PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING
January 30, 2013

NDA# 202049: mannitol inhalation powder (proposed trade name Bronchitol) for oral inhalation sponsored by Pharmaxis, for the management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA# 202049) for mannitol inhalation powder (proposed trade name Bronchitol) for oral inhalation sponsored by Pharmaxis, for the management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package
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DIVISION MEMORANDUM

Date: December 28, 2012

From: Anthony Durmowicz, MD
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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for NDA 202049, dry powder mannitol (proposed name Bronchitol), 400 mg twice daily, indicated for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function.

Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on January 30, 2012. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug product for marketing in the United States. The upcoming meeting is to discuss the New Drug Application (NDA) from Pharmaxis, Ltd., seeking an approval for mannitol inhalation powder (proposed tradename Bronchitol) 400 mg to be administered twice daily for the management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function.

The materials to be discussed in this meeting and the opinions we are seeking are primarily related to the statistical and clinical issues related to the efficacy and safety of mannitol inhalation powder. Keep in mind that in the regulatory decision making process to determine approvability of a product, the Agency takes into consideration various factors in addition to clinical issues, including manufacturing and controls of a product and preclinical considerations. These will not be the focus of this Advisory Committee meeting.

This memorandum summarizes the contents of the Agency background materials and the key issues and topics for discussion at the meeting. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Pharmaxis, Ltd. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this meeting.

Following are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the statistical and clinical briefing documents. Note that, for consistency, in the text and figures in the remainder of this memorandum, the 400 mg mannitol for inhalation study drug product will be referred to as dry powder mannitol

(DPM) and the 50 mg inhaled mannitol control product will be referred to simply as "control".

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 for a very small subpopulation of CF patients that acts on the CFTR, treatment for the great 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."

Product Information

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. As such, mannitol, when inhaled, has the ability to cause severe bronchoconstriction in susceptible subjects. 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 drug product package (14 day supply) includes 280 clear hard gelatin mannitol-filled capsules, which are sealed individually in aluminum blisters (28 blister strips each containing 10 capsules) and two hand held dry powder inhalation devices. 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.

Nonclinical Pharmacology/Toxicology

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.

Clinical Pharmacology

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. 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.

Clinical and Statistical

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 (5mg 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. This resulted in the post hoc creation by Pharmaxis of a "modified" intent to treat population (MITT) that included only ITT patients who attended the week 6 study visit. As a result, patients who dropped out before week 6 of either study are 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.

Another factor that contributed to the problem regarding differential missing data 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, from a statistical perspective, any MMRM estimate of the treatment effect using the continuous change from baseline in FEV1 outcome would not be reliable. Because continuous responder analyses that illustrate the proportion of DPM and control patients who achieve a certain threshold of treatment effect in the primary endpoint represent the true ITT population and account for missing data from both groups, the Agency feels this representation of data is a more accurate reflection of the efficacy of DPM in that patients who cannot tolerate the treatment cannot be expected to receive any efficacy from it.

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

Adapted from FDA statistical briefing document

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. Because the Agency believes analyses that incorporate the true ITT population and are able to account for the missing data as a result of the differential drop-outs are the most appropriate representation of the primary efficacy endpoint, responder analyses are also presented.

- *Modified Intent to Treat Analyses*

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). Note that these analyses do not include the baseline visit and as such, represent an average effect from week 6 to week 26. Analyses that represents an average effect from actual baseline to week 26 by incorporating the change from baseline at baseline estimate the difference between DPM and control from baseline to week 26 as 54.2 mL with 95% CI of (24.7, 83.6).

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]

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

As mentioned above, 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. While a conservative approach, 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.

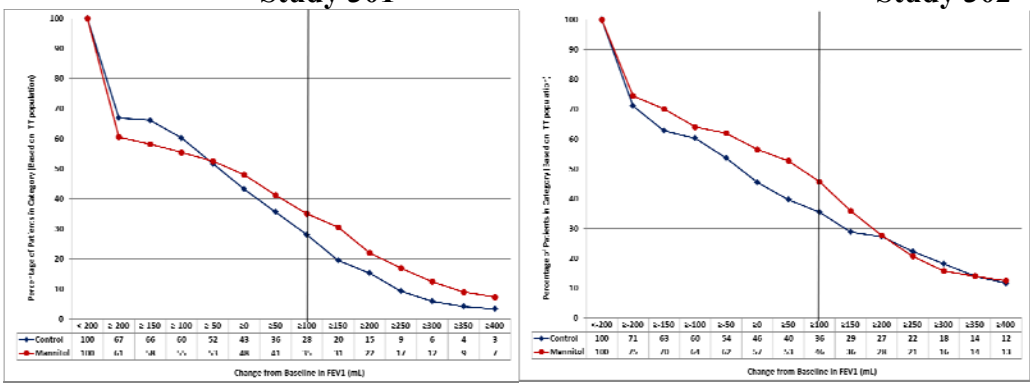
For each analysis, a patient is classified as having been successfully or unsuccessfully treated according a specific threshold for the change from baseline in FEV1 at week 26, in this case from -200 to +400 mL. The x-axis displays the thresholds required to classify a subject as a successfully treated 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

Study 301 **Study 302**



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 5 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 5. 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: FDA's Biostatistical Review, Table 8,]

It is notable that there is inconsistency with regard to the efficacy results when analyses are conducted with and without inclusion of missing data as a result of differential patient drop-out. Results for study 301, which had the greatest differential drop-out, went from demonstrating a statistically significant increase in FEV1 for the MITT population (Table 4) to not significant when missing data were accounted for (Table 5) while results for study 302, which had fewer overall drop-outs, went from statistically equivocal (p=0.059) to results that were statistically significant across the 50, 75, and 100 mL thresholds.

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. The appropriateness and difference in study results based on the use of different analysis study populations will be a significant topic of discussion for the PADAC members.

- *Subgroup Analyses for the Primary Endpoint*

Because the two phase 3 studies differed in terms of the pre-specified statistical analysis methods and there were differences in the early discontinuation rate and pattern, subgroup analyses for the primary efficacy variable, FEV1, based on age, gender, geographic region, rhDNAse use, and disease severity (FEV1 % predicted <50% and ≥50%), were performed separately for each study (Table 6).

Table 6. Responder Analysis Results for FEV1 Absolute Increase ≥100mL at Week 26 (ITT Population)

Response Definition	DPM	Control	Odds Ratio (95%CI)* (DPM vs. Control)	p-value*
Study CF301				
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 CF302				
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 FEV1, and disease severity.

- *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.

Safety Findings

- *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 (Controlled Phase 3 Studies)

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.

Benefit-Risk Assessment

The determination of efficacy based on the 2 phase 3 studies is 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 do 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. The Agency believes, from a statistical standpoint, that responder analyses that incorporate the entire ITT population and therefore account for the missing data from drop-outs, provide a more accurate reflection of the efficacy of DPM in the CF patients enrolled in the studies. Results based on these analyses are not consistent with Pharmaxis' analyses in a modified ITT population. For example, in study 301, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV1 change from baseline for any of the thresholds examined (≥50, 75, or 100 mL) while in study 302 there were statistically significant differences between treatment groups at each of the thresholds examined.

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 bronchospasm in patients treated with DPM and most adverse events with the exception of hemoptysis, were more tolerability issues than major safety issues. 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.

Summary

The purpose of the PADAC meeting is to discuss the efficacy and safety data that have been provided to support the approval of DPM for the management of CF in patients aged 6 years and older to improve pulmonary function. The main issues for the PADAC to consider when considering the overall risk-benefit assessment of DPM 400 mg twice daily are as follows: 1)whether, taking into consideration the high numbers of differential patient dropouts in the DPM group, the various statistical analyses for the primary endpoint and secondary endpoints, the efficacy data presented for the two Phase 3 studies for improvement in lung function (FEV1) in patients with CF meets the standard of substantial evidence; and 2) whether the safety and tolerability profile of DPM, especially the increased incidence of hemoptysis in both children and adults, is sufficient to support its use as a chronic maintenance therapy for CF patients.

At the PADAC meeting, the Applicant will present an overview of the efficacy and safety data for DPM, followed by the Agency's presentation.

Please keep in mind the following discussion points and questions, some of which are voting questions, upon which you will be asked to deliberate, following the presentations and discussion.

Draft Topics for Discussion

1. Discuss the evidence to support the efficacy of DPM at a dose of 400 mg twice daily in improving pulmonary function in patients 6 years and older with cystic fibrosis.
   - **a)** In adults 18 years of age and older
   - **b)** In children and adolescents 6-17 years of age

2. Discuss the overall safety profile of DPM.
   - **a)** In adults 18 years of age and older
   - **b)** In children and adolescents 6-17 years of age

3. 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? **(Voting Topic)**

   - **a)** In adults 18 years of age and older? If not, what further efficacy data should be obtained?
   - **b)** In children and adolescents 6-17 years of age? If not, what further efficacy data should be obtained?

4. Is the safety profile for DPM for the maintenance treatment of patients with cystic fibrosis sufficient to support approval? **(Voting Topic)**
   - **a)** In adults 18 years of age and older? If not, what further safety data should be obtained?
   - **b)** In children and adolescents 6-17 years of age? If not, what further safety data should be obtained?

5. Do the efficacy and safety data provide substantial evidence to support approval of DPM at a dose of 400 mg once daily for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function? **(Voting Topic)**
   - **a)** In adults 18 years of age and older? If not, what further efficacy data should be obtained?
   - **b)** In children and adolescents 6-17 years of age? If not, what further efficacy data should be obtained?

We look forward to a very interesting meeting and again thank you for your time and commitment in this important public health service.

Clinical Review for the Pulmonary-Allergy Drug Advisory Committee Meeting

January 30, 2013

Inhaled Dry-Powder Mannitol
NDA 202,049

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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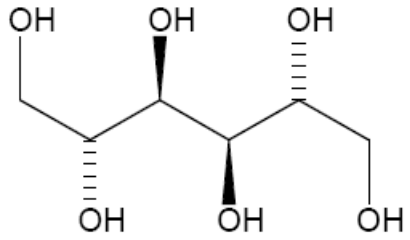
1 Introduction and Background

1.1 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 three morphic forms of mannitol denoted as α, β, δ-mannitol. 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, 2 inhalers are included in each 2-week dose carton.

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.

1.2 Currently Available Treatments for Proposed Indication

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]		

1.3 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.

1.4 Important Safety Issues with Consideration to Related Drugs

The principal 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.

1.5 Other Relevant Background Information

Inhaled dry powder mannitol, 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. In addition to its proposed use for the treatment of CF, chronically inhaled mannitol is also being studied for other indications (to enhance mucociliary clearance in patients with bronchiectasis and COPD). 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.

2 Clinical Data Sources, Review Strategy, and Trial Design

2.1 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 of 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
[Module 5.3.5.3, ISS, Table 1, pg 25/274, and Section 3.1, pages 28- 30]

2.2 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 STUDY DPM-CF-202. 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 Review of Safety.

To orient the reader, the review has been organized in the following manner. The protocols for Studies 202, 301, and 302 are discussed in detail in Section 2.3, "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 3, Integrated 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 4, Review of Safety.

2.3 Clinical Trial Design

2.3.1 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

[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

[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 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).

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.

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
[Ref: Module 5.3.5.1.2, Clinical Study Report DPM-CF-202, Section 9.8, page 50]		

2.3.2 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 (henceforth, they will be referred to as Study 301 and Study 302). 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 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:
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 301 (and subsequent Study 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)					

[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)		

[Module 5.3.5.1.4.16.1.1, Study DPM-CF-301 Protocol Version 5, page 440]

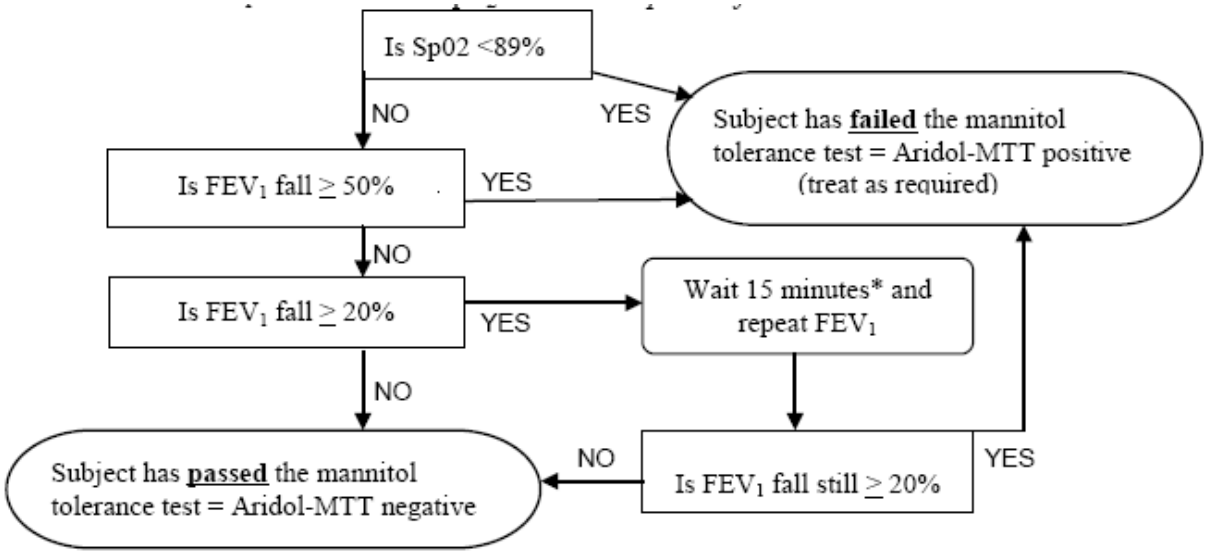
Screening assessments included comprehensive history, demographics, CF sputum microbiology, review of prior and concomitant medications/ treatments, physical exam, vital signs, pulse oximetry, spirometry, report of adverse events, and clinical laboratories. Patients who met all the eligibility criteria 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.

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



. [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[3]		X[3*]

[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 mannitol) 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 aneurysm
- 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 for 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 had 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).

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.

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. 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. 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 briefing document. 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 following definition for pulmonary exacerbation, 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 $\geq$ 38°C
      -anorexia or weight loss
      -sinus pain or tenderness
      -change in sinus discharge
      -FVC or FEV1 decreased by $\geq$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 3, Integrated 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
[Ref: Module 5.3.5.1.3, Clinical Study Report DPM-CF-301, Section 9.8, page 55]		

2.3.3 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 ≥ 40% predicted (from ≥ 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. Blood chemistry and hematology, 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.

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.

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.

Spirometry measurements were conducted in a similar fashion as for Study 301.

No pre-specified key secondary endpoints were identified in the protocol but sputum weight was added as a key secondary endpoint in the SAP. All secondary endpoints listed here were evaluated, and were the same as those in Study 301 unless noted.

- 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%." A brief summary of changes can be found in the table below. . The potential impact of these amendments will be discussed further in Section 3, Integrated Review of Efficacy.

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
[Ref: Module 5.3.5.1.3, Clinical Study Report DPM-CF-302, Section 9.8, page 60]		

2.4 Dose Selection

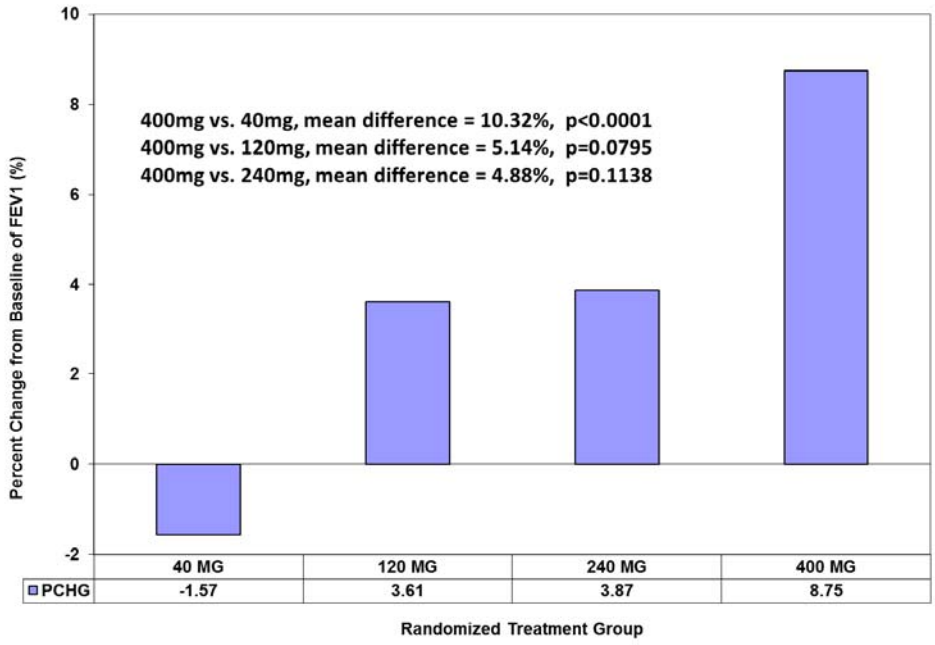
The dose ranging data for the DPM clinical program primarily comes from study 202, in which the effect of 4 different doses of mannitol inhalation powder (40, 120, 240, and 400 mg administered twice daily) on pulmonary function (FEV1) were assessed (refer to Section 2.3.1 for a complete description of 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 7.

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. 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 7: Study 202-Percent Change from Baseline in FEV1, ITT



[Source: FDA's Biostatistical review, Figure 2]

3 Integrated 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 statistical briefing document, because the above analyses do not account for the frequent and treatment-related early discontinuations in the Phase 3 studies, the Agency does not feel the Applicant's pre-specified primary efficacy analyses are an accurate reflection of the efficacy of DPM. Instead, responder curves that allow

inclusion of the entire ITT group, and which illustrate the proportion of DPM and control patients achieving certain FEV1 thresholds are felt to more appropriately account for the treatment-related missing data. In these responder analyses, missing data are presumed to be a treatment failure as it is reasonable to assume patients who drop out would not derive any efficacy. Using these analyses, for study 301, there was no statistically significant difference between treatment groups in the proportion of subjects who achieved any of the increase in FEV1 from baseline thresholds evaluated (≥50, 75, or 100mL). For Study 302, the responder analyses do reveal a statistically significant treatment effect.

Using the Applicant's analyses, while the data between the 2 studies are inconsistent, the benefit appears small for pediatric patients under the age of 18, with a subgroup of patients aged 12-17 years in Study 302 worsening over the 26-week treatment period, and numerical trends in Study 301 indicating that adult patients (aged 18 and older) may have had a better effect than children and adolescents (aged 6-17).

The results for the secondary spirometry endpoints are generally consistent with the results obtained from FDA analyses for the primary endpoint in the ITT population, negative for study 301 and marginally positive for study 302. Regardless, since these 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. Other endpoints failed to demonstrate a statistically significant difference between DPM and control.

3.1 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.

3.1.1 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; see also Guidance for Industry: Special Protocol Assessment, May 2002 *http://www.fda.gov/cder/guidance/index.htm*). Specifically, no agreement was reached regarding choice of endpoints, duration of study, or analysis methods.

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 briefing document 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.

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 a post hoc manner for Study 301 and the integrated data.*
- *To use of the "adjusted baseline" for the presentation of efficacy endpoints in the ISE for Study 302 and for the integrated phase 3 studies.*

While acknowledging the Applicant's post hoc analysis, no agreement was made on the acceptability of the proposals. Instead, the Division noted that pre-specified primary analysis methods are generally relied upon heavily in regulatory decision making while post-hoc analyses are often considered hypothesis generating. The Division stated that the adequacy of the proposed methods would be determined as part of the review of the NDA.

These data analysis issues are described in detail in the FDA's statistical briefing document.

3.1.2 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. A total of 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 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, Dr. Zhou's review

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 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 or, more likely, regional differences in use of the designation "bronchiectasis." 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.

3.1.3 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 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 (i.e., bronchospastic) response to the first dose of DPM, 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. A total of 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 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: 37% 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) for the per protocol (PP) population 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. As such, the validity of the compliance figures is questionable. That being said, 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%

Source: 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

3.1.4 Analysis of Primary Endpoint(s)

Basis for Choice of Endpoint

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 not only with pulmonary outcomes, but with longer term overall morbidity and mortality[1, 2]. The majority of death in the CF population is due to pulmonary causes[1], so improvement in FEV1 is a useful and clinically meaningful endpoint.

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 12

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 (44119) 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 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 the most appropriate 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 statistical review. Because of the unequal (more in the DPM 400mg arm) large dropout of patients in Study 301 before the first efficacy data collection at week 6, the Applicant used a modified Intention-to-Treat (MITT) population to calculate results, excluding those who dropped out before week 6. Interim efficacy analyses were accounted for by adjusting the primary efficacy endpoint to be tested at a 0.0498 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 (MITT)

	DPM 400mg	Control	Treatment-Comparison DPM 400mg - Control		
Weeks			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**

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]

Based on these analyses, for the MITT population in Study 301, there was an 83mL treatment effect that was statistically significant. For study 302, the difference between DPM and control was 54mL, with a p value of 0.059.

In addition, due to differences in the description of the details of the MMRM model used to analyze Study 301, this analysis does not include data for change from baseline to week 6 for that study. The model used for analysis of Study 301 differed from that of Study 302, in that one of the response variables, "change from baseline at baseline," was not included. The overall effect of such is that the treatment effect calculated for Study 301 by the Applicant which demonstrated statistical significance is the average

treatment effect from week 6 to week 26, at 83.1mL. Analyses incorporating the "change from baseline at baseline" into the response variable (as pre-specified in the SAP for Study 301) estimate the difference between mannitol and control in the primary efficacy endpoint as 54.2 mL with 95% CI of (24.7, 83.6). It is important to note that the 54.2 mL estimate is an estimate that represents an average effect from baseline to week 26, as was pre-specified in the SAP for Study 301.

FDA Analyses

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 is reasonable.

Table 13, below, provides the FDA post hoc analyses, which examine 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, none of these parameters achieved statistical significance, although there was a numerical favoring toward DPM 400mg. These results suggest a conclusion which differs from the Applicant's proposed MMRM analysis of the MITT population.

For Study 302, differences between treatment groups using each of these criteria were statistically significant, as noted below.

Table 13: 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 8,]

The Agency also considered the continuous responder curves at each visit prior to week 26; patterns in these data were similar to those for week 26 data.

3.1.5 Analysis of Secondary Endpoints

Both protocols included a list of secondary endpoints which were not specifically ranked to take into consideration multiplicity. In addition, endpoints were not the same for both studies. Most of these endpoints are other spirometric measurements and are listed in Table 14, below. Table 14 provides the responder analysis for these secondary spirometry endpoints at week 26, using a threshold of 5% improvement as the cutoff value.

Table 14: Responder Analysis Results for the Secondary Endpoints at Week 26

Response Definition	DPM	Control	Odds Ratio (95%CI)[1] (DPM vs. Control)	p-value*
Study 301				
ITT[2]	176	118		
FEV1 percent increase ≥5%	64 (36%)	36 (31%)	1.24 (0.74, 2.09)	0.406
%predicted FEV_1 increase ≥5%	37 (21%)	20 (17%)	1.29 (0.69, 2.40)	0.427
Study 302				
ITT[2]	184	121		
FEV1 percent increase ≥5%	86 (47%)	44 (36%)	1.85 (1.09, 3.13)	0.023
%predicted FEV_1 increase ≥5%	55 (30%)	33 (27%)	1.20 (0.69, 2.07)	0.519

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.
[Source: Modified from FDA's Biostatistical Review, Table 9]

These results provide conclusions regarding the treatment effect that are generally consistent with that of the primary efficacy endpoint. Generally, no difference between treatment groups is observed for study CF301 while some marginal differences between treatment groups favoring DPM over control are observed for study CF302. Secondary spirometric endpoints would be expected to trend with FEV1, and therefore add little independent support to the primary endpoint.

Sputum weight post treatment at week 14 was added as a key secondary endpoint for Study CF302 in the SAP, but was neither specified in the Study 302 protocol, nor in the SAP or protocol for Study CF301. Patients in the DPM 400mg group for both studies demonstrated increased expectorated sputum weight at Week 14 over controls. For Study 301, the difference was statistically significant. However, for Study 302, using the SAP-specified procedure to account for multiple endpoints, the significance value to which the p-value would be compared is 0.0167. Since the analysis of sputum weight at baseline was associated with a p-value of 0.041, the results do not represent a statistically significant treatment effect. [data not shown; Source: FDA's statistical review, Table 10]. Nevertheless, 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 11].

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]

The Applicant included a number of additional non-spirometry efficacy endpoints evaluated in the MITT population, none of which demonstrated statistically significant differences between treatment groups (even without adjustment for multiplicity). Table 16 lists these other endpoints below.

Table 16: Non-Spirometry Efficacy Endpoints, MITT Population

DPM 400mg vs. control	Study 301 (N=295)		Study 302 (N=305)	
	Mean/ OR/RR	(95%CI) p-value	Mean/ OR/RR	(95%CI) p-value
Rate for PE	0.86	(0.64, 1.17), p=0.341	0.93	(0.74, 1.17), p=0.551
Hospitalizations for PDPE	0.94	(0.26, 3.42), p=0.924	0.75	(0.42, 1.33), p=0.328
Hospitalizations for PE	0.88	(0.32, 2.39), p=0.800	0.75	(0.45, 1.23), p=0.251
Proportion of patients used rescue Antibiotic for all PE	0.73	(0.39, 1.37), p=0.329	0.91	(0.78, 1.07), p=0.266
Proportion of patients used rescue Antibiotic for all PDPE	0.66	(0.25, 1.76), p=0.407	0.89	(0.69, 1.15), p=0.368
QoL – Respiratory domain scores	0.00	(-1.99, 1.98) p=0.996	2.79	(-0.50, 6.09), p=0.096
QoL increase in respiratory score ≥5 points	0.66	(0.37, 1.17), p=0.156	--	--

PDPE: Protocol defined pulmonary exacerbation; PE: pulmonary exacerbation reported as an AE
[Source: Modified from FDA's Biostatistical Review of Efficacy, Table 12]

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.

3.1.6 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, below.

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 review, Table 14]

3.1.7 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 4, Review of Safety.

4 Review of Safety

Safety Summary

The safety information for DPM 400mg is derived primarily from Studies 301 and 302. As the studies were 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. 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. The full discussion of safety follows.

4.1 Methods

4.1.1 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 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 throughout the review as uncontrolled safety data.

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.

4.1.2 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 Section Discontinuations Due to AE, Prior to Randomization, below, under Section 4.3.3. 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.

4.1.3 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.

4.1.4 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: Failed Challenge Dose of DPM, Clinical Development Program.

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. 3.1.3]	29	[See Sec. 3.1.3]	295
302[i]	342	22	2	[See Sec. 3.1.3]	13	[See Sec. 3.1.3]	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
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 Supportive Safety Results.

4.2 Adequacy of Safety Assessments

4.2.1 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, with additional open-label data for up to an additional 52 weeks, which is a reasonable length of time for a drug planned to be used chronically, as outlined in Guidance ICH E1A. 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). 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.

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 Demographics, and 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.

4.2.2 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 2, above), and while the conduct of study 202 was suboptimal (see the FDA's Biostatistical review), the data collected generally support further evaluation of the safety and efficacy of the 400mg dose.

4.2.3 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

4.2.4 Metabolic, Clearance, and Interaction Workup

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 DPM 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.

4.2.5 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).

4.3 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.

4.3.1 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.

4.3.2 Nonfatal Serious Adverse Events

The Applicant utilized the appropriate definition of Serious Adverse Event throughout the development program, as defined in 21CFR. Data were 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

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 4.3.4. 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 also 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 44125-04) had been receiving study treatment for three and a half months when hospitalized due to an allergic reaction to ceftazidime; study drug was continued, 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 RTI[b]	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
b= Respiratory Tract Infection
[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 4.3.4 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]

4.3.3 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 having AEs 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 4.3.4, Submission Specific Primary Safety Concerns, 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 RTI[c]	0	1 (0.6)
Upper RTI[c]	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
c= Respiratory Tract Infection

[Source: Module 5.3.5.3. ISS Section 8.1.5, Modified from Applicant's Table 42]

4.3.4 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 4.4, 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 4.4.2, 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.

Overall Tolerability

The overall tolerability of DPM 400mg was a significant issue for this program. 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 4.1.4, 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.

Other predictors of overall patient tolerability have previously been discussed in Section 4.3.3, 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%). Three additional patients in the open-label phase discontinued due to cough events. 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.

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 26: 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 26: 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 27, 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 27, 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 27: 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[10]. 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)[11]. A recent case-control study of CF patients in Israel[12] 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[11], 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 of 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 28, 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 28: 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, which demonstrated no statistically significant differences between treatment groups in the proportion of subjects experiencing hemoptysis; however, numerical trends indicate that the risk of

hemoptysis may be increased with mannitol use. Numerical trends 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].

Age notwithstanding, the rate of AE of hemoptysis in patients with FEV1 $\leq$40% predicted who received DPM 400mg was almost double that of patients with low FEV1 who received control, 19% versus 10% (see Section 4.5.3, 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 44120-19 and 61709-16), and one patient from study 302 who received DPM 400mg (patient 10135-01). In addition, Study 301 open-label data included an additional case of massive hemoptysis (patient 44302-03). [Source: Response to IR dated 11-27-2012]

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 29: Incidence of Bronchospasm, Safety Set). 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 29: 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 29, 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.

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 30: Major Safety for Patients <18 years of age, below..

Table 30: 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 would be expected that pediatric patients might 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 events examined for the total safety population are discussed later in this review, under 4.4.1, Common Adverse Events. However, AEs were also evaluated specifically for the 6-17 year old population as well, to assess if events were similar for pediatrics, and are described below in Table 31. The majority of events were the same for the total safety population except that pyrexia and arthralgia were noted more in the total population, and epistaxis occurred at a higher rate in pediatrics than for the population as a whole.

Table 31: Incidence of Adverse Events 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 events 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 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.

4.4 Supportive Safety Results

4.4.1 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 Unique Safety Issue for the Phase 3 Program, and Submission Specific Primary Safety Concerns, 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 32: Common AE by System Organ Class, Double Blinded 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 32: Common AE by System Organ Class, Double Blinded 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 events by preferred term are listed in Table 33, 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. Cough was the most common AE reported in the Phase 3 program. 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 33: Incidence of Adverse Events 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]

Other adverse events 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 31.

4.4.2 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].

4.4.3 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.

4.4.4 Electrocardiograms (ECGs)

ECG monitoring was not conducted as part of the Phase 3 clinical program for DPM 400mg.

4.5 Other Safety Explorations

4.5.1 Dose Dependency for Adverse Events

This is unknown, as only a single dose of 400mg was studied in Phase 3 trials.

4.5.2 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).

4.5.3 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 4.3.4, Submission Specific Primary Safety Concerns, for Pediatrics.

Adverse Events for 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. 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, although the incidences were higher than for FEV1-matched controls. Headache was seen more often in those with low FEV1 on DPM 400mg (23%, versus 5% control), as was incidence of CF exacerbation (55% versus 50% control). Hemoptysis occurred at almost twice the rate in DPM 400mg-treated patients over controls (19% versus 10%).

Table 34: Incidence of Adverse Events 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]

4.5.4 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.

4.5.5 Drug-Drug Interactions

No formal drug interaction studies were conducted with mannitol.

4.6 Additional Safety Evaluations

4.6.1 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.

4.6.2 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.

4.6.3 Pediatrics and Assessment of Effects on Growth

Refer to Section 4.3.4, Submission Specific Primary Safety Concerns, PEDIATRICS, for a discussion of safety in pediatric patients. No formal studies in pediatrics to assess growth were conducted or required for this NDA.

4.6.4 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.

5 Literature Review/References

1. Cystic Fibrosis Foundation Patient Registry. 2009 Annual Data Report to the Center Directors. Bethesda, Maryland. 2010 Cystic Fibrosis Foundation.
2. Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cystic Fibrosis 2008;7(5):450-453.
3. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989, Sep 8; 245(4922):1066-73.
4. Ferkol T, Rosenfeld M, and Milla C. Cystic Fibrosis Pulmonary Exacerbations. J Pediatr 2006; 148:259-64.
5. Konstan MW, Berger M. Current Understanding of the inflammatory process in cystic fibrosis: onset and etiology. Pediatr Pulmonol 1997; 11:481-2.
6. Flume PA et al. Cystic Fibrosis Pulmonary Guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007; 176:957-69.
7. Davis PB, Drumm M, and Konstan MW. Cystic Fibrosis. Am J Respir Crit Care Med 1996; 154:1229-1256.
8. Corey M, et al. Longitudinal Analysis of Pulmonary Function Decline in Patients with Cystic Fibrosis. J Pediatr 1997; 131:809-14.
9. Miller MR, et al. Standardisation of Spirometry. Eur Respir J 2005; 26:319-38.
10. Flume PA, et al. Am J Respir Crit Care Med 2010; 182: 298-306.
11. Flume PA, et al. Chest 2005; 128: 729-38.
12. Efrati O, et al. J Cyst Fibrosis 2008 July;7 (4): 301-6.

Statistical Review for the Pulmonary-Allergy Drug Advisory Committee Meeting

January 30, 2013

Inhaled Dry-Powder Mannitol
NDA 202,049

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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1 EXECUTIVE SUMMARY

The sponsor 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 rhDNase use (yes/no) and region (Australia and Europe in study CF301) or country (Argentina, Canada, Germany, Belgium, France, Netherlands, and US in study CF302)), parallel group (DPM (mannitol 40mg x 10 capsules, BID) or control (mannitol 5mg 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 in a continuous form, as was intended in the protocol and SAP for each study are problematic in that that they do not incorporate the entire ITT group. Patients who dropped out before week 6 are 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 which occurred differentially by treatment group are also present. 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, 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. Therefore, the MMRM estimates of the treatment effect using the continuous change from baseline in FEV_1 outcome may not be accurate. Continuous responder curves 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 more appropriately account for the treatment-related missing data. Statistical hypothesis testing of the treatment effect over the entire range of thresholds is not standardized but analyses at a several single thresholds provide consistent results regarding the qualitative treatment effect within study but not between studies. For study CF301, numerically the results favored the DPM group; however, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined. For study CF302, differences between treatment groups in the proportion of subjects who achieved a 50 mL, 75 mL, or 100 mL threshold in the change from baseline in FEV_1 were associated with p-values smaller than the usual alpha level of 0.05.

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 (test for homogeneity of odds ratio p-value=0.6 for each study).

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Pharmaxis Ltd., the applicant, proposes Bronchitol® (Inhaled Dry Powder Mannitol 400mg capsules (hereafter referred to as DPM)) twice daily (BID), 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 stated the following.

> 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, there was no agreement 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 Sponsor 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 CF-302 (November 7 , 2007)

- The sponsor described 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 but a treatment benefit in reduction in exacerbations in the cystic fibrosis population is not viewed as being appropriate as a separate claim, for description as part of the indication.
- 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 change from baseline in FEV1 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 appear 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 CF-302 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 is 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 CF-302. 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.

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, Muti-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 sponsor regarding the need for additional documents and/or to address possible errors in the electronic datasets and programs. The sponsor'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 true 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 % 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 be 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)

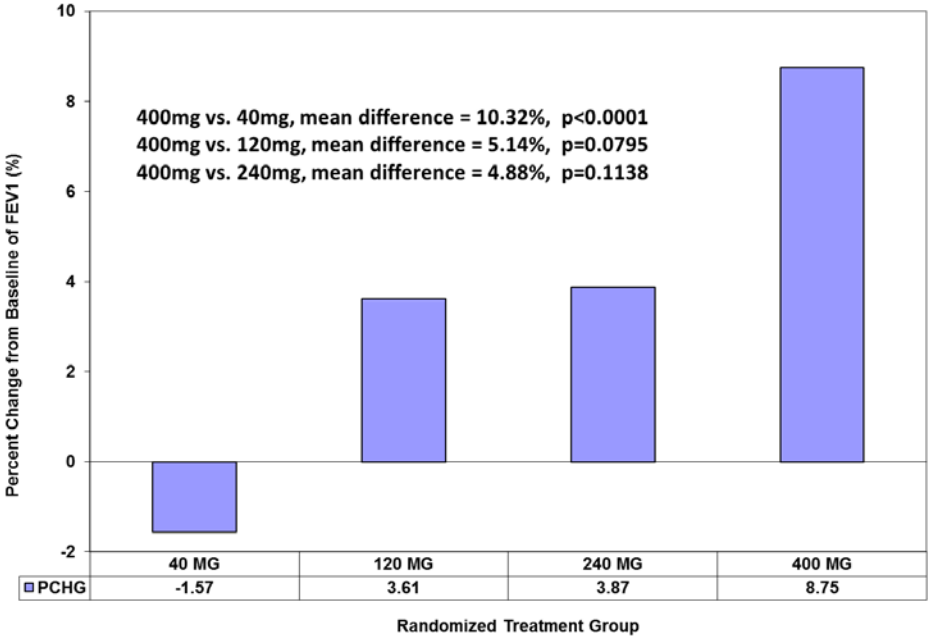
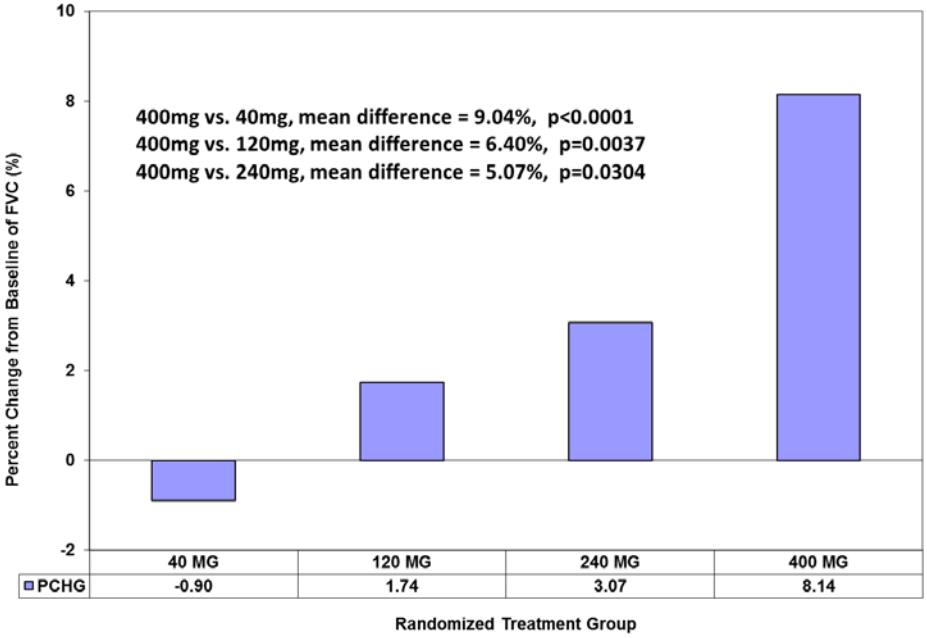


Figure 2: Percent Change from Baseline in FVC for Each Treatment Arm (ITT)



3.2.2 Phase 3 Studies

3.2.2.1 Study Design, Endpoints, and Statistical Methodologies

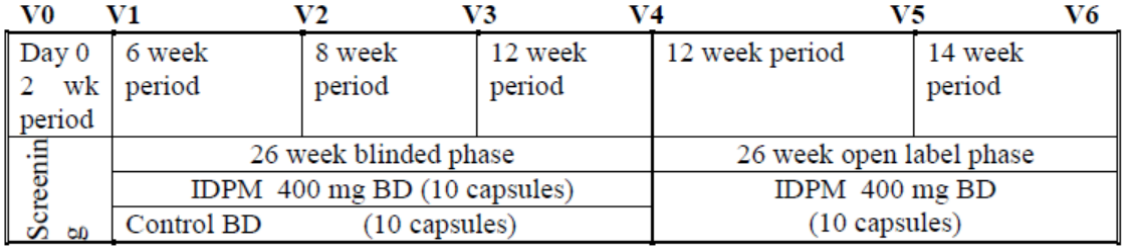
Studies CF301 and CF302 were similar in design. They were double blind, randomized (stratified according to rhDNase use (yes/no) and region (Australia and Europe in study CF301) or country (Argentina, Canada, Germany, Belgium, France, Netherlands, and US in study CF302)), parallel group, controlled, clinical trials with the primary measure of efficacy being the absolute change in FEV_1 from baseline across the 26 week double blind period. As shown in Figure 3, 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 (5mg x 10 capsules, BID mannitol) 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. 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.

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 (visits 1 through 4). All pulmonary function testing was done in the clinic.

The primary efficacy analysis methods were different in each study. However, both studies pre-specified a mixed model for repeated measurements (MMRM) and both specified that the intent-to-treat (ITT) population (defined as all patients randomized who attend the baseline visit and received at least one dose (or part thereof) of study medication) would be used for the primary efficacy analysis. Importantly, missing data were not to be imputed since MMRM was to be employed. This approach to the missing data requires an assumption that missing data occurred at random, unrelated to treatment. If this assumption is violated, MMRM analyses estimating the treatment effect are not reliable. In studies CF301 and CF302, missing data are primarily a result of early study discontinuation likely associated with adverse effects of treatment which clearly violate this assumption. Although the sponsor indicates that the primary efficacy analyses provided in the study report are being conducted using the ITT group, this is not accurate. First, only patients with at least one post-baseline assessment of FEV_1 were included in the analysis effectively reducing the ITT population to a modified ITT (MITT), the ITT patients who did not drop out before the week six visit. And second, additional missing data at weeks 14 and 26 which occurred differentially by treatment group are also present. The extent of the missing data and the differential relationship to treatment assignment is a serious flaw in the outcome of these studies which violates the statistical assumptions underlying the MMRM analyses and therefore make this type of analysis inappropriate, particularly so in study CF301 in which the rate of early discontinuation was even higher than that of study CF302. To address this problem, this review will present responder analyses in which patients with missing data are considered treatment failures. This representation of the missing data is a more accurate reflection of the efficacy of DPM in that patients who cannot tolerate the treatment cannot be expected to receive any efficacy from the product. Although the pre-specified primary efficacy analyses will be fully described and presented in this review, because of the frequent and differential missing data these analyses may not provide reliable estimates of the treatment effect. By assuming 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 and from a statistical perspective, the pre-specified primary efficacy analyses do not appropriately incorporate the frequent and disproportionate early discontinuations and therefore may not accurately reflect the efficacy of DPM in the type of cystic fibrosis patient enrolled in these studies. The post-hoc responder analyses and cumulative responder plots more appropriately incorporate the treatment-related missing data and therefore are more likely to provide an accurate reflection of the efficacy of DPM in the type of cystic fibrosis patient enrolled in these studies.

The following descriptions of the intended MMRM analyses are provided since they were the pre-specified primary analysis methods. From a statistical perspective and as described in the preceding paragraph, these analyses may not be representative of the efficacy of DPM because of the frequent and differential early subject discontinuation rates. Additional statistical issues associated with the MMRM analyses for study CF301 include: (1.) differences between the protocol-specified and SAP-specified analysis methods and (2.) whether or not the change from baseline in FEV_1 at baseline should be incorporated in the response variable. In study CF301 and according to the statistical analysis plan, the absolute change from baseline in FEV_1 was to be analyzed using MMRM. Absolute change from baseline was to be the outcome variable and the model was to include the following predictors: treatment, visit, age, rhDNase use, baseline FEV1, disease severity (baseline FEV1 % predicted), gender, region, and subject (as a random effect). An unstructured variance and covariance structure was assumed to account for the correlation between repeated measures within the same subject. A slightly different model specification was provided in the protocol for study CF301. It was pre-specified in the protocol that treatment, visit, interaction between treatment and visit, age, baseline FEV1, disease severity (baseline FEV1 % predicted), gender, and subject (as a random effect) were to be included in the mixed model. That is unlike the model specified in the SAP; the protocol-specified model did not include a fixed effect for region or rhDNase use and did include an interaction between treatment and visit. The first version of the study report for CF301 provided analysis of the primary efficacy endpoint using the SAP-specified model utilizing measurements taken at weeks 0, 6, 14, and 26 as part of the response variable. That is the response variable included the change from baseline at baseline (i.e., a change of 0 for all subjects). However, analyses provided in the final study report for CF301 are obtained using the SAP-specified model but unlike the first study report, the change from baseline at baseline was not incorporated into the response variable. The results provided by the sponsor in the final clinical study report for study CF301 were obtained by including the change from baseline in FEV1 at weeks 6, 14, and 26 only. This issue was discussed with the Division at the pre-NDA meeting held on December 10, 2010. At the time of that discussion, it appeared that the inclusion of the change from baseline at baseline in the response variable was pre-specified in the SAP; however, available documentation at the time of this review (after amendments to the SAP have been made) indicate that the SAP did not make this specification and one could infer that perhaps the SAP-specified methods were inappropriately applied in developing the first clinical study report. Ultimately it is

unclear at this stage whether or not including the change from baseline at baseline as part of the response variable was a pre-specified analysis method.

The additional statistical issues surrounding the MMRM analysis of the primary efficacy endpoint for study CF301 are two. First, there are discrepancies between the SAP and protocol in model specification (i.e., the protocol-specified model did not include a fixed effect for region or rhDNase use and did include an interaction between treatment and visit). However, both the SAP and protocol were finalized prior to unblinding so that neither model should be considered inappropriate in the sense that it may be a result of data dredging. In addition, in a randomized clinical study, inclusion/exclusion of covariates in the modeling is not critical to understanding the treatment effect as it would be in epidemiology research so that these choices are generally at the discretion of the sponsor (as long as they are specified a priori). In the study report, the sponsor utilizes the SAP-specified model. This is appropriate from a statistical perspective and sensible from a practical standpoint in that of the SAP and protocol, the SAP was the most recently finalized a priori source. In addition, the SAP-specified model included terms for the randomization stratification factors, rhDNase use and region, a desirable feature from a statistical perspective. The second issue with the primary efficacy analysis for study CF301 is whether the change from baseline at baseline should be included in the response variable as invoked in the first but not the second (and final) version of the study report. The MMRM analyses proposed by the sponsor will provide an average response across time. As such, inclusion of the change from baseline at baseline accounts for treatment effects that occur prior to the first post-baseline measurement (assuming the effect is linear). Including the response at baseline, as well as the responses at 6, 14, and 26 weeks, in the response variable will provide an average treatment effect from 0 to 26 weeks. Including only the responses at 6, 14, and 26 weeks will result in an average treatment effect from 6 to 26 weeks. Inclusion of the baseline time point in the response variable in this setting will also result in a smaller treatment effect size as a zero score is registered for all subjects. This reduction in the effect size will be off-set by the corresponding reduction in the variance in that a constant is being included in the response for all subjects. Therefore, assuming the covariance structure utilized in the analysis is sufficient to allow conversion of the estimates, the test of the treatment effect will remain valid regardless of the inclusion or exclusion of baseline from the response variable. Therefore, from a statistical perspective, these inconsistencies and/or inaccuracies in the pre-specified statistical methods alone would not invalidate the results of the primary efficacy analyses.

In study CF302, the FEV1 change from baseline at baseline was not to be included in the response variable and predictors in the MMRM model were to include treatment, visit, the interaction between treatment and visit, age, baseline FEV1, disease severity, use of rhDNase, country, gender, and subject (as a random effect). That is the CF302 model differed from the SAP-specified CF301 model by replacing region with country and adding the visit by treatment interaction term. An unstructured variance-covariance was assumed to account for the correlation between repeated measures within the same subject. The SAP and protocol for study CF302 were consistent regarding the MMRM

model. Therefore, the two additional statistical issues described for study CF301 do not apply to study CF302.

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.

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 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 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 FEF25-75 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 $\geq$ 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 is an endpoint that has been highlighted by the FDA clinical team as being of particular importance so although not corrected for multiplicity, this endpoint 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 over dispersion 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.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

In both studies combined, a total of 719 patients were administered the Mannitol Tolerance Test (MTT). Subsequent to a failed or incomplete MTT or a withdrawal from the study, 642 patients were randomized. Approximately 2-5 weeks elapsed from the time of randomization and the start of study drug administration during which 42 patients (15 (8%) and 14 (11%) DPM and control patients, respectively, in CF301, 8 (4%) and 5 (4%) DPM and control patients, respectively, in study CF302) withdrew from the study prior to receiving any study medication. The reasons provided for these post-randomization but pre-study-drug-administration withdrawals included AE, protocol violation, and withdrawal of consent. Two hundred ninety five and 305 patients received at least one dose of study drug during the 26-week double-blind phase in studies CF301 and CF302, respectively, and form the intent-to-treat (ITT) group. At the time of data analysis, it became evident that early discontinuation of patients before the first post-baseline measurement time point (i.e., week 6) had occurred. In study CF301, 20 (11%) DPM and 6 (5%) control patients withdrew before week 6. In study CF302, 10 (5%) DPM and 2 (2%) control patients withdrew before week 6. The sponsor excludes these patients from efficacy analyses therefore effectively creating a modified intent-to-treat (MITT) analysis group. Note that these early discontinuations occurred more frequently in the DPM groups than the control groups in both studies. 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. In addition, early discontinuation from the double blind period continued to occur after week 6 resulting in missing FEV_1 values for these patients at weeks 14 and/or 26. These discontinuations were more frequent in the DPM group in both studies. In study CF301, 44 (28%) and 26 (23%) additional DPM and control patients, respectively, did not complete the blinded phase. In study CF302, 24 (14%) and 14 (12%) additional DPM and control patients, respectively, did not complete the blinded phase. Using the MMRM analyses, missing primary efficacy endpoint data for these patients is assumed to be similar to that observed for patients who did not discontinue early. This is likely not an appropriate assumption in that the primary reasons for premature discontinuation were adverse event (including exacerbation) and withdrawal by patient. Overall, including discontinuations before week 6 (so that the patient is excluded from the MITT analyses) and discontinuations after week 6 but before week 26 (so that

the MMRM assumptions regarding missing data are applied), early discontinuation occurred in study CF301 in 65 (37%) DPM and 33 (28 %) control patients and in study CF302 in 31 (17%) DPM and 14 (12%) control patients (Table 4).

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 44119 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.

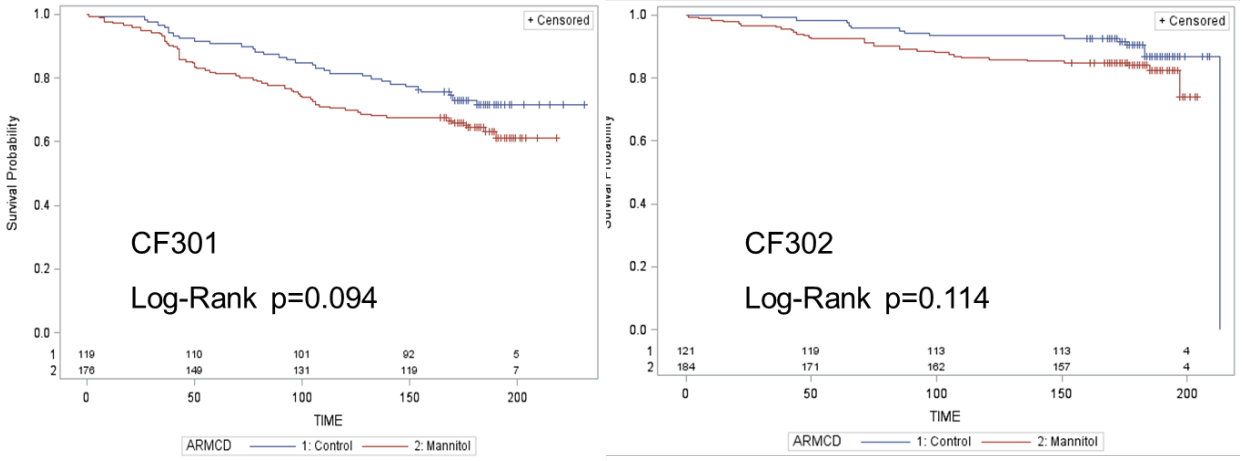
The pattern of withdrawal is shown numerically in Table 5 and graphically with Kaplan- Meier plots of the time to the discontinuation for each study in Figure 4. These illustrate the faster withdrawal in the DPM group than the control group.

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 (44119) 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 rate in these studies raise serious statistical concerns regarding the appropriateness of the pre-specified primary efficacy analyses. Since the early discontinuation rates are differential by treatment group (and likely a result of the assigned treatment) the balance in covariates normally afforded by random treatment assignment in the ITT group in a clinical study is compromised in the MITT group. 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 protocol and SAP specified primary efficacy analyses described in later sections for MMRM analysis of the continuous change from baseline in FEV_1) is not appropriate. Approaches to the analysis of these data that appropriately account for the missing data are needed to provide description of the ITT group. Such analyses (i.e., "responder analyses") are described in the section titled, "Dichotomized Analyses of Primary Endpoint ('Responder Analyses')".

Demographic and Baseline Characteristics

The vast majority of patients in 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 (%)

Demographic Parameter	Study CF301 (N=295)		Study CF302 (N=305)	
	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)
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 (MMRM analyses)

This section provides analysis of the primary efficacy endpoint in a continuous form, as was intended in the protocol and SAP for each study. From a statistical perspective, these analyses may not provide an accurate description of the treatment effect in the type of cystic fibrosis patient enrolled in these studies. These analyses do not incorporate the entire ITT group. Many DPM patients dropped out prior to week 6 (mostly likely due to an inability to tolerate the treatment) so that there is no post-baseline measurement for these patients. These patients are excluded from these analyses (i.e., these analyses are conducting using the MITT population). In

addition, in the MMRM analyses, missing data at weeks 14 and 26 are assumed to be missing for reasons unrelated to treatment. This is likely not an appropriate assumption in that the rates of missing data are differential by treatment group and the reasons for early withdrawal are often AE or withdrawal by patient. Patients who cannot tolerate treatment cannot be expected to receive any efficacy from treatment and therefore should be viewed as cases where treatment failed. The MMRM estimates of the treatment effect provided in this section may not be applicable to a larger cystic fibrosis population or even to the subset of cystic fibrosis patients who can tolerate treatment.

For study CF301, the results of the SAP-specified MMRM model are shown in the upper section of Table 7. The response variable utilized in these analyses does not include the baseline visit. The results provided by the sponsor for Study CF301 include change from baseline in FEV_1 at weeks 6, 14, and 26 only. (See section 3.2.2.1 for further discussion regarding inclusion/exclusion of baseline from the response variable.) Using this analysis, the adjusted mean (least square mean) for absolute improvement in FEV_1 (mL) from baseline in the DPM group was 118.0 mL versus 34.9 mL in the control group for the MITT population. The overall treatment effect averaged across the week 6 to week 26 treatment period statistically significantly favored DPM at 83.1 mL with 95%CI of (39.5, 126.8). Analyses incorporating the change from baseline at baseline into the response variable estimate the difference between DPM and control averaged from baseline to week 26 in the primary efficacy endpoint as 54.2 mL with 95% CI of (24.7, 83.6). As expected, the estimate of the treatment effect from this analysis is smaller than that described in Table 7. It is important to note that the 54.2 mL estimate is an estimate that represents an average effect from baseline to week 26. The difference between treatment groups shown in represents an average effect from week 6 to week 26. Unlike the model specified in the statistical analysis plan, the protocol-specified model did not include a fixed effect for region or rhDNase use and did include an interaction between treatment and time. This analysis incorporated the change from baseline in FEV_1 at weeks 6, 14, and 26 only, not the baseline visit. The qualitative conclusions regarding the primary endpoint for study CF301 using the protocol-specified model are consistent with those previously described using the SAP-specified model. The least square mean for change from baseline in FEV_1 in the DPM group was 113.9 versus 29.1 in the control group with an overall average treatment effect from week 6 to week 26 of 84.8 and $p < 0.001$.

For Study CF302, the adjusted mean (least square mean) for absolute improvement in FEV_1 (mL) from baseline in the DPM group was 106.5 mL versus 53.4 mL in the control group (lower portion of Table 7). The overall average treatment effect numerically favored DPM at 54.1 mL with 95%CI of (-2.0, 110.3). However, strictly speaking, this treatment difference was not statistically significant ($p=0.059$ in comparison to the interim-analysis-adjusted α of 0.0498).

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 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.

As was noted in section 2.1.2, at the pre-NDA meeting, the sponsor made a post-hoc proposal to use an adjusted baseline value for FEV_1 (i.e., the average of baseline FEV_1 and screening FEV_1) to calculate the response variable in the MMRM analyses for study CF302. For this study, the screening FEV_1 was higher than the baseline FEV_1 for only the control group so that the difference between treatment groups in the change from baseline in FEV_1 was larger if the response variable was modified to reflect the change from the average of baseline and screening. The sponsor was informed at the pre-NDA meeting that use of such post-hoc analyses for substantiation of efficacy was not likely to be acceptable for regulatory purposes particularly in the absence of any explanation for the difference between screening and baseline for the control group only. This statement remains valid at the time of this review. From a statistical perspective, it is inappropriate to modify the response variable to incorporate the screening FEV_1 post-hoc. In this review, analyses of study CF302 are presented using the original baseline FEV_1 values only.

Dichotomized Analyses of Primary Endpoint ("Responder Analyses")

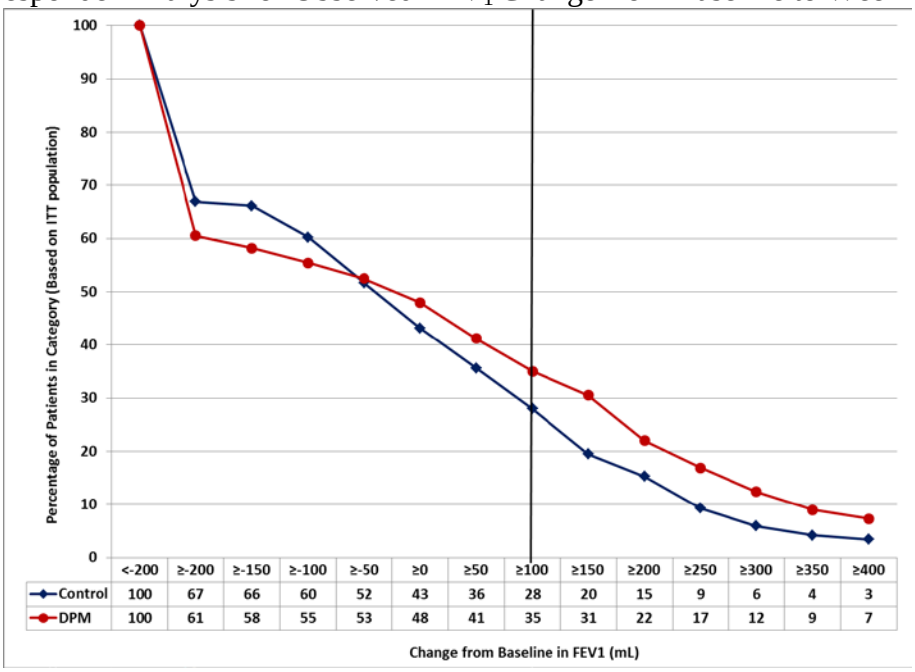
This section provides a post-hoc presentation of the primary efficacy endpoint which incorporates the entire ITT population by assuming that missing data at weeks 6, 14, or 26 represent a failure of the treatment. This is likely an appropriate assumption since patients who cannot tolerate the treatment cannot be expected to receive any efficacy from the treatment. The results in this section can be viewed as representative of the type of cystic fibrosis patient enrolled in these studies since these dichotomized analyses take into account the treatment-related early discontinuations.

Figure 5 and Figure 6 provide continuous responder curves 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.

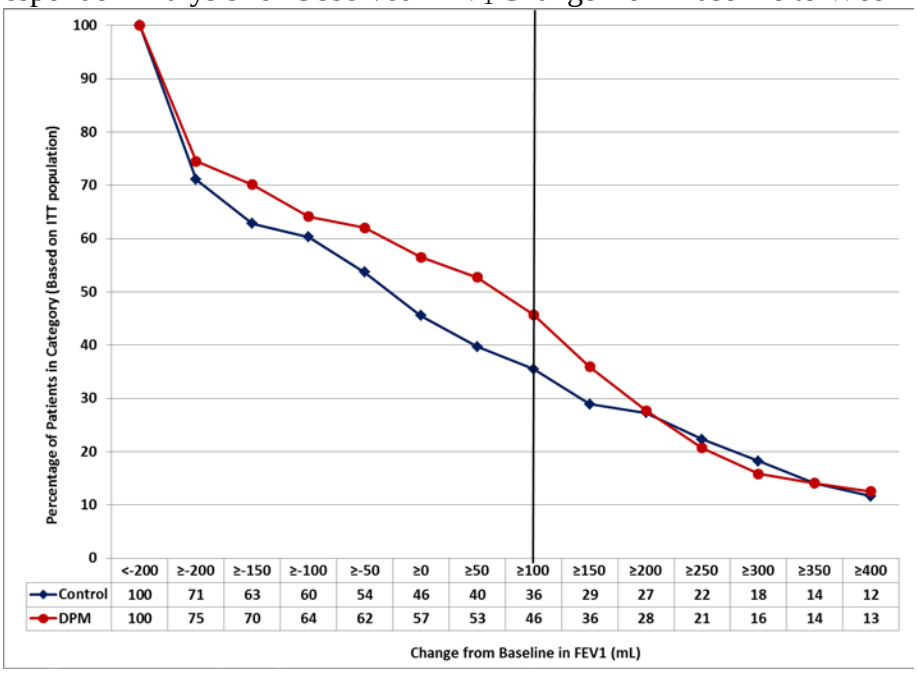
As show in both figures, there is an initial dramatic drop from 100% to approximately 60% in the y-axis, corresponding to the proportion of patients who dropped out since patients with missing data were classified as unsuccessfully treated for all thresholds. Dropouts were more frequent in the DPM group 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 has a numerically higher proportion of patients who achieve the increasing change from baseline in FEV_1 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. The choice of statistical method appropriate for formally testing the difference between treatment groups across a range of thresholds such as is illustrated in these figures have not been standardized. However, one proposal for such test is the Van der Waerden test. Results of this test indicate that the distribution of the proportion of patients achieving the thresholds for the change from baseline in FEV_1 are not statistically significantly different between treatment groups for either study (p=0.7 for study CF301 and p=0.6 for study CF302).

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 Van der Waerden test, the statistical methods used to test for a difference in proportions at a single threshold are straight forward and widely implemented. Table 8 provides a comparison of treatment groups using several such 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 unsuccessfully treated for these analyses.

For study CF301, the results were consistent regardless of the choice of thresholds. Numerically the results favored the DPM group; however, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined. Therefore, when patients with missing data are included in the analysis along with the patients with observed data, the overall effect for DPM in terms of the change from baseline in FEV_1 is not substantiated. For study CF302, the differences between treatment groups using each of these criteria are also consistent with respect to the qualitative conclusions regarding treatment effect. Differences between treatment groups in the proportion of subjects who achieved a 50 mL, 75 mL, or 100 mL threshold in the change from baseline in FEV_1 were associated with p-values smaller than the usual alpha level of 0.05.

Table 8: 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 present in this report for week 26.

Other Spirometry Endpoints

Analysis of the other spirometry endpoints in a continuous form is problematic due to the treatment-related early discontinuations previously described. Therefore, dichotomized responder analyses (e.g., using a relative change of 5%) and cumulative responder plots for the other secondary pulmonary endpoints provide the most appropriate estimates of the treatment effect and are provided in Table 9 and Figure 7 through Figure 10, respectively. These results provide conclusions regarding the treatment effect that are generally consistent with that of the primary efficacy endpoint. Generally, no difference between treatment groups is observed for study CF301 while some marginal differences between treatment groups favoring DPM over control are observed for study CF302.

Table 9: Responder Analysis Results for the Secondary 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		
FEV1 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		
FEV1 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 FEV1 was derived using measured height.

Figure 7: Responder Analysis for FVC (mL) Change from Baseline to Week 26

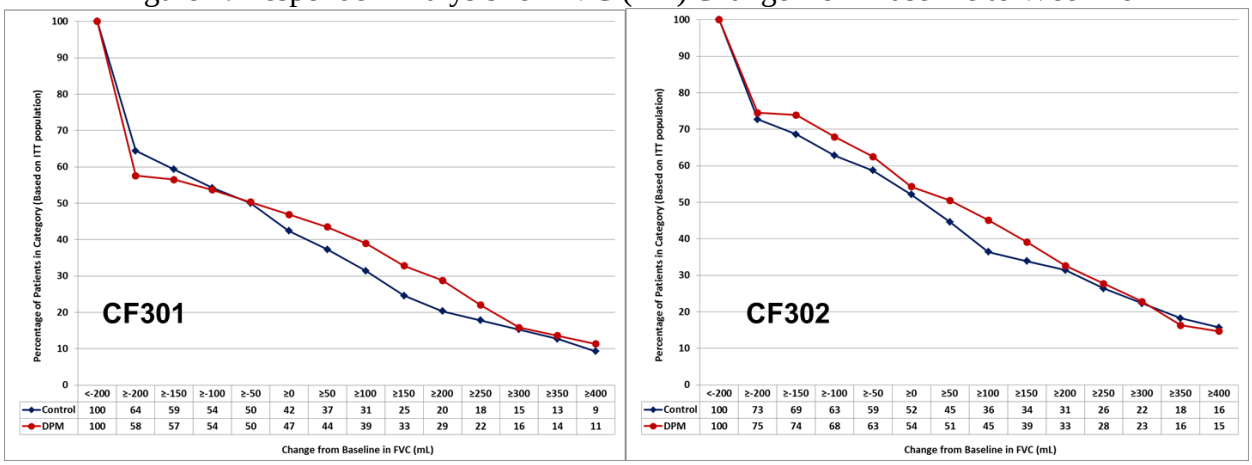


Figure 8: Responder Analysis for Percent Predicted FEV_1 Change from Baseline to Week 26

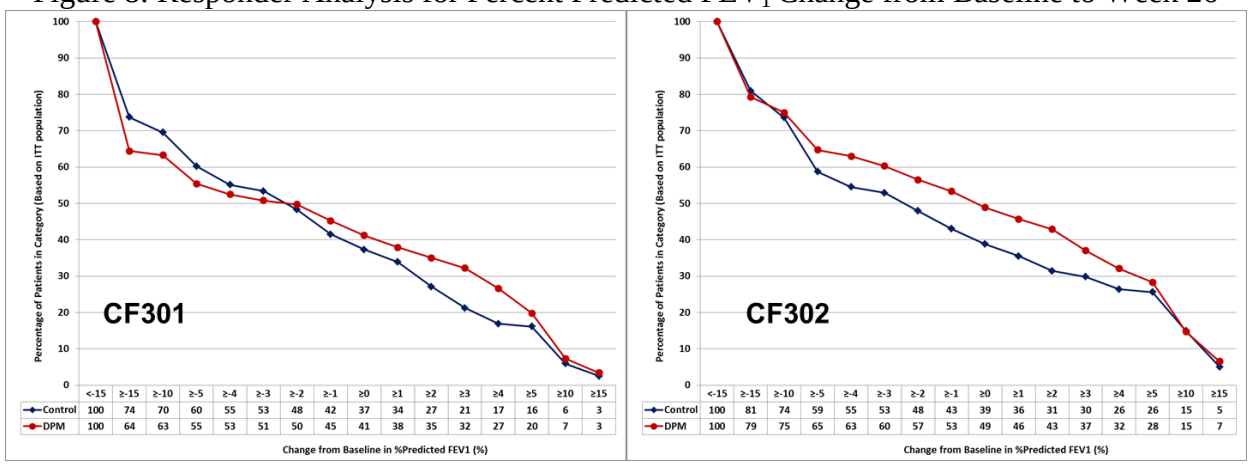


Figure 9: Responder Analysis for FEF_{25-75} (mL) Change from Baseline to Week 26

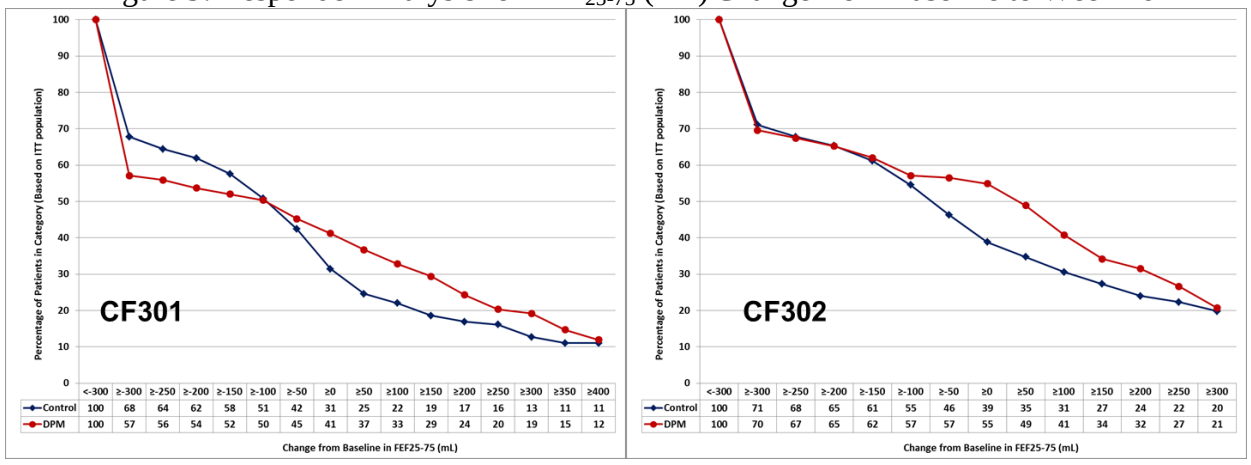
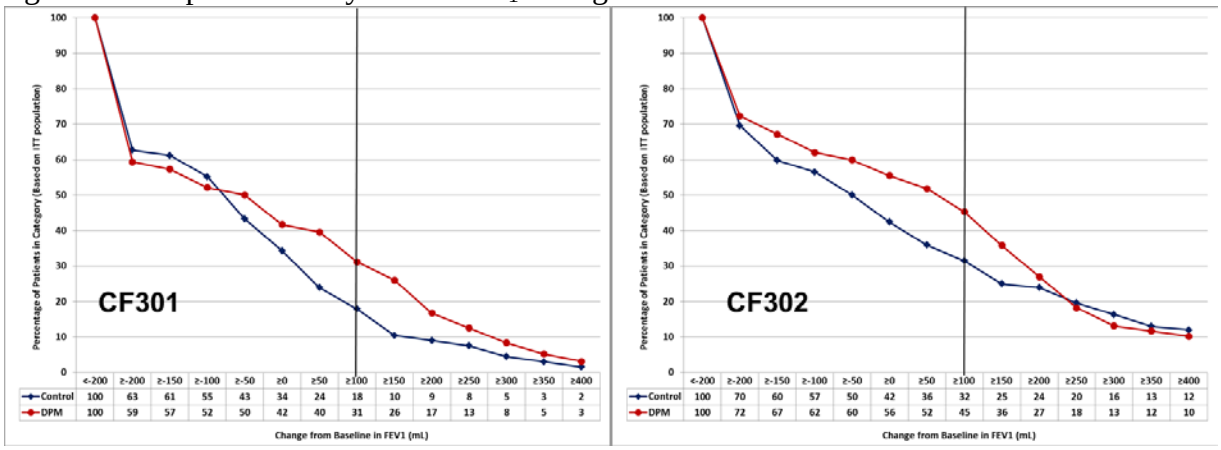


Figure 10: Responder Analysis for FEV_1 Change from Baseline to Week 26 for RhDNase Users



Acute Effects of Treatment on Sputum Weight at Baseline

Effects of treatment on sputum weight at baseline are shown in Table 10. Sputum weight post-treatment at baseline was not specified as a key secondary endpoint in either the SAP or protocol for study CF301 so that the appropriate significance level to which to compare the p-value for this endpoint is unknown. However, from a practical standpoint, the comparison of treatment groups for the sputum weight endpoint are associated with a very small p-value ($p<0.001$) so that this result would stand up to almost any multiple comparison procedure invoked. Although sputum weight post-treatment at baseline was not specified as a key-secondary endpoint in the protocol, it was designated as a key secondary endpoint in the SAP for study CF302. Using the SAP-specified Holm's procedure for multiple endpoints, the significance level to which to compare the p-value for this analysis is 0.0167. Since the analysis of sputum weight at baseline is associated with a p-value ($p=0.041$) that is larger than the multiplicity corrected significance level (0.0167), these results do not represent a statistically significant treatment effect.

Table 10: Sputum Weight (g) (MITT)

		Study CF301		Study CF302	
Weeks		**DPM**	**Control**	**DPM**	**Control**
Baseline	N	160	106	180	114
	Mean (SE)	6.3 (8.2)	2.3 (4.9)	4.9 (6.2)	3.5 (4.4)
	Median (min, max)	3 (0, 40)	1 (0, 39)	2.7, (0, 36)	1.7 (0, 23)
	P-value*		<.001		0.041

*Wilcoxon rank sum test p-value for the comparison of sputum weight between DPM and control group.

Protocol Defined Pulmonary Exacerbation

Results for the protocol defined pulmonary exacerbation (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 the setting of studies CF301 and CF302, this may not a reasonable assumption. 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.

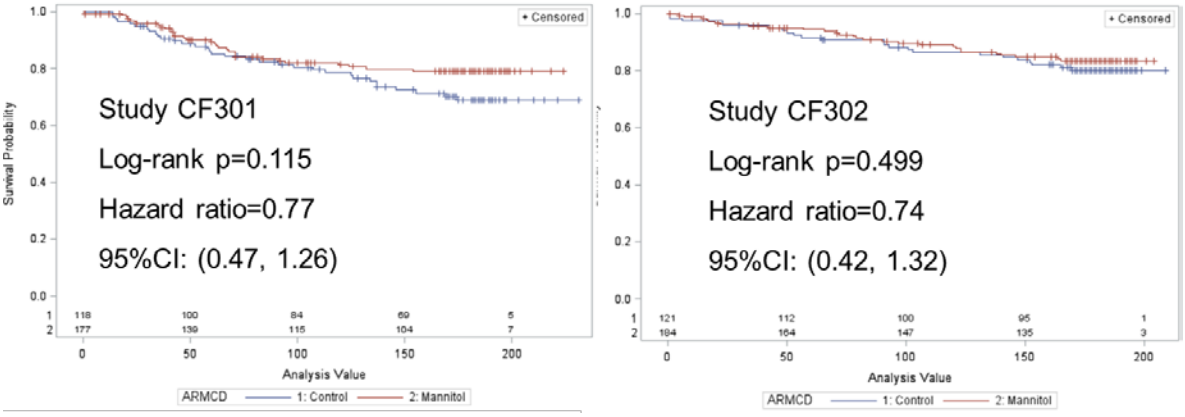
Table 11: Annual Rate of Exacerbation over 26 Weeks of Treatment (ITT)

			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 proportion 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-Meir estimates for the time to first PDPE are provided in Figure 11.

Figure 11: Kaplan-Meir Curve of Time to First PDPE (ITT)



Other Efficacy Endpoints (non-spirometry)

Table 12 provides analysis of several non-spirometry efficacy endpoints. These analyses are conducted in the MITT population and as such are impacted by the treatment-related early discontinuations previously described. This table is included to illustrate that even in such a non-

randomly selected subgroup and without correction for multiplicity, no statistically significant difference between treatment groups was demonstrated for any non-spirometry endpoint, with the possible exception of that previously described for sputum weight.

Table 12: Non-Spirometry Efficacy Endpoints (MITT Population)

	Study CF301 (N=295)		***Study CF302 (N=305)***	
DPM vs. control	Mean/ OR/RR	95%CI p-value	Mean/ OR/RR	95%CI p-value
Rate for PE	0.86	(0.64, 1.17), p=0.341	0.93	(0.74, 1.17), p=0.551
Hospitalizations for PDPE	0.94	(0.26, 3.42), p=0.924	0.75	(0.42, 1.33), p=0.328
Hospitalizations for PE	0.88	(0.32, 2.39), p=0.800	0.75	(0.45, 1.23), p=0.251
Proportion of patients used rescue Antibiotic for all PE	0.73	(0.39, 1.37), p=0.329	0.91	(0.78, 1.07), p=0.266
Proportion of patients used rescue Antibiotic for all PDPE	0.66	(0.25, 1.76), p=0.407	0.89	(0.69, 1.15), p=0.368
QoL – Respiratory domain scores	0.00	(-1.99, 1.98), p=0.996	-3.88	(-8.0, 0.22), p=0.063
QoL increase in respiratory score ≥5 points	0.66	(0.37, 1.17), p=0.156	--	--

PDPE: Protocol defined pulmonary exacerbation; PE: pulmonary exacerbation reported as an AE

[Module 5.3.5.1 Study Report Tables DPM-CF-301: table14.2.1.10; table14.2.2.2, table14.2.3.2, table14.2.4.3, table 14.2.9.2; Study Report Tables PDM-CF302: table14.2.16.3, table14.2.17.2, table14.2.17.4, table14.2.18.3, table14.2.18.4, table14.2.19.14]

Efficacy Conclusion

The extent of the missing data and the differential relationship to treatment assignment is a serious flaw in the outcome of these studies which violates the statistical assumptions underlying the MMRM analyses and therefore make this type of analysis inappropriate, particularly so in study CF301 in which the rate of early discontinuation was even higher than that of study CF302. From a statistical perspective, because of the frequent and treatment-related early discontinuations the pre-specified primary efficacy analyses may not be an accurate reflection of the efficacy of DPM in the type of cystic fibrosis patient enrolled in these studies. The post-hoc responder analyses and cumulative responder plots more appropriately incorporate the treatment-related missing data and therefore are more likely to provide an accurate reflection of the efficacy of DPM in the type of cystic fibrosis patient enrolled in these studies.

Conclusions regarding the treatment effect from the responder analyses for the primary efficacy endpoint in the ITT group are not consistent between studies. In study CF301, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined (e.g., the proportions of subjects who achieved at least a 100 mL increase from baseline in FEV_1 were 35% and 28% for DPM and control, respectively with p=0.312). In study CF302, there were statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined (e.g., the proportions of subjects who achieved at least a 100 mL increase from baseline in FEV_1 were 46% and 36% for DPM and control, respectively with p=0.041).

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 13. 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 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 13: 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

4.1 Gender, Race, Age, and Geographic Region

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 responder analyses by age, gender, region, RhDNase use, and baseline percent predicted FEV_1 are provided in Table 14.

Table 14: Responder Analysis Results for FEV1 Absolute Increase≥100mL at Week 26 (ITT)

Response Definition	*DPM*	*Control*	*Odds Ratio (95%CI)*[1] *(DPM vs. Control)*	*p-value*[1]
Study CF301				
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 CF302				
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.

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 in a continuous form may not be an accurate reflection of the treatment effect of DPM. Responder analyses and continuous responder plots more appropriately account for the treatment-related missing data and therefore may provide a more appropriate estimate of the treatment effect.
- Additional statistical issues regarding the MMRM analyses for study CF301 arise; however the practical impact of these is relatively little next to that of the treatment-related frequent early dropouts. Numerous inconsistencies or inaccuracies in the documentation of the SAP and protocol for study CF301 were identified including (1.) variations in the selection of covariates for inclusion in the MMRM model and (2.) whether or not to include the change from baseline at baseline in the response variable for the primary efficacy endpoints.
- For study CF302, the sponsor made a post-hoc proposal to use an adjusted baseline value for FEV_1 (i.e., the average of baseline FEV_1 and screening FEV_1) to calculate the response variable in the MMRM analyses. The use of such post-hoc

analyses for substantiation of efficacy is not acceptable for regulatory purposes. In this review the practical impact of this issue is none because as previously described the MMRM analyses are generally not acceptable due to 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 in a continuous form, as was intended in the protocol and SAP for each study are problematic in that that they do not incorporate the entire ITT group. Patients who dropped out before week 6 are 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 (95%) DPM patients and 120 of 121 (98%) control patients are included in the MITT group. Additional missing data at weeks 14 and 26 which occurred differentially by treatment group are also present. In study CF301, at week 26, 116 of 177 (66%) DPM patients and 89 of 116 (77%) 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, 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. Therefore, the MMRM estimates of the treatment effect using the continuous change from baseline in FEV_1 outcome may not be accurate. Continuous responder curves 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 more appropriately account for the treatment-related missing data. Statistical hypothesis testing of the treatment effect over the entire range of thresholds is not standardized but analyses at a several single thresholds provide consistent results regarding the qualitative treatment effect within study but not between studies. For study CF301, numerically the results favored the DPM group; however, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined. For study CF302, differences between treatment groups in the proportion of subjects who achieved a 50 mL, 75 mL, or 100 mL threshold in the change from baseline in FEV_1 were associated with p-values smaller than the usual alpha level of 0.05.

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 (test for homogeneity of odds ratio p-value=0.6 for each study).

5.3 Conclusions and Recommendations

The analysis of efficacy data from studies CF301 and CF302 are problematic due to the frequent and treatment-related early discontinuations resulting in systematically missing FEV_1 measurements. The similarities or differences between patients with observed data and patients

with unobserved data in terms of their change from baseline in FEV_1 are unknown. The nature of the most common reasons for early discontinuation suggest that these patients are experiencing an unsuccessful treatment in that if a patient cannot tolerate the product, no efficacy from the product should be expected. From a statistical perspective, this finding of lack of tolerance needs to be incorporated into the efficacy analyses as a failure in terms of efficacy. The responder analyses presented in this review are such analyses. Results of these analyses provide consistent conclusions regarding the qualitative treatment effect within study but not between studies. For study CF301, numerically the results favored the DPM group; however, there were no statistically significant differences between treatment groups in the proportion of patients who achieved the FEV_1 change from baseline thresholds examined. For study CF302, differences between treatment groups in the proportion of subjects who achieved a 50 mL, 75 mL, or 100 mL threshold in the change from baseline in FEV_1 were associated with p-values smaller than the usual alpha level of 0.05.