FDA Briefing Document
Pulmonary-Allergy Drugs Advisory Committee Meeting

May 8, 2019

NDA 202049

Bronchitol

Mannitol inhalation powder for oral inhalation for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

Chiesi

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 Chiesi, for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies to this Advisory Committee in order to gain the Committee's insights and opinions. The background package does 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.

Table of Contents

Table of Tables

Table of Figures

Division Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
M E M O R A N D U M

Date: April 11, 2019

From: Sally Seymour, MD, Acting Division Director
Robert Lim, MD, Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

To: Chair, Members and Invited Guests
Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA) 202049, for mannitol inhalation powder (proposed trade name BRONCHITOL), for oral inhalation sponsored by Chiesi, for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

1 Division Memo

1.1 Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on May 8, 2019. As members of the PADAC, you provide important expert scientific advice and recommendations to the U.S. Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss the New Drug Application (NDA) 202049 from the Applicant, Chiesi, for mannitol inhalation powder (proposed trade name BRONCHITOL), for oral inhalation, for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

The NDA for mannitol inhalation powder was originally submitted in May 2012. The results of the clinical development program were discussed at a PADAC meeting on January 30, 2013. The panel recommended against approval of the NDA at that time because of concerns related to lack of substantial evidence of efficacy, specifically lack of strong statistical evidence, frequent and differential dropouts, and a small effect size. In addition, there were safety concerns regarding hemoptysis, particularly in children. A Complete Response (CR) action was taken on March 18, 2013.

Chiesi responded to the CR action and has submitted the results of a new clinical trial. In addition, the Applicant modified the indication to limit the use of mannitol inhalation powder to adults. We have brought this application back to the AC to discuss whether the submitted data address the issues identified in the original development program. This Division Memorandum provides a brief overview of the application and an introduction to the main issues for discussion. As you read through the Agency background document, you will note that there are continued questions regarding whether there is substantial evidence of efficacy, including issues related to the statistical evidence to support the efficacy and the clinical meaningfulness of the effect size.

1.2 Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States, and approximately 36,000 children and adults in Europe. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is in the 40s. Lack of properly functioning cystic fibrosis transmembrane receptors (CFTR) is responsible for the clinical sequelae of CF. Over time, there is a cycle of lung infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure. Current treatment options include CFTR modulators, inhaled antibiotics, inhaled mucolytics, inhaled bronchodilators, and non-respiratory medications. In this NDA, Chiesi proposes the use of mannitol inhalation powder to improve lung function in adult patients with CF.

Mannitol is a naturally occurring sugar alcohol that is used as a dietary supplement and as an ingredient in numerous drug products. As an inhalation product, mannitol inhalation powder is a

bronchoprovocation agent approved in the Unites States as part of a kit (Aridol) for the assessment of bronchial hyperresponsiveness. Thus, inhaled mannitol, can cause bronchospasm, potentially severe, in susceptible patients. This will be an important consideration for the development program and proposed population for use of mannitol.

Patients with CF have impaired mucociliary clearance in their airways leading to recurrent infections, decrease in pulmonary function, and ultimately respiratory failure. The rationale of developing mannitol for treatment of patients with CF is based on its osmotic property, which encourages the movement of water into the airways and thus improves mucociliary clearance.

The proposed drug product consists of gelatin capsules that contain 40 mg of mannitol without any excipients and a breath actuated hand-held dry powder inhaler capable of processing one capsule at a time. The proposed dose is 400 mg (10 capsules) inhaled twice daily.

Throughout the briefing document, FDA will refer to the product as dry powder mannitol or DPM.

1.3 Regulatory History

The following is a brief summary of the relevant regulatory history for this application:

- The NDA for mannitol inhalation powder was originally submitted on May 18, 2012.
- The results of the clinical development program were discussed at a PADAC meeting on January 30, 2013. The panel recommended against approval (14 no, 0 yes, 0 abstain) of the NDA because of concerns related to substantial evidence of efficacy, specifically lack of strong statistical evidence, lack of support from secondary efficacy endpoints, differential dropouts and a small effect size. In addition, there were safety concerns regarding hemoptysis, particularly in children.
- A Complete Response (CR) action was taken on March 18, 2013. The following is a summary of the clinical CR deficiency:
    - A favorable benefit risk balance was not demonstrated to support the use of DPM in CF patients 6 years and older.
    - The two phase 3 studies were not adequate to determine efficacy given the treatment-related frequent early dropouts in study 301 for which the primary statistical analyses did not account for and the lack of statistical significance in 302 for the primary endpoint.
    - There was no support for efficacy from secondary endpoints.
    - Safety findings raised concerns for hemoptysis, particularly in pediatric patients, which weighed unfavorably against efficacy data in the pediatric population.
    - To support approval, the Applicant should conduct at least one adequate clinical trial in adults showing substantial evidence of efficacy and balancing safety, which includes specified criteria addressing the hemoptysis safety concern.
- May 17, 2013 – Type A meeting to discuss path forward. A third trial was recommended, similar in design to the first two trials, but limited to adult patients because of concerns regarding hemoptysis. The Agency agreed to forced expiratory volume in one second (FEV_1) over 6 months as a primary endpoint but noted that the results must be statistically significant and clinically meaningful. Pulmonary

exacerbation is acceptable as a secondary endpoint, with the expectation that the results would trend in a favorable direction.

- November 29, 2016 – Pre-NDA meeting was held; however, data from new trial were not available for discussion. The Agency noted that pulmonary exacerbations and Cystic Fibrosis Questionnaire – Revised (CFQ-R) would be considered important secondary endpoints.
- The complete response was submitted December 19, 2018.

1.4 Clinical Program

The clinical development program includes three pivotal clinical studies outlined in Table 1. Studies 301 and 302 were included in the original application. Study 303 was submitted in the complete response.

Table 1: Overview of Pivotal Studies

Study	Study Design	Population	Treatments	N	Primary Endpoint†	Countries*
Original NDA Submission						
301	R, DB, PG 26 wks 52 wks OLE	CF patients 6 yrs and older FEV_1 30-90%	DPM 400 mg BID Control (DPM 50 mg BID)	177 118	Δ FEV_1 over 26 wks	UK, Australia
302	R, DB, PG 26 wks 26 wks OLE	CF patients 6 yrs and older FEV_1 40-90%	DPM 400 mg BID Control (DPM 50 mg BID)	184 121	Δ FEV_1 over 26 wks	US, Germany, Canada, Argentina
Complete Response						
303	R, DB, PG 26 wks	CF patients 18 yrs and older FEV_1 40-90%	DPM 400 mg BID Control (DPM 50 mg BID)	209 214	Δ FEV_1 over 26 wks	US, Poland, Russia, Ukraine

Abbreviations: R=randomized; DB=double blinded; PG=parallel group; OLE=open label extension; wks=weeks; yrs=years; DPM=dry powder mannitol; BID=two times per day; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second

† mean absolute change from baseline in FEV_1 over 26 weeks (measured at weeks 6,14, and 26)

*countries contributing ≥10% subjects listed

The Applicant conducted a dose ranging study (Study 202) that evaluated mannitol doses ranging from 40 mg to 400 mg. Although there were some limitations with the design of the dose ranging study, the Applicant chose the highest dose (400 mg) to evaluate in phase 3. The pivotal clinical studies were similar in design – 26 weeks, randomized, double-blind, parallel group, controlled studies in patients with CF. In the clinical program, a low dose of DPM was used as a control to address blinding concerns related to the sweet taste of mannitol. While the pivotal clinical studies were similar in design, there are some differences to note:

- Studies 301 and 302 enrolled CF patients 6 years and older, while Study 303 enrolled adults
- Studies 302 and 303 enrolled patients in the United States, while Study 301 did not enroll U.S. patients

- Studies 301 and 302 were conducted between 2007 and 2010, whereas study 303 was conducted from 2014 to 2017
- Studies 301 and 302 had open label extension periods, while 303 did not

Patients were allowed to continue their baseline chronic medications with the exception of inhaled hypertonic saline. Because of the potential for bronchospasm with mannitol, patients underwent a mannitol tolerance test (MTT) prior to randomization. The MTT required inhalation of successive increasing doses of DPM (from 40 mg to 160 mg) to evaluate for a decline in FEV_1 and oxygen saturation. Patients with a protocol defined decrease in FEV_1 were not randomized. Refer to the Clinical/Statistical Review for a detailed description of the MTT (Section 3.4.1.1).

Because of the potential for bronchospasm, patients were required to take a short acting bronchodilator prior to study medication treatment. Patients administered study medication from a single dose dry powder inhaler with a total of 10 capsules twice daily. Patients assigned to control received 50 mg mannitol (10 x 5 mg mannitol capsules), while patients assigned to DPM received 400 mg mannitol (10 x 40 mg mannitol capsules).

The primary efficacy variable was FEV_1, which is an accepted efficacy variable for CF development programs. The expectation is that the effect on FEV_1 is both statistically significant and clinically meaningful and that there is additional support from other important secondary efficacy variables. Support from secondary efficacy variables would be particularly important when there are questions regarding whether the effect on FEV_1 is clinically meaningful. Given that mannitol is an inhaled product that is proposed to improve mucociliary clearance in the airways, relevant supportive efficacy measures would include exacerbations (antibiotic use, hospitalizations), and the Cystic Fibrosis Questionnaire- Revised (CFQ-R) respiratory domain (CFQ-RRD) score. The DPM program included assessment of some of these measures, including protocol defined pulmonary exacerbations (PDPE).

1.5 Efficacy

1.5.1 Primary Efficacy Variable – FEV_1

To frame the efficacy discussion, a brief overview of the results from the original program is warranted followed by an integrated assessment of efficacy across the three pivotal studies. Because Studies 301 and 302 included adults and children and Study 303 only included adults, *post-hoc* subgroup analyses of adult patients in Studies 301 and 302 are necessary. The adult population is also the most relevant population given the Applicant's proposal to limit the indication to adults. As described in more detail below, in Studies 301 and 302, the analysis of the primary efficacy endpoint using the Applicant's pre-specified statistical method (Mixed Model for Repeat Measures (MMRM)) is problematic because the method makes a strong assumption regarding missing data that is not supported by the data. Alternative methods have been used by FDA statisticians. While only the adult subgroup analyses and *post hoc* statistical methods for Studies 301 and 302 will be presented in this section, the Clinical and Statistical Review provides a more comprehensive discussion of the efficacy results from the original program and Study 303.

Original NDA

In the original program, based upon the Applicant's primary analyses, the treatment difference in the primary efficacy endpoint was statistically significant in Study 301, but was not statistically significant in Study 302. However, there are important statistical considerations regarding validity of the analysis results of Studies 301 and 302. There was differential discontinuation between treatment groups that was more prominent in Study 301, i.e. more patients in the DPM group discontinued compared to the control group. In Study 301, only 63% of DPM and 73% of control patients completed the 26-week treatment period. In Study 302, 83% of DPM and 88% of control patients completed the 26-week treatment period. This is not surprising given the potential for bronchospasm and tolerability issues with DPM. Importantly, in Studies 301 and 302 when patients discontinued, they were no longer followed for efficacy data. The Applicant's statistical analysis utilized an MMRM, which is valid when the missing data occur at random; however, the differential dropout suggested that the missingness was not at random. Because of this issue, the MMRM analysis method was deemed unreliable and likely overestimated the effect size. Sensitivity analyses were performed, but there were limitations with the data imputation methods. Because of these issues, the statistical team determined that there was not clear substantial demonstration of a treatment effect on FEV_1 in Studies 301 and 302.

There were also clinical considerations with respect to the efficacy data, primarily questions regarding the clinical meaning of the effect size and the lack of support from secondary efficacy endpoints. These efficacy issues were a major reason for the PADAC recommendation against approval of the original NDA and the complete response action as described above.

Post-hoc subgroup analyses of Studies 301 and 302 were conducted in adults to compare with results from Study 303. After considering the statistical issues with data imputation methods in the original submission, the FDA statisticians determined that a pattern mixture model is a more appropriate method for Studies 301 and 302. These *post hoc* results are shown in Table 2 below.

Resubmission

In Study 303, 79-82% of patients completed the treatment and 88-89% of patients completed the study, so there was no significant differential discontinuation from the treatment or from the study. The primary efficacy endpoint was the mean absolute change from baseline in FEV_1 over 26 weeks, which is the same as in Studies 301 and 302, although the specific days of FEV_1 assessment differed. Given the lower and non-differential study discontinuation and treatment discontinuation, in Study 303, there was not as much concern regarding interpretation and analysis of the efficacy data. Table 2 shows the results for the primary endpoint for *post-hoc* analyses of the original submission (Studies 301 and 302) and Study 303.

Table 2: Studies 301, 302, 303, Change From Baseline FEV_1 (mL) Over 26 Weeks – Patients ≥18 Years (Adults)

Study (# Patients per Arm)	DPM 400 mg	Control*	Treatment Difference DPM 400 mg – Control		
			LS Mean	95% CI	p-value
Original Submission Post-hoc, ITT, Pattern Mixture Model with MI, 26 weeks (weeks 6, 14 and 26)					
Study 301 (DPM=124, C=85)	93	15	78	21, 135	NR
Study 302 (DPM=97, C=60)	75	-2	78	2, 153	NR
Resubmission ITT, MMRM Model with BOCF using dropout reasons, 26 weeks (days 43, 99, and 183), on study					
Study 303 (DPM=209, C=214)	65	10	55	9, 101	0.018

Abbreviations: MI=multiple imputation; NR=not reported (for the post-hoc subgroup analyses); CI=confidence interval; BOCF=baseline observation carried forward; ITT=intention to treat: all subjects randomized; DPM=dry powder mannitol; LS=least squares
* Control – 50 mg DPM
Source: FDA Statistical Reviewer

Based upon the *post-hoc* analyses of Studies 301 and 302 and the results of Study 303, there is evidence of an effect of DPM on FEV_1 over 26 weeks. While Study 303 was successful in terms of statistical significance of the primary endpoint, the treatment effect is modest. The *post-hoc* analyses of data from adults only in Studies 301 and 302 are also supportive of a modest treatment effect. The clinical meaning of this modest treatment effect was an issue raised during the original application and given the results of Study 303 show a smaller treatment effect, the issue regarding the clinical meaning of the treatment effect remains. We ask the AC panel to discuss the FEV_1 efficacy results and request feedback from the panel on the clinical meaning of the treatment effect.

The review team also considered additional analyses, including analyses of FEV_1 at 26 weeks, responder analyses, and subgroup analyses of U.S. and non-U.S. patients. These are all described in detail in the Clinical and Statistical Review.

1.5.2 Secondary Efficacy Measures

We carefully considered data for other efficacy variables in the DPM program. Of primary interest were the data related to CF exacerbations and the CFQ-RRD, since these have been considered important in benefit-risk determinations.

Exacerbations

Exacerbations are considered an important efficacy variable for CF development programs. The definition of a Protocol Defined Pulmonary Exacerbation (PDPE) in the DPM program was based upon specified signs and symptoms of an exacerbation and treatment with IV antibiotics. This definition was considered acceptable. There are numerous ways to look at exacerbation,

including time to first, rate of, and incidence of hospitalization and antibiotic use associated with exacerbation, which are all described in the Clinical and Statistical Review. Exacerbation rate is of primary interest and Table 3 below provides a summary of the PDPE rate findings.

Table 3: Studies 301, 302, 303, Protocol Defined Pulmonary Exacerbation Rate Over 26 Weeks – Patients ≥18 Years (Adults)

Study (# Patients per Arm)	DPM 400 mg	Control*	Treatment Difference DPM 400 mg – Control	
	Mean Rate	Mean Rate	Rate Ratio	95% CI
Original Submission Post-hoc, ITT, Treated§				
Study 301 (DPM=114, C=76)	0.73	0.95	0.77	0.47, 1.26
Study 302 (DPM=93, C=58)	0.32	0.24	1.35	0.56, 3.24
Resubmission ITT, Treated§				
Study 303‡ (DPM=209, C=214)	0.35	0.23	1.55	0.99, 2.41

Abbreviations: CI=confidence interval; ITT=intention to treat: all subjects randomized; DPM=dry powder mannitol
* Control – 50 mg DPM
§ Only treated patients are included in the statistical analysis using negative binomial model.
‡ This analysis implemented the imputation procedure prespecified for the primary analysis in the statistical analysis plan for study 303 for patients who withdrew from study with no PDPE.
Source: FDA Statistical Reviewer

Results show that the rate of PDPE over 26 weeks are numerically in favor of control in Studies 302 and 303 and numerically in favor of DPM in Study 301. However, given the higher drop-out rate in Study 301 and resultant missing data, the results from Study 301 should be interpreted with caution. We do note that the studies were only 26 weeks in duration, which limits the amount of exacerbation data. However, overall the available PDPE data do not show a benefit of DPM with respect to reduction in exacerbation and some of the results suggest a numerical increase in the rate of exacerbations when compared to control.

CFQ-R Respiratory Domain (CFQ-RRD) Score

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

In Study 303, while the CFQ-R respiratory domain score increased in DPM patients (0.31) and decreased in control patients (-0.56), the difference was neither statistically nor clinically meaningful. The difference between DPM and control treated patients was 0.87 (95% CI: -1.4, 3.1). These CFQ-RRD data are consistent with that observed in Studies 301 and 302, in which there was a small numerical improvement in CFQ-RRD, but the CI overlapped the null.

1.6 Safety

The pivotal clinical studies were similar in design, so the clinical review focused on the pooled safety data from Studies 301, 302, and 303. Because the Applicant's indication is limited to adults, the safety review focused on the adult population. Overall, 414 adult patients were exposed to DPM 400 mg BID and 347 adult patients to control in the pivotal studies with a median exposure of approximately 6 months across studies (mean range 4-6 months). There was additional exposure during the OLE periods. The overall exposure of DPM in this program is considered acceptable given this orphan population. Given the known risk of bronchospasm with mannitol, patients were screened with an MTT and of those adults screened in the phase 3 program, 8% either could not tolerate DPM or did not complete the MTT. The Applicant has proposed the MTT be included in the labeling for DPM to minimize the risk of serious bronchospasm.

There were two deaths in the program, both of which were in the control group. A 19-year-old patient died secondary to CF exacerbation 219 days after the first dose of study medication. A 15-year-old patient died following complications of pneumothorax, partial pneumonectomy, pleurodesis, and lung transplant that occurred 135 days after the first dose of study medication. The serious adverse events (SAEs) were generally balanced although there were numerically more CF exacerbations (coded as condition aggravated) in DPM patients, 55 (13%) compared to control 39 (11%). More patients discontinued treatment in the DPM group, 51 (12%) compared to control, 30 (9%), primarily related to cough. Overall, the most common AEs in this program included condition aggravated, cough, headache, hemoptysis, URTI, nasopharyngitis, and oropharyngeal pain.

CF Exacerbation (Condition Aggravated)

CF exacerbations are an important consideration in CF development programs in terms of efficacy (discussed above) and safety. With regard to safety, investigator-reported adverse events of "condition aggravated" were considered CF exacerbations. For the pooled pivotal studies in adults, condition aggravated was a common AE reported in 32% of DPM patients and 33% of control patients. There was a slight imbalance in condition aggravated SAEs favoring control: 55 (13%) of DPM patients and 39 (11%) control patients and 3% of patients discontinued treatment due to condition aggravated. In subgroup analysis of CF exacerbation in U.S. patients, differences between DPM and control patients were accentuated. This was most notable for SAEs: 23 (21%) U.S. DPM patients and 10 (11%) U.S. control patients reported condition aggravated SAEs.

Hemoptysis

In the original program, hemoptysis was a safety signal identified with DPM and the signal was of particular concern in pediatric patients. Incidence of any hemoptysis in the pooled Studies 301 and 302 from the original submission were: 6-11 years of age – DPM 4 (6%), control 0; 12-17 years of age – DPM 8 (9%), control 2 (3%); adults - DPM 22 (11%), control 11 (8%). Hemoptysis was a safety issue discussed during the 2013 AC meeting and because of the concern in pediatric patients, the Applicant limited Study 303 and the proposed indication to adults. Results from Study 303 did not show a signal for hemoptysis in adult patients treated with DPM. The incidence of hemoptysis was similar between DPM and control – 10% and there was no imbalance for hemoptysis SAEs or hemoptysis AEs leading to discontinuation. In the

pooled pivotal studies in adults, there was no significant imbalance in hemoptysis. Overall, hemoptysis is a safety issue of concern with DPM, but the signal is most prominent in pediatric patients. When limited to adults, hemoptysis is not a prominent safety issue.

1.7 Benefit Risk Considerations

In terms of benefit-risk considerations, in the original NDA submission, there were concerns related to both the efficacy and safety of DPM. With respect to efficacy, Study 302 lost on the primary endpoint and interpretation of the efficacy results from Study 301 were complicated by missing data due differential dropouts, which led to statistical issues with the analyses of the data. Questions were raised about whether the effect size was clinically meaningful and about the lack of support of secondary efficacy endpoints. With respect to safety, hemoptysis was a concern, particularly in pediatric patients.

With the resubmission, the Applicant conducted a third pivotal study and modified the program to address concerns in the original program. Study 303 was larger, and patients were followed after discontinuation of study medication to minimize missing data. Pediatric patients were not enrolled to address the potential hemoptysis safety issue.

Study 303 demonstrated a clear statistically significant difference from control for the primary endpoint of FEV_1; however, the treatment effect of 55 mL (or approximately 1.2% predicted) remains a question regarding the clinical significance. Given the change in patient population and the statistical issues in the original program, a variety of statistical analyses (sensitivity) have been used to understand the treatment effect size and the statistical significance. Overall, a statistically significant improvement in FEV_1 over 26 weeks with DPM is noted in two of the three studies (301 and 303), with a treatment effect size that varies (based on analysis method used). Whether the treatment effect is clinically meaningful is a question we would like the panel to discuss. Other approved CF therapies have typically had a larger treatment effect as well as support from secondary endpoints. In the DPM program, there is a lack of clear support from secondary efficacy variables, such as exacerbations and CFQ-RRD. Some of these efficacy measures, e.g. CF exacerbation rate, were numerically not favorable in some of the studies.

Regarding the safety of DPM, inhaled mannitol is known to cause bronchospasm in persons with airway hyperreactivity. In the DPM clinical development program, all patients were screened with a mannitol tolerance test to identify patients with a significant decrease in pulmonary function with exposure to DPM. Based upon patients randomized in the clinical trials, bronchospasm was not a significant safety issue; however, tolerability issues were noted, e.g. cough and drop outs due to AEs. Treatment discontinuation secondary to CF exacerbations were also noted with DPM. In addition, CF exacerbations reported as SAEs were more common in DPM versus control groups. This was accentuated in the subgroup analysis of U.S. patients. Hemoptysis was a concern in the original NDA submission, but when limited to adults, hemoptysis does not appear to be a prominent safety issue.

We acknowledge that CF is an orphan disease with unmet need for new therapies, but we want to ensure that new products have a favorable benefit-risk assessment for patients. Given the modest treatment effect on FEV_1 and the lack of support from key secondary endpoints (e.g. numerical increase in exacerbations in two of the studies), the benefit of DPM is important to discuss with

the PADAC. We look forward to your input on this application. The following section outlines the Draft Points to Consider.

2 Draft Points to Consider

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

2. Discuss the safety data for mannitol inhalation powder for the proposed use in patients with cystic fibrosis, particularly exacerbations and hemoptysis.

3. Discuss the benefit-risk assessment for mannitol inhalation powder for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

Clinical and Statistical Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Date: April 11, 2019

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To: Chair, Members and Invited Guests
Pulmonary-Allergy Drugs Advisory Committee

Subject: FDA background materials for the New Drug Application (NDA) 202049 for mannitol inhalation powder (proposed trade name BRONCHITOL), for oral inhalation sponsored by Chiesi, for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

3 Clinical and Statistical Review

3.1 Introduction

On May 18, 2012, the Applicant submitted a 505(b)(2) new drug application (NDA) for the use of inhaled dry powder mannitol (DPM) for the management of cystic fibrosis (CF) in patients 6 years of age and older to improve pulmonary function. The proposed dose was 400 mg (10×40 mg capsules) twice daily. During the initial NDA review cycle, the NDA received a Complete Response (CR) action as the data did not provide a favorable benefit-risk for the proposed population due to lack of substantial evidence of efficacy, small effect size, and safety concerns particularly in pediatric patients. This was discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting, where the PADAC voted unanimously against approval. Since the CR action, the Applicant conducted an additional phase 3 study to address the concerns raised in the initial review cycle. These data have been submitted in the Applicant's complete response to the CR action to support the benefit-risk of this product. The focus of this PADAC meeting is to evaluate the benefit-risk of this product in light of the new data.

3.2 Brief Clinical Background

CF is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[1], and approximately 70,000 children and adults worldwide[2]. CF affects all ethnic and racial groups but is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is in the forties.[1]

CF results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which leads to decreased amount or abnormal function of CFTR protein. The CFTR protein is an epithelial chloride ion channel present on the apical surface of epithelial cell membranes. CFTR aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. Over time, the CF lung is exposed to a cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure. Because it is a recessive genetic disease, in order to present with clinical CF disease, one must have two mutations in the *CFTR* gene. To date, approximately 2,000 mutations in CFTR have been identified, with over 300 identified as disease causing.[3]

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

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

There are no FDA approved products for CF that act in a manner similar to DPM. Hypertonic saline, which is widely used by CF patients, may work in a similar manner, but is not FDA approved. A number of drugs are used to treat the symptoms and sequelae of CF, as well as several which treat the underlying cause of CF. Medications used to treat CF patients are summarized in Table 4. Note that not all are FDA approved for use in CF.

Table 4: Treatments for CF

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

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

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

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

3.3 Product Information and Regulatory Background

Product Information

Mannitol, the drug substance, 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.

Mannitol is a well-known, naturally occurring sugar alcohol found in many vegetables. It is used as a nutrient and/or dietary supplement and as an inactive 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 hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. Aridol can cause severe bronchospasm in susceptible individuals and caution is advised in patients with conditions that may increase sensitivity to bronchoconstriction.

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 handheld dry powder inhaler capable of processing one capsule at a time. The product is packaged as a 4-week and 7-day supply which includes 560 and 140 clear hard gelatin mannitol-filled capsules, respectively, which are sealed individually in aluminum blisters (10 capsules per blister strip) and with four or one hand held dry powder inhalation devices, respectively. 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.

Regulatory Background

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

As a result of these concerns, a Pulmonary Allergy Drug Advisory Committee (PADAC) was convened where these issues were discussed (see section 3.8 FDA Division Memorandum From January 2013 PADAC Meeting). The PADAC convened on January 30, 2013 and on the question of whether there was substantial evidence of efficacy, the majority of the PADAC voted "No" (No:11, Yes:3). In the discussion of efficacy, committee members noted concern over the relatively small effect size and difficulty in knowing the true treatment effect given the differential withdrawal between DPM and control groups. Some also commented that there was not strong statistical evidence for efficacy of DPM that would meet the regulatory definition of substantial evidence. The lack of support from secondary endpoints was also cited as a concern. However, several committee members commented that there did seem to be some evidence of efficacy in the adult population. On the question of whether the safety profile was sufficient to support approval, the majority of the PADAC also voted "No" (No:11, Yes: 3). In the discussion of safety, committee members expressed concern over the high occurrence of hemoptysis in patients receiving DPM, especially in children. For the question of whether the safety and efficacy data provided substantial support for approval, the PADAC voted "no" unanimously.

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

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

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

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

Following the CR action, a post-action meeting (type A) between the Applicant and the Agency occurred to discuss a path forward for the development program. At that meeting, the Agency agreed that a primary endpoint of change from baseline in FEV_1 over 6 months was acceptable to

provide substantial evidence of efficacy provided that the FEV_1 change is found to be statistically significant and clinically meaningful. Additionally, to support efficacy, exacerbations would be expected to trend in a positive direction. It was also communicated to the Applicant that conducting a third trial similar in design to the previously completed studies may be the most expedient path forward. This new study should be designed to minimize missing data and patient drop-out and exclude pediatric patients due to safety concerns.

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

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

3.4 Development Program

The DPM clinical development program was relatively small given the disease studied. It consisted of eight clinical studies which included two phase 1, three phase 2, and three phase 3 studies. One phase 1 trial included 18 healthy volunteers, and the remainder of the trials included CF patients. Studies 201, 202 and 203 were used to inform phase 3 dosing; however, the primary support for dose selection was study 202.

Study 202 was a randomized, 2-week treatment period, open-label, cross-over, dose ranging study in 48 CF patients. The study explored four doses (40, 120, 240, and 400 mg administered twice daily). While there were issues with the study, the Applicant selected the 400 mg twice daily dose, which the Agency found acceptable. Percent change in FEV_1 from baseline were -1.6%, 3.6%, 3.9%, and 8.7% for the 40, 120, 240, and 400 mg twice daily doses, respectively. Also, based on the lack of response to 40 mg DPM and the need to meet the requirements of matching taste (mannitol has a sweet taste) and appearance, the Applicant chose a 50 mg inhaled mannitol twice daily dose (5 mg x 10 capsules) as control treatment for phase 3 studies.

The phase 3 program consisted of studies 301, 302, and 303. Studies 301 and 302 were reviewed in the previous NDA review cycle, which received a CR action. Study 303 was completed in an attempt to address the deficiencies included in the CR letter.

3.4.1 Source of Clinical Data

The sources of clinical data reviewed in this document are derived from the phase 3 confirmatory studies. These are summarized in Table 5. Studies 301 and 302 were included in the original application and are highlighted in grey. Study 303 was submitted in the complete response to the CR.

Table 5: Phase 3 Studies

Study	Study Years	Study Design	Duration	Population	Treatments	N	Countries*
301	2007-2010	R, DB, PG OLE 52 weeks	26 weeks	CF patients, ages 6 and older, FEV_1 30-90%	DPM 400 mg BID Control (DPM 50 mg BID)	177 118	UK, Australia
302	2008-2010	R, DB, PG OLE 26 weeks	26 weeks	CF patients, ages 6 and older, FEV_1 40-90%	DPM 400 mg BID Control (DPM 50 mg BID)	184 121	US, Germany, Canada, Argentina,
303	2014-2017	R, DB, PG	26 weeks	CF patients, ages 18 and older, FEV_1 40-90%	DPM 400 mg BID Control (DPM 50 mg BID)	209 214	US, Poland, Russia, Ukraine

Abbreviations: DPM=dry powder mannitol; R=randomized; DB=double blinded; PG=parallel group; OLE=open label extension; BID=two times per day; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second
*countries contributing ≥10% subjects listed

As the protocols for studies 301 and 302 were reviewed in the previous NDA review cycle, only the protocol for study 303 will be reviewed in Section 3.4.1.1. However, key differences from studies 301 and 302 will be highlighted.

3.4.1.1 Study 303

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

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

Study Objectives:

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

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

3.4.1.1.1 Trial Design

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

Table 6: Study 303, Assessment Schedule

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

Table 6: Study 303, Assessment Schedule (continued)

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

[a] The IMP discontinuation visit is used for all subjects that discontinue IMP early but are remaining in the study.
[b] Subjects should be stable and clear of pulmonary exacerbations for at least two weeks prior to visit 1. If a subject has an exacerbation after visit 0 (screening), visit 1 should occur 2 to 5 weeks from the end of the treatment of the exacerbation or the end of the adverse event, whichever is later.
[c] Randomize eligible subjects if compliance with maintenance therapies (antibiotic & rhDNase) is at least 80% in the two weeks prior to visit 1.
[d] IMP accountability and collection must occur at the next scheduled visit for any subjects that withdraw from the study or discontinue from IMP early.
[e] The subject diary should be collected for all subjects, including those who withdraw early from the study.
Source: Study 303 protocol

As inhaled mannitol can induce bronchospasm, to be eligible for participation, patients had to pass a mannitol tolerance test (MTT). The MTT entails receiving successively increasing doses of dry powder mannitol from 40 mg to 160 mg (40 mg, 80 mg, 120 mg, and 160 mg for a cumulative dose of 400 mg). If a patient experienced an SpO_2 <89% within 1 minute after any dose of dry powder mannitol, the patient failed the MTT. If a patient experienced a drop in $FEV_1 \geq 20\%$ of baseline within 60 seconds after the 80 mg, or 120 mg dose, the patient failed the MTT. For the final 160 mg dose, if a patient experienced a drop in FEV_1 of ≥50%, the patient failed the MTT. However, if, at the 160 mg dose, the patients experienced a drop in FEV_1 of 20-50%, the patient was reassessed in 15 minutes. If after 15 minutes the patient continued to have an FEV_1 drop of ≥20%, the patient failed the MTT.

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

Study population

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

Key inclusion criteria:

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

Key exclusion criteria:

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

Study Treatments

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

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

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

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

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

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

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

Study Endpoints

Primary Endpoint:

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

Secondary Endpoints:

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

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

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

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

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

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

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

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

While study 303 was largely similar to previously completed studies 301 and 302, there were several notable differences:

- Study 303 did not have an open-label extension in contrast to studies 301 and 302, which had open label extension phases of 52 and 26 weeks, respectively.
- Study 303 included only adult patients per recommendations made by the Division due to safety/efficacy concerns raised in the initial NDA review cycle.
- While studies 301 and 302 included exacerbation related secondary endpoints, they were not the same as study 303. Endpoints used in the prior studies that were not in study 303 included FEF_{25-75}, sputum weight, and rescue antibiotic use. Antibiotic use and hospitalizations associated with exacerbations were assessed as rates (studies 301 and 302) rather than days (study 303). Importantly, in studies 301 and 302, the secondary endpoints did not have proper adjustment for multiplicity.
- Studies 301 and 302 were conducted between 2007 and 2010, whereas study 303 was conducted from 2014 to 2017. Between 2010 (end of studies 301 and 302) and 2014 (end of study 303), one new therapy, ivacaftor, was approved by the FDA for the treatment of CF patients with a specific mutation.
- In study 303, patients were encouraged to continue participating in study even if they discontinued study treatment, in contrast to studies 301 and 302.
- Study 303 included additional patient contact (telephone) compared to studies 301 and 302.
- In studies 301 and 302, patients were randomized in a 3:2 ratio, whereas in study 303, the randomization ratio was 1:1.

3.4.1.1.2 Statistical Analysis Plan

Analysis Sets

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

- Safety Set (SAF): This set included patients who were administered at least one dose (or part thereof) of randomized study medication. Patients in this set were grouped according to study medication received. This set was used for all analyses of safety endpoints.
- Intent-to-Treat Set (ITT): This set included all randomized patients. Patients were grouped according to randomized study medication. This set was used for all analyses of efficacy endpoints.
- Per Protocol Set (PP): This set included all randomized patients who did not have deviations from the protocol that may have affected the assessment of response to study medication.

Analysis Definitions for Periods

For Safety Data:

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

For Efficacy Data:

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

Estimands

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

Primary Efficacy Endpoint

Primary Analysis: Absolute change from baseline over the 26-week treatment period (with measurements at Week 6, 14, and 26) in Forced Expiratory Volume in 1 second (FEV_1) was compared between the two treatment groups with a restricted maximum likelihood based Mixed Model for Repeated Measures (MMRM) approach. This model included the fixed categorical effects of treatment group, rhDNase use, pooled country, visit, and an interaction term between treatment group and visit, as well as the continuous, fixed covariates of baseline FEV_1 and baseline percent predicted FEV_1. Patient was included in the model as a random effect. An

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

unstructured covariance structure was used to model the within-patient variability. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Least squares (LS) means for each treatment group and mean treatment group difference, standard error (SE), 95% confidence intervals (CIs) and the p-value for the treatment group effect averaged across the study visits, with the same weight applied to each visit, were to be presented. Prior to this analysis, missing data were handled in the following manner:

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

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

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

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

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

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

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

Sensitivity Analysis 4: A responder analysis was performed where a patient was considered to be a responder if (1) the data to determine the change from baseline to Week 26 in FEV_1 were not missing; and (2) the change from baseline to Week 26 in FEV_1 was above a certain threshold. The thresholds considered were (in liters) 0.050, 0.075, and 0.100. The proportion of responders were summarized and compared between treatment groups using a logistic regression model that included the same covariates as in the model for the primary analysis. The treatment group effect odds ratio, as well as the corresponding 95% CI and p-value, were to be presented.

Multiplicity Control Procedure

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

- Absolute change from baseline over 26 weeks in FEV_1
- Absolute change from baseline over 26 weeks in Forced Vital Capacity (FVC)
- Time to first protocol defined pulmonary exacerbation (PDPE)

- Number of days on antibiotics (oral, inhaled, or IV) due to PDPEs
- Number of days in hospital (admissions only) due to PDPEs
- PDPE Rate (per person year)

Primary Analyses for Hierarchical Secondary Efficacy Endpoints

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

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

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

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

Primary Analysis for Other Secondary Efficacy Endpoints:

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

Safety Analyses

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

Key Differences in SAP Compared to Studies 301 and 302

- Analysis Population Definitions
    - Studies 301 and 302

        - The SAPs for Studies 301 and 302 defined the ITT population to include all randomized patients who received at least one dose of study medication
- Primary Analysis for Change from Baseline Over 26 Weeks in FEV_1
    - Studies 301 and 302
        - The SAPs did not reference or define the estimand being targeted
        - Missing measurements for FEV_1 were not imputed, and all missingness was assumed to be at random
        - Treatment discontinuation was not distinguished from study withdrawal
        - The SAPs did not state whether off treatment data would be included
    - Study 301
        - Patients with no post-baseline assessments of FEV_1 were excluded
    - Study 302
        - The SAP did not state whether patients with no post-baseline assessments of FEV_1 would be included
- Primary Analysis for PDPE Rate
    - Studies 301 and 302
        - No imputation was performed for any patients who withdrew from the study, regardless of the number of observed instances of a PDPE
- Family-Wise Type I Error Control
    - Studies 301 and 302
        - Because of a prespecified interim analysis, the primary efficacy endpoint was tested at the two-sided significance level of 0.0498
    - Study 301
        - There was no multiplicity control procedure for the primary efficacy endpoint and the secondary efficacy endpoints
    - Study 302
        - Instead of using an analysis hierarchy, key secondary efficacy endpoints were tested using the Holm's method of correction, at the two-sided significance level of 0.05

Protocol Amendments

Protocol version 1.8 was the first version used dated March 27, 2014. The second version, version 2.0, was dated Oct 13, 2014.

Differences between the two protocol versions were:

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

3.5 Review of Efficacy

3.5.1 Efficacy Review Approach

Studies 301, 302, and 303 serve as the primary support for efficacy. As studies 301 and 302 were previously reviewed, the focus of this document is study 303 data. However, data from

studies 301 and 302 will be discussed and presented when relevant. Given the change in the target population to patients ≥18 years of age, efficacy data from the prior studies in the subgroup of patients ≥18 years are presented when appropriate along with study 303 results.

3.5.2 Patient Disposition

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

The reasons for study withdrawal were balanced between the treatment arms. The most common reason was withdrawal of consent. Other reasons included AEs, lack of efficacy, loss to follow-up, pregnancy, relocation, and other. With regard to treatment discontinuations, adverse events were the common reason, with "subject decision" being the second most common. Other reasons were similar to the reasons noted for study withdrawal. These data are summarized in Table 7.

Table 7: Study 303, Disposition

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

Abbreviations: AE=adverse event; DPM=dry powder mannitol
*Most frequent reason "subject decision" approximately 10 patients (5%) each arm
Source: Study 303 CSR; Table 14.1.1.2, p.143

Withdrawal of consent was explored further, as it was the most common reason for study withdrawal. Reviewer analysis did not reveal an imbalance in reasons cited for withdrawal of consent, which included logistical reasons (insufficient time, travel, study schedule), the desire

to take an alternate medication (hypertonic saline or Orkambi), or patient decision without further clarification.

Note that the study completion data from study 303 are in contrast to those of studies 301 and 302 (overall study population), where a much lower percentage of patients completed. In study 301, only 63% of DPM and 73% of control patients completed the 26-week treatment period. In study 302, the findings were similar, though not as pronounced, where 83% of DPM and 88% of control patients completed the 26-week treatment period. Importantly, in studies 301 and 302 when patients withdrew or discontinued treatment, they were no longer followed for efficacy endpoint data. This resulted in issues related to missing data which complicated analyses and interpretation of efficacy from these studies, as the Applicant's prespecified analysis plan used a mixed model for repeated measures (MMRM). This approach assumes that data missingness occurred at random, which did not appear to be the case for DPM, given the observed differential drop-out and that the product has known side effects which can make it difficult to tolerate for some patients. Given the lower and non-differential withdrawal in study 303, this was not as much of a concern for interpretation and analysis of the efficacy data.

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

Protocol Violations/Deviations

In the randomized patient population, 21 patients in the DPM group (10%) and 31 patients in the control group (14.5%) had major protocol deviations (MPDs). The most common protocol deviation was related to concomitant medication use (5% DPM, 7% control). Other reasons included inadequate compliance and violation of inclusion/exclusion criteria.

3.5.3 Demographics and Baseline Characteristics

In study 303, the demographic characteristics between the two treatment arms were fairly balanced with minimal differences. As expected given the nature of CF, this was a predominantly young (mean age 28) Caucasian (97%) population. The mean height and weight at screening (not shown) were also fairly balanced. The geographic contributions from the study sites are shown; U.S. sites were the largest single country contributor at over 25%. The next highest contribution came from Ukraine, Russia, and Poland at >10% each. Demographic data are summarized in Table 8.

Table 8: Study 303, Demographics

Demographic Parameter	Study 303	
	DPM (N=209)	Control (N=214)
Age		
Mean	26.8 (7.6)	28.6 (10.8)
Median (min, max)	25 (18,59)	25 (18,78)
Geography (≥3% contributors)		
United States	57 (27)	59 (28)
Non-United States	152 (73)	155 (72)
Eastern Europe*	97 (46.4)	98 (45.8)
Canada	7 (3.3)	6 (2.8)
Italy	7 (3.3)	8 (3.7)
Gender		
Female	92 (44)	107 (50)
Race		
Caucasian	202 (96.7)	209 (97.7)
African	4 (1.9)	2 (0.9)

Abbreviations: DPM=dry powder mannitol
*Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia, Ukraine
Source: Study 303 CSR; Table 10-2, 11-2

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

With regard to baseline disease characteristics, in study 303, these were similar between treatment groups. Mean time since CF diagnosis was approximately 20 years, mean baseline FEV_1 percent predicted was 63%, just under half were colonized with *P. aeruginosa*, and the majority (67%) carried at least one *F508del* mutation (Table 9). These baseline characteristics are fairly typical for an adult CF population. However, it should be noted that in the U.S. CF population a larger percentage of patients carry at least one *F508del* mutation (86%). This difference may be related to the fact that approximately 70% of patients were non-U.S. where the mutational composition of the population may differ. Baseline disease characteristics are summarized in Table 9.

Table 9: Study 303, Baseline Disease Characteristics

Characteristics	Study 303	
	DPM (N=209)	Control (N=214)
Mean time since diagnosis	20 years	20 years
Mean age at diagnosis	7 years	9 years
CFTR mutation		
Homozygous F508del	55 (26%)	48 (22%)
Heterozygous F508del	91 (44%)	89 (42%)
At least one other known mutation	28 (13%)	37 (17%)
Both unknown	35 (17%)	40 (19%)
Number of hospitalizations associated with exacerbation in previous 12 month		
0	121 (58%)	135 (63%)
1	57 (27%)	43 (20%)
2	20 (10%)	23 (11%)
3	11 (5%)	9 (4%)
>3	0	4 (2%)
Screening hemoptysis history		
History of hemoptysis	68 (33%)	60 (28%)
Multiple prior hemoptysis events	38 (56%)	27 (45%)
Prior massive* hemoptysis events? yes	3 (4%)	5 (8%)
Lung function at baseline		
Mean FEV_1	2.45L	2.38L
FEV_1 % predicted, mean	63%	63%
CFQ-R respiratory domain scaled score		
Mean	65.4	65.1
Median (min, max)	66.7 (16.7,100)	66.7 (5.6, 100)
Screening sputum microbiology		
Pseudomonas aeruginosa (any)	93 (44.5)	93 (43.5)
Pseudomonas aeruginosa (mucoid)	66 (32)	62 (29)
Pseudomonas aeruginosa (non-mucoid)	41 (20)	46 (22)
Pseudomonas spp. (other)	6 (2.9)	10 (4.7)

Abbreviations: DPM=dry powder mannitol; CFTR=cystic fibrosis transmembrane conductance regulator; CFQ-R=Cystic Fibrosis Questionnaire–Revised

*Massive hemoptysis defined as ≥240 mL in a 24-hour period and/or recurrent bleeding ≥100 mL per day over several days

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

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

Hemoptysis was a significant safety concern in the prior review cycle (see Section 3.6.8). As such, the hemoptysis history at screening was reviewed. No significant imbalances in frequency, timing, or severity of prior events were noted; minor differences were present

showing DPM patients to have a slightly higher frequency of prior multiple hemoptysis events (Table 9). Hemoptysis frequency in study 303 was slightly higher than the previous studies (<20%), understandably given the age differences of the population.

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

Use of rhDNase was approximately 70% in study 303. While rhDNase use was similar between treatment arms, it is worth noting that in the general U.S. CF population, rhDNase is used in approximately 88% of patients. In the subset of patients from U.S. study sites, rhDNase use ranged between 86-91% of U.S. study patients and was consistent with the general U.S. CF population. This difference between the U.S. study population and overall study population may be related to regional variations in rhDNase use and reflective of the multinational nature of this study.

3.5.4 Efficacy Results – Primary Endpoint

The primary endpoint for study 303 was change from baseline in FEV_1 over the 26-week treatment period. FEV_1 is a fairly typical primary efficacy variable used in CF drug development programs and has historically been used to support regulatory decision making. There was a statistically significant difference in change from baseline in FEV_1 over 26 weeks, when comparing DPM to placebo (p=0.018). The adjusted mean difference between DPM and placebo was 55 mL (95% CI: 9 to 101 mL) (Table 10).

Table 10: Study 303, FEV_1 Over 26 Weeks, BOCF Imputation Using Dropout Reason, ITT

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

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

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

related, such as moving. Multiple imputation accounts for statistical uncertainty in parameter estimation due to data missingness. These results were consistent with the primary analysis and supported the robustness of the analysis against assumptions on missing data. Results for the *post-hoc* sensitivity analysis using PMM and Huber-White sandwich estimates for the standard errors are summarized in Table 11.

Table 11: Study 303, Primary Endpoint. FEV_1 Over 26 Weeks, Pattern Mixture Model with MI Using Dropout Reason, ITT

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

Abbreviations: MI=multiple imputation; ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol

Note: These results reflect "on study" estimates, as they include data collected after treatment discontinuation. For each imputed dataset, a linear regression model was fit, and Huber-White sandwich estimates for the standard errors were used for the confidence intervals and p-values.

Source: FDA Statistical Reviewer

A tipping point analysis was also performed to evaluate how robust the primary analysis results are across varying missing data assumptions. In the analysis, missing data with monotone missingness patterns were multiply imputed assuming that missingness was at random among those in the same treatment group and country group, with the same rhDNase use, and with comparable FEV_1 values from screening through Week 26. These imputed values were then shifted for each patient by a value δ that corresponded to the patient's treatment arm. The results over a range of reasonable by-arm shift (δ) values are summarized in Table 12. For the majority of scenarios (shaded in green), though not all (shaded in red), the statistical significance was maintained. This suggests that the primary analysis results are somewhat robust to violations of missing data assumptions, which was expected from relatively low and proportionate missingness rates between treatment groups. If FEV_1 values after study discontinuation in the control arm followed the same trend as those of comparable control patients who remained in the study through Week 26, then in order to tip to a lack of statistical significance, FEV_1 values after study discontinuation in the DPM arm, on average, would have had to be 100 mL lower than those of comparable DPM patients who remained in the study through Week 26.

Table 12: Study 303, FEV_1 Over 26 Weeks, Tipping Point Analysis, ITT

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

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

While the results for the primary endpoint were statistically significant based on the pre-specified analysis and supported by the sensitivity analyses, the magnitude of the effect size was small, corresponding to approximately 1.2% in terms of percent predicted FEV_1. Whether this modest effect is clinically meaningful is an issue we would like the AC panel to discuss.

Studies 301 and 302

The primary endpoint for each of studies 301 and 302 was identical to that for study 303. While these studies were reviewed during the previous NDA cycle, they are presented here for consideration of the totality of the available efficacy data. During the previous NDA review cycle, the Agency found that the effect sizes estimated using Applicant's prespecified MMRM analysis method were unreliable and likely overestimated due to issues regarding missing data. First, the primary analyses excluded patients who had no post-baseline FEV_1 values. In study 301, the number of such patients was notable with over 10% in DPM group and with about 5% in control group, and these patients withdrew mostly due to adverse events within the first month. Second, the MMRM model assumed that data missingness was at random, and patients maintained a treatment benefit even after they discontinued treatments. The assumption was not supported by trial data. About 37% of the DPM group withdrew from the study before 26 weeks, while about 27% of the control group withdrew from study. Last, unlike study 303, these studies did not target a treatment policy estimand, due to patients being withdrawn from the study once they discontinued treatment, with no further data collection that would facilitate the targeting of this estimand, which is an important consideration from a regulatory viewpoint (see section 3.8 FDA Division Memorandum From January 2013 PADAC Meeting for a summary of the statistical issues). Primary endpoint results based on the Applicant's pre-

specified MMRM approach for studies 301 and 302 are summarized in Table 13. Note that this includes patients <18 years of age.

Table 13: Studies 301 and 302, FEV_1 Over 26 Weeks, Patients ≥6 Years, No Imputation, MITT

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

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

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

Studies 301 and 302 – Adults Only (*post-hoc*)
Because in this review cycle, the Applicant has revised their target patient population to include only patients ≥18 years of age, the Division has performed an analysis in the ≥18-year-old patients from study 301 and 302. With the caveats that the concerns regarding missing data and differential drop-out still apply and given that this is a *post-hoc* analysis, results of ≥18-year-old patients in studies 301 and 302 are summarized in Table 14. Note that randomization in studies 301 and 302 was 3:2 (DPM: control). The PMM model with multiple imputation was used in this analysis, as this was felt to handle missing data most appropriately among the proposed sensitivity analyses from the regulatory and statistical perspective. Furthermore, Huber-White sandwich estimates for the standard errors were used to relax the homoscedasticity assumption in the model fits. These results are generally consistent with those of the overall population, though the FEV_1 effect size appears somewhat larger. However, it should be noted that given the *post-hoc* nature of this analysis and previously noted issues with studies 301 and 302, interpretation of these results should be guarded.

Table 14: Studies 301 and 302, FEV_1 Over 26 Weeks, Pattern Mixture Model with MI, ITT, Patients ≥18 Years

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

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

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

3.5.5 Efficacy Results – Secondary endpoints

The secondary endpoints for study 303 were as follows:

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

Secondary endpoints 1-5 (key secondary endpoints) were analyzed in a hierarchical manner such that if the previous endpoint failed to reach statistical significance, the subsequent endpoints were not considered statistically significant. CFQ-R respiratory domain score was a non-hierarchical secondary endpoint.

FVC over 26 weeks

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

Exacerbation related endpoints

In CF development programs, exacerbation related endpoints, when exacerbation is appropriately defined in the protocol, are considered clinically meaningful and weigh heavily in

evaluations of efficacy. In study 303, the definition used for exacerbation for PDPE is appropriate, and statistically significant findings for the PDPE related endpoints would have been considered clinically meaningful.

Results for the PDPE related secondary endpoints for study 303 are summarized in Table 15. As the first hierarchical secondary endpoint failed, none of the PDPE related endpoints can be considered statistically significant. The analyses for these endpoints were performed according to the prespecified primary analysis methods described in the SAP for study 303. This includes the prespecified imputation procedure in the analysis for PDPE rate, for patients who withdrew from the study with no observed PDPEs. The results in Table 15 are consistent with results presented in the Applicant's clinical study report for this study.

Table 15: Study 303, Exacerbation Related Secondary Endpoints, ITT, Treated

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

Abbreviations: ITT=intention to treat: all subjects randomized; HR=hazard ratio; ARR=adjusted rate ratio; DPM=dry powder mannitol; PDPE=protocol defined pulmonary exacerbations; IV=intravenous; CI=confidence interval

‡ This analysis implemented the imputation procedure prespecified for the primary analysis in the statistical analysis plan for study 303 for patients who withdrew from study with no PDPE.

Note: Only treated patients are included in the statistical analysis using negative binomial model.

Source: FDA Statistical Reviewer

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

Studies 301 and 302 also include PDPE rate as a secondary endpoint. The definition used for exacerbation was the same as in study 303. Results from studies 301 and 302 provide context for the study 303 exacerbation related results. Of note, these analyses from 301 and 302 suffered from the same issue as the Applicant's primary analyses for the primary endpoint, as they were done without accounting for the unequal differential drop out of patients seen in

studies 301 and 302. The adjusted rate ratio for PDPE rate per person per year in patients ≥6 years of age (ITT) was 0.74 (0.47,1.18) for study 301 and 0.95 (0.57,1.58) for study 302; however, the numerical difference in exacerbation rate between DPM and control could be a result of the differential early discontinuation rates. Other exacerbation related secondary endpoints were included in studies 301 and 302, however, these data are not presented as there was no correction for multiplicity and results were consistent with PDPE rate (odds/rate ratios with 95% CI including null). Given the focus on adults, an analysis of this subpopulation for studies 301 and 302 for PDPE rate is presented (Table 16).

Table 16: Studies 301 and 302, Adjusted PDPE Rate per Person per Year, No Imputation, ITT, Treated, Patients ≥18 Years

Study 301	**DPM (N=114)**	**Control (N=76)**
Mean rate	0.73	0.95
Adjusted rate ratio (95% CI)	0.770 (0.47 to 1.26)	
Study 302	**DPM (N=93)**	**Control (N=58)**
Mean rate	0.32	0.24
Adjusted rate ratio (95% CI)	1.35 (0.56 to 3.24)	

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

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

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

CFQ-R respiratory domain score

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

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

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

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

3.5.6 Durability of Response

As CF is a chronic condition and DPM would be a chronic therapy, efficacy data should support that the treatment benefit is durable over time. To assess durability of response, the FEV_1 effect was also assessed using landmark analyses (e.g. change from baseline at the end of the 26-week treatment period). In study 303, the change from baseline in FEV_1 at 26 weeks was such that the 95% CI included the null, and the observed treatment effect size was numerically lower in magnitude than that for the primary endpoint and for FEV_1 at the Week 6 and Week 14 timepoints. These data from study 303 suggest that the FEV_1 effect may lack durability. A similar *post-hoc* analysis was performed for adults in studies 301 and 302. In contrast to study 303, in studies 301 and 302, such a waning of effect over time was not observed. Change from baseline in FEV_1 at weeks 6, 14, and 26 in patients ≥18 years are summarized in Table 17.

Table 17: Studies 301, 302, and 303, FEV_1 at Weeks 6, 14, and 24. Pattern Mixture Model with MI, ITT, Patients ≥18 Years

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

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

3.5.7 Additional Analyses

Subpopulations:

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

Additional analyses were performed for subgroups of patients according to whether they were or were not from U.S. sites. These *post-hoc* analyses were undertaken because the U.S. population is ultimately the population of interest, and it is possible that regional differences in standard of care could impact the treatment effect. It appears that the effect size in terms of FEV_1 over 26 weeks in the U.S. population is somewhat numerically larger than that observed in the non-U.S. population, however, the magnitude remains modest, and it may be due to decreases in the control group. As these were *post-hoc* analyses on a relatively small subset of patients, the ability to make definitive conclusions is limited. These data are summarized in Table 18.

Table 18: Study 303, FEV_1 Over 26 Weeks by Region, BOCF Imputation Using Dropout Reason, ITT

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

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

A similar *post-hoc* subgroup analysis was performed for the subgroup of adult patients from U.S. sites from study 302. This analysis was not performed for study 301, as study 301 was entirely non-U.S. As in study 303, the effect size in terms of FEV_1 over 26 weeks in the U.S. population is somewhat larger to that observed in the non-U.S. population. This is summarized in Table 19.

Table 19: Study 302, FEV_1 Over 26 Weeks by Region, Pattern Mixture Model with MI, ITT, Patients ≥18 Years

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

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

These results are consistent with the primary analysis but may also suggest that the FEV_1 effect size in both the U.S. population may be somewhat larger in magnitude compared to non-U.S.

population, however, it is still modest in magnitude. As these were *post-hoc* subgroup analyses in a relatively small subset of patients, the ability to make any definitive conclusion is limited.

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

Given that the subgroup analyses suggested a potential larger effect size in U.S. patients in terms of FEV_1, a *post-hoc* analyses of the U.S. and non-U.S. population were also performed for each of the exacerbation related secondary endpoints for study 303. These results are summarized in Table 20.

Table 20: Study 303, Exacerbation Related Secondary Endpoints, by Region and Overall, ITT, Treated

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

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; PDPE=protocol defined pulmonary exacerbations; HR=hazard ratio; ARR=adjusted rate ratio
Note: Only treated patients are included in the statistical analysis using a negative binomial model. To get by-region estimates, the model was refit with the addition of an interaction term between treatment and region.
[‡] This analysis implemented the imputation procedure prespecified for the primary analysis in the statistical analysis plan for study 303 for patients who withdrew from study with no PDPE.
Source: FDA Statistical Reviewer

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

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

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

numerically diminished treatment effect in the U.S. population. These data are summarized in Table 21. The difference in change from baseline in CFQ-RRD score for DPM versus control in U.S. patients was negative suggesting worsening of symptoms, whereas for non-U.S. patients this difference was positive. However, as these are *post-hoc* analyses in a relatively small subset of patients, the ability to make definitive conclusions is limited.

Table 21: Study 303, Change in CFQ-R Respiratory Domain Scores, by Region and Overall, ITT

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

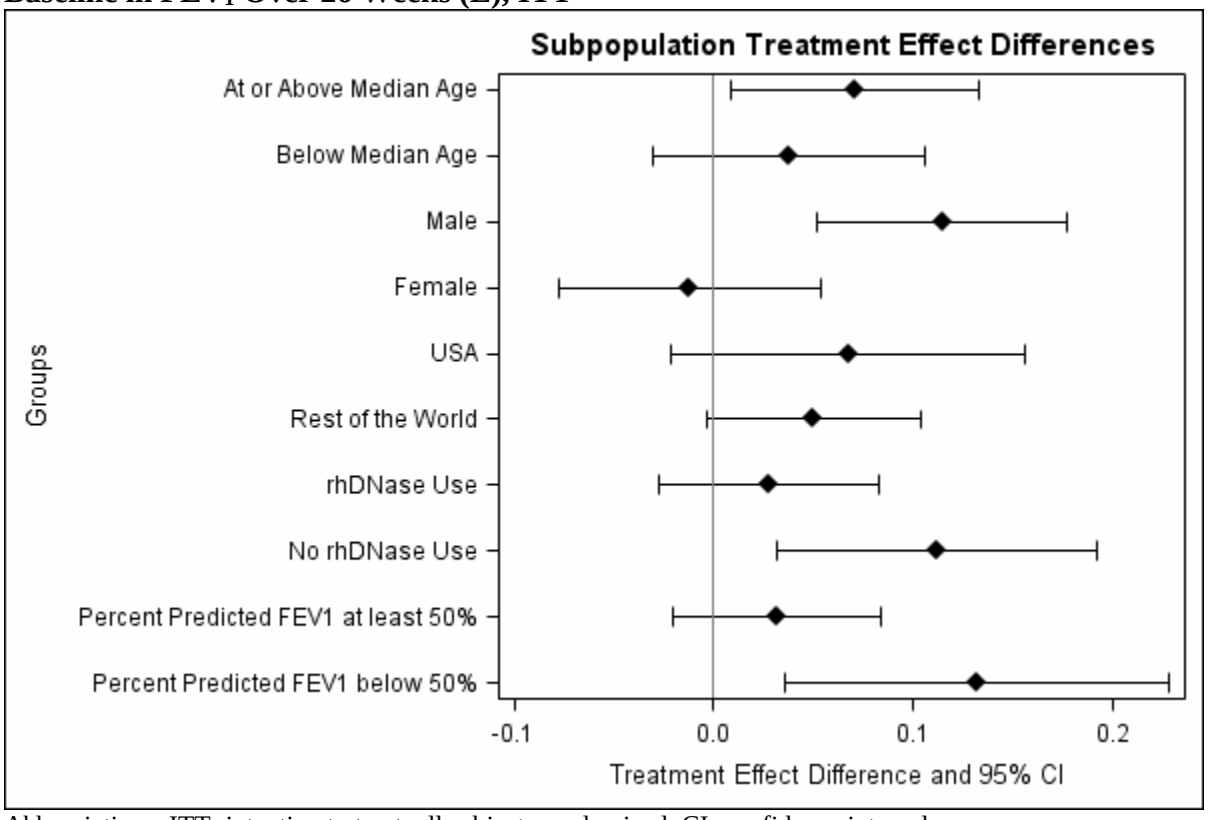
Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; DPM=dry powder mannitol; CFQ-R=Cystic Fibrosis Questionnaire–Revised
Note: By-region results were calculated by refitting the primary analysis model with the addition of an interaction term between treatment and region.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

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

Other subpopulations

Subgroup analyses were also performed on the basis of age, sex, FEV_1, and rhDNase use. These analyses are summarized in Figure 1. In general, these analyses were consistent with the primary analysis, however, the effect appeared diminished in females.

Figure 1: Study 303 Treatment Effect Difference for Subpopulations, Change From Baseline in FEV_1 Over 26 Weeks (L), ITT



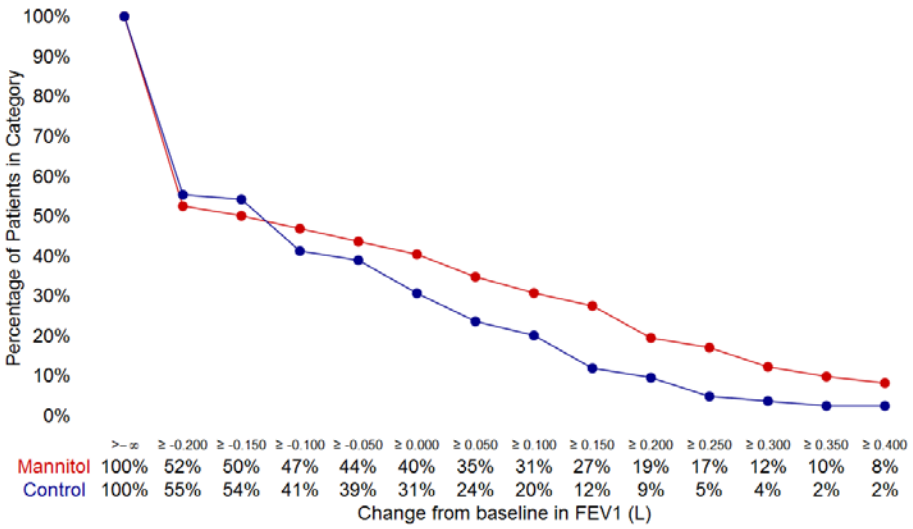
Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval
Source: FDA Statistical Reviewer

Subgroup analyses were also performed based on similar parameters for studies 301 and 302 (data not shown, see attached January 30, 2013 Division Memorandum, Table 6 in the Appendix).

Continuous Responder Analyses:

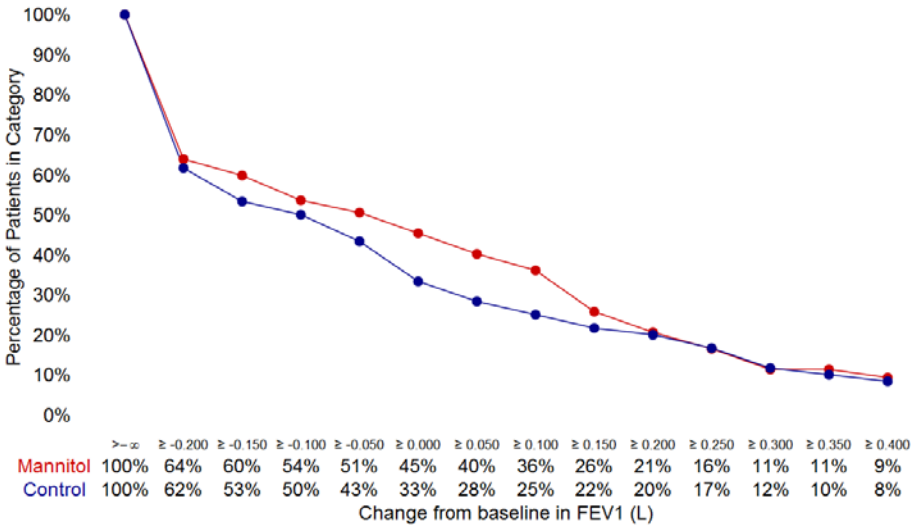
To thoroughly evaluate the treatment response in the setting of the significant dropout related statistical issues for the prior studies, continuous responder analyses were performed for studies 301,302, and 303 (Figure 2, Figure 3, Figure 4, Table 22). These analyses included only those patients ≥18 years of age given the Applicant's target population. For each analysis, a patient is classified as having been successfully or unsuccessfully treated according to a specific threshold for the change from baseline in FEV_1 at week 26, in this case from -200 to +400 mL. The x-axis displays the thresholds required to classify a subject as a successfully treated subject while the y-axis represents the proportion of ITT subjects who achieved the corresponding threshold. The proportion of DPM treated patients achieving each threshold is represented by the red line and proportion of control subjects by the blue.

Figure 2: Study 301 Continuous Responder Analysis, Patients ≥18 Years, ITT



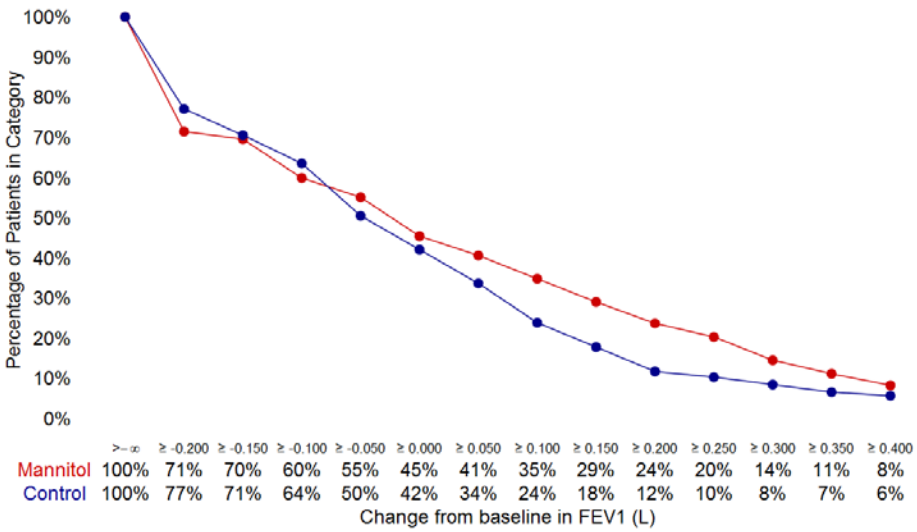
Abbreviations: ITT=intention to treat: all subjects randomized
Source: FDA Statistical Reviewer

Figure 3: Study 302 Continuous Responder Analysis, Patients ≥18 Years, ITT



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

Figure 4: Study 303 Continuous Responder Analysis, ITT



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

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

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

Study	Threshold	DPM	Control	Adjusted Odds Ratio (95% CI)
Study 301		N=124	N=85	
	50 mL	43 (34.7%)	20 (23.5%)	1.67 (0.89 to 3.20)
	75 mL	40 (32.3%)	18 (21.2%)	1.71 (0.90 to 3.37)
	100 mL	38 (30.6%)	17 (20.0%)	1.70 (0.88 to 3.40)
Study 302		N=97	N=60	
	50 mL	39 (40.2%)	17 (28.3%)	1.72 (0.86 to 3.54)
	75 mL	37 (38.1%)	15 (25.0%)	1.86 (0.92 to 3.92)
	100 mL	35 (36.1%)	15 (25.0%)	1.70 (0.83 to 3.58)
Study 303		N=209	N=214	
	50 mL	84 (40.6%)	72 (33.6%)	1.35 (0.91 to 2.01)
	75 mL	76 (36.7%)	62 (29.0%)	1.43 (0.95 to 2.15)
	100 mL	72 (34.8%)	51 (23.8%)	1.71 (1.12 to 2.63)

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

3.5.8 Efficacy Summary

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

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

In summary, while studies 301 (overall population) and 303 achieved statistically significant results for the FEV_1 primary endpoint based on the Applicant's pre-specified analysis, due to

missing data and patient drop-out issues, interpretation of study 301 is complicated. Additionally, while *post-hoc* analyses of patients ≥18 years of age from studies 301 and 302 may suggest a treatment effect in terms of FEV_1, these were *post-hoc* analyses of a trial that lost (302) and a trial with significant statistical issues (301). Moreover, the treatment effect size is modest across all studies. Importantly, these modest in magnitude "wins" on the primary spirometric endpoint are not supported by the exacerbation or symptom related secondary endpoint measures in any of the phase 3 studies.

3.6 Review of Safety

3.6.1 Safety Review Approach

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

3.6.2 Overall Exposure

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

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

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

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

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

Given the disease, the safety database is adequate.

Categorization of Adverse Events

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

3.6.3 Deaths

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

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

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

In study 301, there were no deaths during the course of the study. There were no deaths during the OLP of the two phase 3 studies (301 and 302).

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

3.6.4 Serious Adverse Events

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

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

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

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

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

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

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

Source: SCS, Table 38, p.100

In general, while there were some numerical differences in SAEs between DPM and control groups, these were small in magnitude; less than a 1% difference between arms (unless control arm was higher), with the only exception CF exacerbations (DPM 2% higher than control).

This observation is somewhat consistent with the efficacy results regarding protocol defined pulmonary exacerbations (PDPE), where across multiple PDPE related endpoints trends favored control. Results from the OLP portion of studies 301 and 302 were generally consistent with the DBP results. As hemoptysis had been raised as a safety concern in the prior review cycle, it is worth noting that in the analysis of SAEs in patients ≥18 years of age, the difference between DPM and control groups for hemoptysis was small, though still numerically higher in DPM. A more in-depth discussion of hemoptysis and exacerbations can be found in Section 3.6.8.

3.6.5 Dropouts and/or Discontinuations Due to Adverse Effects

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

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

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

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

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

Results from the OLP portions of 301/302 were generally consistent with the DBP results. The total number of adult OLP patients with TEAEs leading to study withdrawal was 15 of 224 (6.7%). This included 11 of 94 (11.7%) DBP control patients who transitioned to DPM during the OLP and 4 of 130 (3.1%) patients on DPM during the DBP who remained on DPM during the OLP. A possible explanation for this may be that at the end of the DBP the remaining DPM patients were "tolerant" moving forward into the OLP portion thus accounting for low study withdrawal in the OLP (3.1%), whereas control patients who transitioned to DPM in the OLP were not "tolerant" and withdrew at rates similar to DPM in the DBP. Consistent with the DBP, the most frequent AEs in the OLP leading to discontinuation included CF exacerbations, albeit with a lower percentage (1.3%).

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

3.6.6 Severe Adverse Events

During the DBP of studies 301, 302, and 303, in patients ≥18years of age, 13% of DPM and control patients had severe TEAEs. CF exacerbation was the most commonly reported severe TEAE. Between treatment groups, total severe AEs were relatively balanced. These data are summarized in Table 25.

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

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

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

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

Results from the OLP portions were consistent with the DBP results. Approximately 15% of adult OLP patients had a severe TEAE, of which CF exacerbations were the most common

(5.8%). A small numerical increase in exacerbations was noted in control patients transitioning from control to DPM in the OLP (4.5% DBP to 5.3% OLP).

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

3.6.7 Treatment Emergent Adverse Events and Adverse Reactions

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

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

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

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

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

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

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

3.6.8 Submission Specific Safety Concerns

Hemoptysis

Hemoptysis was identified as a safety concern in the initial review cycle based on review of safety data in all patients (pediatric and adult) from studies 301 and 302. Despite the exclusion of patients with >60 mL hemoptysis in the 3 months prior to screening in these studies, hemoptysis AEs, SAEs, and discontinuations due to hemoptysis were consistently observed more frequently in DPM versus control patients. This small but clear signal for hemoptysis occurred even in the youngest age group of 6- to 11-year-olds, raising issues of safety specifically for pediatric patients. While no patients died from hemoptysis events in the safety population during the conduct of studies 301 and 302, the long-term effect of the 2-to-4-fold increase in hemoptysis, when projected to chronic use over the course of a CF patient's lifetime, is unknown. A summary of the safety data from studies 301 and 302 regarding the hemoptysis safety concern is shown in Table 28.

Table 28: Studies 301 and 302, Hemoptysis by Age

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

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

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

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

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

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

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

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

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

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

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

Hemoptysis volume was lower in DPM versus control (mean and median) and more DPM patients reported scant hemoptysis versus control. These data suggest that DPM does not result

in larger volume hemoptysis despite a slightly higher percentage of DPM patients having a history of any hemoptysis and of multiple hemoptysis events at screening.

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

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

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

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

Exacerbations

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

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

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

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

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

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

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

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

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

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

Results for serious CF exacerbations were striking. In the U.S. population, 21% of DPM versus 11% of control patients experienced a serious CF exacerbation. This is in contrast to the non-U.S. and overall population where the differences were much smaller. Similar trends, though not as marked, were observed for AEs leading to drug discontinuation, AEs leading to study withdrawal, and severe AEs. While similar findings were not observed for the category any exacerbation, these findings still raise exacerbation related safety concerns. It is also worth

noting that these exacerbation related safety findings are consistent with the PDPE efficacy data.

Other

Given the known airway effects of inhaled mannitol, analysis of cough events was performed. This analysis was performed grouping the preferred terms "cough" and "productive cough." Based on this grouping the overall frequency of cough events was 14.7%. in pooled studies 301, 302, and 303. In the pooled safety data from all three studies, cough events were seen more frequently in DPM patients versus control. While there were no serious cough events reported, drug discontinuations and study withdrawal due to cough were more frequent with DPM patients. These findings are not unexpected but do suggest some patients may have difficulty tolerating DPM due to cough. These results are summarized in Table 34.

Table 34: Studies 301, 302, and 303 Pooled, Cough, Double Blind Phase Only, Patients ≥18 Years

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

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

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

3.6.9 Safety Summary

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

While there were some numerical differences in certain adverse events, overall the differences between arms did not raise major safety concerns for patients ≥18 years of age. Across the

three phase 3 studies, two deaths occurred, both in control treated patients. With regard to SAEs, overall, they were balanced between arms, however, for the SAE CF exacerbations, events were slightly more common in the DPM versus control treated patients. AEs leading to treatment discontinuation were more common in DPM treated patients compared to control, with cough and CF exacerbations accounting for the majority of events. This suggests that there may be tolerability issues associated with DPM. For severe AEs, overall events were similar between groups, however, there were slightly more severe CF exacerbations in DPM treated patients than control. Common AEs occurring more frequently in DPM patients than control were cough, oropharyngeal pain, hemoptysis, bacteria sputum identified, and pyrexia.

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

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

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

3.7 Benefit/Risk Considerations

The efficacy evaluation of DPM in adult CF patients is based on three phase 3 studies (301, 302, and 303). Studies 301 and 302 included patients ≥6 years of age. Study 303 included only patients ≥18 years of age due to safety concerns raised in studies 301 and 302. Based on the Applicant's pre-specified analyses, results from 302 did not achieve statistical significance in the overall population for the primary endpoint of change from baseline in FEV_1 over 26-weeks, whereas studies 301 (overall population) and 303 did. However, study 301 results are complicated by the extent of differential missing data due to differential drop-out raising concerns regarding the statistical robustness of the results. For the ≥18-year-old population in studies 301 and 302, while *post-hoc* analyses may have suggested an FEV_1 treatment effect, these were *post-hoc* analyses of a trial that lost (302) and a trial with significant statistical issues

(301). Moreover, regardless of the analyses used, the treatment effect size across all studies in all age groups was modest. In study 303, the effect size in terms of the primary endpoint of change from baseline in FEV1 over 26-week was approximately 50 mL. In terms of percent predicted FEV_1, this milliliter value corresponds to approximately 1.2%. In studies 301 and 302, in the *post-hoc* analysis of patients ≥18 years of age, the estimated effect sizes were approximately 80 mL. Whether or not this modest effect size represents a clinically meaningful benefit is uncertain.

To assist in the evaluation of benefit, relevant secondary endpoints were assessed such as exacerbation and CFQ-RRD score. Across all three studies, there were no statistically significant differences between DPM and control groups. Moreover, in the most statistically robust of the three studies (303), for the majority of the exacerbation related endpoints, results numerically favored control over DPM. This unfavorable trend was accentuated in the subgroup analysis of U.S. patients. To add perspective to these data, for the most recently approved CF products, the effect size in terms of percent predicted FEV_1 over a 6-month period ranged from 2.6% to approximately 12%. Additionally, for these products, the FEV_1 improvements were generally further supported by other clinically relevant endpoints such as exacerbation. Overall, while DPM may have an effect on FEV_1, it is modest at best, not supported by other clinically meaningful endpoints, and smaller than observed in other approved CF products.

With regard to risk, based on the adult data from the same three studies, DPM has tolerability issues likely related to its known effects on the airways. The hemoptysis safety concern raised in the previous review cycle have been largely addressed given the proposed patient population (≥18years) and safety data from study 303. Given the unfavorable trends observed for PDPE in study 303, as well a higher incidence of adverse events of CF exacerbation (SAE, AE leading to discontinuation, and severe AEs) observed in DPM versus control patients, and subgroup analyses suggesting that these unfavorable trends were more prominent in the U.S. population, an exacerbation-related safety concern has been raised.

In summary, DPM has a modest effect in terms of lung function, has no clear benefit in terms of other clinically meaningful parameters such as exacerbation, has tolerability issues, and has a potential exacerbation related safety concern. Whether or not the benefit-risk for such a product is considered favorable is the primary purpose of this PADAC meeting.

3.8 Appendix – FDA Division Memorandum From January 2013 PADAC Meeting

DIVISION MEMORANDUM

Date: December 28, 2012

From: Anthony Durmowicz, MD
Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

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.

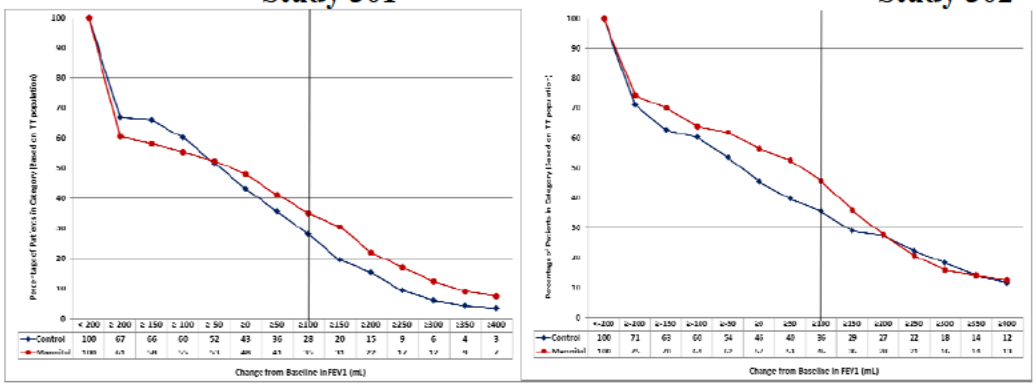
For each analysis, a patient is classified as having been successfully or unsuccessfully treated according a specific threshold for the change from baseline in FEV1 at week 26, in this case from -200 to +400 mL. The x-axis displays the thresholds required to classify a subject as a successfully treated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