Section 7.2.2.7]

Reviewer's Comments:
The Applicant divided Safety events by time of occurrence, classifying events as the "MTT Phase," the "Double-blind Phase," and "Open-label Phase." This review will focus primarily on the 26-week double-blind phase as the best means of comparison of safety between the two groups. The MTT data are important to form a general impression of the overall extent of patients who did not or will not tolerate inhaled DPM, and will be addressed in that light. The open-label data is briefly reviewed to determine if it is supportive of the data from the double-blinded period.

7.3.1 Deaths

There was one death reported during the conduct of the DPM program. The patient was a 15yo man with severe CF lung disease, who was enrolled in Study 302 and received control study drug (50mg inhaled mannitol). He received treatment for approximately 5 months, then study drug was temporarily held for illness progression associated with hospitalization and pneumothorax. When it became evident to the clinicians a month later that the subject's condition was deteriorating (mechanical ventilation, ECMO, lung transplant listing), he was withdrawn from the study, and subsequently died 7 weeks after study withdrawal.

7.3.2 Nonfatal Serious Adverse Events

The Applicant utilized the appropriate definition of Serious Adverse Event throughout the development program, as defined in 21CFR. Data was evaluated from the Applicant's Integrated Summary of Safety, individual study report safety, and the full narrative reports for any patient with a SAE from each of the Phase 3 studies that comprise the safety set. Table 22: SAEs Occurring in More Than One Patient, Any Treatment, Safety Set, lists the total number of patients who experienced SAEs, with specific listings by preferred term for any event occurring in more than one patient. All events, regardless of causality, were evaluated. In general, the SAEs were within what would be expected for a CF population, including CF exacerbations, and other respiratory, GI, and metabolic concerns.

SAEs Reported Before Randomization

When evaluating the data from 729 patients reported after the first challenge dose of mannitol, but before randomization, there were no reported SAEs in the Respiratory, Thoracic, and Mediastinal SOC. CF exacerbations ("condition aggravated") was reported in 14 (4%) of patients in Study 301, and 15 (4%) of patients from Study 302, one of which was evaluated to be "possibly related," and all others as "definitely not related." The overall number of patients who reported an SAE was similar (4.9 vs. 4.7%) in Studies 301 and 302, respectively. [Source: M5.3.5.3, ISS, Section 7.2.1.5, Table 21]. In Study 301, the SAEs of CF exacerbations occurred between 2 days and 5 weeks after the MTT (most over a week after MTT), and were considered unrelated by investigators. There was one patient who tested negative for MTT at screening, and began a course of home IV therapy for an exacerbation (reported as SAE) the same day, but the Investigator considered this exacerbation "definitely unrelated." The only case reported as "possibly related," was a 22 year-old man with baseline FEV1 of 3.5L, who developed shortness of breath, wheezing, chest tightness, increased sputum, and hemoptysis 11 days after the MTT. For Study 302, CF exacerbations occurred from 4 days to 6 weeks after the MTT was administered. There does not appear to be a direct relation between administration of MTT and onset of CF pulmonary exacerbation, with regard to SAEs. [Source: Module 5.3.5.1, CSR 301, Narratives, Section 14.3.3, p 1404-1411, and CSR 302, Narratives, Section 14.3.3, p 665-672]

SAEs During the Double-Blind Period

Serious adverse events during the double-blinded period are described below, in Table 22. The most frequent SAE in both groups was for a CF pulmonary exacerbation (coded as "condition aggravated"), with 17% reported in the DPM group, and 19% in the control group. The second most common event for the treatment group was hemoptysis, with 8 (2%) for the DPM group, versus 2 patients (0.8%) for the control group. Hemoptysis will be explored further under Section 7.3.5 Submission Specific

Primary Safety Concerns. Lower respiratory tract infections occurred in relatively equal numbers of patients in the DPM 400mg and control groups, 4 (1%) and 5 (2%), respectively.

There were a number of serious adverse events which occurred in only once across the Safety population. Those events which occurred in a DPM patient, and not in control, are listed here: pancreatitis, impacted tooth, cholecystitis, bronchopneumonia, cellulitis, pilonidal cyst, bacteria sputum identified, bronchospasm, pleural effusion, antibiotic prophylaxis, central venous catheter, and hospitalization. Based on the known effects and mechanism of action of mannitol, except for bronchospasm, the SAEs listed would not be expected to be the result of inhaled mannitol. There was one reported SAE of drug hypersensitivity in the DPM 400mg group, but it does not appear to be related. A 10 year-old boy in Study 301 (patient (b) (6)) had been receiving study treatment for three and a half months, when hospitalized due to an allergic reaction to ceftazidime; study drug was continued, but ceftazidime was stopped, and the episode resolved one day later [Source: M5.3.5.1, CSR 301, Narratives, Section 14.3.3, p 1447-48].

Table 22: SAEs Occurring in More Than One Patient, Any Treatment, Safety Set

	Phase 3 Controlled Studies Double-Blinded Period	
	DPM 400mg N= 361	Control N= 239
System Organ Class Preferred Term	**Total # of Subjects (%)**	**Total # of Subjects (%)**
Any SAE[a]	77 (21)	65 (27)
General Disorders and Administration Site Cond.	**60 (17)**	**45 (19)**
Condition Aggravated	60 (17)	45 (19)
Respiratory, Thoracic and Mediastinal Disorders	**11 (3)**	**7 (3)**
Hemoptysis	8 (2)	2 (1)
Pleuritic Pain	1 (0.3)	1 (0.4)
Pneumothorax	0	2 (1)
Gastrointestinal Disorders	**4 (1)**	**7 (3)**
Constipation	0	2 (1)
DIOS	2 (0.6)	1 (0.4)
Intestinal Obstruction	0	2 (1)
Infection and Infestations	**7 (2)**	**13 (5)**
Lower Respiratory Tract Infxn.	4 (1)	5 (2)
Pneumonia	0	2 (1)
Metabolism and Nutrition Disorders	**2 (0.6)**	**0**
Diabetes Mellitus	2 (0.6)	0
Surgical and Medical Procedures	**4 (1)**	**0**
Catheterization venous	2 (0.6)	0

a= Events which occurred in only one patient are not listed below this point

[Source: Module 5.3.5.3. ISS Section 7.2.2.5, Modified from Applicant's Table 28]

SAEs in the Uncontrolled Safety Data

There were 430 patients who continued into open-label treatment from the original 600 in the safety population from Studies 301 and 302. Other than for hemoptysis, there were similar types and numbers of patients who reported SAEs in the open-label extension as in the 26-week double-blinded period (Table 23, below). However, while it did not appear as if the incidence of hemoptysis increased over time in patients who received DPM 400mg and continued receiving it in the open-label periods, the number of cases of hemoptysis increased from less than 1% in patients who received control in the double-blind period, to 3% in the open-label extension period adding support to the finding that the increased incidence of hemoptysis seen in the double-blind period was

due to DPM. Hemoptysis will be discussed in more detail in Section 7.3.5 Submission Specific Primary Safety Concerns.

Table 23: SAEs Occurring in More Than 1 Patient, Uncontrolled Open-Label

	Phase 3 Controlled Studies Uncontrolled Open-Label Periods[a]	
	Previous DPM 400mg N= 250	Previous Control N= 180
System Organ Class Preferred Term	**Total # of Subjects (%)**	**Total # of Subjects (%)**
Any SAE[b]	63 (25)	47 (26)
General Disorders and Administration Site Cond.	**49 (20)**	**33 (18)**
Condition Aggravated	49 (20)	33 (18)
Respiratory, Thoracic and Mediastinal Disorders	**7 (3)**	**7 (4)**
Hemoptysis	4 (2)	5 (3)
Cough	1 (0.4)	1 (0.6)
Gastrointestinal Disorders	**6 (2)**	**0**
DIOS	2 (1)	0
Infection and Infestations	**7 (3)**	**8 (4)**
Pneumonia	2 (1)	0
Pneumonia bacterial	0	2 (1)

a= All patients received DPM 400mg BID after previous 26-week DB treatment:
b= Events which occurred in only one patient are not listed below this point

[Source: Module 5.3.5.3. ISS Section 8.1.4, Modified from Applicant's Table 41]

7.3.3 Dropouts and/or Discontinuations

Discontinuations Due to AE, Prior to Randomization

When evaluating the data from 729 patients reported after the first challenge dose of mannitol, but before randomization, there were 29 subjects who withdrew due to an adverse event. The Applicant notes in Study 301 that there were 7 patients who had a "positive MTT" (failed first challenge dose of DPM) who were listed as AE leading to withdrawal, instead of "failed based on MTT." With that in mind, there were 19 subjects who withdrew due to respiratory AEs (some reporting more than one), including bronchospasm (3), cough (12), chest discomfort (6), bronchospasm (3), wheezing (3), and one each for hypoxia, productive cough, and throat irritation. Three subjects withdrew due to CF exacerbation ("condition aggravated"), and 4 for GI complaints, including nausea, vomiting, and retching [Source: M5.3.5.3, ISS, Section 7.2.1.6, Table 22]. From review of the individual study narratives, the majority of the 29 subjects who

withdrew due to an adverse event occurred in association with MTT administration, and most were participants in Study 301. [Source: Module 5.3.5.1, CSR 301, Narratives, Section 14.3.3, p 1460-1466, and CSR 302, Narratives, Section 14.3.3, p 665-672]. Refer also to Section 7.3.5 Submission Specific Primary Safety Concerns, 7.3.5.1 Overall Tolerability, for further discussion.

Discontinuations Due to AE, During the Double-Blind Period

A total of 41 (11.4%) patients from the DPM 400mg group and 15 (6.3%) from the control group withdrew from Phase 3 trials due to adverse events. Most of the discontinuations in the DPM 400mg group were from AEs likely to be associated with inhaled mannitol, including cough, hemoptysis, bronchospasm, chest discomfort, and pharyngolaryngeal pain; see Table 24. No distinct sub-populations were disproportionately represented in the dropouts.

Table 24: AEs Leading to Discontinuation in More Than One Patient, Safety Set

	Phase 3 Controlled Studies Double-Blinded Period	
System Organ Class Preferred Term	**DPM 400mg N= 361 (%)**	**Control N= 239 (%)**
Patients with Any AE Leading to Study Drug Discontinuation[a]	41 (11)	15 (6)
General Disorders and Administration Site Cond.	**12 (3)**	**3 (1)**
Condition Aggravated	8 (2)	3 (1)
Chest Discomfort	3 (1)	0
Respiratory, Thoracic and Mediastinal Disorders	**32 (9)**	**9 (4)**
Hemoptysis	6 (2)	0
Cough	18 (5)	6 (3)
Bronchospasm	2 (0.6)	0
Pharyngolaryngeal Pain	3 (1)	0
Throat Irritation	1 (0.3)	1 (0.4)
Wheezing	0	2 (1)
Nervous System Disorders	**1 (0.3)**	**1 (0.4)**
Headache	1 (0.3)	1 (0.4)
Infection and Infestations	**0**	**2 (1)**
Lower Respiratory Tract Infxn.	0	1 (0.4)
Pneumonia	0	1 (0.4)

a= Events which occurred in only one patient are not listed below this point

[Source: Module 5.3.5.3. ISS Section 7.2.2.6, Modified from Applicant's Table 29]

Discontinuations Due to AEs in the Uncontrolled Safety Data

The data from the two 26-week open-label extensions for Study 301, and the one open-label extension for Study 302, were evaluated for adverse events which led to discontinuation. There were 430 patients who continued into open-label treatment from the original 600 in the safety population; values for discontinuations in the open-label treatment phase are listed below in Table 25. While these events occurred in only a few patients, it is important to note that the change from control treatment to DPM 400mg led to increased numbers of adverse events leading to discontinuation, 16 (9%) versus 5 (2%) for those who continued treatment. In addition, the AE of chest discomfort, CF exacerbation, URTI, LRTI, decreased FEV1, bronchospasm, dyspnea and throat irritation leading to treatment discontinuation all occurred in those who had previously been treated with control in the double-blind period, versus zero AE in these categories for those who had received DPM 400mg in the double-blind period. This most likely represents the inability of these patients to tolerate DPM as a chronic therapy.

Table 25: AEs Leading to Discontinuation in >1 Patient, Uncontrolled Open-Label

	Phase 3 Controlled Studies Uncontrolled Open-Label Periods[a]	
System Organ Class Preferred Term	**Previous DPM 400mg N= 250 (%)**	**Previous Control N= 180 (%)**
Subjects with at least one AE leading to discontinuation[b]	5 (2)	16 (9)
General Disorders and Administration Site Cond.	**1 (0.4)**	**4 (2)**
Condition Aggravated	1 (0.4)	3(2)
Respiratory, Thoracic and Mediastinal Disorders	**4 (2)**	**7 (4)**
Hemoptysis	1 (0.4)	2 (1)
Cough	1 (0.4)	1 (0.6)
Bronchospasm	0	2 (1)
Dyspnea	0	1 (0.6)
Throat Irritation	0	1 (0.6)
Investigations	**0**	**2 (1)**
FEV1 Decreased	0	2 (1)
Infection and Infestations	**0**	**3 (2)**
Lower Respiratory Tract Infxn.	0	1 (0.6)
Upper Respiratory Tract Infxn.	0	1 (0.6)

a= All patients received DPM 400mg BID after previous 26-week DB treatment:
b= All events which occurred in only one patient are not listed below this point

[Source: Module 5.3.5.3. ISS Section 8.1.5, Modified from Applicant's Table 42]

7.3.4 Significant Adverse Events

All significant adverse events are discussed in detail in Section 7.3.5, Submission Specific Primary Safety Concerns, below.

7.3.5 Submission Specific Primary Safety Concerns

The Applicant identified cough, pharyngolaryngeal pain, hemoptysis, bronchospasm, condition aggravated, and infections as "adverse events of special interest." Cough was identified as an adverse event of special interest, as were events of "pharyngolaryngeal pain," since they occurred more frequently in the DPM 400mg group over control, and since the potential local irritant effect of dry powder inhalers is known. These events are not discussed here, but rather are discussed briefly in Section 7.4 Supportive Safety Results. "Condition aggravated" was also identified by the Applicant because of the importance of exacerbations to the progression of CF lung disease, morbidity, and mortality. However, slightly fewer of these adverse events occurred in the DPM 400mg group as compared to controls, and SAEs and AE leading to withdrawal have been discussed in previous sections of this review. Infection, as captured by sputum collection, will be discussed later in Section 7.4.2 Laboratory Findings.

Relevant safety related issues for the DPM 400mg program were overall tolerability of the product, as well as incidences of hemoptysis and bronchospasm. In addition, patients with a low FEV1 were also evaluated to assess if their tolerability of the study drug was different than that of the general population. Each of these will be discussed individually, below.

7.3.5.1 Overall Tolerability

The overall tolerability of DPM 400mg is a specific safety concern. In general, FDA safety reviews assess the risks of a drug across the disease spectrum for a given population. In this case, we are evaluating the use of DPM in patients with cystic fibrosis, with varying levels of lung disease. However, a significant proportion of patients could not tolerate inhaled treatment with dry-powder mannitol, as evidenced by the following:

- Large number of patients who were screened, but did not qualify for randomization
- Large number of patients who discontinued the study before randomization
- Unequal dropout from the treatment group over control, especially within the first 6-week assessment period
- Most of the common adverse events and treatment-related adverse reactions seen are related to respiratory irritation and increased coughing

The number of patients who did not complete the initial test dose or experienced significant drop in pulmonary function after treatment with the test dose (called the MTT

by the Applicant), have been described in Section 7.1.4 Unique Safety Issue for the Phase 3 Program. There were 51 patients who went on to randomization, but reported adverse events prior to randomization. Of these 51 patients, they reported 69 AE which were considered treatment-related. These events included the following: gastrointestinal complaints (11), chest discomfort (7), chest pain (1), condition aggravated (2), dizziness (1), wheeze (5), bronchospasm (3), cough (27), and one each of dysphonia, hypoxia, productive cough, and throat irritation.[source: Module 5.3.5.3, ISS Appendix, table ist13sum1_100, pages 121-122] These episodes demonstrate potential tolerability issues, although these events did not prevent those 51 patients from randomizing. In those who discontinued prior to randomization, 19 subjects discontinued for events with respiratory preferred terms, and 4 for GI preferred terms.

As mentioned in previous sections, one reason for problems with tolerability after randomization might have been that the threshold for a positive mannitol tolerance test (MTT) was too low. The Aridol product which tests for bronchoprovocation, uses a $\geq$15% drop in FEV1 as evidence of reactivity, but the MTT for Studies 301 and 302 used cutoffs of FEV1 decline$\geq$20% to <50% drop at 400mg dose which does not return to <20% of baseline within 15 minutes.

Other predictors of overall patient tolerability have previously been discussed in Section 7.3.3 Dropouts and/or Discontinuations. The incidence of discontinuation due to AE in the DPM 400mg group was almost twice that of the control group, and respiratory events leading to discontinuation occurred in 9% of the DPM 400mg group, versus 4% of the controls. There was also an increased rate of discontinuation in the open-label phase for those patients who initially received control during the double-blind period, then rolled over into open label treatment with DPM 400mg. Subjects in the open-label period withdrew at a rate of 9% for those previously receiving control, versus 2% for those continuing DPM 400mg.

Specific symptoms of cough and throat irritation were also evaluated as part of tolerability. There were no serious adverse events due to cough, productive cough, or aggravated cough during the double-blinded treatment period, but withdrawal due to an AE of cough/productive cough was twice as high for the DPM 400mg group compared to controls (5% vs. 2.5%) See Table 27, below. Three additional patients in the open-label phase discontinued due to cough events. Please also refer to Section 7.3.5.2 Cough, for more detailed description of cough within the DPM program for CF.

Although patients noted events of throat pain and irritation, there were no serious adverse events in either group; there were 3 withdrawals in the double-blind period, and all withdrawals were in the DPM 400mg group. One subject was 8 years old, and the other two patients were adults. There was an additional pediatric patient who withdrew for “throat irritation.” Of the 44 patients treated with DPM 400mg with AE of pharyngolaryngeal pain, 31 completed and continued into the open-label phase, and of those who initially received control, 16 of 18 continued into the open-label phase.

Table 26: Incidence of Local Throat Effects, Safety Set

	Phase 3 Controlled Studies[a] Double-Blinded Phase			Phase 3 Controlled Studies[a] Uncontrolled Open-Label Phase[b]	
Category	**DPM 400mg N=361 (%)**	**Control N=239 (%)**		**Prev. DPM 400 N=250 (%)**	**Prev. Control N=180 (%)**
WD due to AE, Pharyngolaryngeal Pain	3 (0.8)	0		1 (0.4)	0
SAE Pharyngolaryngeal Pain	0	0		0	0
AE Pharyngolaryngeal Pain	44 (12)	18 (8)		13 (5)	12 (7)
Severe AE Pharyngolaryngeal Pain	5 (1.4)	0		1 (0.4)	1 (0.6)
AE Throat Irritation	4 (1)	1 (0.4)		0	2 (0.8)

a=Studies 301 and 302, double-blinded phase was 26 weeks, open-label was 26-52 weeks additional
b=All patients who continued into OL received DPM 400mgBID

[Source: Module 5.3.5.3. ISS, Modified from Applicant's Tables 27, 28, 29, 31, 38, 40, 41, 42; ISS Appendix tables ist20sum1_101 and ist20sum1_101]

As with cough, pain and irritation represent part of the spectrum of tolerability for this product.

7.3.5.2 Cough

Cough was identified by the Applicant as an adverse event of special interest, due to its being reported more often in the treatment group than control, and because it is a common adverse event for an inhaled treatment. The Applicant postulates in this submission that increased cough, because of its potential to mobilize and clear secretions, could actually be a desired effect from DPM; however their clinical program did not evaluate as an efficacy assessment the correlation (if any) of increased cough with increased mobilization of secretions, and those to an improvement in lung function. This reviewer considers that, without pre-defined guidance given to the Investigators to suggest otherwise, if cough was reported as an adverse event in the course of the Phase 3 trials, it would have been determined by the patient/investigator to be untoward, unfavorable or unintended, and should be assessed as such. Add to this that most patients with CF already have a tolerated baseline level of daily cough (and are somewhat desensitized to it), this would suggest that any reported events were in excess of their norm, and therefore adverse. There is no clear way to differentiate from this safety data the timing of cough in relation to study drug use, for example, if the cough was noted immediately after treatment, it might suggest a tolerability issue such as irritant triggering of bronchospasm, if it gradually increased over time with dosing to meet a threshold of irritation (long-term tolerability), or if it occurred later in the treatment

course and might suggest increasing mobilization of secretions (which would be the intended effect). Further complicating the complaint of cough is that cough can occur in patients with CF for a number of reasons, including those due to secretions, irritant exposure, bronchospasm, asthma, gastroesophageal reflux, allergy, nasal polyps, viral illness, etc. Along these lines, the overall effect of DPM to cause irritant cough may have been minimized by comparing treatment to control in these trials, because the control group still received inhaled mannitol via DPI, albeit a much smaller (50mg) dose. The Applicant's choice to evaluate DPM vs. control was reasonable, however, since there was no simple way to maintain the blind and include a no-treatment group, which might have been used to assess this overall tolerability issue.

The Applicant notes that preferred terms of "cough," "productive cough," and "aggravated cough" were assessed in their entire DPM program; for the Phase 3 CF program, there were no AE reports of "aggravated cough." The Applicant did not provide any guidance for Investigators to differentiate "cough" from "productive cough," so again, any potential benefit could not be inferred, as suggested by the Applicant.

Cough was the most common AE reported in the Phase 3 program, with 76 (21%) of patients who received DPM 400mg BID reporting cough, versus 40 (17%) of control-treated patients. Productive cough accounted for another 17 (5%) in the treatment group, versus 9 (4%) of the controls. Incidences of event reporting for all cough episodes are noted below in Table 27: Rates of Reported Cough Events for Phase 3 Program. Post-tussive vomiting has been included in this table, since this can be another unintended effect of excess cough; and is more commonly seen in pediatric patients; this was not included by the Applicant in their analysis of cough events. The post-tussive vomiting AEs are not markedly higher than for controls; if it were, it might have suggested a greater risk to the pediatric patient population, who more commonly present with emesis after coughing, due to a more sensitive gag reflex than in teens and adults.

Table 27: Rates of Reported Cough Events for Phase 3 Program

	Phase 3 Controlled Studies[a] Double-Blinded Phase			Phase 3 Controlled Studies[a] Uncontrolled Open-Label Phase[b]	
Category	**DPM 400mg N=361 (%)**	**Control N=239 (%)**		**Prev. DPM 400 N=250 (%)**	**Prev. Control N=180 (%)**
Withdrawal due to AE- Cough[c]	18 (5)	6 (2.5)		2 (0.8)	1 (0.6)
SAE Cough[b]	0	0		1 (0.4)	1 (0.6)
AE Cough[b]	93 (26)	49 (21)		48 (19)	30 (17)
Severe AE Cough[b]	8 (2.2)	4 (1.7)		0	1 (0.4)
AE Post-tussive Vomiting	8 (2)	2 (0.8)		1 (0.4)	3 (2)

a= Studies 301 and 302, double-blinded phase was 26 weeks, open-label was 26-52 weeks additional
b= All patients who continued into OL received DPM 400mgBID
c= "Cough" includes PT of "cough," "aggravated cough," and "productive cough"

[Source: Module 5.3.5.3. ISS, Modified from Applicant's Tables 27, 28, 29, 30, 38, 40, 41, 42; ISS Appendix table ist20sum1_101]

There were no serious adverse events due to cough, productive cough, or aggravated cough during the double-blinded treatment period, but withdrawal due to an AE of cough/productive cough was twice as high for the DPM 400mg group compared to controls (5% vs. 2.5%). Three additional patients in the open-label phase discontinued due to cough events.

Overall, though cough was seen more frequently in the DPM-treated patients over control, there were no SAE of cough reported, and those who discontinued due to cough would be able to select themselves out of use due to lack of tolerability.

7.3.5.3 Hemoptysis

In the Phase 3 studies of DPM, patients with a previous history of significant hemoptysis episode (>60mL) within the 3 months prior to study were excluded. The rates of serious adverse events, adverse events leading to withdrawal, severe AE, and AE reporting of the preferred term hemoptysis are listed below, in Table 28: Rates of Reported Hemoptysis Events for Phase 3 Program. While none of these events occurs with high frequency, the double-blind treatment period has reports of hemoptysis 2 to 3 times higher in all categories for the DPM 400mg-treated group compared to controls. For patients who continued into open-label treatment, those who received control in the double-blind phase note an increased reporting of hemoptysis events once beginning DPM 400mg that is similar to those patients who received double-blinded DPM 400mg treatment. In addition, those who received DPM 400mg in the double-blind treatment period continued to have rates of hemoptysis higher than the original control arm, but the rate did not continue to rise.

Table 28: Rates of Reported Hemoptysis Events for Phase 3 Program

	Phase 3 Controlled Studies Double-Blinded Phase			Phase 3 Controlled Studies[a] Uncontrolled Open-Label Phase	
Category	**DPM 400mg N=361 (%)**	**Control N=239 (%)**		**Prev. DPM 400 N=250 (%)**	**Prev. Control N=180 (%)**
Withdrawal due to AE- Hemoptysis	6 (1.7)	0		1 (0.4)	2 (1.1)
SAE Hemoptysis	8 (2.2)	2 (0.8)		4 (1.6)	5 (2.8)
AE Hemoptysis	34 (9.4)	13 (5.4)		17 (6.8)	13 (7.2)
Severe AE Hemoptysis	4 (1.1)	1 (0.4)		2 (0.8)	3 (1.7)

a= All patients who continued into OL received DPM 400mg BID

[Source: Module 5.3.5.3. ISS, Modified from Applicant's Tables 24, 27, 28, 29, 38, 40, 41, 42; ISS Appendix table ist20sum1_101]

The Applicant proposes in their Integrated Summary of Safety that hemoptysis is common in CF, and that looking at adverse event reporting itself might not capture the frequency of hemoptysis events, since hemoptysis can be a presenting symptom of pulmonary exacerbation. They performed an additional data capture from the electronic case report forms to identify cases of hemoptysis reported as a symptom of a pulmonary exacerbation but not otherwise reported as an AE. This data is presented in Table 29, below. While the overall totals and total reports for adults are similar, the number for children and adolescents note a disparity that, while not large, may still represent a potentially clinically significant concern.

The Applicant's analysis in Table 29, below, is helpful to identify additional reports of hemoptysis, but any first episode of hemoptysis is an important clinical marker for patients, and would probably have been categorized as an AE/SAE by the clinician. Episodes reported as part of a pulmonary exacerbation are relevant, but would more likely represent repeat episodes in a subject with a prior history of hemoptysis. It should be noted that investigators were not given pre-specified instruction with regard to noting hemoptysis as an AE or as part of the constellation of symptoms of an exacerbation. Even when combining hemoptysis events of AEs or episodes associated with exacerbation, there is still a higher incidence in the pediatric/ adolescent patients who received DPM 400mg versus those who received control. The data for adult patients skews in the opposite direction, and because there are greater numbers of adult patients, pulls the overall incidence to roughly equivalent when examined in the entire safety population. In order to evaluate these episodes in the broader context of CF disease, the rate of hemoptysis in the general CF population needs to be discussed.

Table 29: All Reported Hemoptysis Cases by Age, Safety Set

Subjects with Hemoptysis	Phase 3 Controlled Studies[a] Double-Blinded Period	
	DPM 400mg	Control
All subjects[b]	**N=361**	**N=239**
Reported as AE	34 (9.4)	13 (5.4)
Reported w/ Pulm. Exacerbation	14 (3.9)	19 (7.9)
Total	**48 (13.3)**	**32 (13.4)**
Children 6-11 years old	**N=66**	**N=41**
Reported as AE	4 (6.1)	0
Reported w/ Pulm. Exacerbation	0	1 (2.4)
Total	**4 (6.1)**	**1 (2.4)**
Adolescents 12-17 years old	**N=88**	**N=64**
Reported as AE	8 (9.1)	2 (3.1)
Reported w/ Pulm. Exacerbation	4 (4.5)	5 (7.8)
Total	**12 (13.6)**	**7 (10.9)**
Adults >18 years old	**N=207**	**N=134**
Reported as AE	22 (10.6)	11 (8.2)
Reported w/ Pulm. Exacerbation	10 (4.8)	13 (9.7)
Total	**32 (15.5)**	**24 (17.9)**

a= Studies 301 and 302, 26 weeks
b= includes all reports of hemoptysis as AE or as part of pulmonary exacerbation but not separately for AE

[Source: Module 5.3.5.3. ISS, Section 7.3.3, Modified from Applicant's Table 32, page 82-83.]

In their discussion, the Applicant notes that chronic inflammation and friability of the airways leads to hemoptysis being "commonly observed." This statement as a descriptor of the whole CF population is true, since the pathogenesis of CF hemoptysis is likely caused by airways inflammation and vascular erosion of tortuous bronchial arteries, but in general, most patients presenting with hemoptysis are older, and/or have more significant disease[4]. Hemoptysis is typically noted as scant or minimal, but can be massive (>240mL within a 24-hour period, or recurrent bleeding of >100mL/day over several days)[5]. A recent case-control study of CF patients in Israel[6] identified that 40 patients out of 440 experienced hemoptysis in the 5-year study period, and of these 40, ten were less than 13 years old at first onset of hemoptysis. This represents only 2% of the population reported, which supports the contention that hemoptysis in young children is uncommon. In a review of massive hemoptysis from the CFF database[5], the average age of patients at first episode of hemoptysis was 24.2 $\pm$ 8.7 years, with half of the patients experiencing a massive hemoptysis episode between 18 and 30 years of age. The average lung function at first episode was moderate to severe impairment, with >60% of patients having an FEV1 <40% predicted. This does not exclude the possibility that small hemoptysis might occur earlier, but rather is used to illustrate that hemoptysis in young children is not common or frequently expected.

To further characterize these events of hemoptysis, events that occurred by age group are described in Table 30, below. In the safety population, 4 patients (6.1%) in the DPM 400mg group aged 6 to 11 years reported an AE of hemoptysis, versus none in the control group. In addition, 8 patients (9.1%) of the patients in the DPM 400mg group versus 2 (3.1%) control, aged 12 to 17 years of age, reported hemoptysis. The values between adult groups were similar, at 10.6 vs. 8.2%, respectively. First episode of hemoptysis was not specifically captured in the Applicant's data collection.

Table 30: Hemoptysis Events by Age

	Phase 3 Controlled Studies Double-Blinded Phase		
Category	**DPM 400mg N (%)**	**Control N (%)**	**Total N (%)**
Pediatric (6-11 yr)	**N= 66**	**N= 41**	**N= 107 (18%)**
Any Hemoptysis	4 (6.1)	0	4 (6.1)
Severe AE	1 (1.5)	0	1 (1.5)
SAE	0	0	0
WD due to AE	0	0	0
Adolescent (12-17 yr)	**N= 88**	**N=64**	**N= 152 (25%)**
Any Hemoptysis	8 (9.1)	2 (3.1)	10 (6.6)
Severe AE	1 (1.1)	0	1 (0.7)
SAE	3 (3.4)	1 (1.6)	4 (2.6)
WD due to AE	0	0	0
Adult (≥ 18 yr)	**N= 207**	**N= 134**	**N= 341 (57%)**
Any Hemoptysis	22 (10.6)	11 (8.2)	33 (9.7)
Severe AE	2 (1)	1 (0.7)	3 (0.9)
SAE	5 (2.4)	1 (0.7)	6 (1.8)
WD due to AE	6 (2.9)	0	6 (1.8)

[Source: Module 5.3.5.3. ISS, Section 7.3.3, Modified from Applicant's Table 33]

The Applicant suggests that pediatric patients having a lower baseline FEV1 led to higher rate of hemoptysis. Lower percent predicted FEV_1 at baseline in the younger age groups may be an explanation for why younger subjects (in either treatment group) experience hemoptysis more frequently; however, it is not a reasonable explanation for why the difference between treatment groups in the younger subjects should be larger than that of older subjects.

The FDA Biostatistical review team performed a post hoc exploratory analysis of the frequency of hemoptysis occurring in the MITT population (Table 31, below), which demonstrated no statistically significant differences between treatment groups in the

proportion of subjects experiencing hemoptysis; however, a numerical imbalance indicates that the risk of hemoptysis may be increased with mannitol use. (Note that this exploratory analysis also does not capture patients who discontinued before week 6 for hemoptysis). Numerical imbalances also suggest that the difference between treatment groups in hemoptysis may be more pronounced in patients less than 18 years of age as opposed to patients older than 18 years of age [Source: FDA's Biostatistical Review, Section 3.3, Evaluation of Safety].

Table 31: Frequency of Hemoptysis (MITT Population)

	Study CF301			Study CF302		
	DPM	Control	p-value	DPM	control	p-value
MITT	21/157 (13%)	10/112 (9%)	0.26	13/177 (7%)	3/120 (3%)	0.07
Ages 6 to 11 years	1/28 (4%)	0/17 (0%)	0.43	3/35 (9%)	0/24 (0%)	0.14
Ages 12 to 17 years	4/30 (13%)	1/24 (4%)	0.25	4/55 (7%)	1/39 (3%)	0.32
Ages ≥18 years	16/99 (16%)	9/71 (13%)	0.53	6/87 (7%)	2/57 (4%)	0.39
p-value associated with test for difference between treatment groups in proportion of patients experiencing hemoptysis [Source: FDA's Biostatistical Review, Table 13]						

Age notwithstanding, the rate of AE of hemoptysis in patients with FEV1 ≤40% predicted who received DPM 400mg was almost double that of patients with low FEV1 who received control, 19% versus 10% (see Section 7.5.3 Drug-Demographic Interactions, for additional discussion of severe lung disease AEs).

Massive hemoptysis was also examined in this safety population, to see if there was an increased risk among those treated with DPM 400mg over the control group. The Applicant reports three episodes of massive hemoptysis for this program, two patients in Study 301 (one in each treatment group, patients (b) (6)), and one patient from study 302 who received DPM 400mg (patient (b) (6)). In addition, Study 301 open-label data included an additional case of massive hemoptysis (patient (b) (6)). [Source: Response to IR dated 11-27-2012]

7.3.5.4 Condition Aggravated

"Condition Aggravated" was the preferred term used in the Phase 3 program to identify episodes of CF exacerbation and CF pulmonary exacerbation. For safety reporting, the investigators used clinical judgment to identify and report cases of exacerbation, and no formal safety definition was pre-specified by the Applicant. (There was a pre-specified definition used of efficacy assessments of exacerbation, as described in section 6).

Overall, the number of subjects with at least one AE report of "condition aggravated" was similar, with incidence slightly more favorable in the DPM 400mg group, with 37% versus 40% in the control group. SAEs also slightly favored the DPM group, with 17% versus 19% in the controls. Discontinuation due to AE of "condition aggravated" was slightly higher for the DPM group, 2.2% versus 1.3% in controls. When exacerbations

were broken down by age, the 6-11 year old patients had more exacerbations in the control group (46% vs. 26%), which was the opposite of the 12-17 year olds, who had more exacerbations if they received DPM 400mg (44% vs. 34%). SAEs followed the same pattern. Discontinuations due to adverse events were noted in only one DPM patient 6-11 years old, and in 5% of both treatment and control groups in the 12-17 year age group. The incidence of AE and SAE in adults was similar for both treatment and control groups, and discontinuations were twice as high in the control group as to the DPM 400mg group (8% vs. 4%).

Table 32: All Reported Exacerbations by Age, Safety Set

	Phase 3 Controlled Studies[a] Double-Blinded Phase		
Category	**DPM 400mg N (%)**	**Control N (%)**	**Total N (%)**
Pediatric (6-11 yr)	**N= 66**	**N= 41**	**N= 107 (18%)**
Condition Aggravated AE	17 (26)	19 (46)	36 (34)
SAE	5 (8)	8 (20)	13 (12)
DC due to AE	1 (2)	0	1 (1)
Adolescent (12-17 yr)	**N= 88**	**N=64**	**N= 152 (25%)**
Condition Aggravated AE	39 (44)	22 (34)	61 (40)
SAE	20 (23)	13 (20)	33 (22)
DC due to AE	4 (5)	3 (5)	7 (5)
Adult (≥ 18 yr)	**N= 207**	**N= 134**	**N= 341 (57%)**
Condition Aggravated AE	77 (37)	55 (41)	132 (39)
SAE	35 (17)	24 (18)	59 (17)
DC due to AE	9 (4)	10 (8)	19 (6)

a= Studies 301 and 302, 26 weeks

[Source: Module 5.3.5.3. ISS, Section 7.3.5, and Modified from Applicant's Table 35]

Respiratory infections are an important part of the nature of CF disease, because the frequency and severity of infections, as well as of changes in respiratory colonization and infection, can attribute directly to the morbidity and mortality of CF lung disease. Since mannitol is a sugar and can therefore be a food source for bacteria, there is a concern that inhaled mannitol could act as a substrate for increased microbial growth within the lungs, causing increase in exacerbations or changes in respiratory pathogens as demonstrated by respiratory culture changes. This will be discussed further in Section 7.4.2 Laboratory Findings.

7.3.5.5 Bronchospasm

Because of the known potential for inhaled mannitol to cause acute bronchoconstriction, the Applicant identified bronchospasm as an AE of special interest. The Applicant identified preferred terms of chest discomfort, asthma, asthmatic crisis, bronchial hyperreactivity, bronchospasm, and wheezing. This is a reasonable selection of terms for evaluation, and continues on the theme of overall tolerability of DPM therapy, much as does cough, described above. Overall, the incidence of bronchospastic events was similar between treatment groups, 6% versus 5% (Table 33, below). Individual reports of chest discomfort, bronchospasm and bronchial hyperreactivity occurred more in the DPM 400mg group, whereas asthma and asthmatic crisis were noted more in the control group. It is important to note that all patients in these studies were pre-treated with a bronchodilator prior to study drug administration.

Table 33: Incidence of Bronchospasm, Safety Set

System Organ Class Preferred Term	Phase 3 Controlled Studies[a] Double-Blinded Period	
	DPM 400mg N= 361	Control N= 239
Any bronchospasm-related AE[b]	21 (6)	13 (5)
General Disorders and Administration Site Cond.		
Chest Discomfort	10 (2.8)	4 (1.7)
Respiratory, Thoracic and Mediastinal Disorders		
Asthma	2 (0.6)	3 (1.3)
Asthmatic Crisis	0	1 (0.4)
Bronchial Hyperreactivity	1 (0.3)	0
Bronchospasm	2 (0.6)	0
Wheezing	6 (1.7)	5 (2.1)

a= Studies 301 and 302, 26 weeks
b= includes all patients with at least one AE reported of the following: chest discomfort, asthma, asthmatic crisis, bronchial hyperreactivity, bronchospasm, wheezing

[Source: Module 5.3.5.3. ISS, Section 7.3.4, Modified from Applicant's Table 34; ISS Appendix table ist20sum1 101]

The incidence of bronchospasm was evaluated specifically for the pediatric population as well. For those subjects 6 to 17 years of age, there was one withdrawal due to adverse event of "asthma," in a DPM-treated patient, and one SAE of "asthma crisis," in a control group patient. When evaluating the same adverse events listed in Table 33, but only for pediatric patients, the incidence is 6% (9 patients) for the DPM group, versus 4% (4 patients) for the controls. Specific preferred terms of "bronchospasm" and "bronchial hyperreactivity" were not identified in patients under 18 years of age. So although it was noted, risks of bronchospasm are not high for the pediatric patients in these Phase 3 studies.

7.3.5.6 Pediatrics

The pediatric population (patients less than 18 years old) accounts for 43% of the total population of the safety data base (259 of 600). In general, the number of patients with any AE (95% vs. 92%) and with any SAE (28% vs. 20%) are both higher for the control group over DPM. However, the number of subjects with an AE leading to discontinuation is higher in the DPM 400mg group [double that of the control (6% vs. 3%)]. Reasons for discontinuation in the pediatric treatment group include the following: condition aggravated (2), cough (2), chest discomfort (1), hyperventilation (1), pharyngolaryngeal pain (1), asthma (1), and throat irritation (1). When examined by subgroup of age of 6 to 11 or 12 to 17 years, the findings are similar, as noted in Table 34: Major Safety for Patients <18 years of age, below..

Table 34: Major Safety for Patients <18 years of age

	Phase 3 Controlled Studies[a] Double-Blinded Period	
Subject group	**DPM 400mg N (%)**	**Control N (%)**
Age 6-11 years	N=66	N=41
Subjects with at least one SAE	7 (11)	9 (22)
Subjects with any AE Leading to Study Discontinuation	2 (3)	1 (2)
Subjects with at least one Adverse Event Reported	58 (88)	40 (98)
Age 12-17 years	N=88	N=64
Subjects with at least one SAE	23 (26)	20 (31)
Subjects with any AE Leading to Study Discontinuation	7 (8)	2 (3)
Subjects with at least one Adverse Event Reported	83 (94)	60 (94)
Age 6-17 years	N=154	N=105
Subjects with at least one SAE	30 (20)	29 (28)
Subjects with any AE Leading to Study Discontinuation	9 (6)	3 (3)
Subjects with at least one Adverse Event Reported	141 (92)	100 (95)

a= Studies 301 and 302, 26-weeks

[Source: Module 5.3.5.3.28, ISS Tables 87,106; ISS Appendix B, submitted 11-15-2012]

It might be expected that pediatric patients would discontinue more readily than adult patients, due to less willingness to accept adverse events in children, so it is reassuring that the rate of pediatric discontinuations is lower than that for the adult population, 16% for the DPM 400mg group versus 9% in controls. Likewise, the number of pediatric subjects with one or more SAEs is slightly less than that for the 18 years and older

group, 20 vs. 23% for DPM, and 28 vs. 27 for controls [Source: Module 5.3.5.3, ISS, Table 118].

Adverse drug reactions were examined for the total safety population, and are discussed in 7.4.1 Common Adverse Events. However, these were also evaluated specifically for the 6-17 year old population as well, to assess if events were similar for pediatrics, described below in Table 35. The majority of events were the same for the total safety population, except pyrexia and arthralgia did not meet these criteria for pediatrics, and epistaxis occurred at a higher rate in pediatrics than for the total population.

Table 35: Incidence of Adverse Drug Reactions in >3% of DPM 400mg-Treated Patients aged 6 to 17 and Greater than Control in Controlled Phase 3 Trials of 26 Weeks' Duration

	Phase 3 Controlled Studies[a] Double Blinded Phase	
Event by Preferred Term	DPM 400mg N=154	Control N= 105
Cough[b]	48 (31)	29 (28)
Pharyngolaryngeal Pain	24 (16)	11 (11)
Nasopharyngitis	19 (12)	8 (8)
Vomiting[c]	15 (10)	3 (3)
Hemoptysis	12 (8)	2 (2)
Diarrhea	10 (7)	2 (2)
Epistaxis	6 (4)	1 (1)

a= Studies 301 and 302, 26 weeks
b= Includes the terms "cough," and "productive cough"
c= Includes the terms "vomiting," and "post-tussive vomiting"
[Source: Module 5.3.5.3, ISS Appendix B, Table ist20sum3_101]

Adverse reactions that occurred in DPM 400mg treated group at a frequency of 2-3% where rates exceeded the control group include:
Ear and Labyrinth Disorders: Ear pain
General Disorders and Administration Site Conditions: Chest Discomfort, influenza-like illness
Investigations: Fungus Sputum test positive
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity
Psychiatric Disorders: Insomnia
Reproductive System and Breast Disorders: Dysmenorrhea
Respiratory, Thoracic, and Mediastinal Disorders: Epistaxsis

Overall, the incidences of specific safety issues in pediatric patients have been discussed in the previous section, with rates similar to the overall safety population, with the exception of hemoptysis, which this reviewer feels is clinically significant, due to the young age of these patients and the potential severity of hemoptysis events. This is unfavorable for the overall safety profile in pediatrics.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Applicant's Approach to Eliciting AE in the Development Program

Adverse Events (AE) were defined as any untoward/unfavorable or unintended medical occurrence or change in structure, function, or chemistry of the body of a subject administered a pharmaceutical product, without regard to causal relationship. A clinically-significant increase in symptoms associated with a pre-existing condition was also considered an adverse event. AEs were collected from the start of each study throughout treatment with study drug. In these Phase 3 studies, adverse events were collected from screening through 12 hours after last study visit, or at 7 days from last dose for those patients who discontinued treatment.

Because all patients received a test dose of DPM (called the "Mannitol Tolerance Test" by the Applicant), all adverse events occurring from the test dose until the first randomized dose of study medication were also collected. These are presented separately by the Applicant, and have also been described in Sections 7.1.4 Unique Safety Issue for the Phase 3 Program, and 7.3.5 Submission Specific Primary Safety Concerns, 7.3.5.1 Overall Tolerability.

Incidence of Common AEs

The majority of participants in the double blinded period of Studies 301 and 302 reported at least one AE, which is not unexpected with an underlying disease process such as cystic fibrosis. Table 36: Double Blinded Common AEs by SOC, Safety Set, listed below, demonstrates the number of patients who reported any adverse event. The highest rates of incidence occur in those SOCs which would be expected to have events for this patient population, including respiratory, Infectious, GI, and general disorders (which includes "condition aggravated" for CF pulmonary exacerbations).

Table 36: Double Blinded Common AEs by SOC, Safety Set

	Phase 3 Controlled Studies[a] Double-Blinded Phase	
System Organ Class	**DPM 400mg N=361**	**Control N=239**
Subjects with Any AE	319 (88)	215 (90)
General Disorder & Admin. Site Condition	169 (47)	117 (49)
Respiratory, Thoracic & Mediastinal Disorder	162 (45)	89 (37)
Infections and Infestations	149 (41)	106 (44)
Gastrointestinal Disorders	108 (30)	77 (32)
Nervous System Disorders	79 (20)	59 (25)
Investigations	57 (16)	33 (14)
Musculoskeletal and Connective Tissue Dis.	54 (15)	35 (15)
Injury, Poisoning & Procedural Complications	33 (9)	17 (7)
Skin and Subcutaneous Tissue Disorders	26 (7)	18 (8)
Metabolism and Nutrition Disorders	13 (4)	10 (4)
Ear and Labyrinth Disorders	14 (4)	4 (2)
Psychiatric Disorders	12 (3)	4 (2)
Reproductive System and Breast Disorders	12 (3)	2 (1)
Eye Disorders	6 (2)	2 (1)
Cardiac Disorders	3 (1)	5 (2)
Surgical and Medical Procedures	8 (2)	0 (0)
Hepatobiliary disorders	4 (1)	1 (1)
Renal and Urinary Disorders	2 (1)	3 (1)
Neoplasms benign, malignant & unspecified	3 (1)	0 (0)
Vascular Disorders	3 (1)	0 (0)
Endocrine Disorders	2 (1)	0 (0)
Congenital, Familial & Genetic Disorders	1 (1)	0 (0)
Blood and Lymphatic System Disorders	1 (1)	0 (0)
Immune System Disorders	1 (1)	0 (0)

a= Studies 301 and 302, 26 weeks
[Source: Module 5.3.5.3.28, ISS Appendix Table ist20sum1_101]

Listings of adverse drug reactions by preferred term are listed in Table 37, below. These adverse events occurred in greater than or equal to 4% of DPM 400mg-treated patients with an incidence greater than control in the two Phase 3 clinical trials. Events are listed in order of declining frequency for the DPM 400mg group. Overall, the types of events are what is to be expected in the CF population, however, note that as has been discussed above, AEs such as cough, hemoptysis, pharyngolaryngeal pain, and vomiting are seen more in patients who received DPM.

Table 37: Incidence of Adverse Drug Reactions in >4% of DPM 400mg-Treated Patients and Greater than Control in Controlled Phase 3 Trials of 26 Weeks' Duration

	Phase 3 Controlled Studies[a] Double Blinded Phase	
Event by Preferred Term	DPM 400mg N=361	Control N= 239
Cough[b]	93 (26)	49 (21)
Pharyngolaryngeal Pain	44 (12)	18 (8)
Nasopharyngitis	37 (10.2)	23 (9.6)
Hemoptysis	34 (9)	13 (5)
Vomiting[c]	30 (8)	8 (3)
Pyrexia	24 (7)	15 (6)
Diarrhea	17 (5)	6 (3)
Arthralgia	14 (4)	7 (3)

a= Studies 301 and 302, 26 weeks
b= Includes the terms "cough," and "productive cough"
c= Includes the terms "vomiting," and "post-tussive vomiting"
[Source: Module 5.3.5.3.28, ISS Appendix Table ist20sum1_101]

Adverse reactions that occurred in the DPM 400mg-treated group at a frequency of 2-3%, where rates exceeded the control group, include the following:
Ear and Labyrinth Disorders: Ear pain
General Disorders and Administration Site Conditions: Chest Discomfort, influenza-like illness
Investigations: Fungus Sputum test positive
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity
Psychiatric Disorders: Insomnia
Reproductive System and Breast Disorders: Dysmenorrhea
Respiratory, Thoracic, and Mediastinal Disorders: Epistaxsis

Adverse reactions observed only in patients 6-17 years of age have been previously described in Table 35.

7.4.2 Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology and serum chemistries including liver transaminases. Overall, there were no significant differences in the occurrence of post-baseline laboratory abnormalities throughout the 26-week treatment period between treatment groups. The Applicant reports that most laboratory abnormalities were attributed by the Investigators as due to CF, and the majority of these occurred in the context of a hospitalization for pulmonary exacerbation. There were no laboratory test abnormalities that would be considered unusual for this patient population. Very few were reported as adverse events; "bacteria sputum identified" and "fungus sputum test positive" were reported in the double-blind period and open-label periods, at a rate of 1-2% for each, with no substantial difference

between treatment groups. During the open-label period, one patent previously on control reported an elevated ALT as an AE.

Respiratory Colonization

Respiratory infections are an important part of the nature of CF disease, because the frequency and severity of infections, as well as of changes in respiratory pathogens, can directly contribute to the morbidity and mortality of CF lung disease. Since mannitol is a sugar which could be a food source for bacteria, there is a potential concern that inhaled mannitol could act as a substrate for increased microbial growth within the lungs, causing an increase in exacerbations or changes in respiratory pathogens, as demonstrated by respiratory culture changes.

The Applicant evaluated changes in respiratory culture results as "no growth" (normal flora), or "growth" (any abnormal flora) at each study visit throughout the trials, noting that the majority of subjects (78%) in both control and DPM 400mg groups were noted to have growth of abnormal flora/pathogens. There were some fluctuations throughout the course of the trials, but overall, the percentage of the "no growth" group on DPM 400mg changed from 10% at visit 1 to 8% at week 26, indicating that 20% of those with no growth at baseline grew abnormal flora at week 26. This compares to the control group, of which 10.4% had no growth at visit 1, which decreased to 5.8% at week 26 (52% of the no growth group grew abnormal flora at week 26). So of those patients at baseline not chronically infected with abnormal flora, there was no worsening for the DPM 400mg group. [Source: Module 5.3.5.3, ISS, Section 10.1.2].

In Study 301, there was no substantial change in the percentage of patients whose sputum cultures were growing respiratory pathogens at baseline (week 0) and at week 26 for any of the following: *Burkholderia cepacia*, *Pseudomonas aeruginosa*-mucoid and non-mucoid, *Staphlococcus aureus*, *Candida* species, or *Aspergillus* species [Source: Module 5.3.5.1, CSR 301, Section 12.5, Tables 12-18 and 12-19]. Qualitative microbiology from Study 302 also showed no shifting of pathogens from Visit 1 to Visit 4 (week 26) for any of the organisms listed above; in addition, there was no clinically-meaningful change in the overall rate of Methicillin-resistant *Staphlococcus aureus* (MRSA). While the Applicant also assessed changes for specific bacterial pathogens in terms of Log colony forming units per gram of sputum for samples for Study 302, the overall Phase 3 program was not designed to assess for changes in sputum quantitative microbiology. [Source: Module 5.3.5.1, CSR 302, Section 12.4.3.1, Tables 12.4.3.1.1, 12.4.3.2.1, and 12.4.3.2.2].

7.4.3 Vital Signs

In the Safety set, there were no clinically significant differences between treatment groups in mean systolic or diastolic blood pressure, heart rate, respiratory rate, body temperature, oxygen saturation, weight and BMI at week 0 and week 26. Change from baseline was similar in both treatment groups, as were comparisons of rhDNase user

and non-user subgroups, and pediatric and adolescent subpopulations. [source: Module 5.3.5.3, ISS, Section 11.1.1.1].

The Applicant also assessed differences in respiratory examination from Baseline (visit 0) through week 26 (visit 4). They evaluated respiratory exam reports of crackles, retractions, and decrease in breath sounds/wheezing by treatment group for each parameter. Overall, there were no clinically-relevant changes from baseline at visits 2, 3, or 4. [Source: Module 5.3.5.3, ISS, Section 11.1.1.2].

Reviewer's Comments:
The Applicant postulates that the proportion of patients in the DPM 400mg group with decrease in breath sounds/wheezing was lower at 26 weeks than at baseline, but that the control group was increased, which they feel "…is consistent with a mechanism of improved mucus clearance." While it is reassuring to note that patients who are able to tolerate DPM 400mg do not appear to have worse breath sounds on physical exam at a single visit at week 26, as breath sounds may change rapidly and the determination of breath sounds is somewhat subjective, the clinical significance of this is unknown.

7.4.4 Electrocardiograms (ECGs)

ECG monitoring was not conducted as part of the Phase 3 clinical program for DPM 400mg.

7.4.5 Special Safety Studies/Clinical Trials

Non-CF Bronchiectasis Studies

The Applicant has conducted two Phase 2 dose-ranging studies (DPM-B-201 and DPM-B-202) to evaluate dose-response in bronchiectasis, and has completed one Phase 3 study (DPM-B-301), with a second Phase 3 study ongoing (DPM-B-305). DPM-B-301 is a randomized, double-blinded, parallel-group study to assess the effect of DPM 320mg twice daily for 12 weeks, to determine if benefits in quality of life in subjects with bronchiectasis could be noted, using the St. George's Respiratory Questionnaire. The 12 week treatment period was followed by a 52-week open-label phase. Safety assessments included AEs, clinical laboratory evaluations, vital signs, respiratory and overall physical examinations, and sputum microbiology testing.

The Applicant notes the following pertinent safety information from Study DPM-B-301:
Hemoptysis- 18 patients experienced AE of hemoptysis, 11 (4.7%) in the DPM 400mg group, versus 7 (6.3%) in the control group, one of which was considered severe. Three patients had an AE of hemoptysis that led to study discontinuation, all in the DPM-treated group, and one patient experienced SAE of hemoptysis following first dose of DPM prior to receiving study treatment (patient withdrew).

Bronchospasm- 4 patients (1.7%) in the DPM group and 1 (1%) in control reported AE of bronchospasm. Two events were considered severe, both in DPM-treated patients. Three patients (1.3%) withdrew due to AE of bronchospasm, all in the DPM group. No SAE due to bronchospasm were reported.

Study DPM-B-305 is an ongoing randomized, double-blinded, controlled, parallel-group study, with a primary objective to evaluate difference in rates of graded pulmonary exacerbations in patients with bronchiectasis, randomized in a 1:1 fashion, treated with DPM 400mg BID compared to control. Patients will be treated for up to 52 weeks. Safety assessments will include AEs, clinical laboratory evaluations, vital signs, physical examinations, sputum microbiology, and airway reactivity testing. No safety data was provided from this ongoing study.

7.4.6 Immunogenicity

Immunogenicity was not explored for this program, as mannitol (an alcohol sugar) would not be expected to illicit an immunogenic response.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This is unknown, as only a single dose of 400mg was studied in Phase 3 trials.

7.5.2 Time Dependency for Adverse Events

No specific analysis of time dependency was conducted for adverse events, but as described throughout this review, the adverse events related to tolerability of DPM 400mg occurred early in the double-blinded treatment period, and led to early withdrawals, despite some patients meeting criteria for a negative MTT (first dose of study drug).

7.5.3 Drug-Demographic Interactions

No analyses of AE by race were performed, due to the low percentage of non-Caucasian patients; over 97% of patients in the safety database were Caucasian. No meaningful differences were detected between patients based on sub-group analysis by sex.
Analysis of AE by age has already been discussed in Section 7.3.5.6 Pediatrics.

Patients with Severe Lung Disease (FEV1 < 40%predicted)

Another specific population examined was that of patients with severe CF lung disease. There were 51 patients studied with FEV1 less than or equal to 40% predicted, 31 received DPM 400mg, and 20 received control. In general, similar patterns were seen to the overall safety population in terms of adverse events, except in two important areas. First, discontinuations due to adverse events occurred twice as often in DPM-treated patients with severe lung disease than controls. Second, adverse events of hemoptysis occurred at a rate of 19% in DPM-treated patients with severe lung disease, versus 10% of controls.

Table 38: Incidence of All Adverse Events in Severe Lung Disease (FEV1≤40%)

	Phase 3 Controlled Studies[a] Double-Blinded Period	
Subject group	**DPM 400mg N= 31 N (%)**	**Control N= 20 N (%)**
Deaths	0	0
Subjects with at least one SAE	14 (44)	9 (45)
Subjects who Discontinued from Study for Any Reason	13 (41)	4 (20)
Subjects with any AE Leading to Study Discontinuation	9 (29)	3 (15)
Subjects with at least one Adverse Event Reported	30 (97)	17 (85)

a= Studies 301 and 302, 26-weeks
[Source: Calculated from original datasets by FDA biostatistical reviewer]

As compared to the entire safety population, adverse drug reactions occurred at similar or decreased incidence for cough, vomiting, and pharyngolaryngeal pain in patients with very severe lung disease. Headache was seen more often in those with low FEV1 on DPM (23%, versus 5% control), as was incidence of CF exacerbation (55% versus 50% control).

Table 39: Incidence of Adverse Drug Reactions Occurring in Patients with FEV1 ≤40% at a Rate of ≥5% in DPM 400mg-Treated Patients and Greater than Control in Controlled Phase 3 Trials of 26 Weeks' Duration

	Phase 3 Controlled Studies[a] Double Blinded Phase Patients with FEV1 ≤40% predicted	
Event by Preferred Term	**DPM 400mg N= 31**	**Control N= 20**
Patients with at least one AE	30 (97)	17 (85)
Condition Aggravated (Exacerbation)	17 (55)	10 (50)
Headache[b]	7 (23)	1 (5)
Cough	6 (19)	3 (15)
Hemoptysis	6 (19)	2 (10)
Vomiting[c]	2 (7)	0
Pain in extremity	2 (7)	0
Pharyngolaryngeal Pain	2 (7)	0

a= Studies 301 and 302, 26 weeks
b= Includes the terms "headache" and "sinus headache"
c= Includes the terms "vomiting," and "post-tussive vomiting"

[Source: Module 5.3.5.3.28, ISS Table 133; ISS Appendix A, Table ist163sum1_101]

7.5.4 Drug-Disease Interactions

CF patients with bronchial hyperreactivity or asthma are likely to have an increased bronchoconstrictive response to inhaled mannitol which may be severe and limit a patient's ability to tolerate the drug.

7.5.5 Drug-Drug Interactions

No formal DDI studies were performed with mannitol.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed for this NDA. However, mannitol is believed to be non-carcinogenic based on 2 year dietary carcinogenicity studies conducted by the National Toxicology Program.

7.6.2 Human Reproduction and Pregnancy Data

Mannitol is considered to be non-teratogenic according to the Joint FAO/WHO Expert Committee on Food Additives Monograph. Clinical studies with DPM identified pregnancy and lactation, as well as the inability to comply with appropriate

contraception practices, as exclusion criteria. There were no pregnancies noted in the development program, and there have been no spontaneous post-market reports (from other countries) regarding the use of Bronchitol during pregnancy or lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to Section 7.3.5.6 Pediatrics, for a discussion of safety in pediatric patients. No formal studies in pediatrics to assess growth were conducted or required for this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known pharmacological or psychological potential for the abuse of inhaled mannitol. However, severe bronchospasm may occur in susceptible patients following dosing with inhaled mannitol.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the 120-Day Safety Report on September 18, 2012. Included in the package were the following:

1. Safety data from study DPM-ORB-101, a Phase 1b trial of DPM 400mg administered to healthy subjects, utilizing a different delivery device than that used for the Phase 3 trials of DPM 400mg for the cystic fibrosis indication. Safety data was collected from 21 healthy volunteers who previously demonstrated a negative Aridol bronchial challenge, and
2. Study DPM-B-305, a Phase 3 R, DB, PG study of 12 months' DPM in bronchiectasis. The study is currently ongoing and remains blinded; therefore, no data from this study are presented in this safety update
3. Post-Marketing exposure to DPM 400mg (see Section 8 Postmarket Experience, below for details)
4. Safety data from other clinical use of DPM 400mg across all indications, which Applicant notes were "inadvertently left out of the original submission," including 8 SAEs which were associated with fatal outcome. These are described further below.

The Applicant reports that a total of 467 patients have been supplied DPM 400mg (marketed as Bronchitol) through the "Named Patient Supply" program, through the safety cutoff date of August 18th, 2012. This includes the following:

- 6 CF patients from the US, administered drug under Investigator INDs,
- 7 patients from Belgium under a formal compassionate usage program

- 148 CF patients continuing on DPM 400mg after completion of studies 301 and 302
- 304 bronchiectasis patients continuing on DPM 400mg from studies DPM-B-301 and DPM-B-305
- 2 patients prescribed Bronchitol for other respiratory indications (asthma and plastic bronchitis)

Of these 467 patients, the Applicant reports 55 total AE, including 11 from CF studies, 41 from bronchiectasis trials, (b) (4). Reports by disease (b) (4) include the following:

CF- A total of 11 events, including tinnitus (1), vomiting (1), drug ineffective (1), drug interaction (1), condition aggravated (1), mycobacterial infection (1), infective pulmonary exacerbation of CF (1), asthma (1), hemoptysis (2 reports, 1 serious, 1 non-serious), and respiratory failure (1).

Bronchiectasis- A total of 41 events, including 8 SAE (6 labeled, 2 unlabeled) and 33 non-serious, the most common of which were cough (8), drug effect decreased (3), respiratory failure (2), headache (2), drug ineffective (2), arrhythmia (2), and lower respiratory tract infection (2). The remaining events all occurred in only one report. (b) (4) (b) (4)

These 55 AEs included 14 SAEs, 8 of which (2 each in 4 patients) were associated with fatal outcomes, briefly described below.

CF ((b) (6))- respiratory failure and hemoptysis- 32yo female patient with severe obstructive lung disease and end-stage CF liver disease, stopped drug 1 month prior to death, from respiratory failure due to massive hemoptysis

Bronchiectasis ((b) (6))- respiratory failure, chest infection—65yo male patient with end-stage bronchiectasis who received Bronchitol for 1 month, hospitalized with infection and respiratory failure, drug stopped the next day,patient died 3 days later

Bronchiectasis ((b) (6))- respiratory failure, inclusion body myositis—52yo male patient with end-stage myositis took drug for 60days under special access program in Australia, died 10 days into hospitalization for respiratory failure secondary to myositis

Bronchiectasis ((b) (6))--- MI, arrhythmia--- 73yo woman with bronchiectasis had sudden cardiac event while on airplane; prior history of ectopic heartbeats treated with clopidrogel chronically

Other SAEs deemed "related" to DPM 400mg were the labeled events of lower respiratory tract infection and wheezing, as well as asthma and mycobacterial infection (both unlabelled). [source: 120-Day Update Integrated Summary of Safety, Section 8.2.2, pages 19-32]

Reviewer's Comments:

While it is unusual that the Applicant left these "named patient supply" cases out of the original NDA submission (these deaths occurred between 2007 and 2010), it does not appear that any of the deaths are directly attributable to DPM 400mg. The case of hemoptysis notes that the patient discontinued DPM 400mg (for lack of effect) one month before dying at home from respiratory failure secondary to hemoptysis, so due to the short half-life of treatment effect, the likelihood of this being attributable to DPM is very unlikely.

8 Postmarket Experience

There is not much post-marketing safety data available for DPM 400mg. While it was registered in Australia in March 2011, under the trade name Bronchitol, the product did not launch for sale until reimbursement was granted August 1, 2012, so patients received it free-of-charge under a "Product Familiarization Program" until that time. Bronchitol became available in Europe, in the following countries, recently- UK on May 28, 2012, Germany June 1, 2012, and Austria July 1, 2012.

Table 40: Post-Marketing Exposure to Bronchitol

Country	Product	Total Unit Sales	Dates Available
Australia	14-day pack	68	August 1-18, 2012
	Test kit	10	
Germany	14-day pack	313	June 1-August 18, 2012
	Test kit	492	
Austria	14-day pack	2	July 1-August 18, 2012
	Test kit	0	
United Kingdom	14-day pack	4	May 28-August 18, 2012
	Test kit	9	

[Source: Module 5.3.5.3, 120-Day Integrated Summary of Safety, Section 4.2, Table 1, page 14]

Postmarket and Other Spontaneous AE Reports

The safety data from all sources other than the Sponsor's clinical trials includes information from marketed drug AE reporting, reports from the Patient Familiariazation Program in Australia, the Belgian compassionate usage program, and the "Named Patient Supply," which includes Investigator-initiated studies for CF (b) (4) (b) (4) The data was reported up to the August 18, 2012, safety cut-off. [source: 120-Day Update Integrated Summary of Safety]

Patient Familiarization Program

The Patient Familiarization Program (PFP) is a program in Australia which runs from registration of a drug until reimbursement is granted, so that clinicians can "gain experience" with the drug for free. Clinicians request stock drug for patients within the indication, and continue to receive drug until the drug receives authorization for

reimbursement. 110 patients received drug in this program from March 2011 through August 1, 2012. Reports from this program are unsolicited AEs. There were a total of 4 AE reported from 3 patients, which includes a CF patient with increased blood glucose, a bronchiectasis patient who reported bronchospasm, and a subject who received drug for PFT challenge who reported rhinorrhea and hemoptysis.

Named Patient Supply

The Named Patient Supply population was described above in Section 7.7 Additional Submissions / Safety Issues. This included a total of 467 patients, including 6 for Investigator INDs in US; these data were presented in the 120-Day Integrated Safety Update. Those 55 AE including 14 SAE, of which 8 were associated with fatal outcome, were listed in the post-marketing report data by the Applicant, and have been described in the previous section.

Investigator-initiated studies

The Applicant also provided study drug for 3 Investigator-initiated studies, with the understanding that the Investigators must process and report all AE that occur under the conduct of their study. The Applicant notes that, as of the August 18, 2012, safety cut-off date, 55 patients have received study drug within 3 Investigator-initiated studies. The studies include the following:

- (Dr. Selvaduri) "A double-blind, placebo controlled, randomized study of inhaled mannitol during acute pulmonary exacerbation in children with cystic fibrosis – a pilot studyone for kids with CF during exacerbation," (28 patients enrolled, study completed)
- (Dr. Daviskas) "Inhaled mannitol for the treatment of mucociliary dysfunction in patients with asthma- its effect and mechanisms on the clearance of mucus" (7 patients enrolled, study completed)
- (Dr. Phipps) Pilot study for safety and efficacy of mannitol inhalation to intubated patients (20 patients enrolled, study completed)

For these three studies, 6 SAEs were reported, all unlabelled events, and all occurred in the ICU study (3 of which led to deaths), and include GI perforation, *staphlococcal* endocarditis, Non-Hodgkin's lymphoma, Cerebral vascular accident (CVA), respiratory failure, and ischemia. There were also 5 non-serious AEs reported, all from the CF study, including vomiting (1), dizziness (2), headache (1), and parasthesia (1, unlabeled).

Reviewer's Comments:

Overall, the post-marketing data from Bronchitol is rather small, given its recent approval in other countries. There is no additional signal identified in this data that has not otherwise been described with the CF data submitted for this NDA, and the reports of unusual AE and deaths are more likely related to the indicated population rather than Bronchitol use.

9 Appendices

9.1 Literature Review/References

1. Davis PB, Drumm M, and Konstan MW. Cystic Fibrosis. Am J Respir Crit Care Med 1996; 154:1229-1256.
2. Corey M, et al. Longitudinal Analysis of Pulmonary Function Decline in Patients with Cystic Fibrosis. J Pediatr 1997; 131:809-14.
3. Miller MR, et al. Standardisation of Spirometry. Eur Respir J 2005; 26:319-38.
4. Flume PA, et al. Am J Respir Crit Care Med 2010; 182: 298-306.
5. Flume PA, et al. Chest 2005; 128: 729-38.
6. Efrati O, et al. J Cyst Fibrosis 2008 July;7 (4): 301-6.

9.2 Labeling Recommendations

Based on a recommendation of Complete Response for this NDA, a detailed labeling review and labeling discussions with the Applicant have been deferred.

High-level labeling issues from a clinical perspective include the following:

9.3 Advisory Committee Meeting

On January 30, 2013, the Division and Pharmaxis discussed the findings from the inhaled mannitol NDA at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting.

There were 6 points for discussion and voting:

1. (**DISCUSSION)** Discuss the evidence to support the efficacy of dry powder mannitol (DPM) at a dose of 400 mg twice daily in improving pulmonary function in patients 6 years and older with cystic fibrosis.

2. **(DISCUSSION)** Discuss the overall safety profile of DPM.

3. **(DISCUSSION)** Discuss the support for efficacy and the safety profile of DPM in children and adolescents 6-17 years of age.

4. **(VOTE)** Considering the totality of the data, is there substantial evidence of efficacy for DPM at a dose of 400 mg twice daily for improvement of pulmonary function in patients 6 years and older with cystic fibrosis? If not, what further efficacy data should be obtained?

   VOTE: YES 3 NO 11

5. **(VOTE)** Is the safety profile for DPM for the maintenance treatment of patients with cystic fibrosis sufficient to support approval? If not, what further safety data should be obtained?

   VOTE: YES 3 NO 11

6. **(VOTE)** Do the efficacy and safety data provide substantial evidence to support approval of DPM at a dose of 400 mg twice daily for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function? If not, what further data should be obtained?

   VOTE: YES 0 NO 14

With regard to efficacy, the committee noted concern over the relatively small effect size, and the difficulty knowing the true treatment effect, given the differences in comparator groups due to drop-outs likely due to problems with tolerability. There were some comments that DPM did not show strong statistical evidence that would meet the regulatory definition of substantial evidence, but several members also commented that there did seem to be evidence of efficacy, at least in adults, and that because of the severity of disease that a small treatment effect would be meaningful clinically. Another member noted that the first study which met statistical significance was “plagued with

missing data," had no US patients, and saw no differences in children, while the second study which was free of these issues did not demonstrate statistical significance.

With regard to safety, members expressed concern for high occurrence of hemoptysis in adults and especially children, and noted that there were higher rates of hemoptysis in the mannitol group versus the control group in the randomized trials. Some committee members reported less concern for the safety profile of the drug in patients over 18 years of age. One member noted that the number of hemoptysis cases in the trials can not be underestimated, as hemoptysis is relatively uncommon in pediatrics and is of concern as the lungs of children are still growing and chronic irritants may lead to chronic injury to the airways. In addition, regarding safety in pediatrics, a committee member expressed that if adults were having problems with taking inhaled mannitol, they could simply discontinue treatment, but for a child or adolescent, a parent would be providing/supervising treatments, and may be less willing to discontinue for tolerability issues because they are focusing on potential benefit, and that this situation could lead to more adverse events in children, such as hemoptysis.

With regard to the overall discussion of risk-benefit, one member commented that there is no benefit in the <18 year old population. Another member noted that if the sponsor is using FEV1 as a surrogate for efficacy, then it is a poor surrogate and that there is no evidence that the quality of lives are improved on the basis of their FEV1.

Another member expressed that in the face of a small benefit, the importance of the safety of the drug becomes more prominent, especially for patients that are desperate for a solution, and we should not provide a drug just to give patients something.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A WITZMANN
02/11/2013

ANTHONY G DURMOWICZ
02/11/2013

CLINICAL PHARMACOLOGY REVIEW

NDA Number	202-049 (Related IND 70,277)
Submission Date	05/17/2012 (SDN 0)
Submission Type	505(b)(1)
Review Priority	Standard
Proposed Brand Name	Bronchitol
Generic Name	Mannitol inhalation powder
Sponsor	Pharmaxis Inc.
Route of Administration	Inhalation
Dosage Form	Dry powder capsules and inhaler
Dosage Strength	Each capsule contains 40 mg mannitol
OND Division	Pulmonary, Allergy, and Rheumatology Products
OCP Division	Clinical Pharmacology II
Reviewer	Arun Agrawal, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Proposed Age and Indication	Adult and pediatric patients age 6 years and older. Indicated for the management of cystic fibrosis to improve pulmonary function
Proposed Dosing Regimen	400 mg (10 x 40 mg capsules) twice daily

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendation

NDA 202-049 is acceptable from the viewpoint of the Office of Clinical Pharmacology.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Sponsor markets an approved Aridol™ test kit containing dry powder mannitol capsules in graduated doses (0, 5, 10, 20, and 40 mg mannitol per capsule) and a single patient use inhaler necessary to perform one bronchial challenge test (BCT) [also called as mannitol tolerance test or MTT] to aid in the diagnosis of patients ≥6 years of age with symptoms of or suggestive of asthma (NDA 22-368, approved on 10/05/2010). Previous information regarding this product was submitted under IND 70,277.

Sponsor is now seeking approval of dry powder mannitol capsules and multiple use inhalers as Bronchitol, for the management of cystic fibrosis (CF) in patients ≥6 years of age to improve pulmonary functions, utilizing the 40 mg mannitol capsules and inhaler approved for Aridol™. In support of Bronchitol NDA, data from two Phase 1 clinical pharmacology, three Phase 2, and two Phase 3 clinical studies were submitted. The goals of the clinical pharmacology program were:

1. (a) To determine the absolute bioavailability of mannitol powder for inhalation as compared to mannitol administered intravenously to healthy subjects,
   (b) To determine the relative bioavailability of mannitol powder for inhalation as compared to orally administered mannitol to healthy subjects, and
   (c) To determine the pharmacokinetics (PK) of systemically available mannitol after administration of mannitol powder by inhalation to healthy subjects.

2. To determine the PK of inhaled mannitol after single and multiple dosing to adult, adolescent, and pediatric CF patients.

Relative Bioavailability (Study DPM-PK-101):
This study was previously submitted and reviewed for Aridol™ NDA 22-368. This was an open-label, randomized, three-way crossover study in 18 healthy male subjects aged 19-48 years old. Each subject received three treatments: 635 mg mannitol dry powder by inhalation using a drug powder inhaler, 500 mg mannitol dose administered orally (5 ml of Osmitrol 10% solution), and 500 mg mannitol dose administered by intravenous infusion (5 ml of Osmitrol 10% solution).

The results indicated that the absolute bioavailability of inhaled mannitol as compared to intravenously administered mannitol was 59%, while the absolute bioavailability of orally administered mannitol as compared to intravenously administered mannitol was 61%. The relative bioavailability of inhaled mannitol as compared to orally administered

mannitol was 96%. The median time to reach the mannitol peak serum concentration (Tmax) was 1.5 (1-2) hr for inhaled and 1.4 (1-2) hr for orally administered mannitol (Table 1). Dose normalized mannitol peak serum concentration (Cmax) between inhaled and orally administered mannitol were approximately similar 10,792 and 13,094 ng/mL, respectively. The mean terminal half-life (T1/2) of mannitol was approximately 5 hr regardless of route of administration. Overall, the rate and extent of absorption after inhalation and oral administration were similar. Urinary excretion rates versus time profiles for mannitol were similar for all the three routes of administration.

Table 1. Serum pharmacokinetic parameters for mannitol (mean±SD)

Treatment	Pharmacokinetic Parameters							
	N	T_{max} (hr)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	C_{max}* (ng/ml)	AUC_{0-inf}* (ng.hr/ml)
635 mg inhalation	18	1.5 ±0.5	13,706 ±2,638	4.7 ±1.0	71,457 ±12,586	73,150 ±12,717	10,792 ±2,638	57,599 ±12,717
500 mg oral	18	1.4 ± 0.5	13,094 ±3,085	5.2 ±1.1	59,776 ±13,596	61,414 ±14,059	13,094 ±3,085	61,414 ±14,509
500 mg intravenous	18	0.1 ±0.04	44,322 ±8,775	4.5 ±1.1	98,719 ±21,735	100,236 ±21,516	44,322 ±8,775	100,236 ±21,561

* Dose normalized values to 500 mg

Pharmacokinetics of Inhaled Mannitol Following Single and Multiple Dosing in CF Patients (DPM-PK-102):

This was an open-label, single and multiple dose study to determine PK after single and multiple dosing of inhaled mannitol at 400 mg in CF patients aged 6 years and older. A single dose of inhaled mannitol was administered in the morning of Day 1 and then twice daily from Days 2 to 6, and the last dose in the morning of Day 7.

The results indicated that the serum mannitol levels (mean Tmax values) peaked approximately 0.75 to 2.54 hr post dosing (Table 2). Variability in mean Cmax values between adults, adolescents and pediatric subjects was moderate to high ranging from 15 to 51%. Between subject variability in mean AUC0-inf values (Day 1) ranged from 22 to 47%. Serum mannitol concentrations accumulated following multiple BID dosing over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, pediatric (older), and pediatric (younger) subjects, respectively (Day 7/Day 1 AUC0-12 ratio).

Table 2. Serum pharmacokinetic parameters for mannitol (mean, %CV)

Age group/Dose Day		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-12} (hr*ng/mL)	Day 7/Day 1 AUC_{0-12} Ratio	$AUC_{0-\infty}$ (hr*ng/mL)	$t_{½}$ (hr)	CL/F (mL/hr)	V/F (mL)
Adult (n=6)	**Day 1**	7670 (15%)	2.42 (44%)	41872 (12%)		57594 (22%)	8.9 (54%	7224 (22%)	86653 (33%)
	Day 7	9260 (29%)	1.37 (22%)	50240 (27%)	1.56	NA	12 (70%)	5531 (32%)	86559 (20%)
Adolescent (n=4)	**Day 1**	6768 (51%)	1.57 (65%)	33028 (37%)		41937 (33%)	7.9 (23%)	10719 (45%)	128435 (65%)
	Day 7	7330 (24%)	2.13 (30%)	45358 (16%)	1.21	NA	6 (17%)	7273 (15%)	62882 (20%)
Pediatrics, Older (9-11 yr) (n=2-3)	**Day 1**	4317 (29%)	1.52 (31%)	20918 (27%)		31474*	8.7*	12747*	160836*
	Day 7	8067 (41%)	2.54 (51%)	40857 (28%)	2.18	NA	6.3*	7079*	63987
Pediatrics, Younger (6-8 yr) (n=3)	**Day 1**	7563 (26%)	0.75 (67%)	31593		48370 (47%)	6.2 (44%)	9475 (37%)	77825 (46%)
	Day 7	13200 (26%)	1.33 (22%)	70926 (42%)	2.50	NA	6.1 (27%)	5350 (32%)	50149 (52%)

* Note: Parameter estimates could not be estimated for some subjects. NA: Not applicable

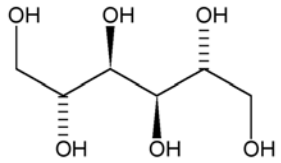
Overall, adequate clinical pharmacology information was provided in support of this NDA.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Mannitol is a hexahydric alcohol with the chemical structure provided below and is provided as spray-dried drug substance in Bronchitol.



Mannitol (C6H14O6, MW 182) is a well-known, naturally occurring sugar alcohol commonly found in vegetable products. It is a Generally Recognized as Safe (GRAS) excipient in the US for food substances at intakes of up to 20 g/day. Mannitol is commonly used as an excipient in the formulation of pharmaceutical products and as a food additive (bulking agent, humectant, and sugar substitute). It is also used as an osmotic agent and is given orally in doses of up to 200 g to induce diarrhea for bowel preparation prior to diagnosis (colonoscopy) or surgery, and intravenously in a dose of 50 to 200 g over a 24 hr period to induce diuresis, or up to 0.25 g/kg (i.e. approximately 17.5 g for a 70 kg subject) over 30 to 60 minutes to treat cerebral edema. Bronchitol contains hard-gelatin capsules each containing 40 mg spray dried mannitol powder for oral inhalation. There are no inactive ingredients in Bronchitol.

2.1.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Dry powder mannitol was included as an inactive ingredient in the formulation of inhaled insulin that was approved for oral inhalation (Exubera™, NDA 21-868). Mannitol was given an orphan designated status for the treatment of CF. Under the same IND (70,277), as for the current Bronchitol, mannitol was also developed as Aridol™ test kit containing dry powder mannitol capsules in graduated doses (0, 5, 10, 20, and 40 mg mannitol per capsule) and a single patient use inhaler necessary to perform one BCT/MTT to aid in the diagnosis of patients ≥6 years of age with symptoms of or suggestive of asthma (NDA 22-368, approved on 10/05/2010). Sponsor is now seeking approval of dry powder mannitol capsules and multiple use inhalers as Bronchitol for the management of CF in patients aged 6 years and older to improve pulmonary functions, utilizing the 40 mg mannitol capsules and inhaler approved for Aridol™.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

More than 1,000 mutations in the CF transmembrane conductance regulator (CFTR) gene have been identified to-date in people with CF. The resulting abnormal channel is subject to rapid intracellular degradation and fails to locate in the cell membrane to transport chloride ions. As a result, cells that line the passageways of the lungs and other organs

produce mucus that is abnormally thick and sticky. The resultant mucociliary dysfunction and abnormal mucus production obstructs the airways leading to the characteristic signs and symptoms of CF.

The treatment of the mucociliary dysfunction consists mainly of physical and pharmacologic therapy in which the aim is to reduce mucus production and to increase its clearance. An increase in clearance of mucus can be achieved by stimulating ciliary activity. Pharmacologic treatment for these diseases currently includes glucocorticoids, beta 2-adrenergic agonists, antibiotics, and mucoactive agents. Osmotic agents, such as ionic hypertonic saline solution, and non-ionic such as mannitol, dextran, and lactose, have been found to increase clearance of mucus and are regarded as promising mucoactive agents. The precise pharmacological mechanism whereby mannitol increases the clearance of mucus remains unclear. Osmotic agents have the potential to increase the amount of water in the airway lumen which might alter the surface properties of the mucus and increase both cilia and cough clearance of the mucus. Mannitol may benefit patients by reducing the mucus load acutely, or it may have a prolonged effect on mucociliary clearance.

2.1.4 What are the proposed dosage(s) and route(s) of administration?
Adults and children 6 years of age and over: 400 mg (10 capsules, each containing 40 mg mannitol) BID oral inhalation using inhaler provided with the drug package.

2.1.5 What is the to-be-marketed formulation?
Bronchitol is supplied as a complete kit containing capsules of dry powder mannitol (40 mg each) in blister packs and a multi-use inhaler.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of clinical pharmacology used to support dosing or claims?
Relative Bioavailability (Study DPM-PK-101): As mannitol-containing foods can affect serum and urinary levels, subjects were instructed to avoid such foods from the time of screening to completion of the study. The objectives of this study were: (1) to determine the absolute bioavailability of mannitol powder for inhalation as compared to mannitol administered intravenously, (2) to determine the relative bioavailability of mannitol powder for inhalation as compared to orally administered mannitol, and (3) to determine the pharmacokinetic parameters of systemically available mannitol after administration of mannitol powder by inhalation. A secondary objective of the study was to provide information on the urinary excretion of mannitol after each of the routes of administration.

Eighteen healthy male volunteers between 19-48 years of age completed the trial. The trial involved administration of the following investigational product in random order: (1) dry powder mannitol for inhalation at 635 mg as a single dose, (2) mannitol at 500 mg dose administered orally (5 mL of Osmitrol 10% solution), and (3) mannitol at 500 mg dose administered as an intravenous bolus (5 mL of Osmitrol 10% solution). The study was an open-label, randomized, three-way crossover design, in which each subject

received mannitol powder for inhalation using a dry powder inhaler, mannitol solution administered orally, and mannitol in a commercial formulation designed for intravenous use. Initially, as a part of the screening process, all patients were screened by receiving 635 mg mannitol powder for inhalation as the Aridol challenge kit. Patients who had a negative MTT result and satisfied all other eligibility criteria were assigned to receive the three study treatments in random order. There was a minimum 7 day washout period between between study drug administrations. During the treatment period, patients attended the study centre for three visits. The visits commenced 12 hr prior to study drug dosing, and were concluded 24 hr after dosing. PK blood and urine samples for the determination of mannitol in serum and urine were taken over the course of each treatment as per following schedule:

- Inhalation and iv administration: Serum samples were collected at -12 and -0.5 hr pre-dose and at 5, 10, 20, 30 min and 1, 2, 3, 4, 8, 12 and 24 hr post-dose.
- Oral administration: Serum aamples were collected at -12 and -0.5 hr pre-dose and at 0.5, 1, 2, 3, 4, 8, 12 and 24 hr post-dose.
- Urine collections were made from -12 hr to -0.5 hr, -0.5 hr to 6 hr, 6 hr to 12 hr and 12 hr to 24 hr.

Patients were to maintain a mannitol-free diet before the first dose administration until the end of the treatment phase. PK parameters (Cmax, Tmax, T1/2, AUC0-24) were determined from serum collected at various time points pre- and post-treatment. The amount of drug excreted in urine was correlated with AUC0-24 values.

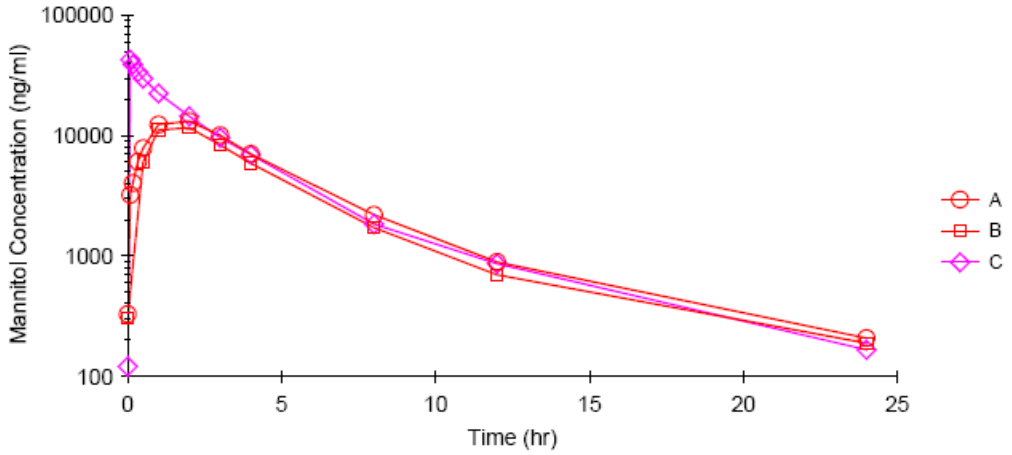
The results indicated that the absolute bioavailability of inhaled mannitol as compared to intravenously administered mannitol was 59%, while the absolute bioavailability of orally administered mannitol as compared to intravenously administered mannitol was 61%. (Table 3). The relative bioavailability of inhaled mannitol as compared to orally administered mannitol was 96%. Intravenous mannitol plasma levels peaked early (0.1 hr) after dosing relative to inhaled, (1.5 hr) and oral (1.4 hr). The dose normalized absorption rates between inhaled and oral mannitol were approximately similar: Cmax, 10,792 ng/mL and 13,094 ng/mL, respectively. The T1/2 of mannitol remained constant at approximately 5 hr regardless of route of administration. The serum profile of mannitol following administration of inhaled, oral and intravenous dose is illustrated in Figure 1.

Table 3. Serum pharmacokinetic parameters for mannitol (mean ± SD)

Treatment	Pharmacokinetic Parameters							
	N	T_{max} (hr)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	C_{max}* (ng/ml)	AUC_{0-inf}* (ng.hr/ml)
635 mg inhalation	18	1.5 ±0.5	13,706 ±2,638	4.7 ±1.0	71,457 ±12,586	73,150 ±12,717	10,792 ±2,638	57,599 ±12,717
500 mg oral	18	1.4 ± 0.5	13,094 ±3,085	5.2 ±1.1	59,776 ±13,596	61,414 ±14,059	13,094 ±3,085	61,414 ±14,509
500 mg intravenous	18	0.1 ±0.04	44,322 ±8,775	4.5 ±1.1	98,719 ±21,735	100,236 ±21,516	44,322 ±8,775	100,236 ±21,561

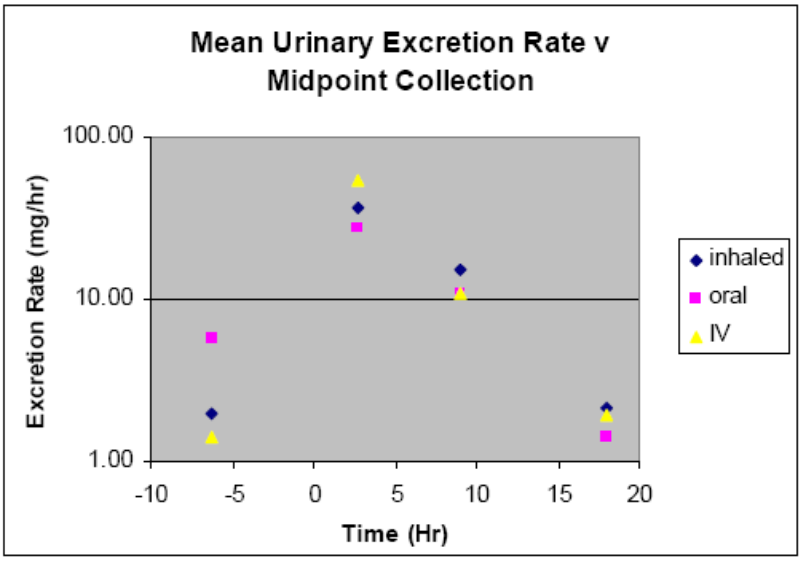
* Dose normalized values to 500 mg

Figure 1. Mean mannitol serum concentrations versus time profiles: A - Inhalation (635 mg), B - Oral (500 mg), C - Intravenous (500 mg)



Urinary excretion rate versus time profile for mannitol was consistent for all routes of administration (Figure 2). When administered intravenously, mannitol is eliminated largely unchanged by kidneys and 87% of the dose is excreted in the urine within 24 hr. The T1/2 was approximately 3.6 hr from urine. The cumulative amount of mannitol eliminated into the urine over the 24 hr collection period was similar for inhaled and oral mannitol. Following inhalation of mannitol 55% of the dose was excreted in the urine and 54% following oral administration. The dose normalized cumulative amount excreted unchanged in the urine following inhalation was 65% which is supported by the 59% oral bioavailability. This indicates that urinary excretion of mannitol is comparable to the serum PK profiles.

Figure 2. Mean urinary excretion rates following inhaled, oral and intravenous doses



Conclusion

The PK data from study DPM-PK101 revealed that systemic exposures of mannitol after inhalation and oral administration were similar. The absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 59%, while the absolute bioavailability of orally administered mannitol as compared to intravenously administered mannitol was 61%. The relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. Furthermore, comparable Tmax and T1/2 values between inhalation and oral routes of administration suggest similar systemic PK of the drug following administration by inhalation and oral routes.

Pharmacokinetics of Inhaled Mannitol Following Single and Multiple Dosing in CF Patients (Study DPM-PK-102):

As mannitol-containing foods can affect serum and urinary levels, patients were to maintain a mannitol-free diet for 2 days before the first dose administration until the end of the treatment phase (after the last PK sample on Day 8). Further, patients were required to have a negative MTT prior to enrollment. This was an open-label, single and multiple dose study. The aim of this study was to determine the PK of mannitol after single and multiple dosing (Day 7) of 400 mg inhaled mannitol to adult (18+ years), adolescent (12-17 years) and pediatric (older 9-11 years, younger 6-8 years) CF patients. A single dose of inhaled mannitol was administered on the morning of Day 1 and then twice daily from Day 2 to 6 and the last dose on the morning of Day 7. PK samples were taken at pre-dose and then at 0.25, 0.5, 0.75 1, 1.5, 2, 3, 4, 8, 12 and 24 hr post-dose for the doses administered on Days 1 and 7. Additional PK samples were taken on the mornings of Days 2 and 8 at 24 hr post-dose, prior to next dose administration.

Single-dose (Day 1–2) and multiple-dose PK parameters (Days 7–8) were compared and summarized for each age group. Accumulation was assessed by calculation of the Day 7/Day 1 AUC0-12 ratio. The mean serum PK parameters of mannitol are presented by age group and dose day in Table 4. Serum mannitol levels (mean Tmax values) peaked approximately 0.75 to 2.54 hr post dosing. Variability in mean Cmax values between adults, adolescents and pediatric patients was moderate to high ranging from 15 to 51%. Between subject variability in mean AUC0-inf values (Day 1) ranged from 22 to 47%. Serum mannitol concentrations accumulated following multiple BID dosing over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, pediatric (older), and pediatric (younger) subjects, respectively.

Table 4. Serum pharmacokinetic parameters for mannitol (mean, %CV)

Age group/Dose Day		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-12} (hr*ng/mL)	Day 7/Day 1 AUC_{0-12} Ratio	$AUC_{0-\infty}$ (hr*ng/mL)	$t_{½}$ (hr)	CL/F (mL/hr)	V/F (mL)
Adult (n=6)	Day 1	7670 (15%)	2.42 (44%)	41872 (12%)		57594 (22%)	8.9 (54%	7224 (22%)	86653 (33%)
	Day 7	9260 (29%)	1.37 (22%)	50240 (27%)	1.56	NA	12 (70%)	5531 (32%)	86559 (20%)
Adolescent (n=4)	Day 1	6768 (51%)	1.57 (65%)	33028 (37%)		41937 (33%)	7.9 (23%)	10719 (45%)	128435 (65%)
	Day 7	7330 (24%)	2.13 (30%)	45358 (16%)	1.21	NA	6 (17%)	7273 (15%)	62882 (20%)
Pediatrics, Older (9-11 yr) (n=2-3)	Day 1	4317 (29%)	1.52 (31%)	20918 (27%)		31474*	8.7*	12747*	160836*
	Day 7	8067 (41%)	2.54 (51%)	40857 (28%)	2.18	NA	6.3*	7079*	63987
Pediatrics, Younger (6-8 yr) (n=3)	Day 1	7563 (26%)	0.75 (67%)	31593		48370 (47%)	6.2 (44%)	9475 (37%)	77825 (46%)
	Day 7	13200 (26%)	1.33 (22%)	70926 (42%)	2.50	NA	6.1 (27%)	5350 (32%)	50149 (52%)

* Note: Parameter estimates could not be estimated for some subjects. NA: Not applicable

Conclusions: Serum mannitol exhibited accumulation following multiple BID dosing over 7 days by approximately 1.21 to 2.50 fold in CF patients. There were no marked differences in the PK of mannitol (Cmax, AUC 0-inf, T1/2 and CL/F) between adult, adolescent, pediatric older and pediatric younger patients and were similar to the PK of mannitol observed in healthy subjects.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Mannitol was measured in serum and urine. Mannitol is being tested as a locally (lungs) acting product and therefore, no exposure response relationship was evaluated/warranted.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

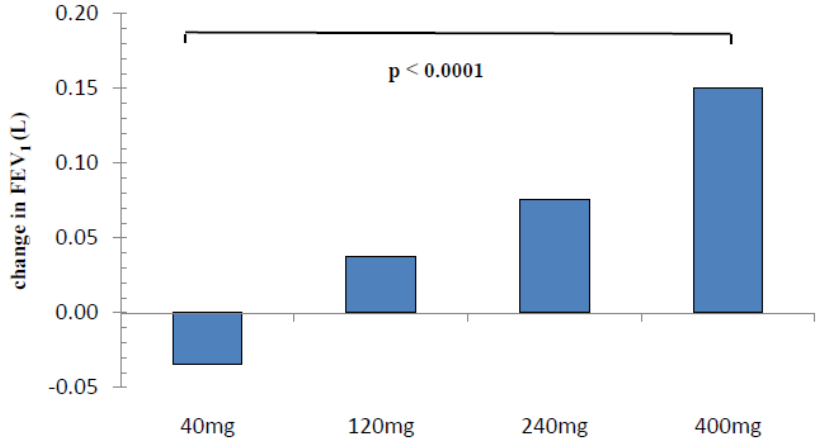
Sponsor submitted following three Phase 2 and two Phase 3 clinical studies:

Table 5. Clinical trials conducted for Bronchitol development program

Phase 2 Studies in CF Subjects (N= 115)		
DPM-CF-201	A Phase 2 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol in CF	49- MTT N=39 (Bronchitol vs. Control cross-over)
DPM-CF-202	Phase 2a Randomized, Open-Label, Dose Response Study to Determine the Optimum Dose of Dry Powder Mannitol Required to Generate Clinical Improvement in subjects with CF	85 MTT N=48 (Bronchitol cross- over dose response)
DPM-CF-203	A cross-over comparative study of inhaled mannitol, alone and in combination with daily rhDNase, in children with CF	40 MTT N=28 (Bronchitol vs. rhDNase vs. Bronchitol + rhDNase cross-over)
Phase 3 Studies in CF Subjects (N= 600)		
DPM-CF-301	Long-term administration of inhaled dry powder mannitol in CF – a safety and efficacy study	389 received MTT N=295 Treated (Bronchitol:177;Control :118)
DPM-CF-302	Long-term administration of inhaled dry powder mannitol in CF – a safety and efficacy study	342 received MTT N=305 treated (Bronchitol:184;Control : 121)

In the Phase 2 Study DPM-CF-202, inhaled dry powder mannitol demonstrated a dose-dependent increase in FEV1 and FVC (measures of improved lung functions) in CF subjects, at doses of 40, 120, 240, and 400 mg BID (Figure 3). Although the highest possible dose was not formally established, the use of more than 10 mannitol capsules for each dose was considered by sponsor to compromise compliance. Mannitol serum levels were not determined in this study. No formal exposure/response studies were conducted to establish the relationship between exposure and response as this is a locally (lungs) acting product and systemic exposures will not be an indicator of local efficacy and safety.

Figure 3. Effect of different doses of inhaled mannitol on FEV1 (L)



The effectiveness of Bronchitol for the management of CF was assessed in two randomized, double-blind, Phase 3 trials in patients with CF. All eligible patients from these trials were rolled over into an open-label extension study. Trial CF-301 evaluated 295 patients ≥6 years of age with baseline FEV1 between 30-90% predicted while Trial CF-302 evaluated 305 patients ≥6 years of age with baseline FEV1 between 40-90% predicted. Patients in both trials were randomized 3:2 to receive either 400 mg of Bronchitol or Control (50 mg mannitol) twice daily for 26 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted. The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in pre-dose FEV1 (mL) through 26 weeks of treatment. In Trial 301, the treatment difference between Bronchitol and Control for the mean absolute change in FEV1 from baseline through Week 26 was 83.14 mL while in Trial 302 the mean absolute change in FEV1 from baseline through Week 26 was 54.14 mL. These changes persisted throughout the 48-72 week open-label extension period. Final assessment of these findings is deferred to the Clinical and Statistical reviewers.

2.2.4 Exposure response

No formal exposure response studies were conducted to establish the relationship between exposure and response as this is a locally (lungs) acting product and systemic exposure will not be an indicator of local efficacy and safety.

2.2.5 Does this drug prolong the QT or QTC interval?

No formal QTc study was conducted.

2.2.6 What are the general PK characteristics of the drug and its major metabolites?

2.2.6.1 What are the single dose PK parameters?

Absolute bioavailability of inhaled mannitol as compared to intravenously administered mannitol was 59%, while the absolute bioavailability of orally administered mannitol as compared to intravenously administered mannitol was 61%. The relative bioavailability of inhaled mannitol as compared to orally administered mannitol was 96%. The Tmax was 1.5 (1-2) hr for inhaled and 1.4 (1-2) hr for orally administered mannitol. Dose normalized Cmax between inhaled and orally administered mannitol were approximately similar 10,792 and 13,094 ng/mL, respectively. The mean T1/2 of mannitol was approximately 5 hr regardless of route of administration. Urinary excretion rates versus time profiles for mannitol were similar for all routes of administration. Overall, the rate and extent of absorption after inhalation and oral administration were similar.

2.2.6.2 What are the multiple dose PK parameters?

Single-dose (Day 1–2) and multiple-dose PK parameters (Days 7–8) were compared and summarized for each age group (adult, adolescent and pediatric). Accumulation was assessed by calculation of the Day 7/Day 1 AUC0-12 ratio. Serum mannitol Tmax peaked approximately 0.75 to 2.54 hr post dosing. Variability in mean Cmax values between adults, adolescents and pediatric (older and younger) subjects was moderate to high ranging from 15 to 51%. Between subject variability in mean AUC0-inf values (Day

1) ranged from 22 to 47%. Serum mannitol concentrations accumulated following multiple BID dosing over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, pediatric older, and pediatric younger subjects, respectively.

2.2.6.3 What are the characteristics of drug absorption?
The rate and extent of absorption after inhalation and oral administration were similar in healthy volunteers, and the results indicated that inhaled mannitol was not accumulated in the lungs (DPM-PK-101). In study DPM-PK-102 serum mannitol Tmax peaked approximately 0.75 to 2.54 hr post dosing. Variability in mean Cmax values between adults, adolescents and pediatric (older and younger) subjects was moderate to high ranging from 15 to 51%. Between subject variability in mean AUC0-inf values (Day 1) ranged from 22 to 47%.

2.2.6.4 What are the characteristics of drug distribution?
In study DPM-PK-102 mannitol concentrations accumulated in serum following multiple BID dosing (400 mg) over 7 days by approximately 1.56, 1.21, 2.18 and 2.50 fold in adults, adolescents, pediatric older, and pediatric younger subjects, respectively (Day 7/Day 1 AUC0-12 ratio). Overall, there were no marked differences in the PK of mannitol between adult, adolescent, pediatric (older) and pediatric (younger) patients.

2.2.6.5 What are the characteristics of drug metabolism?
Mannitol is metabolized in a CYP-independent manner through the glycolytic pathway via dehydrogenation to fructose. Mannitol is primarily excreted unchanged in the urine or feces.

2.2.6.6 What are the characteristics of drug elimination?
When administered intravenously, 87% of the mannitol dose was excreted unchanged in the urine within 24 hrs. The cumulative amount of mannitol eliminated into urine over the 24 hr period was similar for inhaled and oral mannitol. Following inhalation of mannitol 55% of the dose was excreted in the urine and 54% following oral administration.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
No formal studies were conducted to establish dose linearity or nonlinearity.

2.2.6.8 How do the PK parameters change with time following chronic dosing?
Serum mannitol exhibited accumulation following multiple BID dosing over 7 days by approximately 1.21 to 2.50 fold in CF patients.

2.3 Intrinsic Factors

2.3.1 Effect of age
No marked differences in the PK of mannitol were observed between adult (≥18 year old), adolescent (12-17 year old), older pediatric (9-11 year old) and younger pediatric

(6-8 year old) CF patients, however, the total number of patients studied in each age group was very small (see Table 2 for details). Sponsor has requested a pediatric waiver for patients <6 years old stating that clinical studies would be highly impractical with this drug-device combination in this patient population. Clinical studies with Bronchitol did not include sufficient number of patients aged 65 years and older to determine whether they response differently from younger subjects. In general, administration to elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy(ies).

2.3.2 PK in healthy subjects versus patients
PK profiles of inhaled mannitol in healthy subjects and CF patients were similar.

2.3.3 Effect of gender and race
The effect of gender and race on PK of mannitol was not evaluated. However, given the absence of CYP mediated mechanisms of clearance, gender and race are considered unlikely sources of inter-patient variability in mannitol PK.

2.3.4 Renal impairment
No formal studies were conducted to assess the impact of renal impairment on mannitol PK. However, an increase in systemic exposure can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

2.3.4 Hepatic impairment
No formal studies were conducted to assess the impact of hepatic impairment on mannitol PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/ or response and what is the impact of any differences in exposure on pharmacodynamics?
No formal studies were conducted to examine the effect of drugs, herbal products, diet, smoking, and alcohol use on PK of inhaled mannitol.

2.4.2 Drug-drug interactions
No formal drug interaction studies were conducted for inhaled mannitol. Mannitol is not metabolized by CYP enzymes.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?
Not applicable as this is an inhalation product.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

The to-be-marketed formulation was used in the PK and clinical trials.

2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is an inhalation product.

2.6 Analytical Section

2.4.1 Was the suitability of the analytical method supported by the submitted information?

In both PK studies (DPM-PK-101 and DPM-PK-102) the plasma and urine samples were assayed using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays. LC-MS/MS methods used to determine mannitol in human serum and urine met the validation acceptance criteria for selectivity/specificity, linearity, precision and accuracy, sensitivity, dilution integrity, and stability.

Due to dietary intake, mannitol is typically present at low concentrations in human serum. The control matrix used was a surrogate human serum albumin preparation. All references to human serum used to prepare the calibration curve, blank and quality control samples refer to the surrogate human serum preparation. Mannitol in human serum samples was derivatised with acetic anhydride in the presence of pyridine. The range of the assay was 100-100,000 ng/mL using 10 µL of serum. The lower limit of quantification (LLOQ) for serum was 100 ng/mL. The assay accuracy was 84.7% (acceptance criterion: 100±20%), and the precision rate was 4.9% (acceptance criterion: ≤20%) at LLOQ (Table 6).

Table 6. Mannitol assay precision and accuracy in human surrogate serum

LLOQ of Mannitol in Human Surrogate Serum (100ng/ml)

Results expressed as determined concentration (ng/mL)

Replicate	Determined Concentration
1	91.6
2	81.2
3	80.7
4	87.2
5	85.0
6	82.6
Mean	84.7
Precision (%)	4.9
Accuracy (%)	84.7

Precision = Coefficient of variation of mean
Accuracy = Mean determined concentration/actual concentration

Due to dietary intake, mannitol is typically present at low concentrations in human urine. As such, the control matrix used was a synthetic preparation from a published method. All references to human urine used to prepare the calibration curve, blank and quality control samples refer to the synthetic urine mixture. An aliquot of the solution was then derivatised with acetic anhydride in the presence of pyridine. The range of the assay was 200-200,000 ng/mL using 10 µL of urine. The LLOQ for urine was 200 ng/mL. The accuracy was 110.5% (acceptance criterion: 100±20%), and the precision rate was 8.1% (acceptance criterion: ≤20%) at LLOQ (Table 7).

Table 7. Mannitol assay precision and accuracy in synthetic urine

LLOQ of Mannitol in Synthetic Urine (2000 ng/ml)

Results expressed as determined concentration (ng/mL)

Replicate	Determined Concentration
1	a 2450
2	2400
3	2170
4	2030
5	2050
6	2140
Mean	2210
Precision (%)	8.1
Accuracy (%)	110.5

Precision = Coefficient of variation of mean
Accuracy = Mean determined concentration/actual concentration
a = Out of acceptance; included in the calculations

3. Labeling Recommendations

Below are some sections from the proposed labeling. Reviewer suggested changes: ~~double strikethrough~~ text should be deleted from labeling and double underline text should be added to labeling.

7 DRUG INTERACTIONS

No formal drug (b) (4) interaction studies (b) (4) ~~have been~~ conducted with mannitol, the active ingredient in Bronchitol.

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic and Renal Impairment

(b) (4) Bronchitol (b) (4) (b) (4) with hepatic or renal impairment. (b) (4) However, an increase in systemic exposure of mannitol can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

(b) (4)

~~12.2 Pharmacodynamics~~

(b) (4)

4. Appendix

Filing/Survey Form

Office of Clinical Pharmacology

2 *New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	**202-049**	**Brand Name**	**BRONCHITOL**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Mannitol inhalation powder**
Medical Division	**DPARP**	**Drug Class**	**Sugar alcohol**
OCP Reviewer	**Arun Agrawal, Ph.D.**	**Indication(s)**	**BRONCHITOL is indicated for the management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Inhalation Powder: 40 mg capsules and inhaler**
Pharmacometric Reviewer		**Dosing Regimen**	**Adult and pediatric patients age 6 years and older: 400 mg (10 x 40 mg capsules) twice daily**
Date of Submission	**May 17, 2012**	**Route of Administration**	**Inhalation**
Estimated Due Date of OCP Review		**Sponsor**	**Pharmaxis Ltd**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**March 18, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**3**	**3**	**Two PK studies, 2 bioanalytical method validation reports and 2 bioanalytical reports**
Tabular Listing of All Human Studies	**X**	**2**	**2**	**DPM-PK-101 and DPM-PK-102**
HPK Summary	**X**	**2**	**2**	**DPM-PK-101 and DPM-PK-102**
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	**Two bioanalytical method validation reports and 2 bioanalytical reports**
I. Clinical Pharmacology	**X**	**2**	**2**	**DPM-PK-101 and DPM-PK-102**
Mass balance:				
Isozyme characterization:				

Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**2**	**2**	**DPM-PK-101 and DPM-PK-102**
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	**DPM-PK-101**
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	**DPM-PK-102**
multiple dose:	**X**	**1**	**1**	**DPM-PK-102**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	**DPM-PK-101**
Relative bioavailability -	**X**	**1**	**1**	**DPM-PK-101**
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	**DPM-PK-101**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Waiver requested for <6 year old**
Literature References	**X**			
Total Number of Studies	**X**	**3**	**3**	

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/s/

ARUN AGRAWAL
02/08/2013

SURESH DODDAPANENI
02/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 202-049
Supporting document/s:	Sequences 0000
Applicant's letter date:	May 17, 2012
CDER stamp date:	May 18, 2012
Product:	Bronchitol (D-mannitol) Dry Powder Inhaler
Indication:	Cystic fibrosis
Applicant:	Pharmaxis Ltd.
Review Division:	Pulmonary, Allergy and Rheumatology
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.,
Project Manager:	Angela Ramsey

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202-049 are owned by Pharmaxis or are data for which Pharmaxis has obtained a written right of reference. Any information or data necessary for approval of NDA 202-049 that Pharmaxis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202-049.

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1 Executive Summary

1.1 Introduction

The current NDA (NDA 202-049) proposed to register D-mannitol (Bronchitol® inhalation powder) for the cystic fibrosis indication. The NDA referenced the Aridol® application (NDA 22-368) for its nonclinical support. Pharmaxis is the holder of both NDA 22-368 and 202-049.

Aridol® was a 505(b)(2) application that was approved on October 5, 2010. Aridol® is a diagnostic agent indicted for assessing airway hypersensitivity in asthmatics. The maximum recommended human inhalation dose is 635 mg.

The nonclinical program in support of both NDAs 22-368 and 202-049 was completed under IND 70,277. All pivotal nonclinical data that the applicant submitted in support of its current proposal was previously submitted in IND 70,277 or NDA 22-268 and reviewed by the Agency. The current NDA submission contained no significant, new nonclinical data.

1.2 Brief Discussion of Nonclinical Findings

No significant, new nonclinical data were submitted to the current NDA. A brief overview of nonclinical findings of inhaled mannitol, as determined by review of submissions to IND 70,277 and NDA 22-368, is provided below. See Table 1 in Section 3.3 Nonclinical Reviews Referenced for details.

The target organs of toxicity of inhaled mannitol are the respiratory system. Inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively, were conducted. Increased incidences of microphage aggregation and alveolitis were observed in a 3-month study in rats. Coughing, laryngeal ulceration and sinus histiocytosis were observed in a 6-month study in dogs. There were no any neoplastic or pre-neoplastic findings in the respiratory tract. The available nonclinical data in the literature show that mannitol was non-carcinogenic, non-genotoxic, and non-teratogenic.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective, pending labeling. The applicant has completed a bridging toxicology program evaluating the toxicity profile of inhaled mannitol. The program consisted of inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory system as the target organs of toxicity for inhaled mannitol. The organs did not show any neoplastic or pre-neoplastic findings. This toxicology program has satisfied the nonclinical prerequisite for the approval of Bronchitol®.

1.3.2 Additional Non-Clinical Recommendations

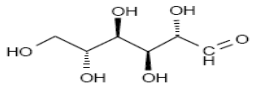
None.

1.3.3 Labeling

A labeling review will be completed at a later time after the review team makes a decision on the recommended clinical dose and indicated population of the product.

2 Drug Information

2.1 Drug

CAS Registry Number:	69-65-8
Generic Name:	D-mannitol
Code Name:	None
Chemical Name:	1,2,3,4,5,6-hexanehexol, or cordycepic acid
Molecular Formula/weight:	$C_6H_{14}O_6$/182.2
Structure:	
Pharmacologic Class:	Sugar

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 22-368 (Aridol), IND 70,277 and DMF (b) (4)

2.3 Drug Formulation

Forty-mg mannitol capsules.

2.4 Comments on Novel Excipients

None. The product contains no excipients.

2.5 Comments on Impurities/Degradants of Concern

(b) (4) was found as a degradant/impurity of D-mannitol. Dr. Kathleen Young conducted a safety evaluation of the impurity in the drug product on May 31, 2011 in IND 70,277. She concluded that there is no safety concern about the impurity. See DARRTS Reference ID# 2953859 for the review.

2.6 Proposed Clinical Population and Dosing Regimen

Patients with Cystic Fibrosis 6 years of age and older will use 400 mg (10 x 40 mg capsules) twice a day.

2.7 Regulatory Background

The current NDA (NDA 202-049) referenced the Aridol® application (NDA 22-368) for nonclinical support. Aridol®, a 505(b)(2) application, was approved on October 5, 2010. Pharmaxis is the holder of both NDA 22-368 and 202-049.

The nonclinical program in support of both NDA 22-368 and 202-049 was completed under IND 70,277. The Division determined that a 6-month inhalation toxicity study of the compound in the most appropriate species was adequate to support registrations of both Aridol® and Bronchitol® products. This determination was based on the extensive use of D-mannitol as an excipient in non-inhalation drug products. Pharmaxis agreed to the nonclinical prerequisite (Ref.: minutes of meetings on June 16, 2005, and February 15, 2006, a telephone conference on October 11, 2006; and correspondence on July 26, 2006 in IND 70,277).

Pharmaxis conducted inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. These studies were submitted previously to IND 70,277 and submitted in NDAs 22-368 and 202-049.

3 Studies Submitted

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

No new nonclinical studies were submitted to the current NDA (202-049). Submitted studies were previously reviewed under IND 70,277 or Aridol NDA 22-368. It is unnecessary to relist the studies or to review them again. See nonclinical reviews referenced in Table 1 below for complete details of previously submitted and reviewed studies.

3.3 Previous Reviews Referenced

This review references a number of nonclinical reviews previously completed by DPARP staff in related IND and NDA applications. Table 1 (below) lists these reviews.

Table 1: Previous Reviews Referenced

Application No.	Author	Review Content	Date of Completion	Reference ID #
NDA 22-368	L. Pei	Original NDA review of Aridol	10/30/2009	NA [a]
NDA 22-368	L. Pei	Nonclinical labeling review of Aridol	11/13/2009	NA
IND 70,277	K. Young	Safety Evaluation of (b) (4) impurity	5/31/2011	2953859
NDA 202,049	L. Pei	Filing review of Bronchitol	7/2/2012	3153685

a. NA, Not available.

4 Pharmacology

Not applicable because no data were submitted.

5 Pharmacokinetics and Toxicokinetics

Not applicable because no data were submitted.

6 General Toxicology

Not applicable because no data were submitted.

7 Genetic Toxicology

The submission contained 3 NTP reports of genetic toxicity testing of mannitol: Chromosomal aberrations and sister chromatid exchanges in the Chinese hamster ovary cell in vitro (NTP Study Report 308644, Gulati et al., *Environ. Molec. Mutag.* 1989;13:133-193), in vivo chromosomal aberration in mice (NTP 741772), and induction of sex-linked recessive lethal mutations and chromosomal reciprocal translocations in germ cells in Drosophila (NTP Study Report 903586). All three reports were completed in the 1980s. None of them contain significant new information about the nonclinical safety evaluation of the mannitol. This document will not review any of the reports.

8 Carcinogenicity

The submission contained the NTP study report of two-year carcinogenicity of mannitol in rats and mice (NTP TR-236). It is not necessary to review the report because the finding of the report has been described in the labeling review of Aridol.

9 Reproductive and Developmental Toxicology

Not applicable because no data were submitted.

10 Special Toxicology Studies

Not applicable because no data were submitted.

11 Integrated Summary and Safety Evaluation

The application has adequately evaluated the toxicity profile of inhaled mannitol. The evaluation included inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. These studies identified the respiratory system as the target organ of toxicity. The studies did not reveal any neoplastic or pre-neoplastic findings. These studies are considered adequate to support the registration of mannitol for the cystic fibrosis indication (Bronchitol). The approval of Bronchitol is recommended from the nonclinical perspective, pending labeling review.

Mannitol is used as a nutrient and/or dietary supplement and an ingredient in numerous drug products. As a dietary supplement, mannitol is considered generally recognized as safe [GRAS, 21CFR§582.5470]. Mannitol has been used as both an active and inactive ingredient in numerous medicinal products.

As an active ingredient of drug products, mannitol is a laxative, diurectic, and diagnostic agent (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). These products are administered by inhalation or parental administration. Aridol (NDA 22-368, approved on October 5, 2010) is a mannitol inhalation product. Each capsule contains 40-mg mannitol. Many mannitol injectables products are currently on the market. These products contain 10 – 40% (w/v) of mannitol.

As an inactive ingredient, mannitol is present in numerous products (http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm). These products are used by oral, parenteral, topical and inhalation administration. Exubera® (inhaled insulin product, NDA 21-868, approved on January 27, 2006) is the only inhalation product that contains mannitol as an inactive ingredient.

The mannitol toxicity by non-inhalation routes of administration is well understood. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. The National Toxicology Program found mannitol non-carcinogenic and non-mutagenic (http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr236.pdf). F344/N rats and B6C3F1 mice fed with up to 5% D-mannitol in diet for 103 weeks did not reveal any evidence of tumorigenicity. No evidence of mutagenicity was found in a battery of testing: a bacterial mutation assay, an *in vitro* mouse lymphoma cell assay, an *in vivo* mouse micronucleus assay and other assays. D-mannitol is non-teratogenic, according to the Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol (http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm).

A bridging toxicology program was designed to evaluate the toxicity profile of mannitol after the inhalation route of administration, due to the available extensive clinical and nonclinical data on mannitol. This program focused on effects of inhaled mannitol, particularly its effect on the respiratory system. The program consisted of inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. These studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol. The studies did not reveal any neoplastic or pre-neoplastic findings in the respiratory system, as the nonclinical review completed by Dr. Luqi Pei October 30, 2009 concluded. The completed toxicology program has adequately evaluated the toxicity profile of inhaled mannitol. The current review recommends the approval of the Bronchitol® application, pending the labeling review.

Unresolved toxicology issues (if any): None.

Recommendations: Approval of Aridol is recommended, pending labeling review, from the nonclinical perspective.

12 Appendix

Nonclinical review completed by Dr. Luqi Pei on October 30, 2009 in NDA 22-368.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-368
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	February 26, 2009
PRODUCT:	Aridol (Mannitol)
INTENDED CLINICAL POPULATION:	Test kit for bronchial hyper-responsiveness in patients 6 years of age and older
SPONSOR:	Pharmaxis Ltd.
DOCUMENTS REVIEWED:	Not applicable
REVIEW DIVISION:	Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER:	Luqi Pei, Ph.D.
PHARM/TOX SUPERVISOR (acting):	Jean Wu, M.D., Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Miranda Raggio
Date of review submission to DARRTS:	October 30, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Approval of Aridol is recommended from the nonclinical perspective. The applicant has completed a bridging toxicology program evaluating the toxicity profile of inhaled mannitol. The program consisted of inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory system as the target organs of toxicity for inhaled mannitol. The organs did not show any neoplastic or pre-neoplastic findings. This toxicology program has satisfied the nonclinical prerequisite for the approval of Aridol.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Labeling review will be completed at a later time after the review team decides what labeling format will be used for the product.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The target organs of toxicity of inhaled mannitol are the respiratory system. Inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively, were conducted. Increased incidences of microphage aggregation and alveolitis were observed in a 3-month study in rats. Coughing, laryngeal ulceration and sinus histiocytosis were observed in a 6-month study in dogs. There were no any neoplastic or pre-neoplastic findings in the respiratory tract. The available nonclinical data in the literature show that mannitol was non-carcinogenic, non-genotoxic and non-teratogenic.

B. Pharmacologic activity

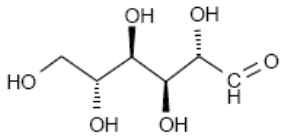
Aridol inhalation may provoke bronchoconstriction in some patients. D-mannitol inhalation results in hyper-osmosis in the airways. The hyper-osmosis induces histamine release from mast cells. Histamine in turn provokes bronchoconstriction.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number:	22-368
Review Number :	1
Sequence number/date/submission type:	000/27-FEB-2009/Original NDA
Information to the Sponsor:	Yes ( ), No (x)
Sponsor/or Agent:	Pharmaxis Ltd, 1840 Gateway Dr., San Mateo, CA 94404
Manufacturer of the Drug Substance:	(b) (4)
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
Review Completion Date:	October 30, 2009
Drug:	
Trade Name:	Aridol
Generic Name:	D-Mannitol
Code Name:	None
Chemical Name:	1,2,3,4,5,6-hexanehexol, or cordycepic acid
Structure:	
CAS Register Number:	69-65-8
Mole File Number:	Not available
Molecular Form and Weight:	$C_6H_{14}O_6$/182.2
Relevant IND/NDAs:	MDF# (b) (4) IND 70,277
Drug Class:	Diagnostic (Broncho-provocation) agent
Intended clinical population:	Asthmatic patients 6 years of age and older
Route of Administration:	Inhalation

Clinical Formulations: Capsules filled with 5, 10, 20 and 40 mg of D-mannitol powder. Mannitol will be delivered by a dry powder inhaler.

Proposed Clinical Dose: up to 635 mg/patient, single time use.

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies reviewed within this submission: None.
Studies not reviewed within this submission:

Study No.	Description	Location in submission	Review # [a]
XIS 001/033434	Single-dose inhalation toxicity of mannitol in rats	4.2.3.1	1
XIS 002/033951	14-day inhalation toxicity study of mannitol in rats	4.2.3.2	1
XIS 004/034088	Mannitol eye irritation study in rabbits	4.2.3.6	1
XIS 003/034081	Effect of mannitol on bovine corneal opacity and permeability in vitro	4.2.3.6	1
XIS 005 / 043185	13-week inhalation toxicity study with 4-week recovery in rats	4.2.3.2	2
26050	2-week inhalation study in dogs	4.2.3.2	2
26482/ 666958	Investigative inhalation study in rats	4.2.3.2	2
26966/ 667108	26-week inhalation toxicity study in dogs	4.2.3.2	4
NTP 821315	In vitro mouse lymphoma assay	4.2.3.3	5[b]
NTP 315204	Bacterial reverse gene mutation assay	4.2.3.3	5
NTP 90264	In vivo micronucleus assay	4.2.3.3	5
NTP No. 236	2-year dietary carcinogenicity studies in rats and mice	4.2.3.4	5

a. Reviews 1, 2 and 4 were completed by Dr. Luqi Pei on 18-MAR-05, 21-JUL-06 and 31-JUL-07, respectively, under IND 70,277. See Appendices for the reviews.

b. The National Toxicology Program conducted these gene toxicity studies. Some were peer-reviewed and cited in available data bases such as the Hazardous Substances Data Bank (http://toxnet nlm nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+69-65-8). Another review is not needed.

Drug History:

This NDA application was developed under IND 70,277 under which the original application was filed on November 22, 2004. As the Sponsor of the IND, Pharmaxis is developing mannitol dry powder as two products (b) (4). The products are Aridol and Bronchitol. The former is a diagnostic agent for provoking bronchoconstriction. The latter will be indicated for (b) (4) pulmonary cystic fibrosis. As such, Aridol and Bronchitol have different dosages and use durations. The Aridol NDA is currently under review while the Bronchitol program is in a clinical phase-3 development stage.

Pharmaxis and DPAP have held a number of meetings to discuss the development of mannitol programs. Four meetings dealt with nonclinical issues of Aridol development: the 19-NOV-04 Pre-IND meeting, the 16-JUN-05 guidance meeting, the 15-FEB-06 EOP2 meeting, and the 12-MAR-08 pre-NDA meeting. The pre-IND, EOP2 and pre-NDA meetings discussed the Aridol program. The guidance meeting discussed the Bronchitol program. The EOP2 meeting also discussed the Bronchitol program. Minutes of the meetings are available in DARRTs.

Through these meetings, Pharmaxis and the Division agreed on the following regarding the nonclinical requirement of mannitol inhalation products:

1. Two 14-day inhalation toxicity studies of mannitol in two animal species (one in each species) are needed for the registration of Aridol.
2. A 6-month inhalation toxicity study in a most appropriate species is needed to support the development and registration of Bronchitol. The dog was considered the most appropriate species later as discussed in Pharmacology and Toxicology Review No. 4 of IND 70,277 completed by Dr. Luqi Pei on November 19, 2007.

3. No studies of carcinogenicity, genetic toxicity, reproductive and developmental toxicity are needed for either Aridol or Bronchitol.

Pharmaxis has completed mannitol inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. These studies have been previously submitted and reviewed under IND 70,277. See Pharmacology and Toxicology Reviews (Appendices) completed by Dr. Luqi Pei on November 29, 2007 (Review# 4), July 21, 2006 (Review# 3), and March 18, 2005 (Review# 1).

DPAP requested in the pre-NDA meeting that Pharmaxis address the safety qualifications of impurities, leachables and extractables in the Aridol NDA. The current review will not address these issues because they were addressed separately through Chemistry Consultation Requests and Reviews. A Chemistry Consultation Request was filed by Dr. Deepika Arora on June 4, 2009 and a Pharmacology and toxicology Review of the Request was completed by Dr. Luqi Pei on August 5, 2009. Refer to the appropriate documents for additional information.

This NDA was submitted on February 26, 2009 (letter date) and accepted by the Agency on March 1, 2009. DPAP held a filing meeting on April 13, 2009. Dr. Luqi Pei completed a nonclinical fileability review on April 15, 2009.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Inhalation of D-mannitol provokes bronchoconstriction through inducing histamine release from mast cells. No pharmacology studies were performed under IND 70,277 or the current NDA. A literature review was performed as requested in the pre-NDA meeting. The review indicated that mannitol could induce the release of histamine from cultured human lung mast cells and blood basophils. The histamine release was apparently attributed to the hyper-osmosis (2 – 3x normal) associated with mannitol. Mannitol treatment also enhances histamine release from mast cells induced by IgE. In the current application, inhaled mannitol delivered into the airways is responsible for inducing an osmotic gradient into airways.

2.6.2.2 Primary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.3 Secondary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.4 Safety pharmacology

Not applicable because no data was submitted.

2.6.2.5 Pharmacodynamic drug interactions

Not applicable because no data was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No separate pharmacokinetic studies of inhaled mannitol were conducted in animals. Mannitol levels in the plasma and bronchoalveolar lavage fluid (BALF) were measured in some inhalation toxicity studies. Mannitol does-concentration relationship was seen in the plasma/serum but not in BALF. Figure 1 (below) shows the time course of mannitol plasma/serum concentration in dogs (Report No. 667108).

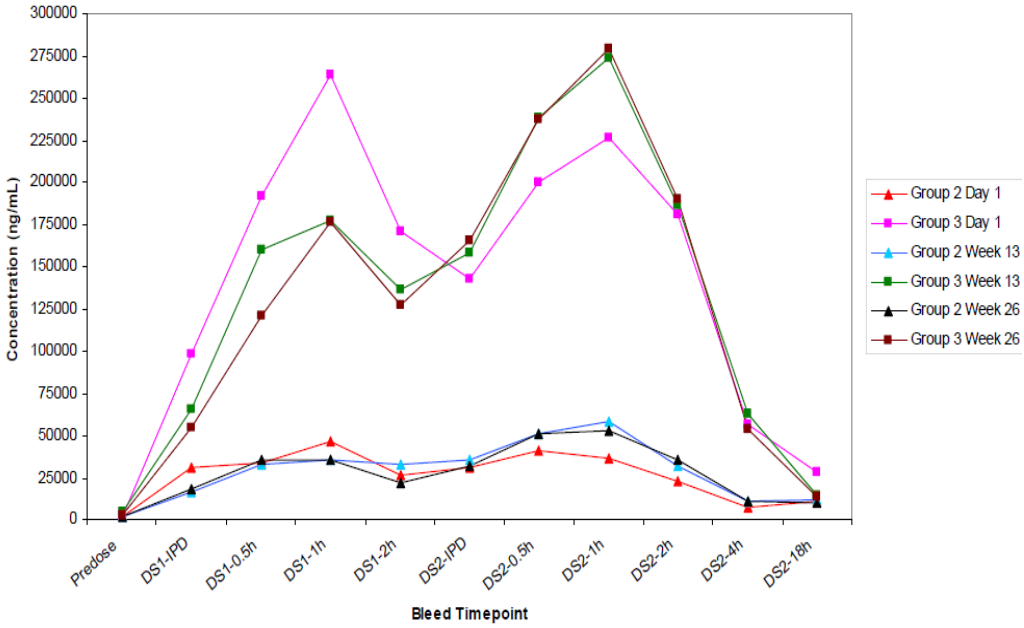


Figure 1 Serum mannitol concentrations after inhalation exposures in dogs. The estimated pulmonary deposits were 43 and 178 mg/kg/day for Groups 2 and 3, respectively. Each daily dosing consisted of two episodes (60 minutes each) of exposures with an interval of at least 2 hours between them. DS1 and DS2 indicate first and second episodes of the day, respectively (Source: P/T review #4, page 7).

Mannitol concentrations in BALF were determined in both rats and dogs. In a 13-week inhalation study in rats (Study XIS 005/0413185), the mean mannitol level in BALF was 0, 3.8 and 3.2 µg/ml in the control, LD (pulmonary deposit dose,12.4 mg/kg/day) and HD (pulmonary deposit dose, 21.0 mg/kg/day) groups, respectively. In the 26-week dog study

(Report No. 667108), BLAF mannitol concentrations were below the limit of quantitation (0.1 μmol/L) for both low (43 mg/kg/day) and high dose (178 mg/kg/day) groups.

2.6.4.2 Methods of Analysis

Mannitol levels were analyzed by liquid chromatography-tandem mass spectrometry using TurboIonSpray in positive ion mode. The data were quantified by comparing peak area ratios (test item to internal standard) of the samples to the appropriate calibration lines using weighted (1/x2) least squares regression. The assay lower limit of quantification (LLOQ) for Mannitol in dog serum was 100 ng/mL. The method was found to give linear calibration lines for Mannitol in dog serum and lung lavage wash samples over the range *ca* 100-100000 ng/mL.

2.6.4.3 Absorption

Not applicable because no data was submitted.

2.6.4.4 Distribution

Not applicable because no data was submitted.

2.6.4.5 Metabolism

Not applicable because no data was submitted.

2.6.4.6 Excretion

Not applicable because no data was submitted.

2.6.4.7 Pharmacokinetic drug interactions

Not applicable because no data was submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable because no data was submitted.

2.6.4.9 Discussion and Conclusions

Not applicable because no data was submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data was submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because new data was submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Mannitol is non-carcinogenic, non-mutagenic and non-teratogenic. Comprehensive summaries of D-mannitol toxicology are available. See the National Toxicology Program Technical Report No. 236 (1982) at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr236.pdf and the Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol at http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm.

Mannitol is used as a nutrient and/or dietary supplement and an ingredient in numerous drug products. As a dietary supplement, mannitol is considered generally recognized as safe [GRAS, 21CFR§582.5470]. Medically, mannitol is used as active and inactive ingredients. As an active ingredient, mannitol is a laxative and diurectic. As an inactive ingredient, mannitol is an excipient in numerous products. The routes of administration of these products included oral, parenteral (e.g., IV, and IP), topical and inhalation. Exubera® (an insulin product, NDA 21-868, approved on January 27, 2006), however, is an only inhalation product that uses a small amount of mannitol as an inactive ingredient. The toxicology program of Aridol and Bronchitol focused on effects of inhaled mannitol on the respiratory system due to the extensive nonclinical data available on mannitol.

General Toxicology:

The mannitol toxicology program consists of inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. Table 1 (below) presents an overview of these toxicity studies. The studies identified the respiratory system as the target organ of toxicity for inhaled mannitol. Increased incidences of microphage aggregation and alveolitis were observed in a 3-month study in rats. Coughing, laryngeal ulceration and sinus histiocytosis were observed in a 6-month study in dogs. The NOAEL in the 6-month inhalation study in dogs was 43 mg/kg/day (pulmonary deposits).

Table 1 Overview of Inhalation Toxicity Studies of Mannitol

Study #	Species	Duration	Mannitol (mg/kg/day) [a]	NOAEL
26482/666958[b]	Rat	7 days	57.3, 97.9	None
XIS 002/033951	Rat	2 weeks	0, 0.9, 2.5, & 6.9	6.9
XIS 005/0413185	Rat	13 weeks	0, 12.4, 21.0	None [c]
26050/666386	Dog	2 weeks	0, 25, 100, 197	None [d]
26966/667108	Dog	26 weeks	0, 43, 178	43 [e]

a. Estimated pulmonary deposits. The pulmonary deposit was considered 10% (rat) and 25% (dog) of the inhaled dose (reported).
b. A non-GLP compliant investigative dose-ranging study that did not examine the lung tissue microscopically.
c. The review is in agreement with the study report regarding the NOAEL determination.
d. The report states that the 197 mg/kg/day dose is "well-tolerated."

e. The study report and the DPAP disagree on the NOAEL. DPAP considers the NOAEL the low dose (43 mg/kg/day, pulmonary deposition) but the study report deemed the high dose (710 mg/kg/day, inhaled dose) as the NOAEL.

Rats:

Three inhalation toxicity studies of mannitol were completed in rats. The treatment duration of these studies was 1, 2 and 13 weeks, respectively. In a 3 month study, rats at ≥ 12.4-mg/kg/day (pulmonary dose) mannitol showed increases in the incidence of microphage aggregation in the lung and eosinophilic inclusion in olfactory epithelium in nasal cavity. Rats receiving 21.0-mg/kg/day mannitol also showed an increase in the incidence of alveolitis in the lung.

In a 7-day non-GLP dose-ranging study, Sprague-Dawley rats (5/sex/dose) were exposed nose-only to approximately 5 or 9 mg of mannitol/L of air for 120 to 240 minutes/day for 7 days. The rats were sacrificed immediately after the last exposure. The amount of mannitol delivered to the lung was determined by measuring mannitol concentrations in the bronchoalveolar fluid (3/sex/dose). The respective estimated achieved dose of mannitol was 573 and 979 mg/kg/day for the low-dose and high-dose groups, respectively. The respective mean mannitol concentration in BALF for the low and high dose groups was 36.7 and 42 μg/ml in males and 43.6 and 33.4 μg/ml in females. Necropsy did not reveal any treatment-related effect. Microscopic examination was not done.

In a 2-week study (XIS 002/033951), CD-1 rats (10/sex/dose) were given via nose-only inhalation pulmonary deposited doses of 0, 0.9, 2.5 and 6.9 mg/kg of mannitol for 14-days. Histological evaluations of the respiratory system were done in every group. The remaining organs were examined in the control and high-dose groups only. No significant, treatment-related effects were observed. The NOAEL was 6.9 mg/kg/day.

In a 13-week study (26050/666386), Sprague-Dawley rats (10/sex/group) were given via nose-only inhalation air (C), 12.4 (LD), or 21.0 (HD) mg/kg/day (pulmonary deposition) for 13 weeks. Additional rats (5/sex) were included in the control (RC) and high dose (RHD) groups to evaluate reversibility of lesions after a recovery period of 4 weeks. The duration of exposure was 180 minutes/day. D-mannitol concentrations were 0, 1.83 or 2.89 mg/L for the control, LD and HD groups, respectively. The estimated pulmonary deposition of D-mannitol was 0, 12.4 and 21.0 mg/kg/day for the control, LD and HD groups, respectively. D-mannitol contents in the bronchoalveolar fluid were approximately 0, 3.8 and 3.2 μg/ml for the control, LD and HD groups, respectively. Both the LD and HD females showed statistically significant decreases in body weight gain (approximately 20%). Clinical pathology examinations revealed minimal decreases (approximately 50% or less) in white blood cell numbers and increases (12-30%) in serum phosphorus in the HD group. Microscopic examinations revealed increases in the incidence of alveolar macrophage aggregation and alveolitis. The respective incidence of alveolar macrophage aggregation in the C, LD, HD, RC and RHD was 3/10, 6/10, 9/10, 0/2 and 1/2 in females and 4/10, 5/10, 3/10, 1/1 and 3/4 in males. The increase in the incidence of alveolitis was observed in the high-dose male only (incidence: 0/10-C, 0-/10-MD, 1/10-HD, 0/1-RC, and 2/4-RHD, respectively). The most significant, treatment-related effect, but of no safety concern for the intended use of mannitol, was seen in the nasal cavity. Both the low and high-dose rats showed increases in the incidence of eosinophilic inclusion in olfactory epithelium of the

nasal cavity (Incidence: 3/20-Air, 15/20-LD, and 13/20-HD). This finding is not considered relevant to humans because minimal nasal exposure is expected from the intended clinical use. The study failed to establish NOAEL.

Dogs:

Two inhalation toxicity studies of mannitol were completed in dogs. The treatment duration of these studies was 2 and 26 weeks, respectively. Dogs receiving 178-mg/kg/day (pulmonary dose) for 26 weeks mannitol showed increases in the incidence of minimal laryngeal ulceration and sinus histiocytosis in mediastinal lymph node.

In a 2-week study (XIS 005/0413185), beagle dogs (3/sex/group) were exposed by inhalation via a face mask to air (C), 25 (LD), 100 (MD) or 197 (HD) mg/kg/day of D-mannitol (pulmonary deposition) for 14 days. Coughing occurred during and immediately after dosing in all treated groups (Incidence for M + F: 0/6-C, 1/6-LD, 4/6-MD and 4/6-HD). Spongy (4/6) and froth-filled lung (3/6) were reported in the HD group during necropsy. Microscopic examination revealed the following: lung congestion/hemorrhage (2/6-HD), and pigment in submandibular lymph node (3/6-HD); bronchoalveolitis (2/3 apiece for MD and HD males); peribronchiolar infiltration (Incidence: 0/3-C, and 3/3 apiece in LD, MD and HD in males; and 1/3-C, 1/3-LD, 2/3-HD and 0/3-HD in females); foamy alveolar macrophages in all treated females and HD males (respective incidence in control, LD, MD and HD: 1/3, 0/3/, 0/3/ and 2/3 in males and 0/3, 2/3, 2/3 and 1/3 in females) and inflammatory foci and focal hyperplasia in trachea carina (1/3-HD female). The high dose males and females also showed increases in lung weight. The study did not establish a NOAEL. The findings, however, were absent in the 26-week study at a dose (178 mg/kg/day, see below) similar to the high dose of the 2-week study.

The 26-week study ((b) (4) Study #667108) was conducted to evaluate the toxicity of inhaled mannitol. Beagle dogs (4/sex/dose) were exposed via a face mask to air, 43 or 178 mg/kg/day of D-mannitol for 26 weeks. The control and HD groups also included two additional dogs per sex to study reversibility of any lesions after a recovery period of 4 weeks. In addition to the routine toxicological evaluations, the study measured respiratory parameters, EKG, chest auscultation, and the cell numbers in the bronchoalveolar lavage fluid. Coughing occurred in both LD and HD groups while the histological changes occurred in the HD group only. Histological changes in the HD group included laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node; but incidences were low (1/4 in each sex) and severity was minimal. Both lesions were reversible after a recovery period of 4 weeks. The review NOAEL was 43 mg/kg/day.

Genetic toxicology:

Mannitol is non-genotoxic. Studies conducted by the National Toxicology Program showed that D-mannitol tested negative in bacterial gene mutation assays, an *in vitro* mouse lymphoma assay, and an *in vivo* mouse micronucleus assay. Mannitol also tested negative in a dominant lethal assay in rats, an *in vivo* rat bone marrow study and an *in vitro* study using WI-38 human cells.

Carcinogenicity:

Mannitol is non-carcinogenic. The National Toxicology Program conducted 2-year dietary carcinogenicity studies of D-mannitol in F344/ N rats and B6C3F1 mice. Groups of 50 rats and 50 mice of each sex were fed diets containing 0%, 2.5% or 5% D-mannitol for 103 weeks. These concentrations correspond to nominal doses of 0, 3,750, 7,500-mg/kg/day. No evidence of carcinogenicity was found in either rats or mice of either sex.

Reproductive Toxicity:

Mannitol is non-teratogenic. According to the Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol, "Mannitol was tested for teratogenic effects in mice, rats, and hamsters. Pregnant mice and rats given oral doses of mannitol up to 1.6 g per kg for 10 consecutive days and hamsters up to 1.2 g per kg for 5 consecutive days showed no effects on maternal or fetal survival." http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm.

Local Tolerance:

Mannitol tested negative in an eye irritation study in rabbits (Report No. X1S 003/134081) and an *in vitro* corneal opacity and permeability study in bovine eyes (Report No. X1S 003/034088).

2.6.6.2 Single-dose toxicity

Not applicable because no new data were submitted.

2.6.6.3 Repeat-dose toxicity

The application contained inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. These studies have been reviewed previously by Dr. Luqi Pei under IND 70,277. See Pharmacology and Toxicology Reviews 1, 2 and 4 (Appendix).

2.6.6.4 Genetic toxicology

The applicant submitted 3 reports of genetic toxicity tests of mannitol. These tests were conducted by the National Toxicology Program. The tests included a bacterial reverse gene mutation assay (NTP 821315 and others), an *in vitro* mouse lymphoma assay (NTP 315204), and an *in vivo* mouse micronucleus assay (NTP 90264). Each report concluded that mannitol tested negative in the assay. No detailed review of the reports is necessary based on the following considerations. It appeared that at least the bacterial gene mutation had been considered previously during the assessment of D-mannitol carcinogenicity. The National Toxicology Program Technical Report 236 (1982) which concludes that mannitol is non-carcinogenic states:

> "D-Mannitol was not mutagenic for *Salmonella typhimurium* G-46 or TA 1530 or for *Saccharomyces cerevisiae* D-3 when tested without metabolic activation (Green, 1977). Mutagenesis testing results of the National Toxicology Program at three different laboratories showed that D-mannitol was not mutagenic for *Salmonella typhimurium* TA 98, 100, 1535, and 1537 (NTP Tech. Bull., 1981). Results of a dominant lethal assay in rats at doses of 20, 200,

2,000, and 5,000 mg/ kg of D-mannitol by gavage were negative. No increases in chromosome aberrations were observed in an *in vivo* rat bone marrow study or in an *in vitro* study using WI-38 human cells (FDA, 1974). (http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr236.pdf, page 15)

It also appears that the mouse lymphoma cell assay and the *in-vivo mouse* micronucleus assay (NTP 90264) were done recently to reflect the ICH standard test battery of genotoxicity testing. Each report concluded that D-mannitol tested negative in the assay. The following information is provided for the purpose of documentation.

D-Mannitol Bacterial Reverse Mutagenesis Test [NTP Studies 315204 (1981), 79044 (1981), 4632 (1979), and 27050 (1981)]

The Four histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535 and 1537) were used to evaluate the mutagenic potential of the test item D-mannitol both in the presence and absence of metabolic activation using the preincubation method. No statistically or biologically significant increases in the number of revertants were noted in any strain of the bacterium, either with or without metabolic activation (S9). D-mannitol was considered negative under the experimental conditions.

D-Mannitol Mouse Lymphoma TK Assay (NTP Study 851315)

Mannitol at concentrations of up to 5000 µg/mL failed to consistently increase the mutation frequencies in mouse lymphoma L5178Y cells in the presence or absence of metabolic activation. D-mannitol was considered negative in the mouse lymphoma/TK+/- assay under the testing conditions.

D-Mannitol *In-vivo* Micronucleus study (NTP Study 90264)

Male Balb/C mice were given D-mannitol up to 3000 mg/kg/day (ip) for 3 consecutive days did not cause any significant increase in structural chromosome aberrations in bone marrow or circulating polychromatic erythrocytes in male mice. D-mannitol was considered negative in the mouse micronucleus assay under the testing conditions.

2.6.6.5 Carcinogenicity

No new data were submitted. The applicant submitted reports of 2-year carcinogenicity studies of D-mannitol in F344/ N rats and B6C3F1 mice completed by the National Toxicology Program (Technical Report 236, 1982). Groups of 50 rats and 50 mice of each sex were fed diets containing 0%, 2.5% or 5% D-mannitol for 103 weeks. No evidence of carcinogenicity was found in either rats or mice of either sex. It was concluded that D-mannitol is non-carcinogenic based on the NTP report.

2.6.6.6 Reproductive and developmental toxicology

No data was submitted. Information in Section 2.6.6.1 was based on the Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol (http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm).

2.6.6.7 Local tolerance

The application contained an eye irritation study in rabbits (Report No. X1S 003/134081) and an *in vitro* corneal opacity and permeability study in bovine eyes (Report No. X1S 003/034088). Dr. Luqi Pei reviewed both studies previously in a pharmacology and toxicology review completed on March 18, 2005 under IND 70,277. See Appendix 1 for the review.

2.6.6.8 Special toxicology studies

Not applicable because no data was submitted.

2.6.6.9 Discussions and Conclusion

The application has adequately evaluated the toxicity profile of inhaled mannitol. The Division previously determined that a 6-month inhalation toxicity study of the compound in the most appropriate species is adequate to support registrations of both Aridol and Bronchitol products. This determination was based on the extensive use of D-mannitol as an excipient in non-inhalation drug products. Pharmaxis has agreed to the non-clinical pre-requisite (ref.: IND 70,277, minutes of meetings on June 16, 2005, and February 15, 2006, a telephone conference on October 11, 2006; and the letter on July 26, 2006). Specifically, the agreements were:

- No additional or new studies of genetic toxicity, carcinogenicity, reproductive and developmental toxicity of mannitol are needed.
- A 6-month inhalation toxicity study in a most appropriate species is needed to support the clinical trials of 3 months or longer in the treatment duration and registration of Bronchitol®.
- Additional studies could be needed if these studies reveal safety concerns.

The above testing strategy was formed after considering the available information of D-mannitol. As being alluded to earlier, mannitol is a nutrient and/or dietary supplement and an ingredient in numerous drug products. As a dietary supplement, mannitol is GRAS compound. Medically, mannitol is used as active and inactive ingredients. As an active ingredient, mannitol is a laxative and diurectic. As an inactive ingredient, mannitol is an excipient in numerous products. The routes of administration included oral, parenteral, topical, as well as inhalation administration. Consequently, comprehensive summaries of D-mannitol toxicology are available.

Pharmaxis has submitted inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. These studies have been summarized in Section 2.6.6.1 (Overall Toxicology Summary, page 8). The studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol. They did not reveal any neoplastic or pre-neoplastic findings in the respiratory system. The completed toxicology program has adequately evaluated the toxicity profile of inhaled mannitol and no additional toxicity studies are needed. The following discussions focus on the information relevant to the labeling review of Aridol.

There are currently numerous mannitol drug products approved and currently marketed in the US. These products are exclusively for the intravenous route of administration. Their labels do not describe the carcinogenic, genotoxic and reproductive toxicity potential of mannitol due to historic reasons: nonclinical studies were conducted after the approval of the listing reference product. Aridol is for the inhalation route of administration. It is reasonable to include the available nonclinical information in its labeling.

Carcinogenicity: Dietary mannitol is non-carcinogenic in laboratory animals. The National Toxicology Program conducted 2-year dietary carcinogenicity studies of D-mannitol in F344/ N rats and B6C3F1 mice. Groups of 50 rats and 50 mice of each sex were fed diets containing 0%, 2.5% or 5% D-mannitol for 103 weeks. These concentrations correspond to nominal doses of 0, 3,750, 7,500-mg/kg/day mannitol. No evidence of carcinogenicity was found in either rats or mice of either sex. See the NTP Technical Report No. 236 (1982) at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr236.pdf. The nominal dose was provided by the Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol at http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm.

Additional studies have been completed recently using alternative animal models. An example is a 9-month dietary study in transgenic DNA repair-deficit Xpa-/- mice and double transgenic Xpa-/- p53+/- mice by Lina et al (*Toxicol Pathol,* 2004;32:192-201). Mannitol doses were 2%, 5% and 10% of diet. The study did not reveal any carcinogenic potential of mannitol. The study contained other 3 compounds: haloperidol, reserpine and phenacetin. The study assumed that D-mannitol was non-carcinogenic and used mannitol as a negative control.

A shortcoming of the available data is that the carcinogenicity studies may not reflect the effect of inhaled mannitol on the respiratory system. This concern has been alleviated by the finding that inhalation toxicity studies up to 6 months in treatment duration submitted did not reveal any evidence of pre-neoplastic or neoplastic change. The carcinogenicity evaluation of the inhaled mannitol is now considered adequate.

It is recommended that the Aridol labeling includes the NTP studies only. This recommendation is consistent with the applicant's proposal. The Lina study should not be used because it considered D-mannitol non-carcinogenic in the study design.

Mutagenicity: Assays assessing mutagenic potential and their results were summarized in Section 2.6.6.4 (page 11). All assays were conducted by the National Toxicology Program and FDA. The tests included a bacterial reverse gene mutation assay, an *in vitro* mouse lymphoma assay, and an *in vivo* mouse micronucleus assay, a dominant lethal assay in rats, an in vivo chromosomal aberrations assay in rat bone marrow and an *in vitro* test using WI-38 human cells. The applicant proposed to include the following 3 assays: a bacterial reverse gene mutation assay, an *in vitro* mouse lymphoma assay and an *in vivo* mouse micronucleus assay. The remaining assays should also be mentioned in the labeling.

Developmental Toxicology: This application did not conduct or submit any developmental toxicity studies. This is considered acceptable because D-mannitol is a GRAS compound. The Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol states:

> "Mannitol was tested for teratogenic effects in mice, rats, and hamsters. Pregnant mice and rats given oral doses of mannitol up to 1.6 g per kg for 10 consecutive days and

hamsters up to 1.2 g per kg for 5 consecutive days showed no effects on maternal or fetal survival." See http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm.

The applicant in Section 2.4.5.5 also provided the following summary information from literature review:

"As part of an embryotoxicity study, rats were administered mannitol intravenously at a dose rate of approximately 150 mg/kg once a day from days 6 to 15 of gestation. Mannitol was administered in combination with tartaric acid (0.06 mg/mL) and acted as the vehicle control. All pregnant females were euthanized on gestation day 20 and a complete uterine, placental and foetal examination was carried out. No significant compound-related effects were detected in the dams or in embryonic development.

A single dose of mannitol (550 mg/kg) was administered subcutaneously to pregnant rabbits on gestation day 12. On gestation day 29 the pregnant rabbits were euthanized and fetuses examined. No gestational and developmental toxicity as a result of treatment was seen. It can therefore be concluded that mannitol had no effect on embryonic development in rabbits after a single 550 mg/kg dose of mannitol".

Mannitol developmental toxic potential was evaluated in a chick embryo neural retina cell assay. Mannitol did not affect *in vitro* cell aggregation, growth or differentiation at concentrations up to 40 mM. It was therefore concluded that mannitol did not exhibit developmental toxic potential and did not have any effect on embryonic cell development."

The applicant proposed to include in the Aridol labeling oral teratogenicity studies in mice, rats (b) (4). The review agrees with the proposal to include the mouse and rat study although the treatment duration was slightly shorter than the currently acceptable standards.

(b) (4)

2.6.6.10 Tables and Figures

Not applicable because no data was submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The application has adequately evaluated the toxicity profile of inhaled mannitol. The applicant has submitted inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory system as the target organs of toxicity. The study did not reveal any neoplastic or pre-neoplastic findings.

The completed studies are considered adequate to support the registration of Aridol. The approval of Aridol is recommended from the nonclinical perspective.

Mannitol is used as a nutrient and/or dietary supplement and an ingredient in numerous drug products. As a dietary supplement, mannitol is considered generally recognized as safe [GRAS, 21CFR§582.5470]. Medically, mannitol has been used as active and inactive ingredients. As an active ingredient, mannitol is a laxative and diurectic. As an inactive ingredient, mannitol is an excipient in numerous products. The routes of administration included oral, parenteral (e.g., IV, and IP), and topical administration. Mannitol was also present as an inactive ingredient of an inhaled insulin product, Exubera® (NDA 21-868, approved on January 27, 2006).

The mannitol toxicology by non-inhalation use is well understood. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. The National Toxicology Program evaluated carcinogenicity and mutagenicity of D-mannitol. It concluded that F344/N rats and B6C3F1 mice fed with up to 5% D-mannitol in diet for 103 weeks did not reveal any evidence of tumorigenicity. Mannitol was non-genotoxic in a bacterial mutation assay, an *in vitro* mouse lymphoma cell assay, an *in vivo* mouse micronucleus assay and other assays. The Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol considered D-mannitol non-teratogenic.

Due to the extensive clinical and nonclinical data available on mannitol, the toxicology program of the current application focused on effects of inhaled mannitol, particularly its effect on the respiratory system. The Division determined in the 19-JUL-2004 pre-IND meeting that 14-day inhalation toxicity studies in 2 species (one in each species) were needed to support the registration of Aridol.

Pharmaxis has submitted inhalation toxicity studies of mannitol up to 3 and 6 months in rats and dogs, respectively. These studies were reviewed previously and summarized in detail in Section 2.6.6.1. Briefly, the studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol. The studies did not reveal any neoplastic or pre-neoplastic findings in the respiratory system. The completed toxicology program has adequately evaluated the toxicity profile of inhaled mannitol and no additional toxicity studies are needed.

Unresolved toxicology issues (if any): None.

Recommendations: Approval of Aridol is recommended pending labeling review from the nonclinical perspective.

Luqi Pei, Ph.D.
Senior Pharmacologist

Appendix:
1. Pharmacology review No. 4
2. Pharmacology review No. 2
3. Pharmacology review No. 1

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number: 70,277
Review Number : 4
Sequence number/date/submission type: 035/ 31-JUL-07/ IT
036/ 1-AUG-07/ SM
037/ 6-AUG-07/ SM
Information to the Sponsor: Yes ( ), No (x)
Sponsor/or Agent: Pharmaxis Ltd, 1840 Gateway Dr., San Mateo, CA 94404

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: November 29, 2007

Drug:
Trade Name: Bronchitol®, Aridol®
Generic Name: D-Mannitol
CAS Register Number: 69-65-8

Drug Class: Sugar

Intended clinical population: Cystic fibrosis (b) (4)

Route of Administration: Inhalation (DPI)

Clinical Formulations: Blisters filled with 40-mg D-mannitol powder.

Proposed Clinical Protocols: Pharmaxis submitted two new clinical protocols as Requests for Special Protocol Assessments on August 1 and 8, 2007 (Serial 036 and 037). (b) (4) Protocol DPM-CF-302 is a cystic fibrosis trial in patients 6 years and older. Mannitol doses will be (b) (4) 400 mg, bid, in (b) (4) cystic fibrosis diseases, respectively. The treatment duration is 6 months for protocols. Table 1 provides an overview of these protocols.

Table 1 Overview of the Proposed Clinical Trials of Mannitol

Protocol No.	Submission Date	Disease	Mannitol		Patient		
			mg/day	Treatment (mo.) [a]	Number	Sex	Age (yr)
(b) (4)							
DPM-CF-302	06-AUG-07	Cystic fibrosis	800	6	250	M/F	≥ 6

a. The treatment may be extended to 12 months.

Previous Human Experience: The sponsor is conducting clinical trials of Bronchitol® (320 or 400 mg, bid for up to 9 months) in Australia. The sponsor states that a 3-month trial involving 343 bronchiestasis patients was completed. (b) (4) cystic fibrosis trials

involving 250 patients for 6 months and 118 patients for 9 months in are currently ongoing. Mannitol doses were 640 and 800 mg/day for the (b) (4) cystic fibrosis indications, respectively. Aridol® (single-dose broncho-provoking diagnostic agent) is currently marketed in Australia (the March 28, 2006 submission, Serial No. 017).

Drug History:

Pharmaxis is developing Bronchitol® (mannitol dry powder) for (b) (4) cystic fibrosis indications. (b) (4) are in clinical phase-2 developmental stage in this country and phase-3 development outside the country. (b) (4) In the cystic fibrosis program, both 3- and 6-month clinical trials (one each) are currently on-going (Serial No. 37). Mannitol doses were (b) (4) for (b) (4) cystic fibrosis trials, respectively.

In planning phase-3 clinical trials for (b) (4) cystic fibrosis indications, Pharmaxis submitted two clinical protocols as Special Protocol Assessment requests. (b) (4) Protocol DPM- DPM-CF-302 a 6-month clinical trial in cystic fibrosis patients. (b) (4) may be extended to 12 months. Table 1 (previous page) provides an overview of these protocols.

This is the first time that the Division handled Protocol DPM-CF-302, but the Division had reviewed a similar protocol previously. Submitted on 15-AUG-2006 (Serial No. 026), Protocol DPM-CF-301 proposed to treat patients of cystic fibrosis 6 years of age and older with 50 – 400 mg mannitol, bid, for 6 months. Dr. Luqi Pei completed a nonclinical safety evaluation of the protocol on 05-OCT-2006. The review found that Pharmaxis had not complied with the nonclinical pre-requisite for the proposed clinical trial. Specifically, Pharmaxis had not submitted any 6-month toxicity study that is necessary to support the proposed clinical study. The review recommended placing the protocol on a Clinical Hold. The Division informed Pharmaxis of the hold decision via a telephone conference on October 11, 2006. Pharmaxis withdrew the protocol on the same day and is currently conducting the study outside of the country.

Pharmaxis submitted a draft report for a 6-month inhalation toxicity study of mannitol in dogs as pivotal nonclinical data to support the proposed clinical trials on July 31, 2007 (Serial No. 035). This document: 1) reviews the toxicity study; 2) determines whether the study satisfies the pre-requisite of the 6-month study; and 3) determines whether the study support nonclinically the safety of the proposed clinical protocols.

Studies Submitted and Reviewed in the Review:

Mannitol 26 weeks inhalation toxicity study in beagle dogs with a 4-week recovery period ((b) (4) report# 26966 and Study# 667108). Submitted on 31-JUL-2007 (Serial No. 035), electronic submission.

Studies Submitted but Not Reviewed in this Review:

Mannitol investigative dose inhalation toxicity study in rats ((b) (4) report# 26482 and Study# 66985). Submitted on 31-JUL-2007 (Serial No. 035), Vol. 35.1, attachment 2.

Mannitol 2 weeks inhalation toxicity study in dogs with ((b) (4) report# 26050 and Study# 666357). Submitted on 31-JUL-2007 (Serial No. 035), Vol. 35.1, attachment 3.

These two final study reports were not reviewed because Dr. Luqi Pei had reviewed their draft reports previously. (See Pharmacology and Toxicology Review No. 2 completed on 21-JUL-2006.) There were no changes in study results and conclusions between the draft and final reports. A review of the final reports is not necessary.

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

2.6.6.1 Overall Toxicology Summary

Repeat-Dose Toxicology:

A 6-month inhalation toxicity study in dogs ((b) (4) Study #667108, Serial No. 035) was conducted to evaluate the toxicity inhaled mannitol. Beagle dogs (4/sex/dose) were exposed via a face mask to air, 43 or 178 mg/kg/day of D-mannitol for 26 weeks. The control and HD groups also included two additional dogs per sex to study reversibility of any lesions after a recovery period was 4 weeks. In addition to the routine toxicological evaluations, the study measured respiratory parameters, EKG, chest auscultation, and the cell numbers in the bronchoalveolar lavage fluid. Coughing occurred in both LD and HD groups while the histological changes occurred in the HD group only. Histological changes in the HD group included laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node although their incidences were low (1/4 in each sex) and severity was minimal. Both lesions were reversible after a recovery period of 4 weeks. The review NOAEL was 43 mg/kg/day.

2.6.6.3 Repeat-Dose Toxicity

Study Title: Mannitol 26 weeks inhalation toxicity study in beagle dogs with 4 weeks recovery period. Submitted on 31-JUL-2007 (Serial No. 035), electronic submission.

Key findings:

- Beagle dogs (4/sex/dose) were exposed by inhalation to 0, 43 and 178 mg/kg/day (pulmonary deposit) of mannitol for 26 weeks.

- The HD dogs coughed throughout the study and showed low incidence (1/4 in each sex) of minimal ulceration in the larynx and sinus histiocytosis in the mediastinal lymph node.
- All findings were reversible after a recovery period of 4 weeks.
- The NOAEL was 43 mg/kg/day.

Study number:	(b) (4) Study #667108 and Report #26966
Volume #, and page #:	Not available for electronic submission (31-JUL-07, Serial 035)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 18, 2006
Study complete date:	April 11, 2007
Report date:	N/A
GLP compliance:	Yes, with an unsigned GLP statement
QA reports:	Yes, with an unsigned GLP statement
Drug lot # & purity:	Batches # 3M021, 3M24, 3M28, EXP001 - 5, EXP007; purity: 98- 102%
Formulation/vehicle:	Mannitol dry powder

Method:

Beagle dogs (4/sex/dose) were exposed by inhalation to 0, 43 and 178 mg/kg/day (pulmonary deposit) of mannitol for 26 weeks. The control and HD groups also included two additional dogs per sex to study reversibility of any lesions after a recovery period was 4 weeks. The exposure was achieved via a face mask through inhaled air containing 0, 0.20 and 8.7 mg/L of mannitol particles for the control, low and high dose groups for 120 minutes/day.[1] The daily exposure was divided into two episodes of 60 minutes, with an interval of at least 2 hours between the episodes. The mean mass median aerodynamic diameter (MMAD) was 3.2 and 3.3 μm in LD and HD groups, respectively. Pulmonary and achieved doses were calculated from measured minute volumes, chamber mannitol concentrations, body weights and MMADs and applicable theoretic deposition factors. [See footnote a in Table 2] In addition to the routine toxicological evaluations, the study also measured respiratory parameters, EKG, chest auscultation, and the cell numbers in the bronchoalveolar lavage fluid. A complete list of organs and tissues were examined microscopically in both the main section and recovery dogs.

Species/strain:	Dogs, Beagle
#/sex/group:	4
Age:	Approximately 5.5 - 6 months
Weight:	M: 7.0 – 10.9 kg; F: 6.3 – 9.6 kg

(b) (4)

Doses in administered units: 0, 43, or 178 mg/kg/day (pulmonary deposits)
Route, form: Inhalation via a face mask, dry powder, 120 minutes/day (60 minute/episode, 2 episodes/day, ≥ 120 minutes between episodes)

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Daily
Ophthalmoscopy:	Pretreatment and Weeks 7, 13, 26 and end of recovery
Respiratory system:	Respiratory rate, tide volume and minute volume at pretreatment and weeks 1, 7, 13 and 26
ECG:	Immediately after dosing at pretreatment and weeks 7, 13 and 26
Chest Ausculation:	Biweekly
Hematology:	Pretreatment and weeks 7, 13 and 26
Clinical chemistry:	Pretreatment and weeks 7, 13 and 26
Urinalysis:	Pretreatment and weeks 7, 13 and 26
Bone marrow smear:	Not evaluated although samples were collected at necropsy
Bronchoalveolar lavage:	Right lobe at necropsy
Gross pathology:	Sacrifice time
Sacrifice method:	Pentobarbitone (IP)
Organs weighed:	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, pancreas, pituitary, prostate, salivary gland, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus
Histopathology:	A complete panel – all animals in all groups were examined. Adequate Battery: yes (x), no ( ) Peer review: yes (x), no ( )
Toxicokinetics:	Day 1 and weeks 13 and 26, at hours 0.5, 1, and 2 after 1st and 2nd dose; and hours 4 and 18 (2nd dose only)

Results

Dose estimates: Table 3 (below) presents the dose estimates of the study. The estimated pulmonary deposition was 43 and 178 mg/kg/day for the low and high dose groups, respectively.

Table 2 Estimated Pulmonary Deposits in the 26-Week IH Study in Dogs

Treatment	Dose	Aerosol			Exposure (mg/kg/day)	
		MMAD (μm) [a]	GSD	Drug (mg/L)	Achieved Dose [a]	Pulmonary Deposit [b]
Air	0	-	-	-	-	-
Mannitol	LD	3.22	2.17	2.0	171.2	43
	HD	3.29	2.18	8.7	712.8	178

a. Achieved dose in the study report. Achieved delivered dose levels were estimated using the formula: Dose (mg/kg/day) = (MV x T x CC)/BW; where MV = Minute volume (overall group mean value from actual recorded results in the study), T = Duration of exposure (minutes), CC = Gravimetric chamber concentration of Mannitol = mg/L, and BW = Mid-week individual body weight in kg.

b. Converted from the achieved dose using a deposition factor (0.25). Pulmonary deposits (mg/kg/day) = Achieved dose (mg/kg/day) x 0.25 (pulmonary deposition factor). For example, the pulmonary deposition for the HD = 99 x 0.25 = 25 mg/kg/day.

Mortality: None.

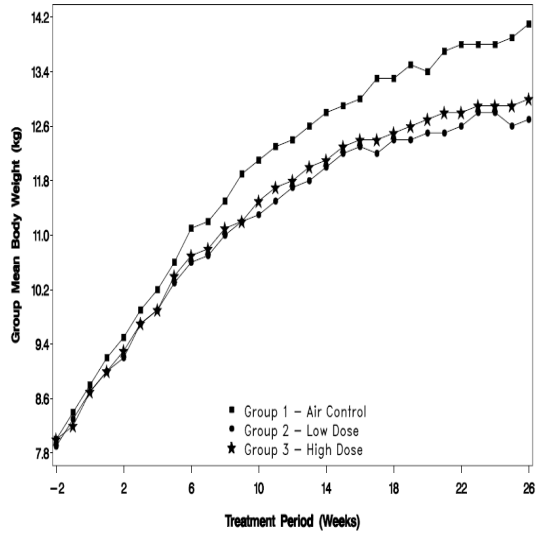
Clinical Signs: Cough mostly occurred in the HD dogs. Table 3 (below) presents the incidence of coughing at major milestones of the study. Coughing occurred during and post dosing in the HD group throughout the study, but only in the first week in the LD group

Table 3 Coughing In the 26-Week Inhalation Toxicity Study in Dogs

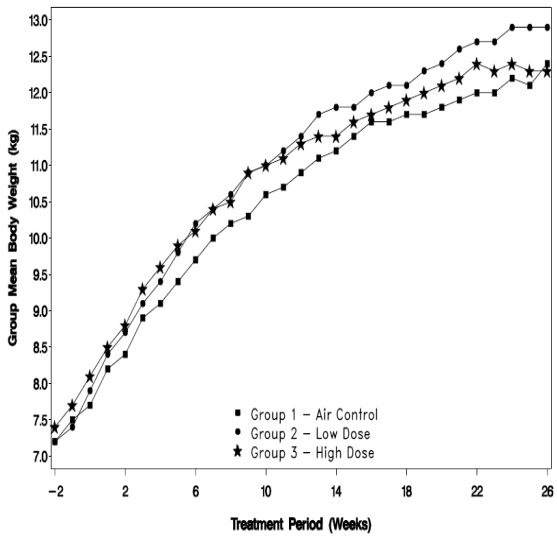
Time	Incidence of Coughing (M & F combined) [a]							
	43 mg/kg/day Mannitol (n = 56)				178 mg/kg/day Mannitol (n = 84)			
	Minimal	Moderate	Marked	Total	Minimal	Moderate	Marked	Total
Week 1 [b]				10				50
Week 4	0	0	0	0	2	8	3	13
Week 9	0	0	0	0	0	22	1	23
Week 13	1	0	0	1	18	7	1	26
Week 17	0	0	0	0	26	6	1	33
Week 22	0	0	0	0	14	5	3	22
Week 26	2	0	0	2	11	11	0	11

a. The control group is not listed because no coughing was observed in either sex at any time.
b. The severity of cough was not graded in Week 1.

Body Weight: Figure 1 presents the body weight-time course of the study in both sexes. Both LD and HD male dogs showed decreases in body weight throughout the study. The females, however, did not show significant changes in body weight from the control group. At the end of the study, the decrease in the mean body weight of the male LD and HD groups was 9.9% and 7.8%, respectively. [The actual body weight was 14.1, 12.7 and 13.0 kg for the C, LD and HD groups, respectively].



Males



Females

Figure 1. Body weight in 26-week inhalation toxicity study of mannitol in dogs ((b) (4) Study #667108). Mannitol dose (pulmonary deposits) was 0, 43 and 178 mg/kg/day for the control, low dose and high dose groups, respectively.

Food Consumption: No treatment-related effect was observed.

Ophthalmoscopy: No treatment-related effect was observed.

Respiratory parameters: No treatment-related effect was observed in respiratory rate, minute volume and tidal volume.

ECG: No treatment-related effect was observed.

Hematology: No treatment-related effect was observed.

Clinical Chemistry: No treatment-related effect was observed.

Urinalysis: No treatment-related effect was observed.

Organ weight: No treatment-related effect was observed.

Gross pathology: No treatment-related effect was observed.

Histopathology: Microscopic changes were limited to the respiratory system in the HD group. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node (1/4 each in both sexes) were observed. No abnormalities were observed in the recovery dogs.

Blood mannitol concentrations: Mannitol was detected in the blood of both LD and HD dogs (Figure 2). The mannitol concentrations appear to dose-related. There is no significant change in the blood mannitol concentrations with increased dosing duration.

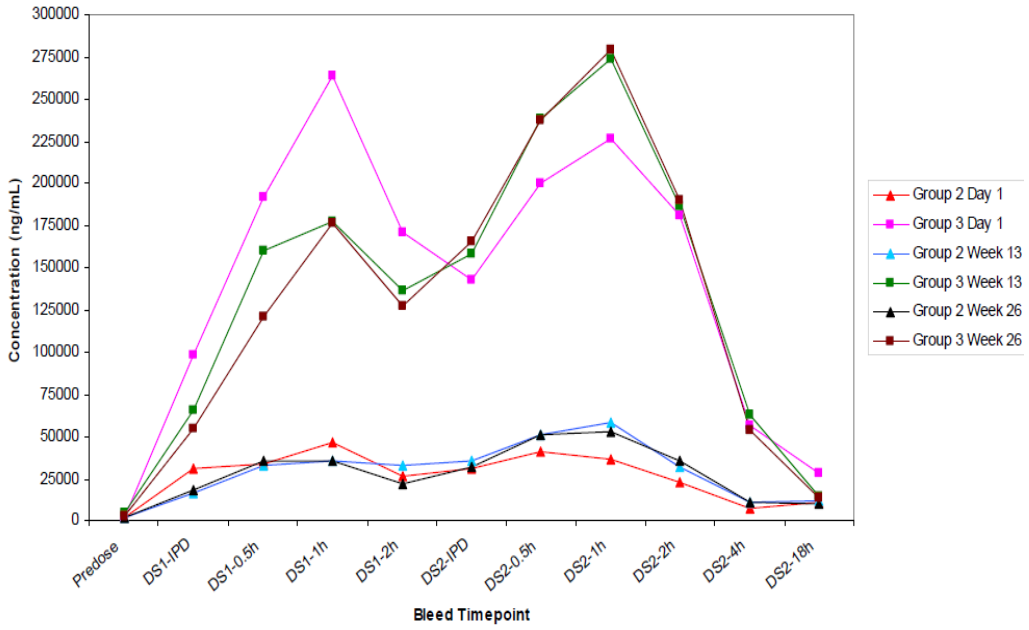


Figure 2. Plasma mannitol concentrations after inhalation exposures in dogs. The estimated pulmonary deposits were 43 and 178 mg/kg/day for Groups 2 and 3, respectively. DS1 and DS2 indicate first and second dosing episodes of the day, respectively. Each episode lasted 60 minutes.

2.6.6.9 Discussions and conclusions

The following discussion focuses on the selection of the appropriate species for the safety evaluation of inhaled D-mannitol. The discussion concludes that the dog may be accepted as the most appropriate species despite of some minor deficiency in the nonclinical data of the application.

The Division previously determined that a 6-month inhalation toxicity study of the compound in the most appropriate species is adequate to support the safety of clinical trials exceeding 13 weeks in the treatment duration and product registration. This determination was based on the extensive use of D-mannitol as an excipient in non-inhalation drug products. Pharmaxis has agreed to the non-clinical pre-requisite (ref.: minutes of meetings on June 16, 2005, and February 15, 2006 and a telephone conference on October 11, 2006; a letter issued on July 26, 2006). Specifically, the Division and Pharmaxis agreed:

- No additional or new studies of genetic toxicity, carcinogenicity, reproductive and developmental toxicity of mannitol are needed.
- A 6-month inhalation toxicity study in a most appropriate species is needed to support the clinical trials of 3 months or longer in the treatment duration and registration of Bronchitol®.
- Additional studies could be needed if these studies reveal safety concerns.

Pharmaxis and the Division, however, have not reached an agreement on the choice of species for the 6-month inhalation toxicity study. Pharmaxis initially argued that the rat was the most appropriate species (Prior to March 6, 2006, Serial No. 012). The division responded that the appropriateness of the rat should be supported by adequate data. Pharmaxis quickly changed its position and argued that the dog was the most appropriate species (the March 30, 2006 submission, Serial No. 016). Pharmaxis reasoned that the dog was the most appropriate species because higher exposures of mannitol could be achieved. On June 21, 2006, Dr. Luqi Pei completed a review of Pharmaxis' rationales (Ref.: Pharmacology and Toxicology Review #3). The review concluded that Pharmaxis had not demonstrated that the dog was the species of choice for the 6-month study. On July 26, 2006, the Division issued a letter stating the following:

> "We are currently unable to concur with your proposal to study dogs for chronic administration of mannitol in order to support chronic clinical administration and a marketing application. In order to support selection of the most appropriate species, we recommend that you conduct a 2- or 13-week GLP-compliant inhalation toxicity study of D-mannitol in dogs."

On 11-OCT-2006, the Division via a telephone conference reiterated the necessity for a 6-month inhalation toxicity study in the most appropriate species in support of the long-term clinical trial. The meeting minutes state that "the selection of the most appropriate species should be based on the results of 2- or 13-week GLP compliant inhalation toxicity studies of D-mannitol in 2 species with comparable characteristics, and identification of a NOAEL."

In the 31-JUL-2007 submission, Pharmaxis submitted a draft report of the 6-month inhalation toxicity study in dogs and a document entitled "*Summary of Completed Mannitol Nonclinical Studies and Justification of Species Selection*". The results of the dog study have

been discussed earlier in the review. The document argues that the dog is the most appropriate species in the nonclinical safety evaluation of inhaled mannitol. The position was based on the following: 1) Higher inhaled dose of mannitol can be delivered to the pulmonary region in dogs than in rats, whether on a basis of mg/kg body weight, mg/g lung weight or on a mg/m^2 lung surface area, although both rat and dog studies employed the maximum feasible dose. 2) The low delivery rate in rats was attributed to both the respiratory physiology and the aerosol generating apparatus. For example, the same device (i.e., a rotating brush aerosol generator) generated only 25% respirable particles in rats. In comparison, approximately 85% or more particles were respirable in dogs. 3) The dogs (including the high dose group) in the 6-month study showed no treatment-related toxicity other than coughs immediately after dosing. As such, the sponsor concludes that the high dose is the NOAEL. The review disagrees with the sponsor since the HD dogs also showed histological changes in larynx (ulcer) and mediastinal lymph node (histiocytosis). Thus, the NOAEL dose in the 26-week dog study is the low dose (43 mg/kg/day) rather than the high dose (178 mg/kg/day).

The sponsor's arguments have merits, but also apparent deficiencies. The completed and submitted inhalation toxicity studies of mannitol include 1, 2 and 13-week studies in rats and 2 and 26-week studies in dogs. Table 4 (below) presents the major characteristics of the completed inhalation toxicity studies of mannitol. The dogs apparently achieved higher inhaled doses than rats, but it is unknown whether both rats and dogs used the maximal feasible dose although the sponsor claimed so. The lower fraction of respirable particles in rats could be attributed more to the aerosol generating device and exposure system than species physiology.

Table 4 Characteristics of Mannitol Inhalation Toxicity Studies

Species	Rat [c]			Dog	
Study duration	1-WK	2-WK	13-Wk	2-WK	26-WK
Report No.	26482	33951	413185	26050	26966
GLP compliance	No	Yes	Yes	Yes	Yes
Conducting laboratory	[redacted] (b) (4)				
n/sex/dose	5	10	10	4	4 (2)[b]
Treatment duration (min./d)	120 - 240	60	180	120	120
Mannitol					
Aerosol concentration (mg/L)	5.2, 9.1	0, 0.26, 0.88, 2.8	0, 1.8, 2.9	0, 1.1, 3.2, 9.2	0, 2.0, 8.7
Pulmonary deposit (mg/kg/day)	54, 98	0, 0.9, 2.5, 6.9	0, 12.4, 21.0	0, 25, 100, 197	0, 43, 178
BALF concentration (µg/ml)	40.2, 37.7	-	0, 3.8, 3.2	-	-
MMAD (µm)	2.9, 3.6	0, 2.4, 3.7, 4.7	0, 3.9, 4.4	0, 2.6, 2.6, 0.9	0, 3.2, 3.3
NOAEL(mg/kg/day)	< 54	6.9	< 12.4	< 25	43

a. [redacted] (b) (4) - = not determined.
b. Number of animals in the recovery groups (control and HD only). The recovery period was 4 weeks in duration.
c. Source: Pharmacology and toxicology review (#2) completed by Dr. Luqi Pei on July 26, 2006. An exception is the 26-week study that is from the current review.

As discussed in the pharmacology and toxicology review (#2) completed by Dr. Luqi Pei on July 26, 2006, the completed toxicity studies vary in a number of areas: study designs, GLP-

compliance, mannitol aerosol concentration, daily exposure duration, estimated pulmonary deposition, mannitol concentrations in the BALF, aerosol MMAD and identification of NOAEL values. These variations make it difficult to compare the dose-response and species sensitivity to inhaled mannitol between rats and dogs. Ideally, studies in both rats and dos comparable treatment duration and pulmonary deposited dose should be submitted so that the most appropriate species can be determined based on sound science. That means that additional 2- or 13-week inhalation toxicity study of D-mannitol in dogs, even a 6-month inhalation study in rats, should be completed and submitted. However, due to the many factors indicated above, it is uncertain if the most appropriate species can be truly determined. Neither is it clear how much added values these studies would provide should they be completed. The review, thus, considers that the dog study has fulfilled the requirement of the 6-month inhalation toxicity study in the most appropriate species.

OVERALL EVALUATION AND RECOMMEDATION

Summary

This review finds no significant safety concerns about the (b) (4) proposed clinical protocols. The proposed clinical dose of mannitol (b) (4) cystic fibrosis patients, respectively. The sponsor has completed a toxicology bridging program to support chronic inhalation administration of mannitol by conducting a 6-month toxicity study in dogs in addition to shorter-term studies in rats and dogs. The Division considers this toxicology program to be adequate. The NOAEL in the 6-month inhalation toxicity of mannitol in dogs is 43 mg/kg/day. The NOAEL provides safety margins of 2.7 – 3.4 on a mg/kg basis. These margins are smaller than the generally accepted safety margin of 6, but are considered acceptable since the dose-response curve of inhaled mannitol is rather shallow in dogs. At a high dose (178 mg/kg/day) that is four times the NOAEL, a low incidence (1/4 in each sex) and minimal in severity of laryngeal ulceration and histiocytosis in mediastinal lymph node was observed. These findings are completely reversible after a recovery period of 4 weeks. Laryngeal ulceration is also considered a clinically monitorable response. Histiocytosis in mediastinal lymph node is considered a defense (clearance) mechanism of the inhaled particles. The histological changes associated with the mannitol inhalation in dogs are not considered significant safety concerns regarding the proposed use of the drug.

Finally, clinical experience at the proposed doses and in the disease populations is available to evaluate the safety of the proposed of the drug. The sponsor is conducting up to 9-month clinical trials of Bronchitol® (320 or 400 mg, bid) in Australia. (b) (4) cystic fibrosis trials involving 250 patients for 6 months and 118 patients for 9 months in are currently ongoing. Mannitol doses were 640 and 800 mg/day for the (b) (4) cystic fibrosis indications, respectively. Aridol® (single-dose broncho-provoking diagnostic agent) is currently marketed in Australia (the March 28, 2006 submission, Serial No. 017). Overall, the review finds the available nonclinical data supportive of the proposed clinical protocols. It is recommended that these clinical protocols be allowed to proceed.

In addition to the 6-month dog study, the sponsor conducted inhalation toxicity studies up to 13 weeks in rats and dogs. Table 5 (below) presents an overview of these toxicity studies, including the 6-month study. These studies identified the respiratory system as the target organ of toxicity for inhaled mannitol.

Table 5 Overview of Inhalation Toxicity Studies of Mannitol

Study #	Species	Duration	Mannitol (mg/kg/day) [a]	NOAEL
26482/666958[b]	Rat	7 days	57.3, 97.9	None
XIS 002/033951	Rat	2 weeks	0, 0.9, 2.5, & 6.9	6.9
XIS 005/0413185	Rat	13 weeks	0, 12.4, 21.0	None [c]
26050/666386	Dog	2 weeks	0, 25, 100, 197	None [d]
26966/667108	Dog	26 weeks	0, 43, 178	43 [e]

a. Estimated pulmonary deposits.
b. A non-GLP compliant investigative dose-ranging study. The study did not show the dose-related increase in the concentration of mannitol in the bronchoalveolar fluid. Neither did it examine the lung tissue microscopically.
c. The review is in agreement with the study report in determination of NOAEL.
d. The report states that the 197 mg/kg/day dose is "well-tolerated."
e. The report considers the NOAEL as 178 mg/kg/day.

A 7-day non-GLP dose-ranging inhalation study was conducted to investigate the achievement of pulmonary delivery of mannitol to the lung in Sprague-Dawley rats. Rats (5/sex/dose) were exposed nose-only to approximately 5 or 9 mg of mannitol/L of air for 120 to 240 minutes/day for 7 days. The rats were sacrificed immediately after the last exposure. The amount of mannitol delivered to the lung was determined by measuring mannitol concentrations in the bronchoalveolar fluid (3/sex/dose). The respective estimated achieved dose of mannitol was 573 and 979 mg/kg/day for the low-dose and high-dose groups, respectively. The respective mean mannitol concentration in BALF for the low and high dose groups was 36.7 and 42 μg/ml in males and 43.6 and 33.4 μg/ml in females. Necropsy did not reveal any treatment-related effect. Microscopic examination was not done.

In a 2-week rat study (XIS 002/033951), CD-1 rats (10/sex/dose) were given via nose-only inhalation pulmonary deposited doses of 0, 0.9, 2.5 and 6.9 mg/kg of mannitol for 14-days. Histological evaluations of the respiratory system were done in every group. The remaining organs were examined in the control and high-dose groups only. No significant, treatment-related effects were observed. The NOAEL was 6.9 mg/kg/day.

In a 2-week dog study (XIS 005/0413185), beagle dogs (3/sex/group) were exposed by inhalation via a face mask to air (C), 25 (LD), 100 (MD) or 197 (HD) mg/kg/day of D-mannitol (pulmonary deposition) for 14 days. Coughing occurred during and immediately after dosing in all treated groups (Incidence for M + F: 0/6-C, 1/6-LD, 4/6-MD and 4/6-HD). Spongy (4/6) and froth-filled lung (3/6) were reported in the HD group during necropsy. Microscopic examination revealed the following: lung congestion/hemorrhage (2/6-HD), and pigment in submandicular lymph node (3/6-HD); bronchoalveolitis (2/3 apiece for MD and HD males); peribronchiolar infiltration (Incidence: 0/3-C, and 3/3 apiece in LD, MD and HD in males; and 1/3-C, 1/3-LD, 2/3-HD and 0/3-HD in females); foamy alveolar macrophages

in all treated females and HD males (respective incidence in control, LD, MD and HD: 1/3, 0/3/, 0/3/ and 2/3 in males and 0/3, 2/3, 2/3 and 1/3 in females) and inflammatory foci and focal hyperplasia in trachea carina (1/3-HD female). The high dose males and females also showed increases in lung weight. The study did not establish a NOAEL.

In a 13-week rat study (26050/666386), Sprague-Dawley rats (10/sex/group) were given via nose-only inhalation air (C), 12.4 (LD), or 21.0 (HD) mg/kg/day (pulmonary deposition) for 13 weeks. Additional rats (5/sex) were included in the control (RC) and high dose (RHD) groups to evaluate reversibility of lesions after a recovery period of 4 weeks. The duration of exposure was 180 minutes/day. D-mannitol concentrations were 0, 1.83 or 2.89 mg/L for the control, LD and HD groups, respectively. The estimated pulmonary deposition of D-mannitol was 0, 12.4 and 21.0 mg/kg/day for the control, LD and HD groups, respectively. D-mannitol contents in the bronchoalveolar fluid were approximately 0, 3.8 and 3.2 µg/ml for the control, LD and HD groups, respectively. Both the LD and HD females showed statistically significant decreases in body weight gain (approximately 20%). Clinical pathology examinations revealed minimal decreases (approximately 50% or less) in white blood cell numbers and increases (12-30%) in serum phosphorus in the HD group. Microscopic examinations revealed increases in the incidence of alveolar macrophage aggregation and alveolitis. The respective incidence of alveolar macrophage aggregation in the C, LD, HD, RC and RHD was 3/10, 6/10, 9/10, 0/2 and 1/2 in females and 4/10, 5/10, 3/10, 1/1 and 3/4 in males. The increase in the incidence of alveolitis was observed in the high-dose male only (incidence: 0/10-C, 0-/10-MD, 1/10-HD, 0/1-RC, and 2/4-RHD, respectively). The most significant, treatment-related effect, but of no safety concern for the intended use of mannitol, was seen in the nasal cavity. Both the low and high-dose rats showed increases in the incidence of eosinophilic inclusion in olfactory epithelium of the nasal cavity (Incidence: 3/20-Air, 15/20-LD, and 13/20-HD). This finding is not considered relevant to humans because minimal nasal exposure is expected from the intended clinical use. The study failed to establish NOAEL.

Pharmaxis uses the following to justify the adequacy of nonclinical data in support of the proposed clinical protocols: (b) (4) Neither the cover letters of the three recent submissions nor the document acknowledged the previous communications between the Agency and Pharmaxis regarding the nonclinical requirements for Bronchitol® development. Nor did the submissions calculate safety margins based on pulmonary depositions in animals and proposed clinical dose in humans. The review does not address any of the above arguments or deficiencies.

Recommendations:

Internal recommendations:

1. It is recommended that the proposed clinical protocols ((b) (4) DPM-CF-302) in (b) (4) cystic fibrosis patients to be allowed to proceed.

2. The sponsor has fulfilled the nonclinical requirement of the 6-month inhalation toxicity study in the most appropriate species for the development of Bronchitol®.

External recommendations: None.

Luqi Pei, Ph.D.
Senior Pharmacologist/toxicologist

Linked Applications	Sponsor Name	Drug Name
IND 70277	PHARMAXIS LIMITED	ARIDOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUQI PEI
11/29/2007
Non-Clinical Reviewer

TIMOTHY J MCGOVERN
11/29/2007
Non-Clinical Reviewer
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number:	70,277
Review Number :	2
Sequence number/date/submission type:	008/ 13-JAN-06/ IN 009/ 17-JAN-06/ IT 012/ 06-MAR-06/ IT 016/ 30-MAR-06/ IT 017/ 28-APR-06/ IT
Information to the Sponsor:	Yes (x), No ( )
Sponsor/or Agent:	Pharmaxis Ltd, 1840 Gateway Dr., San Mateo, CA 94404
Manufacturer of the Drug Substance:	(b) (4)
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Products
Review Completion Date:	July 21, 2006
Drug:	
Trade Name:	Aridol®, Bronchitol®
Generic Name:	D-Mannitol
Code Name:	None
Chemical Name:	1,2,3,4,5,6-hexanehexol, or cordycepic acid
CAS Register Number:	69-65-8
Mole File Number:	Not available
Molecular Form and Weight:	$C_6H_{14}O_6$/182.2
Relevant IND/NDAs:	DMF# (b) (4)
Drug Class:	Sugar
Intended clinical population:	Cystic fibrosis (b) (4)
Route of Administration:	inhalation

Clinical Formulations: Capsules filled with 5, 10, 20 and 40 mg of D-mannitol powder. Mannitol will be delivered by a dry powder inhaler.

Proposed Clinical Protocol: None.

Previous Human Experience:

The Sponsor states that 39 cystic fibrosis patients (b) (4) patients have received (b) (4) 400 mg Bronchitol for 12 days, respectively. The sponsor also states that a 3-month clinical trial of Bronchitol (400 mg, bid) is ongoing in Australia.

Studies Submitted and Reviewed in the Review

Mannitol toxicity study by inhalation administration to CD rats for 13 weeks followed by 4 week withdrawal period, Study No. XIS 005 / 043185, submitted on January 17, 2006.

2-Week inhalation toxicity study of mannitol in dogs, Study No. 26050, submitted on March 6, 2006.

Mannitol: Investigative dose inhalation toxicity study in rats. Report Nos. 26482 & 666958, submitted on April 28, 2006.

Studies Submitted but Not Reviewed in this Review: None.

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Drug History:

Pharmaxis is developing D-mannitol powder as two drugs for (b) (4) indications in this IND. The two drugs will have an identical dosage form (i.e., 40 mg capsules) but two names: Aridol® and Bronchitol®. Different names are used to distinguish the indications. Aridol® is a diagnostic agent for provoking bronchoconstriction in asthmatics while Bronchitol® is a therapy for (b) (4) cystic fibrosis. The Aridol® program is currently in Phase-1 clinical development stage while the Bronchitol® program is under active discussions.

The IND was opened on November 19, 2004. The original submission proposed to study efficacy of D-mannitol as a provoking agent (Aridol®) for eliciting bronchoconstriction. The submission proposed to give approximately 130 asthmatic subjects 6 – 50 years of age, in a dose-raising schedule, up to 635 mg of mannitol to provoke bronchoconstriction. The proposal was allowed to proceed based on available clinical experience with the inhaled mannitol.

The Division has met Pharmaxis three times in the past two years to discuss the nonclinical development plan of D-mannitol. These meetings were held on July 19, 2004, June 16, 2005, and February 16, 2006, respectively. The first meeting discussed nonclinical studies needed to support the development and registration of Aridol®. The last two meetings discussed requirements for Bronchitol®. Minutes of these meetings are available.

Through these meetings, Pharmaxis and the Division agreed on the following: 1) 14-day inhalation toxicity studies in two animal species are needed for the registration of Aridol®, 2) no studies of carcinogenicity, genetic toxicity, reproductive and developmental toxicity are needed for either Aridol® or Bronchitol®, 3) a 6-month inhalation toxicity study in a most appropriate species are needed to support the development and registration of Bronchitol®, and 4) additional studies could be needed if these studies reveal safety concerns.

Pharmaxis and the Division, however, have not reached agreement on the choice of species for the 6-month inhalation toxicity study. Pharmaxis initially proposed and argued for the rat

as the species of choice. The Division was deferring its decision of the species of choice until the completion of a review of the available studies. While the Division's review is ongoing, Pharmaxis changed its mind and elected to use dogs instead of rats in the March 30, 2006 submission (Serial No. 016). The Division has not responded to the new proposal yet.

The discussions on rats as the species of choice for the 6-month inhalation toxicity studies have been well documented in the minutes of June 16, 2005, and February 16, 2006 meeting. In their submissions as late as March 6, 2006 (Serial No. 012), Pharmaxis repeatedly argued that the rat be considered the most appropriate species. Pharmaxis cited inhalation toxicity studies on 2 weeks in rats and dogs and 13 weeks in rats to support its position. Only the report for the 2-week rat study was submitted prior to the June 8, 2005 meeting. Reports of the 2-week dog and 13-week rat studies have not been submitted after the February 16, 2006 meeting. The Division maintained a position that it could not concur with Pharmaxis' position without reviewing the results of these studies. Pharmaxis submitted reports for the 2-week dog and 13-week rat studies on 17-JAN-06 and 06-MAR-06, respectively.

While the Division was reviewing the reports and Pharmaxis' rationale for conducting the 6-month study in rats, Pharmaxis submitted a new proposal on March 30, 2006. The new proposal elects to replace the rat with the dog as the species of choice for the 6-month inhalation toxicity study. Pharmaxis reasoned that their newly collected data indicate an achievement of significantly higher pulmonary deposition of mannitol in dogs than in rats. The referenced data are a 7-day non-GLP compliant dose-ranging study in rat conducted by the laboratory which conducted the 2-week dog study. The submission provided a summary of the study only; the study report was not provided. The Division requested the study report on April 14, 2006. Pharmaxis provided a draft report of the study (Report No. 26482 or 666958) in the 28-APR-2006 submission (Serial No. 017).

The 30-MAR-2006 submission also contains a document entitled, "Justification for using the dog, as opposed to the rat, in a 26-week D-mannitol inhalation toxicity study". The current review evaluates reports of the 7-day rat, 2-week dog and 13-week rat inhalation toxicity studies and Pharmaxis' new proposal to conduct the 6-month inhalation toxicity study of D-mannitol in dogs.

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2.6.6 TOXICOLOGY

2.6.6.1 Overall Toxicology Summary

Repeat-Dose Toxicology:

Repeat-dose Inhalation toxicity of D-mannitol was evaluated in rats and dogs for the treatment duration of up to 13 weeks. Table 1 (below) presents an overview of these toxicity studies. The studies identified the respiratory system as target organs of toxicity for inhaled mannitol.

Table 1. Overview of Inhalation Toxicity Studies of Mannitol

Study #	Species	Duration	Mannitol (mg/kg/day) [a]	NOAEL
26482/666958[b]	Rat	7 days	57.3, 97.9	None
XIS 002/033951	Rat	2 weeks	0, 0.9, 2.5, & 6.9	6.9
XIS 005/0413185	Rat	13 weeks	0, 12.4, 21.0	None [c]
26050/666386	Dog	2 weeks	0, 25, 100, 197	None [d]

a. Estimated pulmonary deposits.
b. A non-GLP compliant investigative dose-ranging study. The study did not show the dose-related increase in the concentration of mannitol in the bronchoalveolar fluid. Neither did it examine the lung tissue microscopically.
c. The review is in agreement with the study report in determination of NOAEL.
d. The report states that the 197 mg/kg/day dose is "well-tolerated."

A 7-day non-GLP dose-ranging inhalation study was conducted to investigate the achievement of pulmonary delivery of mannitol to the lung in Sprague-Dawley rats. Rats (5/sex/dose) were exposed nose-only to approximately 5 or 9 mg of mannitol/L of air for 120 to 240 minutes/day for 7 days. The rats were sacrificed immediately after the last exposure. The amount of mannitol delivered to the lung was determined by measuring mannitol concentrations in the bronchoalveolar fluid (3/sex/dose). The respective estimated achieved dose of mannitol was 573 and 979 mg/kg/day for the low-dose and high-dose groups, respectively. The respective mean mannitol concentration in BALF for the low and high dose groups was 36.7 and 42 μg/ml in males and 43.6 and 33.4 μg/ml in females. Necropsy did not reveal any treatment-related effect. Microscopic examination was not done.

In a previously reviewed 2-week rat study (XIS 002/033951), CD-1 rats (10/sex/dose) were given via nose-only inhalation pulmonary deposited doses of 0, 0.9, 2.5 and 6.9 mg/kg of mannitol for 14-days. Histological evaluations of the respiratory system were done in every group. The remaining organs were examined in the control and high-dose groups only. No significant, treatment-related effects were observed. The NOAEL was 6.9 mg/kg/day.

In the 2-week dog study (XIS 005/0413185), beagle dogs (3/sex/group) were exposed by inhalation via a face mask to air (C), 25 (LD), 100 (MD) or 197 (HD) mg/kg/day of D-mannitol (pulmonary deposition) for 14 days. Coughing occurred during and immediately

after dosing in all treated groups (Incidence for M + F: 0/6-C, 1/6-LD, 4/6-MD and 4/6-HD). Spongy (4/6) and froth-filled lung (3/6) were reported in the HD group during necropsy. Microscopic examination revealed the following: lung congestion/hemorrhage (2/6-HD), and pigment in submandicular lymph node (3/6-HD); bronchoalveolitis (2/3 apiece for MD and HD males); peribronchiolar infiltration (Incidence: 0/3-C, and 3/3 apiece in LD, MD and HD in males; and 1/3-C, 1/3-LD, 2/3-HD and 0/3-HD in females); foamy alveolar macrophages in all treated females and HD males (respective incidence in control, LD, MD and HD: 1/3, 0/3/, 0/3/ and 2/3 in males and 0/3, 2/3, 2/3 and 1/3 in females) and inflammatory foci and focal hyperplasia in trachea carina (1/3-HD female). The high dose males and females also showed increases in lung weight. The study did not establish a NOAEL.

In the 13-week rat study (26050/666386), Sprague-Dawley rats (10/sex/group) were given via nose-only inhalation air (C), 12.4 (LD), or 21.0 (HD) mg/kg/day (pulmonary deposition) for 13 weeks. Additional rats (5/sex) were included in the control (RC) and high dose (RHD) groups to evaluate reversibility of lesions after a recovery period of 4 weeks. The duration of exposure was 180 minutes/day. D-mannitol concentrations were 0, 1.83 or 2.89 mg/L for the control, LD and HD groups, respectively. The estimated pulmonary deposition of D-mannitol was 0, 12.4 and 21.0 mg/kg/day for the control, LD and HD groups, respectively. D-mannitol contents in the bronchoalveolar fluid were approximately 0, 3.8 and 3.2 μg/ml for the control, LD and HD groups, respectively. Both the LD and HD females showed statistically significant decreases in body weight gain (approximately 20%). Clinical pathology examinations revealed minimal decreases (approximately 50% or less) in white blood cell numbers and increases (12-30%) in serum phosphorus in the HD group. Microscopic examinations revealed increases in the incidence of alveolar macrophage aggregation and alveolitis. The respective incidence of alveolar macrophage aggregation in the C, LD, HD, RC and RHD was 3/10, 6/10, 9/10, 0/2 and 1/2 in females and 4/10, 5/10, 3/10, 1/1 and 3/4 in males. The increase in the incidence of alveolitis was observed in the high-dose male only (incidence: 0/10-C, 0-/10-MD, 1/10-HD, 0/1-RC, and 2/4-RHD, respectively). The most significant, treatment-related effect, but of no safety concern for the intended use of mannitol, was seen in the nasal cavity. Both the low and high-dose rats showed increases in the incidence of eosinophilic inclusion in olfactory epithelium of the nasal cavity (Incidence: 3/20-Air, 15/20-LD, and 13/20-HD). This finding is not considered relevant to humans because minimal nasal exposure is expected from the intended clinical use. The study failed to establish NOAEL.

2.6.6.3 Repeat-Dose Toxicity

Study Title: Mannitol Investigative Dose Inhalation Toxicity Study in Rats (draft)

Key findings: Rats (5/sex/dose) exposed to approximately 5 or 9 mg of mannitol/L of air for 120 to 240 minutes/day for 7 days showed detectable amounts of mannitol in the bronchoalveolar fluid. The mannitol concentration in the BALF was, however, variable and no dose-concentration relationship was observed. The respective mean mannitol concentration for the low and high dose groups was 36.7 and 42 μg/ml in males and 43.6 and

33.4 μg/ml in females. No treatment related effect was identified on the limited parameters evaluated. The study did not establish a NOAEL because microscopic examinations were not done in any groups.

Study number:	26482 and 666958
Volume #, and page #:	Volume 13.1, Page 3 - 68
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 31, 2006
Study complete date:	February 27, 2006
Report date:	N/A
GLP compliance:	No.
QA reports:	No.
Formulation/vehicle:	Mannitol dry powder

Methods:

Young adult Sprague-Dawley rats (5/sex/group) were exposed by nose-only inhalation to air containing 5 or 9 mg/L mannitol for 120 to 240 minutes/day for 7 days (Table 2). The amount of mannitol delivered to the respiratory tract (3 rats/sex/dose) was determined. Specifically, rats were sacrificed immediately after the last treatment. The lung was removed, weighed, and washed with 5 ml saline twice. Mannitol concentrations in the first wash BALF fluid were determined. Method of analysis was not given. The report states samples "were analysed using appropriate methodology developed for lung lavage washes from dogs." Other parameters measured included clinical signs (daily), body weight (every 3 days), hematology (day 7), lung weight and necropsy.

Table 2. Duration of Daily Exposure in Rats

	Duration of Exposure (min.) [a]	
Time (Day)	Low-dose Group	High-Dose Group 2
1 - 5	240	240
6	240	120
7	120	120

a. The exposure duration for the last two days was reduced out of concerns about insufficient supplies of the testing material.

Results:

Exposure: The estimated achieved dose of mannitol was 573 and 979 mg/kg/day for the LD and HD groups, respectively. The respective estimated achieved doses ranged 565 – 674 and 619 – 738 mg/kg/day for low-dose males and females and 829 – 1272 and 926 – 1421 mg/kg/day for high-dose males and females (Table 3).

Table 3. Estimated Achieved Doses of Mannitol in Males and Female Rats

	Estimated achieved doses for both males and females (mg/kg/day) [a]								
Days	1	2	3	4	5	6	7	8	Mean
LD Group	595	592	642	623	665	706	365	392	572.5
HD Group	878	1069	1308	1347	1017	575	659	-	979

a. Source: page 29 of submission S017.

The estimated pulmonary deposited dose of mannitol was 57.3 and 97.9 mg/kg/day for the LD and HD groups, respectively, based on deposition fraction of 0.1. The calculation was based on the fraction (11.3 – 78.7%) of aerosol particles with aerodynamic diameters smaller than (b) (4). The MMAD ranged 2.85 ± 3.19 (range: 1.44 ± 4.05 to 4.20 ± 2.39) and 3.62 ± 3.2 (range: 3.31 ± 4.2 to 4.00 ± 1.76) μm for Groups 1 and 2 respectively.

Clinical signs: Rat nostrils were occasionally "caked up" in both groups.

Body weight: No treatments-related effects were observed.

Hematology: No treatments-related effects were observed.

Lung weight: No treatment-related effects were observed.

BALF mannitol concentration: Mannitol was detected in every rat in the LD and HD group, but no dose-response relationship was observed (Table 4).

Table 4. Mannitol Concentrations in BALF in Rats

		Mannitol (mcg/ml)			
Group	Sex	Rat A	Rat B	Rat C	Mean
1 (Low Dose)	Male	12.6	70.4	27.2	36.7
	Female	50.2	60.1	20.5	43.6
2 (High Doe)	Male	10.4	58.9	57	42.1
	Female	11.7	50.6	37.9	33.4

Necropsy: No treatment-related effects were observed.

Study Title: Mannitol toxicity study by inhalation administration to CD rats for 13 weeks followed by 4 week withdrawal period.

Key findings:

- Rats were exposed to D-mannitol at estimated pulmonary deposition of 0, 12.4 and 21.0 mg/kg/day for 13 weeks.
- D-mannitol levels in bronchoalveolar fluid were approximately 0, 3.8 and 3.2 μg/ml for the control, LD and HD groups, respectively.
- Both the LD and HD females showed statistically significant decreases in body weight gain (approximately 20%).
- Microscopic examinations revealed increases in the incidence of alveolar macrophage aggregation and alveolitis. The respective incidence of alveolar macrophage aggregation in the control, low-dose, high dose, recovery control and recovery high-dose groups was 3/10, 6/10, 9/10, 0/2 and 1/2 in females and 4/10, 5/10, 3/10, 1/1 and 3/4 in males. The increase in the incidence of alveolitis was observed in the high-

dose male only (incidence: 0/10-C, 0-/10-MD, 1/10-HD, 0/1-RC, and 2/4-RHD, respectively).

- The most significant and treatment related effects were seen in the nasal cavity. Both the low and high-dose rats showed increases in the incidence of esinophilic inclusion in olfactory epithelium of the nasal cavity (Incidence: 3/20-Air, 15/20-LD, and 13/20-HD).
- The study did not establish a NOAEL.

Study number:	XIS 005/0413185
Volume #, and page #:	Volume 7.1, Page 1 - 666
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 16, 2004
Study complete date:	April 6, 2005
Report date:	September 2, 2005
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Drug lot # & purity:	3M08, 3M09, 3M10, 3M11; purity: 98- 102%
Formulation/vehicle:	Mannitol dry powder

Methods:

Sprague-Dawley rats (10/sex/group) were exposed via nose-only inhalation to air, 12.4 or 21 mg/kg/day of D-mannitol powder (pulmonary deposition) for 13 weeks. The duration of exposure was 180 minutes/day. The MMAD was 3.9 and 4.4 μm for the LD and HD groups, respectively. Additional male rats (5/group) were included for analysis of bronchoalveolar lavage fluid for the presence of inflammatory cells and mannitol concentration (Table 5). More rats (5/sex/group) were included in the control and high dose group to evaluate reversibility of lesions after a recovery period of 4 weeks. Rats of the main section of the study were sacrificed 24 hours after the last dosing. The recovery rats were sacrifice 4 weeks after the last dosing. Rats in both the main study section and the recovery arm underwent pathological evaluations.

Table 5. Design of the completed 13-week inhalation toxicity study of mannitol in rats

Group	Treatment	Mannitol [a] (mg/kg/day)	Rat Distribution (n/sex)				
			Main [b] Study	Recovery Section	Lung Lavage Section [c]		
					Day 1	Week 7	Week 13
1	Air	0	10	5	5 M	5 M	5 M
2	Mannitol	12.4	10	-	5 M	5 M	5 M
3	"	21.0	10	5	5 M	5 M	5 M

a. Estimated pulmonary deposition. (See Table 6 for details.)

b. Each group also included 2 additional and reserve rats/sex/group.
c. Additional rats for bronchoalveolar lavage study only.

Doses: 0, 12.4 and 21.0 mg/kg/day (Table 3, below)

Table 6. Estimated Pulmonary Deposits in the 13 Week IH Study in Rats

Treatment	Dose	Aerosol			Exposure (mg/kg/day)	
		MMAD (μm) [a]	GSD	Drug conc. (mg/L)	Achieved Dose [b]	Pulmonary Deposit [c]
Air	0	-	-	-	-	-
Mannitol	LD	3.9	2.19	1.83	124	12.4
	HD	4.4	2.37	2.89	210	21.0

a. The report states that the MMAD was slightly larger than the ideal range of 1 - 3 μm because it used the formulation as supplied without any modification, (b) (4) .
b. Achieved dose (mean of males and females) reported by the sponsor. The estimated achieved dose assumed 100% deposit of inhalable particle (particles with diameters < 7 um). The percentage of inhalable particles was 77% and 70% for the low and high dose groups, respectively. For example, the dose in female low dose group was obtained as: [1.53 (mg/L, mean aerosol mannitol concentration) x 160 (ml/min, RMV) x 180 (min, exposure duration/day) x 0.77 (fraction of particles < 7 μm in diameter)]/ 248 (g, mean body weight) = 137 mg/kg/day (report page 435).
c. Converted from the achieved dose. Pulmonary deposits (mg/kg/day) = Achieved dose (mg/kg/day) x 0.1 (pulmonary deposition factor). For example, the pulmonary deposition for the HD = 124 x 0.1 = 12.4 mg/kg/day.

Species/strain:	Rats (Crl:CD® (SD) IGS BR),
#/sex/group:	10
Satellite groups:	5/sex in control and high dose group, 15 males/group for lung lavage analysis on weeks 1, 4 and 13
Age:	6 - 7 weeks
Weight:	M: 273 - 343g; F: 191 – 241 g
Doses in administered units:	0, 12.4 and 21.0 mg/kg/day (See Table 5 (above) for dose estimates)
Route, form:	Nose-only IH, dry powder, 180 minutes/day

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Pretreatment and Week 13
EKG:	Not assessed
Hematology:	Weeks 6 and 13
Clinical chemistry:	Weeks 6 and 13
Urinalysis:	Weeks 6 and 13
Bone marrow:	Week 13 and end of recovery period for RBC morphology analysis
Lavage:	Weeks 1, 7 and 13 (5 males/time point). Each lung was weighed. The lung was then washed with 8.0 ml of saline 3 times. WBC count,

differential WBC count and mannitol content in each washout fluid were measured.

Gross pathology: Sacrifice

Sacrifice method: Pentobarbitone (IP)

Organs weighed: Adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, salivary glands, seminal vesicles, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus

Histopathology: Adrenals, brain, femur, heart, kidneys, liver, lungs, ovaries, spleen, spinal cord, sternum, stomach, testes, thyroid (with parathyroids) and uterus in control and high dose groups + respiratory tract of all animals of the main study section; tissues with gross abnormalities in the LD and all recovery rats. The design is considered acceptable because the toxicity of mannitol by non-inhalation routes of administration is a well understood compound. The interest of the currently application is primarily the respiratory system.

Adequate Battery: yes (x), no ( )

Peer review: yes ( ), no (x)

Toxicokinetics: None

Other: Aerosol concentration and particle size distribution were measured in each exposure period from representative animal exposure positions. Particles were generated by a scraper from a compressed powder and a streamed air flowing over the scraped dust. Particle sizes were determined with an Anderson cascade impactor.

Results

Mortality: None.

Clinical Signs: No treatment-related effects were observed.

Body Weights: Females showed statistically significant decreases in body weight gain (Table 7). The decrease was no longer apparent after a recovery period of 4 weeks. There was no apparent treatment effect in absolute body weight.

Table 7. Body Weight and Weight Gains in Rats

Parameter	Time	D-mannitol (mg/kg/day)					
		Male			Female		
		0	12.4	21.0	0	12.4	21.0
N		17	12	17	17	12	17
Body weight (g)	Week 0	312 ± 18	312 ± 13	310 ± 16	210 ± 13	213 ± 6	217 ± 12
	Week 13	499 ± 37	471 ± 44	497 ± 37	280 ± 21	268 ± 11	275 ± 17
Weight gain (g)	Weeks 0 - 13	191 ± 23	159 ± 38	187 ± 30	70 ± 13	55 ± 9**	58 ± 15**
as % of control	Weeks 0 - 13	-	83	98	-	79	83
as % of control	Rec. period	-	-	99	-	-	105

**, $p < 0.01$.

Hematology: No remarkable findings were noticed. The HD group showed statistically significant but toxicologically unremarkable increases (< 50% increase) in white blood cell

count (Table 8). The increase was primarily attributed to increases in lymphocyte numbers. The increase was reversible; the recovery groups showed no difference. Other changes were not only small in magnitude but also observed only in one sex. The hematological changes are, therefore, considered unremarkable.

Table 8. Notable Hematological Changes in the 13-Week Rat Study

Sex		Male			Female		
D-mannitol (mg/kg/day)	Week	0	12.4	21.0	0	12.4	21.0
WBC (x 10^9/L)	6	11.1	12.2	16.0**	7.9	8.9	10.4**
	13	10.7	11.7	14.2*	6.7	8.1	8.4
Lymphocytes (x 10^9/L)	6	7.5	9.1	11.1**	6.4	7.4	9.0**
	13	7.9	8.6	10.2*	5.3	6.8	6.9
Monocytes (x 10^9/L)	6	0.22	0.23	0.32**	0.14	0.11	0.15
	13	0.21	0.23	0.29*	0.14	0.11	0.15
Platelets (x 10^9/L)	6	1017	1068	872*	1039	1023	1096

*, $P < 0.05$; **, $p < 0.01$.

Clinical chemistry: The high dose group showed statistically significant increases in serum phosphorus levels (Table 9). The increase was reversible. Potassium level was increased in the high dose males during week 6, but it is not considered toxicologically significant. The increase was absent in other time points of the treatment in males and any time point in the females.

Table 9. Notable Clinical Chemistry Changes in the 13-Week Rat Study

Sex		Male			Female		
D-mannitol (mg/kg/day)		0	12.4	21.0	0	12.4	21.0
K (mmol/L)	Week 6	3.8	3.8	4.1*	3.3	3.6	3.4
Phosphorus (mmol/L)	Week 6	2.20	2.17	2.47*	1.77	1.93	2.22**
	Week 13	2.17	2.12	2.28	1.55	1.87	2.02**

*, $P < 0.05$; **, $p < 0.01$.

Urinalysis: Not remarkable. The females showed dose-related decrease in urinary chloride concentration (Table 10), but the results were variable and appear to be within background levels. The recovery control group showed a mean of 34 mmmol/L while the HD group showed values of 33 – 42 mmol/L during the exposure period.

Table 10. Urinary Chloride Levels during the Study

	Urinary Cl (mmol/L)					
	Male			Female		
Mannitol (mg/kg/day)	0	12.4	21.0	0	12.4	21.0
Week 6	45.4	58.7	44.7	60.2	46.7	42.4*
Week 13	45.3	44.6	37.1	70.4	48.5*	32.6**
Recovery	41.0	-	36.0	34.0	-	56.7

Bone marrow smear: No treatment-related effects were observed.

Bronchoalveolar lavage Fluid:

White blood cell count: No treatment-related effects were observed.

Differential white blood cell count: No treatment-related effects were observed.

Mannitol content: Mannitol was detected in the bronchoalveolar lavage fluid of treated groups, but it lacked a dose-concentration relationship. Table 11 (below) presents individual and mean mannitol concentrations in week 7. This time point was selected because it had the most consistent values between individual and groups. Data from other time points (day 1 and week 13) were more variable although similar trends existed. The highest mannitol concentration was found in the first wash. The mannitol concentration declined as more washes were carried out. The mean mannitol concentration in the low and high dose groups was 3.8 and 3.2 μg/ml. One control sample showed a detectable amount of mannitol (3 μg/ml) on one occasion.

Table 11. Mannitol Concentration in Week 7

	Mannitol (μg/ml)									
Group	LD					HD				
Rat No	A	B	C	D	E	A	B	C	D	E
Wash 1	6	4	8	8	4	8	3	7	3	4
Wash 2	3	4	4	3	2	4	BLQ [a]	4	3	2
Wash 3	2	2	3	2	2	2	2	4	0	0
Individual mean	3.7	3.3	5.0	4.3	2.7	4.7	2.5	5.0	2.0	2.0
Group Mean	3.8					3.2				

a., BLQ, below the limit of quantitation (2 μg/ml). Data were extracted from vol. 2, p 586.

Organ weights: No treatment-related effects were observed in either pathologically examined or lung lavaged rats.

Gross pathology: Congested lymph nodes were observed in the treated groups (Table 12). The other findings listed, though slightly increased, are not considered to be definitively treatment-related.

Table 12. Noticeable Gross Pathology findings of the 13-Week inhalation Study of Mannitol

Sex	Male					Female				
Study Section	Main Study			Recovery		Main Study			Recovery	
Group	Cont.	LD	HD	Cont	HD	Cont.	LD	HD	Cont	HD
N	10	10	10	5	5	10	10	10	5	5
Lung and bronchi: pale areas	4	6	2	1	3	2	3	7	2	2
Congested	0	1	2	0	1	0	0	0	0	0
Lymph node/mandibular: Enlarged	4	2	7	1	2	2	0	0	0	0
Congested	1	1	3	0	2	0	2	3	0	3
Uterus: fluid distension	-	-	-	0	0	2	1	4	3	3

Histopathology:

Increases in the incidence of alveolar macrophage aggregation and alveolitis (Table 13) were observed. The respective incidence of alveolar macrophage aggregation in the control, low-dose, high dose, recovery control and recovery high-dose was 3/10, 6/10, 9/10, 0/2 and 1/2 in females and 4/10, 5/10, 3/10, 1/1 and 3/4 in males. The increase in the incidence of alveolitis was observed in the high-dose male only (incidence: 0/10-C, 0-/10-MD, 1/10-HD, 0/1-RC, and 2/4-RHD, respectively). The most significant and treatment related effects were seen in

the nasal cavity. Both the low and high-dose rats showed increases in the incidence of eosinophilic inclusion in olfactory epithelium of the nasal cavity (Incidence: 3/20-Air, 15/20-LD, and 13/20-HD) that were reversible. This finding, however, is not considered relevant to humans because minimal nasal exposure is expected from the intended clinical use. Increases in the incidence of inflammation cells in the kidney and cysts in the thyroid and pituitary glands were seen in the high dose group, but the significance of these findings is unknown given the lack of systemic toxicity of mannitol from non-inhalation route of administration.

Table 13. Noticeable Microscopic Pathology findings

Sex	Male					Female				
Study Section	Main Study			Recovery		Main Study			Recovery	
Group	Ctr	LD	HD	Ctr	HD	Ctr	LD	HD	Ctr	HD
N	10	10	10	5	5	10	10	10	5	5
Lung: Alveolar MΦ aggregation	4	5	3	1/1	3/4	3	6	9	0/2	1/2
Alveolitis	0	0	1	0/1	2/4	0	0	0	0/2	0/2
Alveolar hemorrhage	0	1	1	0/1	0/4	0	0	0	0/2	0/2
Lymph node/Mandibular: plasmacytosis	5	7	8	1/1	2/3	4	8	4	-	1/3
Hemorrhage	5	4	7	0/1	2/3	2	2	4	-	2/3
Apoptosis	1	0	2	0/1	0/3	0	0	0	-	0/3
Mediastinal: paracortex cellularity	0/9	4	3	-	-	0	2/9	1/7	-	-
Nasal turbinate: Olfactory epithelial ↑ esinophilic inclusion	1	8	6	-	-	2	7	7	-	-
Trachea: sub-mucosal inflame. cell	3	4	4	0/1	0/4	1	1	3	-	-
Kidney: Inflammation	2	1/2	6	0/1	- [a]	2	-	1	-	-
Pituitary: developmental cyst(s)	0	-	2	-	-	0	-	1	-	-
Thyroid: prominent ultimobranchial cyst	2	-	7	-	-	4	-	3	-	-

a. -, not examined. For the recovery groups, the review does not consider organs without reported findings microscopically examined because the protocol calls for microscopic examinations of tissues with gross findings only.

Study Title: Two-Week Inhalation Toxicity Study of Mannitol in Dogs (Draft).

Key findings: Beagle dogs (3/sex/group) exposed to ≥ 25 mg/kg/day (pulmonary deposition) of D-mannitol via inhalation for 14 days showed dose-related pathological changes in the respiratory system. The changes included spongy lung and froth-filled trachea; lung congestion or hemorrhage, peribronchiolar infiltration, alveolitis, alveolar foamy macrophages; and focal hyperplasia of trachea carina.

- D-mannitol doses were air, 25, 100 or 197 μg/kg/day (pulmonary deposition).
- Spongy (4/6)[1], froth-filled lung (3/6), lung and congestion/hemorrhage (2/6), and pigment in submandicular lymph node (3/6) were observed in HD group.
- Bronchoalveolitis was observed in the MD (2/3) and HD (2/3) males.
- Peribronchiolar infiltration was observed in all treated males. (The respective incidence in control, LD, MD and HD was 0/3, 3/3/, 3/3 and 3/3 in males, and 1/3, 1/3, 2/3 and 0/3 in females.)

[1] Numbers in the parenthesis following changes indicate incidence.

- Foamy alveolar macrophages were observed in all treated females and HD males. (The respective incidence in control, LD, MD and HD groups was 1/3, 0/3/, 0/3/ and 2/3 in males and 0/3, 2/3, 2/3 and 1/3 in females).
- Inflammatory foci and focal hyperplasia was observed in one HD female.
- The lung weight was increased in both HD males and females. It is unclear whether the increase in lung weight was a result of inflammation or mannitol accumulation or both.
- The study did not establish the NOAEL.

Study number:	26050 and 666387 (histopathology)
Volume #, and page #:	Volume 13.1, Page 7 - 278
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 17, 2005
Study complete date:	Not available
Report date:	N/A
GLP compliance:	Yes, with a unsigned GLP statement
QA reports:	Yes, with a unsigned GLP statement
Drug lot # & purity:	3M15, 3M16; purity: 98- 102%
Formulation/vehicle:	Mannitol dry powder

Methods:

Beagle dogs (3/sex/group) were exposed by inhalation via a face mask to air, 25, 100 or 197 mg/kg/day of D-mannitol for 14 days. Each daily dose was divided into two exposure sessions. Each session was approximately 60 minutes. The interval between two exposure sessions in one day was at least 120 minutes long. Standard batteries of clinical observation, clinical pathology and histological pathology examinations were carried out during and at the end of study.

Species/strain:	Dogs, Beagle
#/sex/group:	3
Age:	Approximately 5 months
Weight:	M: 8.1 – 11.1 kg; F: 6.8 – 10.9 kg
Doses in administered units:	0, 25, 100, or 197 mg/kg/day
Route, form:	Inhalation via a face mask, dry powder, 120 minutes/day (60 minute/episode, 2 episodes/day, ≥ 120 minutes between episodes)

Observations and times:

Clinical signs:	Daily
Body weights:	Twice weekly
Food consumption:	Daily
Ophthalmoscopy:	Pretreatment and Day 14

Respiratory system:	Respiratory rate, tide volume and minute volume at pre-treatment and days 7 and 14.
ECG:	Days 1 and 14 (within 15 minute post second dosing)
Hematology:	Pre-dosing and day 14
Clinical chemistry:	Pre-dosing and day 14
Urinalysis:	Pre-dosing and day 14
Bone marrow smear:	Day 14 at necropsy
Bronchoalveolar lavage:	Right lobe at necropsy
Gross pathology:	Sacrifice time
Sacrifice method:	Pentobarbitone (IP)
Organs weighed:	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, pancreas, pituitary, prostate, salivary gland, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus
Histopathology:	A complete panel – all animals in all groups were examined. Adequate Battery: yes (x), no ( ) Peer review: yes ( ), no (x)
Toxicokinetics:	Day 1 and 14 at hours 0.5, 1, and 2, 4 (2^{nd} dose only) and 18 (2^{nd} dose only) post dosing

Results

Dose estimates: Table 14 (below) presents the dose estimates of the study. The estimated pulmonary deposition was 25, 100 and 197 mg/kg/day for the low, mid and high dose groups, respectively.

Table 14. Estimated Pulmonary Deposits in the 2-Week IH Study in Dogs

Treatment	Dose	Aerosol			Exposure (mg/kg/day)	
		MMAD (μm) [a]	GSD	Drug (mg/L)	Achieved Dose [a]	Pulmonary Deposit [b]
Air	0	-	-	-	-	-
Mannitol	LD	2.6	2.2	1.05	99	25
	MD	2.6	2.4	3.15	251	100
	HD	0.9	2.5	9.22	789	197

a. Achieved dose used by the study report. The estimated achieved dose assumed 100% deposit of inhalable particle (< 7.3 μm). The inhalable particle was approximately 92%, 91% and 85% of the test aerosols for the low, mid and high dose groups, respectively. The achieved dose was calculated by the formula: D = (MV x T x CC)/BW. Where, D is in mg/kg/day, MV = minute volume (overall group mean value per sex based on actual recorded results from the study), T = the duration of exposure in minutes, CC = gravimetric chamber concentration in mg/L, and BW = mid-period individual body weight in kg. Extracted from pages 53 and 54 of the report.

b. Converted from the achieved dose using a deposition factor (0.25). Pulmonary deposits (mg/kg/day) = Achieved dose (mg/kg/day) x 0.25 (pulmonary deposition factor). For example, the pulmonary deposition for the HD = 99 x 0.25 = 25 mg/kg/day.

Mortality: None.

Clinical Signs: Coughing occurred during and immediately post dosing throughout the study. The combined incidence of males and females that coughed was 0/6, 1/6, 4/6 and 4/6 for the control, low, mid and high dose groups, respectively.

Body Weight: No treatment-related effect was observed.

Food Consumption: No treatment-related effect was observed.

Ophthalmoscopy: No treatment-related effect was observed.

Respiratory parameters: No treatment-related effect was observed in respiratory rate, minute volume and tidal volume.

ECG: No treatment-related effect was observed.

Hematology: No treatment-related effect was observed.

Clinical Chemistry: No treatment-related effect was observed.

Urinalysis: No treatment-related effect was observed.

Organ weight: The high-dose group showed increases in lung weight (Table 15). The increase was apparent in both absolute and relative lung weight. Only was the increase in lung weight relative to body weight, however, reached statistically significance in the males. The small sample size (n = 3) probably accounts for the lack of statistical significance.

Table 15. Absolute and Relative Lung weight in Dogs

	Male				Female			
	Cont'l	LD	MD	HD	Cont'l	LD	MD	HD
Body weight (kg)	11.0	11.1	11.6	11.1	9.9	9.3	9.4	10.0
Lung weight (g)	108.7	118.2	112.3	132.0	94.5	89.7	97.1	104.9
Lung weight relative to body (%)	0.99	1.02	1.05	1.19*	0.97	0.97	1.03	1.05

Gross pathology: The high-dose group showed spongy lung and froth-filled trachea (Table 16, below). The respective gender-combined incidence in the control, low, mid and high dose groups was 0/6, 0/6, 0/6 and 4/6 for spongy lung and 0/6, 0/6, 0/6 and 3/6 for frost-filled trachea.

Table 16. Notable Necropsy Findings in Dogs

	Male				Female			
	Cont'l	LD	MD	HD	Cont'l	LD	MD	HD
Lung: dark focus	0	0	2	0	0	0	0	0
Spongy	0	0	0	2	0	0	0	2
Trachea: froth-filled	0	0	0	2	0	0	0	1

Histopathology: Microscopic changes were limited to the respiratory system. The changes included congestion or hemorrhage, peribronchiolar infiltration, alveolitis, alveolar foamy macrophages and focal hyperplasia of trachea carina (Table 17). Congestion/hemorrhage (MD and HD), pigmentation and hyperplasia in the lymph node (HD), foamy alveolar macrophages, and inflammation/focal hyperplasia in trachea carina (HDF) were observed in one or both sexes in a dose-dependent manner (i.e., mid and/or HD groups). Peri-bronchiolar infiltration was observed in all treated males while the incidence of alveolitis was increased

in all treated females. The gender-combined incidence for the control, low, mid and high-dose groups was 0/6, 0/6, 1/6 and 2/6 for congestion/hemorrhage; 1/6, 4/6, 5/6 and 3/6 for peribronchiolar infiltration; 1/6, 2/6, 2/6 and 3/6 for foamy alveolar macrophages; and 1/6, 5/6, 2/6 and 3/6 for alveolitis.

Table17. Notable Microscopic Findings in Dogs [a]

	Male				Female			
	Cont'l	LD	MD	HD	Cont'l	LD	MD	HD
Lung: Agonal congestion/hemorrhage	0	0	1	1	0	0	0	1
Alveolitis, minimal focal	0	2	0	0	1	3	2	3
Broncho-alveolitis	0	0	2	2	1	0	0	0
Perivascular infiltrates	3	3	3	3	3	3	3	3
Peri-bronchiolar infiltration	0	3	3	3	1	1	2	0
Foamy alveolar mΦ	1	0	0	2	0	2	2	1
Lymph node: submandicular/pigment	0	0	0	2	0	0	0	1
/ lymph hyperplasia	0	0	0	0	0	0	0	1
Retropharyngeal/ lymph hyperplasia	0	0	0	1	0	0	0	0
Trachea: inflammatory foci	0	0	0	0	0	0	0	1
- carina: focal hyperplasia	0	0	0	0	0	0	0	1

a. n = 3/group.

Toxicokinetics: Results not available yet.

2.6.6.9 Discussion and Conclusions

This section discusses selection of the most appropriate animal species for evaluating the inhalation toxicity of D-mannitol. The Division and the sponsor agreed that a 6-month inhalation toxicity study of mannitol in a most appropriate species is needed for registration of Bronchitol®. The two sides, however, have not agreed on the species of choice for the study. The sponsor is currently proposing to conduct the study in dogs. (Note that the sponsor previously proposed a rat study.) The sponsor states that their completed toxicity studies (up to 13 weeks in rats and 2 weeks in dogs) support the proposal. The review finds the available data insufficient to support their current proposal, due to a number of deficiencies discussed below.

Results of the completed toxicity studies have been summarized previously in Section 2.6.6.1 (page 5). Table 18, next page, summarizes characteristics of the studies. These characteristics demonstrate that the completed toxicity studies have little in common. They differ in study designs, GLP-compliance, mannitol aerosol concentrations, daily exposure duration, estimated pulmonary deposition, mannitol concentrations in the bronchoalveolar lavage fluid (BALF), MMAD and NOAEL values. These differences make it impossible to determine the most appropriate animal species.

Study quality: The completed inhalation toxicity studies of mannitol in rats and dogs differ in quality. The 7-day rat study (Study 26482) is non-GLP compliant and poor in quality. It lacked any control groups. The duration of exposure varied from 120 to 240 minutes per day. The daily MMAD ranged from 1.44 to 4.2 μm. The GSD ranged from 1.76 to 3.2. Mannitol concentrations in the bronchoalveolar lavage fluid lacked any dose-response relationship. There was no microscopic examination of any animals. These deficiencies demonstrate that the study is not a valid study and it should not be relied upon for choosing the species for the pivotal 6-month study.

Some of the above deficiencies also exist in the GLP-complaint studies. For example, at mannitol concentrations in BALF in the 13-week rat study lacked any dose-response relationship.

Table 18. Characteristics of Mannitol Inhalation Toxicity Studies

Species	Rat			Dog
Study duration	1-wk	2-WK	13-Wk	2-WK
GLP compliance	No	Yes	Yes	Yes
n/sex/dose	5	10	10	4
Treatment duration (min./d)	120 - 240	60	180	120
Mannitol				
Aerosol concentration (mg/L)	5.2, 9.1	0, 0.26, 0.88, 2.8	0, 1.8, 2.9	0, 1.1, 3.2, 9.2
Pulmonary deposit (mg/kg/day)	54, 98	0, 0.9, 2.5, 6.9	0, 12.4, 21.0	0, 25, 100, 197
BALF concentration (μg/ml)	40.2, 37.7	-	0, 3.8, 3.2	-
MMAD (μm)	2.9, 3.6	0, 2.4, 3.7, 4.7	0, 3.9, 4.4	0, 2.6, 2.6, 0.9
NOAEL (mg/kg/day)	< 54	6.9	< 12.4	< 25

Study Designs: These completed studies differ not only in treatment duration but also in exposure levels. The respective treatment durations were 1, 2 and 13 weeks in rats and 2 weeks in dogs. The respective duration of daily exposures varied from 60 minutes to 240 minutes in rats and 120 minutes in dogs. The respective mannitol aerosol concentration was up to approximately 9.0, 2.8 and 2.9 mg/L for the 1-, 2- and 13-week studies in rats and 9 mg/L in 2-week study in dogs. When mannitol aerosol concentrations are similar (i.e., 9 mg/L in both 2-week studies in rats and dogs), aerosol particle sizes differed significantly; the MMAD was (b) (4) in rats and dogs, respectively. This variation may result in a significant difference in estimated pulmonary exposure. The respective estimated pulmonary deposition for the 2-week studies ranged from 0.9 – 6.9 mg/kg/day in rats and 25 – 197 mg/kg/day in dogs, respectively. The true difference in pulmonary exposure may be even greater because of the difference in MMAD. Overall, there is little similarity in the design of these studies.

Study Results: The toxicological profiles of inhaled mannitol in rats and dogs appear to be similar; however, the NOAEL values vary significantly pending the species and duration of treatment. The respective NOAEL is <54, 6.9, and <12.4 for the 1-, 2-, and 13-week studies in rats and <25 mg/kg/day for the 2-week study in dogs. It is unknown how low the actual 2-week NOAEL in dogs could be, and whether it is greater than, smaller than, or similar to the NOAEL of 6.9 mg/kg/day identified in the 2-week rat study?

The differences in study designs, exposure levels and the NOAELs make it impossible to determine whether dogs or rats are the most appropriate species in evaluating toxicity of mannitol for a chronic administration. Rats and dogs appear to possess similar toxicological profiles. The similarity in toxicological response indicates that most appropriate species should be the most sensitive species. Unfortunately, there is insufficient information to determine whether rats or dogs are more sensitive.

The sponsor argues that the dog is the most appropriate species because higher exposures of mannitol can be achieved in this species. The sponsor states that their proposal is supported by the results of the 7-day rat study and the 2-week dog study. At nominal mannitol concentrations of approximately 9.0 mg/L, the estimated pulmonary exposure was 98 and 197 mg/kg/day in rats and dogs, respectively. This argument ignores an important flaw of the studies - large differences in MMADs. The MMADs were (b) (4) μm in rats and dogs, respectively. Such a big difference in MMAD can result in marked differences in pulmonary deposition. In addition, the apparent flaws of the 7-day rat study render the argument invalid. The issue in question is not exclusively which species can be administered higher doses, but also which is most sensitive to the observed toxicities. Thus, additional data is needed before a sound comparison can be made.

The sponsor should conduct an additional inhalation toxicity study of mannitol that possesses characteristics similar to the completed 2- or 13-week studies in dogs. If a 2-wk dog study identifies a NOAEL lower than the 2-wk rat NOAEL, they could choose the rat for chronic dosing. On the other the hand if the dog NOAEL is smaller than the rat NOAEL, they could conduct a dog study. Alternatively, a 13-wk study in dogs with a NOAEL greater than that in the 13-wk rat would support the rat for chronic dosing. A pivotal characteristic should be comparable estimated pulmonary exposures based on pulmonary deposits. Mannitol concentrations in BALF could also be used if the data is of good quality.

The above discussion demonstrates that the available nonclinical information in this application is insufficient to support the sponsor's assertion that the dog is the species of choice for the 6-month inhalation study of mannitol in laboratory animals. Additional information is needed to support this assertion. The additional study should be either 2 or 13 weeks in treatment duration in dogs and should identify a NOAEL. The study should also have comparable estimated pulmonary exposures to some of the completed studies. Pulmonary exposures may be based on estimated pulmonary deposits or mannitol concentrations in BALF.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The available nonclinical information in this application is insufficient to support the sponsor's assertion that the dog is the species of choice for the 6-month inhalation toxicity study of mannitol in laboratory animals (Serial Nos. 016 and 17, Submitted on 30-MAR-06 and 28-APR-06). Additional information is needed to support this assertion. The additional study should be either 2 or 13 weeks in treatment duration in dogs and identify a NOAEL. The study should also have designs comparable to some of the completed studies in rats, especially regarding the estimated pulmonary exposure. Pulmonary exposures may be based on theoretically estimated pulmonary deposits or high quality characterization of mannitol concentrations in BALF.

Internal Comments

Pharmaxis has not submitted sufficient information to support its recent proposal for the 6-month inhalation toxicity study on March 30, 2006 (Serial No. 016). The proposal replaces the previous proposal that used the rat as the species of choice (Serial No. 009, submitted on 13-JAN-06). Pharmaxis presented its rationales for the current proposal in a document entitled, "Justification for using the dog, as opposed to the rat, in a 26-week D-mannitol inhalation toxicity study" (Serial No. 017, submitted on 28-APR-06). The document argues that dogs be used as the species of choice because higher pulmonary exposure can be achieved. Table 19 summarizes the sponsor's evaluation of dosimetry of mannitol in rats and dogs.

Table 19. Comparison of Dosimetry and Respiratory Responses to Mannitol

Parameters	Rat [a]	Dog [b]
Fraction (%) of respirable particles with MMAD of ≤ (b) (4) μm	< 25%	> 85%
Evidence of drug-related effect: ↑ lung weight at 5 – 9 mg/l	No	Yes
Occurrence of caking at nares (limiting pulmonary deposition)	Yes	No
Dose-dependence of BALF mannitol concentration	No	Unknown

a. Non-GLP 7-day investigative study (Study no. 26482).
b. 14-day GLP toxicity study (Study no. 26050).

Briefly, the sponsor argues that: 1) the fraction of respirable particles (i.e., aerosol particles with MMAD of ≤ (b) (4) μm) was higher in dogs than in rats, 2) there was no "pharmacological evidence of (in the form of induced osmosis) significant D-Mannitol exposure in the trachea or lung at either 5 or 9 mg/L" in rats, 3) the lower pulmonary exposure in rats was attributed to the high nasal deposition indicated by caking as nares, and 4) the mannitol concentration in BALF in rats lacked a dose-concentration relationship.

The above arguments are based on the results of a 7-day non-GLP toxicity study in rats and 2-week GLP study in dogs. As discussed in Section 2.6.6.9 (toxicology discussion and conclusion), the 7-day non-GLP rat study is not a valid study and it provides little scientific value. As to the dog study, there is no quantitative determination of pulmonary exposures of mannitol. While there may have been a difference in the fraction of respirable particles with an MMAD of < (b) (4) μm in the two studies, this issue relates to how the particles were generated and not to the appropriateness of the tested species. It is presumed that an aerosol with a smaller MMAD could be generated for a rat study as well as a dog study. Mannitol concentration data in the plasma or BALF fluid have not been submitted either. Consequently, there is no quality information to support the statement that, at similar concentrations, more mannitol was delivered to pulmonary regions in rats than in dogs. Theoretically, higher pulmonary deposition can be achieved in dogs at similar achieved doses due to a larger fraction of pulmonary deposition of inhaled particles (F_{dog}= 0.25 vs. F_{rat} = 0.1). However, the deposition fraction is only one of factors determining the pulmonary exposure. Other factors such as the duration of treatment per episode of exposure is equally important in determining the pulmonary exposure.

The most appropriate species should be based on an overall evaluation of the sensitivity and dose-response relationship between species. Currently, there is insufficient data to determine whether rats and dogs are more sensitive to inhaled mannitol. The completed studies differ in study designs, GLP-compliance, aerosol mannitol concentration, daily exposure duration,

estimated pulmonary deposition, mannitol concentrations in the bronchoalveolar lavage fluid (BALF), MMAD and the NOAEL values. Therefore, an additional study of either 2 or 13 weeks in dogs with estimated pulmonary exposures comparable to some of the completed studies should be conducted to identify a NOAEL. Pulmonary exposures may be based on estimated pulmonary deposits or mannitol concentrations in BALF. This study will allow a direct comparison to the previously conducted studies in rats and enable the selection of the most appropriate species to be studies for long-term effects on mannitol.

External comments

We are currently unable to concur with your proposal to study dogs for chronic administration of mannitol in order to support chronic clinical administration and a marketing application. In order to support selection of the most appropriate species, we recommend that you conduct a 2- or 13-week GLP-compliant inhalation toxicity study of D-mannitol in dogs. The study should possess characteristics comparable to the completed 2- or 13-week studies in rats regarding pulmonary exposure and should identify a no-observed-adverse-effect-level NOAEL. Pulmonary exposures may be based on theoretically estimated pulmonary deposits. Mannitol concentrations in the bronchoalveolar lavage fluid (BALF) could be also used if the data are of good quality. The Division can provide comments on a study protocol prior to study initiation if you desire.

This recommendation is based on our determination that your recent submissions have not provided sufficient nonclinical data to support your assertion that the dog is species of choice for the 6-month inhalation toxicity study of D-mannitol. Your completed toxicity studies (up to 13 and 2 weeks in rats and dogs, respectively) vary in a number of areas: study designs, GLP-compliance, mannitol aerosol concentration, daily exposure duration, estimated pulmonary deposition, mannitol concentrations in the BALF, aerosol MMAD and identification of NOAEL values. These variations make it difficult to compare the dose-response and species sensitivity to inhaled mannitol between rats and dogs.

Luqi Pei, Ph.D.
Pharmacologist/toxicologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Luqi Pei
7/21/2006 02:10:49 PM
PHARMACOLOGIST

Timothy McGovern
7/21/2006 04:00:58 PM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number:	70,277
Review Number :	1
Sequence number/date/submission type:	000/19-NOV-04; Stamp date: 22-NOV-04; Original submission
Information to the Sponsor:	Yes ( ), No (x)
Sponsor/or Agent:	Pharmaxis Ltd, 1840 Gateway Dr., San Mateo, CA 94404
Manufacturer of the Drug Substance:	(b) (4)
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
HFD #:	HFD-570
Review Completion Date:	March 18, 2005
Drug:	
Trade Name:	Aridol
Generic Name:	D-Mannitol
Code Name:	None
Chemical Name:	1,2,3,4,5,6-hexanehexol, or cordycepic acid
CAS Register Number:	69-65-8
Mole File Number:	Not available
Molecular Form and Weight:	$C_6H_{14}O_6$/182.2
Relevant IND/NDAs:	MDF# (b) (4)
Drug Class:	Diagnostic (Broncho-provocation) agent
Intended clinical population:	Asthmatic patients
Route of Administration:	inhalation

Clinical Formulations: Capsules filled with 5, 10, 20 and 40 mg of D-mannitol powder. Mannitol will be delivered by a dry powder inhaler.

Proposed Clinical Protocol: Each of 130 asthmatic subjects 6 – 50 years of age will receive up to 635 mg of mannitol to provoke bronchoconstriction. A rising dose schedule will be employed and a total dose of mannitol per patient will be 5, 15, 35, 75, 155, 315, 475 and 635 mg. Dose-escalating will stopped when bronchoconstriction occurs.

Previous Human Experience:

The sponsor states that approximately 1240 asthmatic adults and 160 asthmatic children have been given up to 635 mg of mannitol dry powder by inhalation (p 1.068).

Studies Submitted and Reviewed in the Review

Study #	Description	Vol. #	Page #
	Summary of nonclinical information	2	1
XIS 001/033434	Single-dose inhalation toxicity of mannitol in rats	2	007
XIS 002/033951	14-day inhalation toxicity study of mannitol in rats	2	112
004/034088	Mannitol eye irritation study in rabbits	3	001
003/034081	Effect of mannitol on bovine corneal opacity and permeability in vitro	3	020

Studies Submitted but Not Reviewed in this Review: None.

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Drug History:

A pre-IND meeting was held on July 19, 2004 to discuss the development program of mannitol indicated as a bronchial provocation agent in asthmatics. Nonclinical information available then included a literature review of mannitol toxicology and summaries of sponsor-completed studies. These studies included inhalation toxicity studies up to 14 days in rats, an ocular irritation study in rabbits, a (cow) cornea irritation study in vitro (planned). The Division informed the sponsor of the following:

1) The available data is adequate to open an IND.
2) Inhalation toxicity studies up to 14 days in a second animal species are also needed for the NDA filing.
3) Additional toxicity study(ies) in rats with higher mannitol doses may be needed, pending the review of completed studies.

Mannitol is used as a food additive, a drug and an excipient in drug products. As a food additive, mannitol is considered Generally-Regarded-As-Safe (GRAS). Medically, mannitol has been used as a laxative, diurectic and excipient. As an excipient, mannitol is present in many oral, parenteral (e.g., IV, and IP), and topical products. The sponsor states that inhaled mannitol at doses up to 635 mg/patient has been given to approximately 1,400 asthmatics and normal volunteers. No significant adverse effects associated with the use of mannitol were observed. Mannitol is non-carcinogenic and non-mutagenic.

TABLE OF CONTENTS

2.6.2 PHARMACOLOGY

Inhalation of hyper-osmotic D-mannitol may provoke bronchoconstriction by stimulating the release of histamine from mast cells. The submission contains no individual pharmacology study reports. It does contain a brief literature review. According to the review, hyper-osmotic mannitol (2 – 3x normal) induced the release of histamine from cultured human lung mast cells and blood basophils. Mannitol treatment also enhances histamine release from mast cells induced by IgE.

2.6.3. PHARMACOKINETICS AND TOXICOKINETICS

No data on pharmacokinetic and toxicokinetic data of inhaled mannitol in animals are provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall Toxicology Summary

General toxicology:

Inhalation toxicity studies of 1 and 14 days were conducted via a nose-only exposure system in rats. Respective D-mannitol doses (pulmonary deposition) in the low, mid and high dose groups were 2, 8 and 10 mg/kg/day in the single-dose study and 0.9, 2.5 and 6.9 mg/kg/day in the 14-day study. Table 1 (next page) presents an overview of the two toxicity studies. In the single-dose study, the rats were dosed on day one and sacrificed on day 15 for histologic evaluations. In the 14-day study, the rats were sacrificed 24 hours after the last dose. Histological evaluations of the respiratory system were done in every group and in the remaining organs of the control and high-dose groups only. No significant, treatment-related effects were observed in either study. The NOAEL was 10 and 6.9 mg/kg/day for the single-dose and 14-day repeat-dose exposure.

Table 1. Overview of Mannitol toxicity studies

Study #	Species	Duration	Route	Mannitol (mg/kg/day) [a]	NOAEL
XIS 001/033434	Rat	1 time	IH	0, 2, 8 & 10	10
XIS 002/033951	Rat	14 days	IH	0, 0.9, 2.5, & 6.9	6.9

a.. Estimated Pulmonary deposits.

Special toxicity:

Two studies were conducted to evaluate the eye irritation potential of mannitol. The studies are a Draize eye irritation test in rabbits and a bovine corneal opacity and permeability test in vitro. No significant irritation was observed in either assay. The results demonstrate that mannitol is non-irritating to the eye.

2.6.6.2 Acute Toxicity Study

Single-dose Toxicity Study of by Inhalation Administration to Rats.

Key findings: This is a preliminary acute toxicity study in rats which revealed no abnormal findings at single inhalation mannitol doses up to 10 mg/kg. CD-1 rats (5/sex/dose) were given via nose-only inhalation single pulmonary deposited doses of 0, 2, 8, and 10 mg/kg of mannitol. The rats were sacrificed after an observation period of 14 days.[1] Parameters assessed included clinical observations (clinical signs, food consumption and body weight) and autopsy. No histological examination was conducted. No treatment-related abnormalities were found. This study is not very informative given its design. A detailed review of the study is omitted. The following is the administrative information about the study.

Study number:	XIS 001/033434
Volume #, and page #:	Volume 1.2, Page 2-007
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 1, 2003
Study complete date:	January 19, 2004
Report date:	April 30, 2004
GLP compliance:	Yes, Signed GLP statement

[1] The pulmonary dose was calculated by multiplying the reported achieved doses by 0.1 (deposition fraction). The report states that the achieved doses are 17.6, 80.0 and 98.1 for the low, mid and high dose groups, respectively. The achieved doses were calculated from aerosol mannitol concentrations of 0.48, 2.84 and 3.72 mg/L. At least 71% of the aerosol has MMAD of (b) (4) The duration of exposure was 60 minutes.

QA reports:	Yes,
Drug lot # & purity:	3M05, 98- 102% purity

2.6.6.3 Repeat-Dose Toxicity

Study Title: Toxicity Study by Repeated Daily Inhalation Administration to CD rats for 2 weeks

Key findings: CD-1 rats (10/sex/dose) were given via nose-only inhalation pulmonary deposited doses of 0, 0.9, 2.5 and 6.9 mg/kg of mannitol for 14-days. The rats were sacrificed after 24 hours after the last dosing. No treatment-related abnormalities were found. The NOAEL is 6.9 mg/kg/day.

Study number:	XIS 002/033951
Volume #, and page #:	Volume 1.2, Page 2-112
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 6, 2003
Study complete date:	February 27, 2004
Report date:	June 14, 2004
GLP compliance:	Yes, Signed GLP statement
QA reports:	Yes,
Drug lot # & purity:	3M05, 98- 102% purity
Formulation/vehicle:	

Methods: Animals were dosed by oral inhalation once per week for 6 weeks.

Dosing:

Species/strain:	Rats (Crl:CD® (SD) IGS BR),
#/sex/group:	10
Age:	6 - 7 weeks
Weight:	M: 26. – 324g; F: 168 - 205g
Doses in administered units:	(See Table 2, next page, for dose estimates)
Route, form:	Nose-only IH, dry powder, 60 minutes/day

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	None
EKG:	Pre-treatment and week 5
Minute volume:	For 15 minutes pretreatment using Buxco Electronics LS-20 system

Hematology:	Week 2
Clinical chemistry:	Week 2
Urinalysis:	Week 2
Gross pathology:	Sacrifice
Sacrifice method:	Pentobarbitone (IP)
Organs weighed:	Adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, salivary glands, seminal vesicles, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus
Histopathology:	A complete panel for the control and high dose groups; respiratory system for all groups.
Toxicokinetics:	None
Other:	Aerosol concentration and particle size distribution were measured in each exposure period from representative animal exposure positions. Particles were generated by a scraper from a compressed powder and a streamed air flowing over the scraped dust. Particle sizes were determined with an Anderson cascade impactor.

Results

Dose estimates: Table 2 (below) presents the dose estimates of the study. The estimated pulmonary deposition was 0.9, 2.5 and 6.9 mg/kg/day for the low, mid and high dose groups, respectively.

Table 2. Estimated Pulmonary Deposits in the 14 day IH Study in Rats

Treatment	Dose	Aerosol			Exposure (mg/kg/day)	
		MMAD (μm)	GSD	Drug (mg/L)	Achieved Dose [a]	Pulmonary Deposit [b]
Air	0	-	-	-	-	-
Mannitol	LD	2.4	2.37	0.264	9.0	0.9
	MD	3.7	2.46	0.877	25.2	2.5
	HD	4.7	2.80	2.796	69.3	6.9

a. Achieved dose reported by the sponsor.
b. Converted from the achieved dose. Pulmonary deposits (mg/kg/day) = Achieved dose (mg/kg/day) x 0.1 (pulmonary deposition factor). For example, the pulmonary deposition for the HD = 69.3 x 0.1 = 6.9 mg/kg/day.

Mortality: None.

Clinical Signs: No treatment-related effects were observed.

Body Weights: No treatment-related effects were observed. The respective terminal mean body weight was 329, 340, 345, 343 grams in males and 215, 204, 200 and 201 grams in females.

Clinical pathology: No remarkable findings were noticed.

Hematology: No treatment-related effects were observed.

Clinical chemistry: No treatment-related effects were observed.

Urinalysis: No treatment-related effects were observed.

Organ weights: No treatment-related effects were observed.

Gross pathology: No treatment-related effect was observed.

Histopathology:

No significant abnormalities were observed in the respiratory system in the treatment groups (Table 3). Increased incidences of inflammation cells in the heart and kidney were seen in the high dose group, but the significance of these findings is unknown given the lack of systemic toxicity of mannitol from non-inhalation route of administration.

Table 3. Noticeable Pathology findings of the 14 –day inhalation Study of Mannitol

	Male				Female			
Mannitol (mg/kg/day, Pulmonary)	**0**	**0.9**	**2.5**	**6.9**	**0**	**0.9**	**2.5**	**6.9**
N	10	10	10	10	10	10	10	10
Adrenal: cortical vacuolation	8	-	-	10	10	-	-	6
Brain: vascular inflammation	0	-	-	1	0	-	-	0
Epididymides: inflammation cells	6	-	-	9				
Heart: Inflammation cells in myocardio.	1	-	-	4	0	-	-	2
Kidney: cortical tubular basophilia	1	-	-	4	1	-	-	2
Interstitial inflammatory cells	2	-	-	5	2	-	-	2
Lungs: Sub-pleural inflammation cells	2	7	4	6	6	5	4	9
Spleen: prominent extramedullary hemapoiesis	4	-	-	7	10	-	-	10

- indicates not examined.

2.6.6.4 Special toxicity studies

Study Title: Eye Irritation to the Rabbits (Report No. 004/034088)

Three white New Zealand rabbits were administered 78 mg (0.1 ml in volume) of mannitol in one eye and observed for ocular irritation for 72 hours post administration. The opposite eye served as a control. Parameters evaluated include corneal opacity, iridial lesions, and conjunctival redness and chemosis. No remarkable findings were observed in any of the rabbits. Mannitol is considered non-irritant to the eye under the conditions tested.

Study Title: Bovine Corneal Opacity and Permeability Assay (Report No. 003/034081)

This assay assessed the ocular irritancy potential of mannitol *in vitro*. It is not a standard test. Some consider it an alternative to the Draize *in vivo* eye irritation test. Isolated bovine corneas (obtained from slaughter houses) were incubated with mannitol powder, 20% imidazole (positive control) or 0.9% saline on the anterior side but the culture medium on the posterior side at 32^{o}C for 4 hours. Opacity was determined by the light transmission through the cornea. Permeability was measured by the rate of sodium fluorescein crossing the cornea

with a spectrophotometer. (Cornea was incubated at 5 mg/ml sodium fluorescein at 32^{o}C for 90 minutes.) A composite score was derived for each cornea based on its opacity and permeability reading. A score value of less than 25 was considered non-irritant. A score of greater than 25 was considered irritant. The composite score of 0.2, 152.4 and not applicable was obtained for the mannitol, imidazole and saline, respectively. The report states that mannitol is classified as "a negative potential eye irritant" according to the criterion.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The available nonclinical data of this application is insufficient to support the safety of the proposed clinical trial of mannitol. The deficiency is primarily the lack of appropriate inhalation toxicity studies in a non-rodent species and the lack of adequate safety margins between the observed-no-adverse-effect-level in animals and the proposed clinical dose in humans. The lack of sufficient safety margin is indicated by the proposed clinical dose (635 mg/patient, or 12.7 mg/kg/day) being greater than the NOAEL in monkeys (6.9 mg/kg/day from a 14-day inhalation toxicity study). However, significant clinical experience of the proposed use of mannitol exists. The clinical experience appears to support the proposed use of mannitol.

Toxicology:

The toxicology of non-inhalation use of mannitol is well understood. Mannitol is non-carcinogenic and non-mutagenic. F344/N rats and B6C3F1 mice fed with up to 5% D-mannitol in diet for 103 weeks did not reveal any evidence of tumorigenicity. Mannitol used as a nutrient and/or dietary supplement in animal drugs, feeds, and related products is generally recognized as safe [21 CFR 582.5470 (4/1/97)]. Medically, mannitol has been used as a laxative, diurectic and excipient. As an excipient, mannitol is present in many oral, parenteral (e.g., IV, and IP), and topical products.

However, toxicological characterization of inhaled mannitol is limited. There is no information in the literature regarding to the toxicity of inhaled mannitol. The sponsor conducted inhalation toxicity studies of mannitol in rats for the treatment duration of up to 14 days. Respective D-mannitol doses (pulmonary deposition) for the low, mid and high dose groups were 2, 8 and 10 mg/kg/day in the single-dose study and 0.9, 2.5 and 6.9 mg/kg/day in the 14-day study. No significant, treatment-related effects were observed in either study. The NOAEL was 10 and 6.9 mg/kg/day for the single-dose and 14-day repeat-dose exposure.

Clinical Experience

According to the sponsor, approximately 1,400 asthmatics and normal volunteers received via inhalation up to 635 mg mannitol/patient. No significant adverse effects associated with the mannitol treatment were observed.

Conclusion

The proposed trial of mannitol is safe from the nonclinical viewpoint. The application does not contain sufficient nonclinical data to support the safety of all the proposed clinical doses of mannitol. The inadequacy includes the lack of toxicity studies in a second species (a non-rodent species) and the lack of adequate safety margins between the NOAEL in rats and the portion of the proposed clinical doses (> 35 mg/kg/day), based on a NOAEL of 7 mg/kg/day (7 mg/kg/day ÷ 10 safety factor x 50 kg/patient = 35 mg/patient). However, sufficient clinical experience appears to support the safety of all the proposed doses and compensates the inadequacy in nonclinical data. Also, the expected adverse effect associated with the proposed use of mannitol – bronchoconstriction – is readily monitorable clinically. The proposed trial is reasonably safe.

Recommendation:

The initial IND protocol is considered to be reasonably safe to proceed.

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Pharmacologist/toxicologist

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/s/

Luqi Pei
3/18/05 01:44:54 PM
PHARMACOLOGIST

Timothy McGovern
3/21/05 09:28:53 AM
PHARMACOLOGIST
I concur.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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