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SUMMARY

The FDA's Pulmonary-Allergy Drugs Advisory Committee meeting on Pharmaxis' Bronchitol, an inhalable dry powder mannitol for cystic fibrosis, was somewhat contentious, and the outcome was not positive for the company. The panel recommended against approval, finding the drug was neither safe nor effective.

Trends-in-Medicine
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FDA Advisory Committee Rejects Pharmaxis' Bronchitol for Cystic Fibrosis

White Oak, MD
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The FDA's Pulmonary-Allergy Drugs Advisory Committee voted unanimously (14-0) that Pharmaxis' Bronchitol (inhalable dry powder mannitol, DPM) for cystic fibrosis should ***not*** be approved. The panel also voted 11-3 that it is ***not*** safe or effective, saying the pivotal trial did not prove any significant effect on FEV_1, had a high dropout rate, and raised safety concerns because of an increased risk of hemoptysis.

Pharmaxis conducted two Phase III trials (Studies 301 and 302), but one of these trials missed the primary endpoint. Before the vote, the panel was divided, with some members arguing that the FDA standards on the definition of efficacy (two studies meeting primary endpoints) should be waived – one even suggested "updating" the standards – in the case of this drug. Others suggested use could be restricted (i.e., to children under 18) by labeling. Some members argued that a 1%-2% improvement in FEV_1 could be considered efficacy. On the other hand, the statisticians flatly said that the data were not good enough.

The discussion was, at times, somewhat tense and contentious, with an FDA medical officer rebutting statements made by the company, including exacerbation claims. It was clear that the FDA team had had many discussions with the company and was rebuffed all along the road, and they were not allowing the company to make claims that weren't backed with evidence. When a U.K. clinician hypothesized that the incidences of hemoptysis may be due to the sheer force of mucus being coughed up as a result of the drug, calling it a possible "benefit," one panel member warned that a chronic irritant could cause tremendous injury, especially to children with growing airways.

In briefing documents prepared for the panel ahead of the meeting, FDA reviewers said that determining efficacy was problematic because of frequent treatment-related patient dropouts, leading to missing data. They said that a statistically significant effect of DPM on the primary endpoint was not shown and that the overall effect of the drug in cystic fibrosis patients can't be confirmed. The company used a modified intent-to-treat (mITT) population, which showed a modest but statistically significant increase for the primary endpoint of change from baseline in FEV_1 over 26 weeks in only one of the two Phase III trials (Study 301).

The FDA did an analysis using the entire intent-to-treat population, which it said was a more accurate reflection of DPM's efficacy, and results were not consistent with the company's analyses. In the FDA analysis, there was no statistically significant difference

between DPM and control patients in Study 301, but there were statistically significant differences shown in the other Phase III trial (Study 302). This put the company's analyses into question.

As for safety, there did not seem to be a significant increase in bronchospasms in patients taking DPM vs. control, and most adverse events had more to do with intolerability than safety. The exception was hemoptysis, which occurred more frequently in patients taking DPM vs. control.

The FDA wanted the panel to determine whether the company's efficacy data meet the standard of substantial evidence (especially in light of a high dropout rate) and whether the safety and tolerability profile of the drug, especially the increased incidence of hemoptysis in both children and adults, is good enough to support its use as a chronic maintenance therapy for cystic fibrosis patients. Obviously, the panel did not find the data satisfactory.

OVERVIEW

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal genetic disease most common in Caucasians. It occurs in about one out of every 3,500 children born in the U.S. Patients do not have a properly functioning cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, which is responsible for the clinical sequelae of cystic fibrosis, including malabsorption of nutrients and the presence of tenacious respiratory secretions that are difficult to mobilize, leading to recurrent/chronic pneumonia and lung damage.

There is no cure for cystic fibrosis, and until the recent approval of a drug for a very small subpopulation of cystic fibrosis patients that acts on the CFTR, treatment is limited to alleviation of symptoms and treatment of complications for most cystic fibrosis patients. The median age of survival is the early to mid-30s, and most die because of respiratory failure. Medications available include mucolytics such as inhaled DNase and hypertonic saline (not approved in the U.S.), beta-agonist bronchodilators, pancreatic enzyme supplements, and inhaled corticosteroids.

D-mannitol is a well-known, naturally occurring sugar alcohol found in most vegetables. It is used as a nutrient/dietary supplement and as such is generally recognized as safe. The exact mechanism of its action in the lungs of cystic fibrosis patients is unknown, and the company's hypothesis is that when inhaled, the hyperosmotic agent may increase hydration of mucus and the periciliary fluid layer, helping clear secretions. It is a known bronchial irritant, and increased cough resulting from inhalation may also help get rid of mucus.

As an inhaled product, it is a bronchoprovocation agent approved in the U.S. as part of a kit for the assessment of bronchial hyperresponsiveness in patients age ≥6 who do not have clinically apparent asthma. Mannitol, when inhaled, can cause severe bronchoconstriction in susceptible subjects. The studies showed that the respiratory tract is the target organ of toxicity of inhaled mannitol. The proposed product is hard gelatin capsules containing 40 mg of mannitol and a breath-actuated, handheld dry powder inhaler capable of processing one capsule at a time.

The investigational new drug (IND) application for DPM was opened in November 2004. The cystic fibrosis indication was given orphan drug status on July 13, 2005, and fast track status on November 8, 2006. However, over the years, the FDA met with the Australian company (which has one other approved product in the U.S. – a test) to discuss a myriad of problems, including study duration, endpoints, pooling of data, definitions, and missing data. In 2010, the company proposed several post hoc changes to the statistical analysis plan, which the FDA called "post hoc manipulations," saying they were "generally not acceptable for regulatory purposes."

FDA PERSPECTIVE

Pre-Meeting FDA Briefing Documents

The FDA reviewers noted there was a discrepancy between the screening and baseline FEV_1 for control vs. placebo in Study 302, "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."

The company also proposed to change the analysis of the primary efficacy endpoint for Study 301. While not commenting on the "adequacy" of the proposed methods, the FDA reviewers said, "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."

The FDA reviewers also questioned testing the drug in children as young as 6 before studies in adults were completed, and it asked the company to justify using the same dose for children as for adults.

Efficacy

The company submitted data from two Phase III studies (301 and 302). The primary endpoint was absolute change from

baseline in FEV_1 at Week 26. Other efficacy endpoints included additional spirometry assessments, pulmonary exacerbations, protocol-defined pulmonary exacerbations, quality of life, rescue antibiotic use, and days in hospital due to pulmonary exacerbation.

The FDA reviewers pointed out data analyses were "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 that included only intent-to-treat 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 dropouts is more pronounced for Study 301 and results in only 88% of DPM patients being included in the modified intent-to-treat analysis compared to 95% of control patients. In Study 302, 96% of DPM patients and 99% of control patients were included in the modified intent-to-treat population."

The FDA reviewers said that another thing contributing to the problem of missing data was that "throughout the conduct of the studies there were additional missing data as a result of differential dropout at Weeks 14 and 26, when efficacy assessments were made." The reviewers mentioned the company's pre-New Drug Application (NDA) meeting proposal to change the baseline FEV_1 level, noting that that kind of manipulation "creates a large regulatory obstacle to overcome."

About 66% of enrolled patients finished Study 301, a 26-week double-blind study, and 85% completed Study 302. The biggest reasons for dropping out were adverse events, including cystic fibrosis exacerbations, and withdrawal by patient.

Regarding efficacy results, the company gave mixed model for repeated measures analyses for the modified intent-to-treat population, which the FDA reviewers called "problematic in that they do not include the entire intent-to-treat population, and the mixed model for repeated measures model does not appropriately account for the differential rates of patient dropout that is higher in the DPM groups. Because the Agency believes analyses that incorporate the true intent-to-treat population and are able to account for the missing data as a result of the differential dropouts are the most appropriate representation of the primary efficacy endpoint, responder analyses are also presented." Dropouts were more frequent in the DPM group vs. control in both studies, but markedly so in Study 301.

The FDA reviewers said that responder analyses of the primary endpoint were done for the entire intent-to-treat population. It was assumed that missing data at Weeks 6, 13, or 26 represented failed DPM treatment. For each study, the DPM group had a numerically higher proportion of patients who had an increasing change from baseline in FEV_1 thresholds vs. control, but the changes were not statistically different between treatment groups (p=0.7 for Study 301 and p=0.6 for Study 302). Using a different way of looking at it, changes for Study 301 were not significant, but for Study 302, there was statistical significance.

The FDA reviewers wrote, "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 dropout. Results for Study 301, which had the greatest differential dropout, went from demonstrating a statistically significant increase in FEV_1 for the modified intent-to-treat population, while results for Study 302, which had fewer overall dropouts, went from statistically equivocal 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…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 cystic fibrosis patients in terms of the change from baseline in FEV_1 in the intent-to-treat 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 committee members.

Regarding dose selection, the FDA reviewers called the dose study (302) design "problematic in that all patients began their treatment sequence with two weeks of treatment with the highest (400 mg) BID dose with subsequent randomization to the other two-week dosing treatment periods. As a result, the value of this open-label dose-finding study is limited."

Primary Analysis – Absolute Change from Baseline FEV_1 (mITT) – Average Effect from Week 6 to Week 26

Study	DPM 400 mg	Control	p-value
Study 301	15.3%	17.4%	<0.001
Study 302	22.4%	25.6%	0.059
Study 301			
	n=176	**n=118**	
FEV_1 absolute increase ≥50 mL	41%	36%	0.420
FEV_1 absolute increase ≥75 mL	37%	30%	0.259
FEV_1 absolute increase ≥100 mL	35%	28%	0.312
Study 302			
	n=184	**n=121**	
FEV_1 absolute increase ≥50 mL	53%	40%	0.008
FEV_1 absolute increase ≥75 mL	50%	36%	0.007
FEV_1 absolute increase ≥100 mL	46%	36%	0.041

Safety

The FDA reviewers did not have many problems with the safety data, but a red flag was raised about hemoptysis. In the combined safety population, 719 patients were assessed for airway hyperreactivity to find out eligibility. Of these, 77 patients either failed the test immediately because of decreased FEV_1, couldn't tolerate the dose, or otherwise withdrew, leaving 642 patients to be randomized. Forty-two more patients withdrew in the 2-5 weeks before the first dose, leaving 600 patients who received at least one dose of the drug. There was one death – a 15 year old with severe cystic fibrosis lung disease in the Study 302 control group who received treatment for about five months. His illness progressed, and the study drug was stopped after hospitalization and pneumothorax (collapsed lung). He continued to deteriorate and died of respiratory failure.

More patients taking control had serious adverse events vs. DPM patients, 27% vs. 21%. Most events occurred in just one or two patients. Cystic fibrosis exacerbations were the most frequent serious adverse event and occurred in 19% of control and 17% of DPM patients. Other serious adverse events were infrequent and mostly related to other systemic manifestations of cystic fibrosis, including diabetes, respiratory infections, and intestinal obstruction.

Although patients with a history of significant hemoptysis episode were excluded, in the double-blind controlled phase of the studies, the occurrence of hemoptysis was two to four times higher for serious adverse events, adverse events leading to withdrawal, severe adverse events, and adverse events in patients taking DPM vs. control. Hemoptysis was also increased in children taking DPM vs. control.

Patients taking DPM had more cystic fibrosis exacerbations vs. control – 20% vs. 18% respectively. Other adverse events in patients taking DPM included cough, pharyngolaryngeal pain, bronchospasm, and pulmonary infection.

FDA Formal Presentation to the Panel

Anthony Durmowicz, MD, a clinical team leader in the FDA's Division of Pulmonary, Allergy, and Rheumatology Products, Center for Drug Evaluation and Research (CDER), gave an overview of inhaled mannitol powder for cystic fibrosis. The substance is a commonly used and recognized sugar alcohol used as an osmotic diuretic in medicine and is generally recognized as safe. The indication is for the management of cystic fibrosis in patients 6 years and older to improve pulmonary function. The dose is 400 mg (10 capsules) by inhalation BID. Other mucus clearance agents used for cystic fibrosis are inhaled hypertonic saline and DNase.

Dr. Durmowicz described the trials, saying that the "most problematic issue was the one of missing data," and sensitivity analyses were required to assess the study results. The treatment effect was also "somewhat questionable…At the end of the day it appears there is a single study that shows efficacy and another study that is negative or equivocal. A treatment effect is in the range of 50-80 mm, and one question is: Is it clinically significant in this population? There is a safety issue, and there is an incidence of hemoptysis. Pediatrics is also part of the discussion."

The three main topics for discussion were:

- **Efficacy** – Is there substantial evidence of efficacy, taking into account missing data and dropout as well as the clinical relevance of the range of clinical effects?
- **Safety** – Potential safety concerns include hemoptysis and other respiratory events.
- **Data** – Are there sufficient data to suggest that there is evidence of efficacy and safety?

Overview of therapies

Kimberly Witzmann, MD, a clinical reviewer in the FDA's Division of Pulmonary, Allergy, and Rheumatology Products, CDER, and a pediatric pulmonologist, gave an overview of cystic fibrosis therapies. She said that the IND application for DPM was filed November 22, 2004, and it was given orphan drug and fast drug status. On Feb 15, 2006, at the end of the Phase II meeting, it was decided that the Phase III study depended on the primary outcome and that one-year safety data were needed. An FEV_1 variable was chosen as a primary endpoint, but small changes in FEV_1 over short periods of time would not be sufficient to support approval, and additional co-primary or secondary outcomes would be required. On December 10, 2010, the company proposed post hoc changes to statistical analyses, and the FDA said those kinds of studies are generally frowned upon.

Dr. Witzmann said the design of the dose selections study was problematic, but a dose response was observed: 400 mg was the highest dose evaluated and had the best response. A 40 mg dose resulted in a negative response.

Dr. Witzmann described the two Phase III studies. The control was a 50 mg BID dose of DPM.

Phase III screening procedure differences

Feng Zhou, MS, a statistical reviewer from the FDA's Division of Biometrics II, Office of Biostatistics, Office of Translational Sciences, CDER, said that the screening procedures were different in the two Phase III studies, and the studies were not

conducted concurrently. A mixed model for repeated measurements analysis was used. For secondary endpoints, Study 301 did not apply multiple adjustments to the secondary endpoints, and Study 302 used the Holm's method to control the Type 1 error for following key secondary endpoints at 26 weeks: mean change in absolute forced vital capacity (FVC) from baseline, mean change from baseline in % predicted FEV_1, sputum weight post-treatment, mean change from baseline in absolute FEV_1, mean change from baseline in absolute FEV_1 in rhDNase use group, and mean change in absolute forced expiratory flow (FEF) 25-75 from baseline.

Zhou discussed the differential early study discontinuation rates, "The most common reasons for early study discontinuations were 'withdrew by patient' and adverse events." She said the company's treatment analysis "may be inaccurate." The primary efficacy endpoint result was statistically significant in Study 301, but not in Study 302. She said the mITT population excluded patients with no post-baseline data and statistical analysis methods, assuming that the missing data are missing at random. She said there are very serious areas of concern regarding the treatment effect with the drug.

Zhou said none of the sensitivity analyses was perfect, and she criticized the sensitivity analysis for the primary endpoint (baseline observation carried forward) for its assumptions.

An FDA post hoc analysis of the primary efficacy endpoint assumed that patients who withdrew were non-responders. In both plots showing change from baseline in FEV_1 at Week 26 (for the two Phase III studies), the control and DPM lines both drop and head down in steep curves.

Another post hoc analysis of the two Phase III studies including all intent-to-treat patients suggested a beneficial impact of DPM vs. control. (*This finding was made despite one study failing the primary endpoint.*)

Zhou summarized:

- **Early study discontinuation –** an overriding concern:
  - 64% of DPM and 73% of control subjects completed the 26-week treatment period in Study 301.
  - 83% of DPM and 88% of control subjects completed the 26-week treatment period in Study 302.
- **Primary efficacy endpoint:**
  - Pre-specified mixed model for repeated measures. Statistical models may not provide an accurate estimate of the treatment effect.
  - Cumulative responder analyses suggest numerical differences in efficacy between treatment groups.
- **Secondary efficacy endpoints:** No statistically significant differences between treatment groups in non-spirometric endpoints were seen in either study, but numerically the results sometimes favored DPM. Zhou said, "This statement may seem contradictory to what the company presented today."
- **Subgroup analyses** of the primary efficacy endpoint in pediatrics: In Study 301, numerical differences between treatment groups in the cumulative responder plots for the primary efficacy endpoint appear to be smaller in the 6-17 age group compared to that in the age 18-and-over group. The trend is not replicated in Study 302.

Statistical issues

Thomas Permutt, PhD, director of the FDA's Division of Biometrics II, CDER, told the panel that "the statistical issues here are crucial to the understanding of the drug, and it is appropriate to give you my perspective on it as well. Statisticians usually lay heavy status on the pre-specified analysis, and we do not have it here."

He summarized:

- Pre-specified analysis is insufficient.
- Effect in tolerators is important but difficult.
- Sensitivity analyses are persuasive.
- Effect is better described by a responder profile.

In an elegant, slightly rambling, professorial, and brilliant speech, Dr. Permutt said that the pre-specified analysis using mixed model for repeated measures, which is an average of available observations, is a "sound method but a wrong question…You want to find out what happened to your lost patients. That is not what we have here. We have a substantial arm of patients who were unable to tolerate the treatment. We know what happened; they stopped the treatment…More specifically, a patient who tolerates a drug up to the first visit and then has to discontinue contributes a good score to the analysis but has not had a good outcome…Most patients did tolerate the treatment, and we can ask how much the pulmonary function improved in the tolerators. This is what we want to know? I think it might be. This is not chemotherapy, where the question has to be: How did everybody do? You made a strong argument that what counts is what happens to people who tolerate it."

Dr. Permutt said that an analysis of completers would have to be compared to people in the control group, "but you can't figure out who in the control group is like the tolerators… Certain elements are excluded. So, in this case the pre-specified analysis on its own is not persuasive to us."

He said that the sensitivity analyses are important but include some with bad scores for dropouts, "We believe that the effect on FEV_1 is real but not large and probably overestimated by the primary analysis."

Dr. Permutt said, "What we would like to see…is an analysis that incorporates the good feature of the other analyses with the baseline that it does not impute benefit to the patients who might get better for a while and then drop out…We are confident that the sensitivity analyses taken as a whole support a positive result in Study 301…We do think that the effect on FEV_1, while not zero, is probably overstated – a smaller value, probably 15-16 ml…If you consider all the possible dichotomies, you actually get all the information back, and once you convince yourself that there is an effect, if you do that, it is that these curves are a very useful way of looking at what that effect is."

He showed a graph of all patients randomized in Study 301, and dropouts were on the left side of the curve, "If you look at 100 ml, about 35% of patients on active drug and about 28% patients on control had improvement of ≥100 ml FEV_1. It is a difference of about 7%. For every 100 patients treated, seven might have improvement of that magnitude attributable to the drug…You can see similar results at control, or 200 ml, or other values. There is uncertainty, which is difficult to portray in this type of graph…but we are reasonably confident that it is going in the right direction…Study 302, you see rather different-looking curves, and the FDA and applicant agree that the results are not statistically significant…They add weak support to 301 and tell a similar story."

Dr. Witzmann returned to summarize the FDA statistical team's presentation, review safety data, and give a risk: benefit assessment.

Efficacy findings

Dr. Witzmann said that in the sponsor's primary efficacy analysis, using the mixed model for repeated measures in a modified intent-to-treat population, Study 301 showed a statistically significant result but Study 302 did not. An additional sensitivity analysis conducted by the FDA was consistent with the company's results and "supports the idea that the positive results for 301 were not the result of how missing data were handled."

Dr. Witzmann asked, "How do we interpret these data?…The change with chronic use should be improved pulmonary outcome. That meaningful improvement should be reflected in other endpoints, such as fewer infections, hospitalizations, exacerbations, and better quality of life. In this light, Studies 301 and 302 showed positive trends but no significant changes in incidence or time to first pulmonary exacerbation, rescue antibiotic use, days in the hospital due to exacerbation, or quality of life scores. It may have been because the study length was only 26 weeks.

FEV_1 in the context of DPM for cystic fibrosis:

- Inhaled mannitol – not a bronchodilator
  - Facilitates airway clearance, and chronic use should result in improved pulmonary outcome.
- FEV_1
  - Measure for overall improved pulmonary function.
  - Meaningful improvement should be reflected in other endpoints, resulting in fewer infections, hospitalizations, exacerbations, and better quality of life.
  - Studies 301/302 numerical, but no significant changes.
    - **a.** Incidence or time to first pulmonary exacerbation.
    - **b.** Rescue antibiotic use.
    - **c.** Days in the hospital due to exacerbation.
    - **d.** Quality of life scores.

Regarding pediatric efficacy, for patients 6-17 years, in Study 301, there is little separation of the curve, suggesting a lack of effect for pediatric patients in the study, "So, Study 301, which showed statistical significance overall, does not show benefit for patients 6-17 years old."

Dr. Witzmann reviewed what is known from the two studies from a clinical perspective:

- Study 301
  - Missing data due to differential dropout (36% DPM and 27% control).
  - Primary analysis met statistical significance.
  - Sensitivity analyses – effect not due to chance alone. FEV_1 point estimates ranged from 59 to 83 ml.
- Study 302
  - Missing data not as problematic (17% DPM and 12% control).
  - Primary analysis does not meet usual standard for statistical significance (p=0.059).
  - Sensitivity analyses – FEV_1 point estimates range from 49 to 63 ml.
- Secondary endpoints: Sometimes numerically favors DPM, but not statistically significant.

- Pediatrics: Study 301 suggests a problem for efficacy in pediatrics; Study 302 cannot confirm. Study 302 failed to meet statistical significance: 49-63 ml.

Dr. Witzmann said, "Because of the small change and statistical significance in only one study, it is important to look at secondary endpoints. Sometimes they numerically favor DPM, but none reached statistical significance, so the secondary endpoints provide small support. Last, when we examine the pediatric efficacy data…there appears to be variability between results in each study, with 301 suggesting a lack of benefit and 302 suggesting similarity to the general population. [This] is concerning."

Safety

Dr. Witzmann said, "Overall, the exposure is reasonable for the disease. There were no deaths…The number of patients who discontinued for any reason and for an adverse event was higher in the DPM group. Discontinuation for any reason includes patient withdrawal for any reason, which they don't have to divulge."

Almost twice as many DPM patients withdrew due to adverse events vs. control. Tolerability of DPM was an issue even in the open-label part of the trials.

Dr. Witzmann described special safety concerns: bronchospasm, hemoptysis, and overall tolerability. She said that 10% of screened patients failed to complete their test doses, so they were not included in the intent-to-treat population. There was a slightly higher increase of symptoms vs. control in the studies. All patients were pretreated with a bronchodilator prior to treatment.

Pediatric patients

Dr. Witzmann said the number of patients with an adverse event leading to discontinuation was higher in the DPM group and double that of control (6% vs. 3%), "So, we see chronic tolerability issues in this group. The findings for hemoptysis were more pronounced in pediatrics…This is especially concerning given the expectation that these patients have better lung function. Looking at the age groups, the rate of any hemoptysis in pediatrics is four times that of control, and the risk of serious events with hemoptysis is twice that of control …Looking at the subgroups continues to show this disparity – with hemoptysis even in the youngest patients. The sponsor suggests that pediatric patients have lower baseline FEV_1… However, it is not a reasonable explanation for why the difference between treatment groups should be larger in younger patients than that in older subjects."

Safety summary:

- **Bronchospasm**
  - 10% of enrolled patients could not complete first dose (modified intent-to-treat).
  - Once randomized, little difference between DPM and control.
- **Hemoptysis**
  - Significant issue, twice as many serious adverse events vs. control.
- **Overall tolerability**
  - An issue if one can "pass" modified intent-to-treat.
  - Adverse events due to cough, throat pain, vomiting.

Risk:benefit

- **Benefit**
  - Study 301 positive, Study 302 negative/equivocal.
  - Missing data makes it difficult to estimate effect on FEV_1. Is the range of effect clinically meaningful?
  - Some secondary endpoints show numerical trend, but support not robust.
- **Risk**
  - Poorly tolerated by many patients.
  - Unable to complete initial dose.
  - Adverse events including cough, throat pain, hemoptysis, and vomiting.

For patients with severe lung disease (FEV_1<40% predicted), Dr. Witzmann said adverse events were similar to the general population except in two important areas – discontinuation due to adverse events occurred twice as often vs. control, and adverse events of hemoptysis occurred in 19% of severe lung disease patients vs. control.

PHARMAXIS PERSPECTIVE

Ron Dundore, PhD, vice president for U.S. regulatory affairs for Pharmaxis, said mannitol is generally recognized as safe. He said mannitol has been shown to improve airway clearance but noted that dry powder mannitol (DPM) has limitations of use: It has not been studied in patients with an FEV_1 <30% predicted or in patients with a history of recent significant hemoptysis. The risk:benefit in patients with FEV_1 <40% is not clearly established.

Felix Ratjen, MD, a pediatric pulmonologist from the University of Toronto Hospital for Sick Children and a Pharmaxis consultant, said that more options are needed for cystic fibrosis treatment. He told the panel that cystic fibrosis is a life-shortening genetic disease and cystic fibrosis patients have an estimated life expectancy of 38 years. It is a multi-organ disease, but 75% of all hospitalizations are caused by pulmonary morbidity. Lung disease is progressive, and lung function declines over time. Cystic fibrosis therapy's goal is to delay decline in lung function, but exacerbations and infections lead to lung function decline. Dr. Ratjen said there are many challenges of nebulized therapy: It takes a lot of time, it limits patients' mobility, requires setup and cleaning, and only a third of patients follow recommended cleaning procedures, leading to bacterial contamination of the devices.

Dr. Ratjen said that options that can be added to cystic fibrosis therapy include improving airway clearance by enhancing mucociliary clearance, and he argued that any incremental FEV_1 improvements are regarded as clinically meaningful.

Howard Fox, MD, chief medical officer at Pharmaxis, said that despite missing data, the Phase III Study 301 showed efficacy, and that despite the primary endpoint narrowing missing statistical significance in Phase III Study 302, there was "meaningful effect."

Dr. Fox said that the primary endpoint, significant improvement in lung function, was met in Study 301, with patients on DPM achieving an 83.1 ml change from baseline vs. control (p=0.001) over 26 weeks. For Study 302, the change from baseline was 54.1 ml vs. control, but it was not statistically significant, with a p-value of 0.059. However, Dr. Fox argued that the change was "clinically meaningful improvement."

Reasons for Withdrawal in Bronchitol Trials

Reason for withdrawal	DPM	Control
Study 301		
Subject withdrew consent	15.8%	18.6%
Adverse event	16.4%	9.3%
Physician decision	3.4%	0
Sponsor decision	0.6%	0
Other	0.6%	0
Total withdrawals	36.7%	28.0%
Study 302		
Subject withdrew consent	7.1%	5.8%
Adverse event	7.1%	4.1%
Physician decision	1.1%	0.8%
Other	0.5%	0.8%
Protocol violation	0.5%	0
Subject lost to follow-up	0.5%	0
Total	16.8%	11.6%

Dr. Fox argued that the FDA's dichotomous approach was "limited," saying that there is a large loss of power using that approach vs. the ANCOVA cystic fibrosis approach. Looking at DPM completers, he said, "[Although] we cannot use data using only completers…we acknowledge that DPM is not a treatment for all patients but cystic fibrosis treatment is highly individualized."

Dr. Fox concluded that DPM showed "meaningful and sustained" FEV_1 improvements in both studies, which also showed trends in exacerbation reduction, forced vital capacity, and sputum weight evidence, and a clinically meaningful benefit.

Brett Charlton, MBBS, PhD, Pharmaxis medical director, told the panel that DPM is safe, with most adverse events being those of tolerability. He said hemoptysis will be addressed in label and post-approval. The company's risk management plan includes distribution through specialty cystic fibrosis pharmacies, training for physicians including guidance for minimizing and managing hemoptysis, and a registry for gathering hemoptysis data and assessing ongoing risk.

Dr. Charlton said that hemoptysis is a "common event" in cystic fibrosis patients, "Events are usually mild…Incidence is reported to increase with disease severity and age."

He said the company agrees with the FDA that hemoptysis is associated with patients aged 6-17 years. Of the hemoptysis episodes in patients in that age group, he said it was reported as mild/moderate in 10-12 patients. There were three serious adverse events, including one massive hemoptysis. Dr. Charlton said the incidence of massive hemoptysis, based on the registry data, is expected to be 0.4% to 1.4%, "All in all, there were very few events. So, there is a signal for increased hemoptysis on DPM, and it is more in the 6- to 17-year age group…We are proposing guidelines for physicians in the

Serious Adverse Events in Bronchitol Phase III Trials

Serious adverse event	DPM n=361	Control n=239
≥1 serious adverse event	21.3%	27.2%
Condition aggravated	16.6%	18.8%
Lower respiratory tract infection	1.1%	2.1%
Discontinuations due to serious adverse events		
Any	11.4%	6.3%
Cough	5.0%	2.5%
Condition aggravated	2.2%	1.3%
Hemoptysis	1.7%	0
Severity of hemoptysis adverse events		
Mild	52.5%	76.9%
Moderate	37.5%	15.4%
Severe	10.0%	7.7%

labeling…It would include withholding DPM in the event of massive hemoptysis. There would also be a limitation for patients with FEV_1 ≤40%."

Patrick Flume, MD, a pulmonologist from the Medical University of South Carolina and a Pharmaxis consultant, told the panel, "We need therapies that address the physiology farther upstream…When I look at a new medication for my patients, there are three questions I ask: What is the efficacy, what is the safety profile, and how will I introduce the therapy into my patient's current regimen…We need options for our patients."

Dr. Flume said, "I feel comfortable that DPM shows efficacy." He added that he believes DPM is comparable to other cystic fibrosis treatments.

Looking at safety, particularly bronchospasm and hemoptysis, Dr. Flume said, "For me, the risk of bronchospasm is not a major concern and remains manageable." As for hemoptysis, he said, "It is a sign of pulmonary exacerbation…and the overall DPM rate is not higher than what we usually see in our practice."

He also said the rate of massive hemoptysis is similar to the existing registry data,"Physicians see hemoptysis as a sign of exacerbation and treat it as such."

As for a hemoptysis signal in younger patients, Dr. Flume said, "There is a signal…The children who had hemoptysis also had severe lung disease…These children had more than we usually see in our patient population. No patients withdrew from the trial as a result of a hemoptysis event. So, knowing all this information, how do I weigh the risk:benefit? Pediatric patients should have the opportunity to achieve better lung function, and I believe that outweighs the risk."

Dr. Flume concluded, "When you look at the totality of the evidence for DPM, it improves lung function and reduces the frequency of pulmonary exacerbations. The overall safety profile is acceptable to me…Treating physicians know how to monitor massive hemoptysis if it should occur."

PANEL QUESTIONS FOR THE COMPANY AND THE FDA

Asked what the dose was in the tolerance test, Dr. Fox said that it was 400 mg.

David Jacoby, MD, a pulmonologist from Oregon Health and Science University and the panel chair, asked how the capsules were given, "I'm assuming not everyone reached the 400 mg; is that correct?" Dr. Fox replied, "That is correct."

Screening

Dr. Jacoby asked, "It looks from the data that…one might be concerned about…people being treated without appropriate screening…And so, how bad can this be? There is 25% who failed, and it was at different doses, not all 400 mg. So, perhaps anecdotally, what is the worst reaction, the worst-case scenario." Pharmaxis' Dr. Charlton responded, "We have a lot of experience with Aridol [Pharmaxis' lung function test]. It is fairly quickly reversible. The worst was 53%, and that was a patient who recovered in 30 minutes with bronchodilator. In the Phase II program, they screened with a higher dose – 74 were screened with a 635 mg dose without a pre-bronchodilator, and the largest fall was 25%. Six had falls greater than 20%."

Panel member Jeff Wagener, MD, a retired pediatrician from the University of Colorado Medical School, asked if they looked at the patients who had a 10% fall, and Dr. Charlton said, "We looked at bronchoconstriction events…and we saw that falls 10% or greater were split 50/50 between DPM and control."

Pre-treatment

Panel member Robert Castile, MD, a pediatric pulmonologist from Nationwide Children's Hospital and Ohio State University, asked who was pretreated and how long after pretreatment was the first dose given, "For testing, going forward, we are going to need that data." Dr. Charlton said that a short-acting beta-agonist was given 5-15 minutes before mannitol or control. The default was four puffs of albuterol.

- *Dr. Castile:* "Why did you pick 20% as a drop? Generally…we think about 10%-12% change being a significant change. I, as a clinician, was concerned about giving a patient a drug that produced a 20% drop in lung function twice a day or between a 10%-20% drop…My further thought is: Those patients in the 10%-20% range, were they the ones who dropped out, had more adverse events, or had no improvement? The cutoff seems high to me."

- *Pharmaxis' Dr. Fox:* "The drop in FEV_1 after drug administration despite having pre-dose albuterol is a very temporary drop, and it normalizes within half an hour… That's an important distinction. We did look at patients… Are the patients who were more twitchy during their tests, are they more likely to have adverse events going forward? And their adverse event rate was the same as the others… We also did not see any predictors of who would respond."
- *Diana Bilton, MD, a consultant to Pharmaxis from Royal Brompton Hospital in London who treats 600 cystic fibrosis patients:* "The threshold of 20% is a standard one in cystic fibrosis practice …We stick at 20% as a safety limit, and some of the patients in my clinical experience now in Europe using this drug will have drops that are asymptomatic, and we discuss with them that 20% is our safety threshold. I feel comfortable with 20%, and, of course, it has to be reversible as you sit with the patient."
- *Dr. Castile:* "Do you have concerns about starting the drug in patients with asthma?…Do you screen those patients?"
- *Dr. Bilton:* "The difficulty with cystic fibrosis is that there is a lot of patient variability…Although a patient may pass the mannitol tolerance test, there may be events. But I haven't seen this, and the Australian experience is similar. The test selects out the patients who do not get the treatment."
- *Dr. Fox:* "Asthmatic patients were not excluded from these studies…and there were more numerically in the DPM arm."

Panel member James Tracy, DO, an allergist from Omaha NE, asked whether they ever saw patients who forget to premedicate with albuterol, and Dr. Bilton said, "They are likely to miss something on a busy day. I haven't had a patient say they forgot their albuterol and then felt terrible, but, in my clinical practice, we haven't had a bronchospasm, and my Australian colleagues have not had people collapsing because of bronchospasm because of that issue."

Dropouts

Panel member Kathryn Blake, PharmD, a senior research scientist at Nemours Children's Clinic in Jacksonville FL, asked what happened to the patients who did not reach six weeks, "I'm trying to get a way to maybe better pick patients…and I want to tie it in to pediatric patients…They are more likely to take the drug twice a day because the parent will give it to them…For them, can we come up with a better way to predict who will not tolerate it well?"

- *Pharmaxis' Dr. Fox:* "The test itself is very effective."
- *Dr. Blake:* "Do you recommend that they hydrate well before taking? And are drugs taken in a certain order?"
- *Pharmaxis consultant Dr. Bilton:* "We did learn from the U.K. and European experience…that talking with the patients about having a drink before using the inhaler, getting the flow rate right – if they do it too fast, they cough a lot more than they need to…I feel that is a reason why the withdrawal rate is different across the two studies."

Panel member Peter Terry, MD, a pulmonologist from Johns Hopkins University, noted that a significant number of patients had improvement in their FEV_1 but still withdrew. Dr. Fox said, "It would be a good idea to look at those specific patients."

Post-exposure data

Dr. Wagener asked if there were post-exposure data.

- *Dr. Fox:* "We looked at post-exposure to the drug, and we looked to see how patients reacted to albuterol afterwards."
- *Dr. Charlton:* "The proportion of patients improving from visit 1-3 was more than 50%…1.4% of patients had a 20% or more fall on one occasion vs. 0.4% patients on control."
- *The FDA's Dr. Durmowicz interjected:* "The bar for a positive tolerance test after albuterol is -20%. It is notable that the test of bronchial reactivity is -15%, so it is less. The other issue, and Dr. Blake alluded to it: Once you get past the tolerance test, you aren't out of the woods. And you can see that by the great number of differential dropouts throughout the whole program compared to control. That is a tolerability issue and in some ways a safety issue…But the issue, and we discussed it in the efficacy section, is that it messes around with the efficacy combination, and that is why we are doing all these sensitivity analyses…Regardless, all these differential dropouts create a population that is different – the population of patients screened out over 26 weeks are all the non-tolerators. These people have lead pipes for airways, and they are going to tolerate it. You are comparing to a control group in which you don't know who might be a responder and who might not be…and that is not addressed by the sensitivity analysis, as far as I know."
- *Dr. Wagener:* "You don't say whether you stopped the drug. You don't want to overburden your patient if it doesn't work."
- *Dr. Bilton:* "Yes, we would stop the drug."

Statistical analysis of responders

Panel member Amy Herring, ScD, a biostatistician from the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill, asked if there was a statistical analysis that could be used to determine responders, "You might be able to use some of the data from your challenge test. You have some nice data there that could be used for that purpose…Then I'd like to ask some questions about the analysis subset. That population is problematic…and it seems to be due to exacerbations…So, it is leaving you with a healthier subset in the DPM group…And, so, you really need to keep that initial population. As far as I can tell, there are two important issues that I don't see handled simultaneously that I'd like to see…There are other models in the literature, and I wonder if you used any of those."

- *Pharmaxis' Dr. Fox:* "I acknowledge what you are saying – that we can't know what the patients are doing. All I know is that based on their last FEV_1, it seems very unlikely that all these patients have worsened…It seems reasonable to think that a simple approach like baseline carried forward seems a reasonable thing to do."
- *Dr. Herring:* "You can predict…only on the data you see. We can't see what happens when they disappear. So, a plot like this could never be used to rule out missing at random …Now, about that observation carried forward…I agree that it is a conservative approach…but the key line will be too small because it doesn't take into account variance."

Hemoptysis in children

Rodney Mullins, the national director of Public Health Consultants and Advocates in Duluth GA and the panel's consumer representative, asked about the incidence of hemoptysis in children.

- *Pharmaxis' Dr. Flume:* "We know a lot about hemoptysis in cystic fibrosis patients. It is a common event associated with more Stage 1 patients, and in terms of cataloging the frequency of those events, there are very few publications looking at this. A review from an Israeli center looked at 44 patients with hemoptysis, and 44% of them were under age 13…There are no clinical trials looking at how to measure hemoptysis. They don't exist. But we were able to generate what to do when it happens." He said hemoptysis occurred in 10.4% of children 6-17 years old vs. 7.6% in control.
- *Mullins:* "It just seemed rather high vs. control."
- *Dr. Flume:* "Ten percent, to me, for a mild complication is an acceptable risk."

Mullins asked about efficacy for the 6- to 17-year-old subgroup, and Dr. Fox showed the pooled Phase III data, "The adolescent group seems to have a lesser effect (vs. adults). There may be something going on in the adolescent population."

Indication to begin treatment

Panel member Richard Parad, MD, a neonatologist from Harvard Medical School and Brigham and Women's Hospital, asked what the indication is for starting the drug and in what order, compared to other drugs. Regarding children, he said, "It's a broad age range and not a great number of patients. Young children are different from older cystic fibrosis patients – 80 ml to me means a different thing to a 15 year old than to a 4 year old. Do you have the data broken down by age? At least below the adolescents? And lastly, do you have data either from those who went to open-label after 26 weeks or retested after the 52-week period? What effect persisted, or what was the decline after stopping the drug?"

- *Dr. Fox:* "In terms of the open-label data, we don't have data of what happens when patients discontinue, so do they go back to baseline or not?"
- *Dr. Parad:* "It was not a large number of children," looking at the percentage change and percentage of predicted data.
- *Panel member Dr. Blake:* "Going back to children, parents of very young children under the age of 11 are very motivated, so I think that monitoring will be important. Your plan for proposed questionnaires falls a bit short, and in this electronic age you really have a duty to collect all the information you can, from the parents as well [as physicians], and that would be more robust."
- *Dr. Fox:* "One thing about the cystic fibrosis database is that data are collected on every visit."

Secondary endpoints

Asked why secondary endpoints were not delineated from the start for the Phase III studies, the FDA's Dr. Durmowicz said, "Back in 2005, we told the sponsor what was required for different endpoints. An exacerbation endpoint would require a study of at least a year. We didn't select the endpoints for the sponsor; we gave them requirements, and they selected them, including the absolute change vs. predicted change. In 2005, since FEV_1 is not a bronchodilator and would be reflective of longer-term, clinically meaningful endpoints, we told them they need robust support from secondary endpoints…They are not powered for every endpoint that they could have. But especially for 301, they didn't specify any secondary endpoints…show not favorable light on the FEV_1. That alone is really supporting benefit in that trial. That is the general framework we were operating under."

Sensitivity analysis

Panel member Paul Greenberger, MD, an allergist/immunologist from Northwestern University Feinberg School of Medicine, asked about the sensitivity analysis, and the FDA's Dr. Permutt said, "About 35% of people in the active group had response in Study 301, and only 28% in control had such a response (100 ml), so our best estimate of number needed to treat is about 14, but there is some difference in the number of responders in active compared to control. In Study 302, they are about equally apart at 100. The separation at 100, where the vertical line is, is about the same, a little more – 35 ml or so."

PUBLIC SPEAKERS

All nine public speakers urged the panel to recommend approval of dry powder mannitol (DPM), saying that it fills an unmet need and that physicians need as many tools as possible to manage cystic fibrosis.

Carroll Jenkins, executive director of the non-profit Cystic Fibrosis Research and the mother of a 38-year-old cystic fibrosis patient, told the panel that her son Alex spends four hours a day treating his disease. She said that mucus is extremely thick in cystic fibrosis patients, "Any drug that can help the patient clear the mucus will give a better quality of life…Physicians should have all the available armaments in their toolbox…Right now, there are very few products for mucillary clearance…We need more options now."

Emily Schaller, a 30 year old with cystic fibrosis and founder of the non-profit Rock CF Foundation, said she was diagnosed in 1983, when her parents were told that she probably wouldn't live past high school. She said she is alive because of new cystic fibrosis treatments, "These drugs are great that I take, but I spend hours a day taking these drugs …I couldn't be more excited when I heard about this drug and its potential."

Moira Aitken, MD, the principal investigator in the Bronchitol Study 302, said she was speaking on her patients' behalf and not on behalf of the company. She said she wanted to stress the burden of care that cystic fibrosis patients have, explaining that pulmonary therapy takes up to 180 minutes day. She told the panel that during the open-label phase of the study, all the patients at her site taking mannitol were clinically improved. She showed photos of three of her patients, who told her that mannitol "really cleaned [them] out."

Michael Boyle, MD, who runs the Johns Hopkins adult cystic fibrosis program, which has ~300 adults enrolled, asked the panel to recommend approval of the drug, saying there haven't been many developments in the last 10 years with regard to lung clearance. He added that hypertonic saline is his patients' least favorite drug because it is hard to tolerate, it burns, and it takes too long to deliver. He said prescriptions are filled only 40% of the time. Dr. Boyle said that physicians are going to use Bronchitol to treat patients who have low tolerance for hypertonic saline, "This is the type of drug where we can find some efficacy, find the right subgroup; it will empower them."

Bruce Marshall, MD, vice president of clinical affairs for the Cystic Fibrosis Foundation, spoke of the treatment burden for cystic fibrosis patients and noted the advantage that DPM might have over hypertonic saline.

Jerry Cahill, a 56-year-old cystic fibrosis patient on disability, said he is one of the fortunate ones to be living and breathing at his age. He had a double lung transplant nine years ago, "I was basically drowning in my own mucus… People with cystic fibrosis need more drug therapies…If you can spend less time on therapies and more time living life, that's a blessing."

Ahmet Uluer, DO, a pulmonologist and director of the adult cystic fibrosis program at Brigham and Women's Hospital and Boston Children's Hospital Cystic Fibrosis Center, where 600 patients are treated, told the panel, "Every day we look in our patients' eyes, and we try to think what else we have for our patients, and I think this fills an unmet need…If an option exists…that may reduce their treatment burden, we would be in favor of that…And it would be a welcome addition." He added that a simple-to-use and easy-to-store treatment would be an improvement over current therapies.

Ronnie Sharpe, a 32-year-old cystic fibrosis patient, calling himself the chief community servant at Cysticlife.org, told the panel that new medications allowed him to still be alive, "Decades older than the expiration date given to my mom when I was born…Current medications aren't enough… As a community, we need more…Options are important… One thing that you can bless me with today is more time."

Emily Grumbine, a 32 year old with cystic fibrosis, said she is taking DPM through the compassionate use program and it has improved her life. She said that in 2009 she participated in a clinical trial. In the open-label part, she said, "I was blown

away by how much mucus I was able to cough up [on treatment]…Three minutes, twice a day, [compared to] 10-20 minutes is what I am used to with hypertonic saline." The day she took her first dose of DPM on the compassionate use program in February 2012 "was the happiest day of my life…It is so much more effective than hypertonic saline was for me… Because of mannitol, I was able to run a 10K in August, and I'm able to sing in church choir every week without having a coughing attack…I have stable lung function and have been able to maintain my lung function this past year."

PANEL DISCUSSION

Before the vote, the panel was divided. Some panel members argued that the FDA standards on the definition of efficacy (two studies meeting primary endpoints) should be set aside – one suggested "updating" the standards – in the case of this drug, and some thinking they can restrict the drug's use (i.e., to children under 18) in the labeling. Some members argued that a 1%-2% improvement in FEV_1 could be considered efficacy, but the statisticians flatly said that the data were not good enough.

It is interesting to note that a U.K. clinician hypothesized that the incidences of hemoptysis may be due to the sheer force of mucus being coughed up as a result of the drug, calling it a possible "benefit." Panel member Dr. Wagener pounced on that, warning that a chronic irritant could cause tremendous injury, especially to children with growing airways.

The discussion grew contentious when the FDA's Dr. Durmowicz rebutted statements made by the company, including exacerbation claims. It was clear that the FDA team had had many discussions with the company and had been rebuffed all along, and they were not allowing the company to make claims that weren't backed with evidence. The panel chair, on the other hand, continued to let the company stand up and present its data.

Dr. Durmowicz said, "The big question for us is: Is there substantial evidence for efficacy? There are compounding factors including the impact of missing data/differential dropout, sensitivity analyses suggesting a range of effect on FEV_1, and clinical relevance of treatment effect. Also, are there sufficient data [to demonstrate]…acceptable safety in the pediatric population?" He brought up the Efficacy Standard, which says that the drug must have "substantial evidence consisting of adequate and well controlled investigations."

Referring to the standard as "regulator-ese," Dr. Durmowicz continued, "But what does that mean? It means that you need replicate, well-designed, well-controlled studies demonstrating an efficacy finding. This means two studies, with an appropriate endpoint, both winning statistically and clinically. One positive study does not meet that bar. However, there are times when one study can suffice. A excellently designed, multicenter study showing highly reliable, statistically strong evidence on an important clinical benefit, such as survival, can suffice. Or, a single study demonstrating statistically and clinically meaningful benefit in multiple, unrelated, pre-specified endpoints. One example is the cystic fibrosis drug ivacaftor [Vertex Pharmaceuticals' Kalydeco]. That would be an example of the type of study you would need to fit into that category."

Dr. Durmowicz laid out the safety standard and then described the risk:benefit, "It is noted that cystic fibrosis is a serious, fatal disease. What are the acceptable risks for benefit? But we still need to meet that substantial evidence of efficacy bar, and that is true for all drugs, including orphan disease."

FDA QUESTIONS FOR THE COMMITTEE

QUESTION 1. Discuss. 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.

Panel member comments included:

- *Dr. Wagener, pediatrician:* "I would prefer if we separated the above 18 and below 18, but having taken care of more than 1,000 cystic fibrosis patients in my career, I can certainly understand the statements of [the public speakers]. At the same time, approval is based on statistical evidence of efficacy, and if we follow that thought, there is nothing that will meet those guidelines. However, there may be a few things that are different with this drug. There is no FDA-approved drug that works in this fashion…So, this would really be a first drug in class. My question is whether that may change what you define as statistically proven efficacy. The second thing is that this drug has some unique properties in its evaluation in that it creates a side effect in that patients will discontinue the drug because of that side effect. We assume that the 10% dropout rate is that side effect. In the case of adults, I don't find that as a big problem…But in this situation, perhaps the evaluation of just the patients who stayed in the trial makes it different…I think there is evidence of efficacy. It may not be based on some of the statistics that we have used historically, but here you have a life-threatening disease…I would be willing to stretch the definition of efficacy beyond the pure statistics, which I admire, but I think you have to go one step further in this case."

- *Consumer rep:* "From the standpoint of public health…What do they deserve? Do they deserve something, or do they deserve something safe? I have concerns about efficacy and safety. Once a drug is approved and has a high level of toxicity, and there are indications of intolerance, and there are indications of serious concern about exacerbations and adverse effects, once they are out there, they are out there …The public believes that when we say safe, they believe it is safe…Decisions we make here should take into account a group of patients who are desperate…Saying that we are almost there or yes later but not right now is something we should consider. To make a decision on desperation, just to do something – we have done that in the past, and some of those decisions have come back to haunt you. To take that sense of desperation and prey upon them, I would say to you that we have a significant responsibility, and rather than lower the bar, I would raise the bar."
- *Dr. Greenberger, allergist/immunologist:* "I think it might be time for the Agency and industry to take a look at the 1998 standards we just saw and perhaps bring them up to date."
- *Dr. Parad, neonatologist:* "This is my first panel experience… and there appears to be efficacy with some patients, [but] I don't have a good sense that if [what] Mr. Mullins says is true, how does this labeling control that? What could we put in the labeling that might channel the use of the drug?"
- *The FDA's Dr. Durmowicz:* "The intended use is the indication. So, even if you think that it's good for adults and bad for children, that is the indication proposed for use right now. There is a caveat there that you could say, 'I think it's good for adults but not for children.'…There are warnings and precautions, contraindications, and they can be modified and made more appropriate…We, on purpose, do not want to go into labeling too much today, although we would like to hear your suggestions…But the first bar is the indication, and if you think it could be used safely regarding contra-indications or something like that, then we would like to hear from you."
- *Badrul Chowdhury, MD, PhD, director of the FDA's Division of Pulmonary, Allergy, and Rheumatology Products, CDER, interjected:* "There is no specific limitation [in the indication]… We need to look at substantial evidence, meaning, in most situations, replicated [studies]. For efficacy, you go back to a (historical) standard…Do you have confidence that it improves FEV_1?"
- *Dr. Blake, research scientist:* "In looking at the regulatory requirements that you have two trials that meet the primary endpoint, the first one does and the second one doesn't, but looking at them, they are very close…I wonder if one of the countries affected the outcome of Trial 302?"
- *The FDA's Zhou:* "I don't believe that one country would have pulled the study down."
- *Dr. Herring, biostatistician:* "Study 301 was a study with a very small p-value – no patients for the U.S. and no difference in the children…And then the study that followed, 302, they learned they did not have missing data but [it] was not statistically significant. To me, the results are really mixed. I'd love the sponsor to find a group that it helps…I would love to see that study, that population found, and if so, I would be very supportive."
- *Consumer rep:* "I would feel much better about saying yes if, rather than the presentation against a panacea, that there was a profile of efficacy…Children will be forced to take it… and it concerns me."
- *Michelle Harkins, MD, a pulmonologist from the University of New Mexico*: "It was underwhelming data for efficacy…and it would have been nice if there were efficacy in both studies."
- *Consumer rep:* "All of our children do not have cystic fibrosis centers, and they would be very vulnerable…That's why our assessments have to take into consideration that."
- *Dr. Tracy, allergist:* "I practice in a rural state, and they don't go every day, but they do get to a cystic fibrosis center very often. And we take care of people, not statistics…That said, the data are not particularly overwhelming."
- *John Connett, PhD, a biostatistician from the University of Minnesota:* "The data are weak. I think approving the drug on weak evidence for a surrogate…Analyses could have been done that were not here."
- *Dr. Castile, pediatric pulmonologist:* "There is a borderline effect on FEV_1 that is in the 2%-4% rate…Beyond that there is no evidence at all of the clinical effect. In the data there is a suggestion, a significant subset that may benefit from the drug, and what I gleaned from looking at all the data is that the subset may have an FEV_1 between 40 and 70 in adults… So, it is quite a dilemma. You want to provide that kind of therapy, and the testimony from the public who were adults with cystic fibrosis and doctors, and they have the sense it works…So, I have quite a dilemma…I don't see it in my patients, but if I did, I'd want the option."
- *Dr. Parad:* "I concur with Dr. Castile about the efficacy issue…If you are just looking for p-values, it is not the whole story, and looking at effect size, it is not the whole story…The cystic fibrosis story over the last years are incremental improvements…Personally, I would say a 2%-5% increase in FEV_1 doesn't sound like a big effect size, but adding it to the other things may make a significant difference to some patients…We have to agree on how we define

efficacy. I wonder if that degree of FEV_1 is a good definition."

- *Dr. Wagener:* "One approach is 'anything is better than nothing,' in which case a 1 mm would be considered acceptable. Conversely, I would argue that adding something if it has no burden, that may be true, but everything we do – we heard that it has less burden than hypertonic saline, but we may add more burden…And if you do that, then you have lost. That is where the risk is in accepting very small steps, because you could be doing worse."
- *Dr. Castile:* "The company tested it on a very broad population, and this is no longer a virgin population – 50%-70% were already on something. So, a 2%-4% increase…If the improvement were between 7% and 10%, I don't think it's likely if you take that non-virgin population and add a hydrating agent. The problem I have is with the breadth of the study and what subpopulation it really helps the most."
- *The FDA's Dr. Durmowicz:* "Given the issues with dropout and the data itself, the subpopulations you want to know most about are the population of tolerators taking the control medication. You would have to give the test, put everyone on the drug for a period of time, define the tolerators, and then randomize to drug or control. That would be the comparative group."

QUESTION 2. Discuss. Discuss the overall safety profile of DPM.

Asked by the consumer rep about the hemoptysis signal, Pharmaxis' Dr. Fox answered, "We recognize this as a signal, particularly in children, and we take the signal very seriously. What we do not know is the size of the risk and if it is manageable." Pharmaxis consultant Dr. Ratjen said that hemoptysis is rare, "These episodes were transient; they did not lead to long-term problems with these patients…So, that is the question of the risk vs. the benefit. I, as a clinician, would say that the risk is acceptable for the potential benefit."

- *Consumer rep:* "When you look at the data, the clarity of the adverse events is very pronounced; the clarity of the benefits, as it speaks to efficacy, is quite vague. But when we talk about hemoptysis and several other issues related to the toxicity of this treatment, it is very pronounced; there is no lack of clarity there. If the benefits were so pronounced and clear to me and my peers, there would be an overwhelming gesture of support for this therapy, but that is where I have this consternation. If we put the population at risk with this therapy, where is the win for them?"
- *Dr. Ratjen:* "Patients with cystic fibrosis – the overwhelming majority – are being cared for by experts."

The FDA's Dr. Witzmann said there were serious adverse events in the DPM patients, "There is a difference in that group, and the patients were all randomized. These patients in the pediatric group…had episodes of hemoptysis. However, the pediatric group was randomized; therefore, there is still an increased number of patients in the DPM who had episodes of hemoptysis vs. control. This was not the analysis interpreting reported by the investigators as adverse events…Even when you take that number of patients who may be having an exacerbation and also had hemoptysis, there was still a number greater in the pediatric population than the control population." Pharmaxis' Dr. Charlton said some patients were hospitalized for exacerbations.

Panel member Dr. Tracy, an allergist, asked what the company thought about hemoptysis in children, and Pharmaxis consultant Dr. Bilton said, "People with cystic fibrosis come into my clinic, and they want to know what it is when they cough up blood. There is a signal here in children that we need to take seriously…I think that it relates to getting up a lot of thick sputum and thick structures, and I wonder if, [as] they are coughing that up, they are exposing a grazed airway…The majority were not recurrent. Clearly, we need to clear this up. A registry would be good, but I'm thinking that it might be due from coughing the mucus up. So, it might be part of the efficacy…With children you have to be careful, but that is one of my theories."

- *Dr. Wagener, pediatrician:* "I find the issue of safety to be the biggest thing…With hemoptysis, it is a relatively uncommon thing with children…So, that's one thing…The second is a longer-term question of safety. Since these studies were just six months long and even the extension study I don't know how long it has gone on, a chronic irritant may create chronic injury to the airway, particularly on children with a growing airway. I would worry that if approved, this will not just be limited to the severe lung disease patient, it will be used in all degrees of lung disease, and people will interpret it the opposite of what we are…If there is a long-term adverse effect creating inflammation, then we are going to be creating a real problem that we won't recognize for a few years."
- *Dr. Greenberger, allergist/immunologist:* "My question is on safety from the eight sites in Argentina, with an excessive number of safety findings there. The efficacy data did not coincide with the others around the world."
- *Pharmaxis' Dr. Fox* said that he didn't have specific safety data by country, but he asked Dr. Ratjen to speak about his experience in South America. Dr. Ratjen said, "The overall level of care in Argentina is different from North America. The outcome of those patients is much less favorable than it is in North America."

- *Consumer rep:* "I would caution against shifting the burden of safety to the consumer. There is a lot of discussion about if you live near a cystic fibrosis center or have the luxury of the care by my colleague Dr. Tracy…There are a lot of people in America. We are struggling…Our ability to give them something where that burden is not shifted on them."

Pharmaxis' Dr. Flume referred again to the Israeli paper looking at hemoptysis in cystic fibrosis patients. He said that 25% of those patients were under the age of 13. Dr. Witzmann responded, saying that some of the data were skewed.

- *Dr. Greenberger:* "Severe acute hemoptysis – can someone tell me how many patients had to have bronchoscopies because of it?"
- *Pharmaxis' Dr. Charlton:* "Two had medical treatment out of 16. None was hospitalized because of hemoptysis, three were hospitalized with antibiotics to treat the exacerbation. This group of children and adolescents represent probably less than half of what you would normally see in the clinic."
- *The FDA's Dr. Durmowicz sharply reacted, almost scolding Dr. Charlton:* "You can't say that nobody was hospitalized due to hemoptysis – because that is part of the definition of exacerbation. So, I don't buy that comment, I'm sorry." Dr. Charlton shrugged his shoulders.

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

Comments included:

- *Dr. Wagener, pediatrician:* "I was told that you can't divide by zero. So, in this subpopulation, you cannot find benefit in the under 18 year olds, so if there is any risk, it is there."
- *Dr. Ratjen showed the pooled 6- to 17-year-old subgroup:* "There is not a significant effect…but the totality of the data all go in the same direction of benefit…There is not an indication that there is less efficacy with the drug in children."
- *Dr. Terry, pulmonologist:* "You are using FEV_1 as a surrogate for efficacy, and I would argue that there is no evidence that the quality of these people's lives is improved."
- *Pharmaxis consultant Dr. Flume:* "When you look at all the endpoints, FEV_1 is the one we use in the clinic; it is monitored very closely, so you can carve that several ways…I want to comment about exacerbations…Keeping in mind the study wasn't powered to measure exacerbations…what you see is a clear signal in where we are going with exacerbations."
- *The FDA's Dr. Durmowicz, again responding sharply, almost exasperatedly:* "We don't think that you can make anything of the exacerbation data. We told the company that you need one-year data for exacerbations. Secondly, you don't pool exacerbations. Thirdly, the exacerbation data suffer the same issues as the general data. So, I don't believe that there is any benefit shown in exacerbations in this clinical program, although you can show some nominal changes."
- *Pharmaxis' Dr. Fox, continuing to argue:* "Reductions for less than 50% are still considered meaningful."
- *Pharmaxis' Dr. Flume:* "When we talk about exacerbation, in a U.S. population last year, that is 20,000 events – 20,000 admissions for antibiotics…So, when you start talking about reductions in that, is a 20% reduction relevant? In our patient population, that is a big difference."

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

VOTE: 3 Yes, 11 No

The Yes votes were Dr. Harkins, a pulmonologist; Dr. Parad, a neonatologist; and Dr. Wagener, a pediatrician.

Panel member comments included:

- *Dr. Herring, biostatistician:* "I voted no. The sponsor does not meet the standard for efficacy. It has not shown the drug is effective in children and adolescents."
- *Dr. Tracy, allergist:* "I agree about the comments on lack of evidence. There is no doubt that a subset will benefit greatly from this drug; we don't know who they are."
- *Dr. Greenberger, allergist/immunologist:* "There is a huge unmet need. However, based on regulatory standards, the data did not support substantial evidence."
- *Dr. Terry, pulmonologist:* "I voted no for the same reasons as Dr. Herring."
- *Panel chair:* "The evidence did not meet the standards for approval."
- *Dr. Blake, research scientist:* "I voted no. If we had been given the opportunity to vote for adults, I would have voted for that."
- *Dr. Connett, biostatistician:* "It was interesting that the first trial had poor follow-up rates and missing data yet positive signal. The second trial some improved, but the efficacy

went away. I couldn't go with the complete range [of ages]."

- *Dr. Harkins, pulmonologist:* "I voted yes because of the unmet need."
- *Dr. Wagener, pediatrician:* "Using the modified intent-to-treat approach in 301 supported efficacy. The FDA review somewhat supported efficacy for adults but not for children."
- *Dr. Parad, neonatologist:* "I voted yes. I wanted to answer a different question. I believe Study 301 showed overall effect, and Study 302 is marginal. I don't see this for children, but I would accept 2%-4% efficacy in adults."
- *Dr. Castile, pediatric pulmonologist:* "The FEV_1 data were borderline, and there was no supporting clinical evidence."
- *Mary Cataletto, MD, a pediatric pulmonologist from Winthrop University Hospital in Mineola NY:* "I was very impressed by the clinical anecdotes from the public and the cystic fibrosis centers, but the data didn't merit."

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

VOTE: 3 Yes, 11 No

The Yes votes were different this time – Dr. Greenberger, an allergist/immunologist; Dr. Herring, a biostatistician; and Dr. Tracy, an allergist.

Panel member comments included:

- *Dr. Castile, pediatric pulmonologist:* "The data showed an increased risk in hemoptysis, which is not explained yet."
- *Dr. Parad, neonatologist:* "I would have voted yes for 18 and above, but more investigation is needed."
- *Dr. Wagener, pediatrician:* "In reviewing the animal data, there is need for a longer-term study."
- *Dr. Harkins, pulmonologist:* "I voted no solely for the pediatric signal in hemoptysis, and it should be monitored longer term, but I would not have a problem in the adult population."
- *Dr. Connett, biostatistician:* "I voted no for the hemoptysis, but to me it looked as if it occurred more in people with low FEV_1.
- *Dr. Blake, research scientist:* "This is a new drug class for children; we have to be especially careful."
- *Dr. Terry, pulmonologist:* "There was insufficient evidence."
- *Dr. Greenberger, allergist/immunologist:* "I voted yes. I thought there was sufficient weight of evidence to understand the safety profiling."
- *Consumer rep:* "My vote is based on concerns with the lack of probability and the dropout rate, and I was looking for some understanding of those who dropped out and the overall high occurrence of hemoptysis."
- *Dr. Tracy, allergist:* "I voted yes. I thought there was sufficient evidence looking at the regulatory requirements."
- *Dr. Herring, biostatistician:* "I also voted yes. While I have concerns about the children, it didn't include any irreversible adverse events."

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

VOTE: Unanimously No (14-0)

Everyone said they voted No for the same reasons they gave on the other voting questions. Specific panel member comments included:

- *Dr. Blake, research scientist:* "I was very moved by the stories from the patients and clinicians. I believe it has a place for adults, and I voted no because of the pediatric safety concerns."
- *Dr. Connett, biostatistician:* "I wish I could have voted yes. There is a need for the drug."
- *Dr. Harkins, pulmonologist:* "I had a split vote, so I had to vote no. It is an unmet need. I feel confident in the adult population."
- *Dr. Wagener, pediatrician:* "If it were just for adults, it could be reasonably approved, but we need more study in children, particularly long term."
- *Dr. Castile, pediatric pulmologist:* "There was a lack of clarity in both the safety and efficacy data…It is unfortunate because I think it has a role, but based on the data presented and the questions asked, I had to vote no."
- *Dr. Cataletto, pediatric pulmonologist:* "I think there is a place for a drug like this, but further studies are necessary."

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