FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

(PADAC)

Wednesday, May 8, 2019

8:03 a.m. to 4:33 p.m.

FDA White Oak Campus

Building 31 Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Chee, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

David H. Au, MD, MS

(Chairperson)

Professor of Medicine

University of Washington

Director, Health Services Research and Development Center of Innovation

VA Puget Sound Health Care System, Seattle Division

Seattle, Washington

John M. Kelso, MD

Staff Physician

Division of Allergy, Asthma, and Immunology

Scripps Clinic

San Diego, California

David J. Lederer, MD, MS

Associate Professor of Medicine and Epidemiology

Division of Pulmonary, Allergy and Critical Care Medicine

Columbia University Medical Center

New York, New York

Gailen D. Marshall Jr., MD, PhD, FACP
The R. Faser Triplett Sr MD Chair of
Allergy and Immunology
Medical Director, UMMC Clinical Research
Support Program/Clinical Research and Trials Units
Professor of Medicine, Pediatrics and Pathology
Vice Chair for Research, Department of Medicine
Director, Division of Clinical
Immunology and Allergy
Chief, Laboratory of Behavioral Immunology Research
The University of Mississippi Medical Center
Jackson, Mississippi

Loretta G. Que, MD
Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Allergy and Critical Care
Medicine
Duke University Health System
Durham, North Carolina

Carrie A. Redlich, MD, MPH

Professor of Medicine, Pulmonary Section &

Occupational and Environmental Medicine

Director, Yale Occupational and Environmental

Medicine Program

Yale University School of Medicine

New Haven, Connecticut

Richard W. Weber, MD

Professor Emeritus

Department of Medicine

National Jewish Health

Denver, Colorado

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Stuart Green, MD

(Industry Representative)

Vice President

Respiratory and Immunology

Merck Research Laboratories

Rahway, New Jersey

TEMPORARY MEMBERS (Voting)

Kathryn Blake, PharmD, BCPS, FCCP, CIP
Director, Center for Pharmacogenomics and
Translational Research
Principal Research Scientist
Associate Professor of Pharmacy, Mayo Clinic
College of Medicine and Science
Nemours Children's Specialty Care
Jacksonville, Florida

Erica Brittain, PhD
Mathematical Statistician
Deputy Branch Chief
Biostatistics Research Branch
National Institute of Allergy and Infectious
Diseases (NIAID)
National Institutes of Health (NIH)
Bethesda, Maryland

Mary Cataletto, MD, MMM
Professor of Clinical Pediatrics
Stony Brook University
School of Medicine
Stony Brook, New York

Scott S. Emerson, MD, PhD
Professor Emeritus of Biostatistics
Department of Biostatistics
University of Washington
Seattle, Washington

Daniel L. Gillen, PhD
Professor and Chair
Department of Statistics
University of California, Irvine
Irvine, California

Erin Moore, BS
(Patient Representative)
Hummelstown, Pennsylvania

Richard B. Parad, MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Department of Pediatric Newborn Medicine
Brigham and Women's Hospital
Connor's Center for Women
Boston, Massachusetts

Karen S. Schell, DHSc, RRT-NPS, RRT-SDS
RPFT, RPSGT, AE-C, CTTS
(Acting Consumer Representative)
Clinical Assistant Professor
University of Kansas Medical Center
School of Health Professions
Respiratory Care Education
Kansas City, Kansas

James M. Tracy, DO

Managing Partner

Allergy, Asthma and Immunology Associates, PC

Associate Clinical Professor of Pediatrics

University of Nebraska College of Medicine

Omaha, Nebraska

FDA PARTICIPANTS (Non-Voting)

Sally Seymour, MD

Acting Director

Division of Pulmonary, Allergy, and

Rheumatology Products (DPARP)

Office of Drug Evaluation II (ODE II)

Office of New Drugs (OND), CDER, FDA

Robert H. Lim, MD

Clinical Team Leader

DPARP, ODE II, OND, CDER, FDA

Yongman Kim, PhD

Biostatistics Team Leader

Division of Biometrics II (DB II)

Office of Biostatistics (OB)

Office of Translational Sciences (OTS)

CDER, FDA

Khalid Puthawala, MD

Clinical Reviewer

DPARP, ODE II, OND, CDER, FDA

Cesar Torres, PhD

Statistical Reviewer

DB II, OB, OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:03 a.m.)

Call to Order

Introduction of Committee

DR. AU: Good morning. I would like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so.

I also want to remind attendees of today's meetings that there may be multiple people with cystic fibrosis in this room. If needed, we have items recommended by the Cystic Fibrosis Foundation available outside of the meeting room. People with CF and their families should be aware that individuals with CF might choose to attend this advisory committee without notifying the staff. Therefore, we cannot guarantee that you will not encounter others with CF at this meeting.

I would also like to identify the FDA press contact, Nathan Arnold. If you are present, please stand, at the back of the room there.

My name is David Au. I am the chairperson

for the Pulmonary Allergy Drugs Advisory Committee. I will be chairing this meeting. I will now call today's Pulmonary Allergy Drugs Advisory Committee to order. We'll start by going around the table and introduce ourselves. We will start with the FDA to my left and go around the table.

DR. SEYMOUR: My name is Dr. Sally Seymour. I'm the acting director for the Division of Pulmonary Allergy and Rheumatology Products.

DR. LIM: Bob Lim, clinical team leader, DPARP.

DR. PUTHAWALA: Khalid Puthawala, clinical reviewer, DPARP.

DR. KIM: Yongman Kim, statistical team leader, FDA.

DR. TORRES: Cesar Torres, statistical reviewer.

DR. TRACY: Jim Tracy, University of Nebraska.

DR. BLAKE: Kathryn Blake from Nemours Children's Specialty Care.

DR. MARSHALL: I'm Gailen Marshall,

University of Mississippi Medical Center.

DR. LEDERER: Good morning, Dave Lederer, Columbia University in New York.

LCDR CHEE: Hi. Cindy Chee, DFO for Pulmonary Allergy Drugs Advisory Committee

DR. AU: David Au, the VA Puget Sound Healthcare System and the University of Washington.

DR. KELSO: John Kelso. I'm an allergist at Scripps Clinic in San Diego.

DR. QUE: Loretta Que. I'm at Duke University in North Carolina.

DR. REDLICH: Carrie Redlich, Yale University.

DR. WEBER: Richard Weber, National Jewish Health, Denver, Colorado.

DR. SCHELL: Karen Schell, University of Kansas Medical Center. I'm a consumer representative.

MS. MOORE: I'm Erin Moore. I'm the patient rep today.

DR. PARAD: I'm Richard Parad from Harvard Medical School.

DR. EMERSON: Scott Emerson, biostatistician, University of Washington.

DR. BRITTAIN: Erica Brittain. I'm a statistician at National Institute of Allergy and Infectious Diseases, NIH.

DR. GILLEN: Daniel Gillen, Department of Statistics, University of California at Irvine.

DR. GREEN: Stuart Green, Merck Research Laboratories. I'm the industry representative.

DR. AU: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are held quite strongly. Our goal is that today's meeting will be a fair and open forum for these discussions and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I will now pass it to Lieutenant Commander Cindy Chee, who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR CHEE: The Food and Drug Administration is convening today's meeting of the Pulmonary Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other

agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a specific government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application 202049 for mannitol inhalation powder for oral inhalation, submitted by Chiesi, USA, Inc. 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.

This is a particular matters meeting during which specific matters related to Chiesi's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the

committee members and temporary members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Stuart Green is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Green's role at this meeting is to represent industry in general and not any particular company. Dr. Green is employed by Merck Research Laboratories.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for

the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. AU: Thank you. We will now proceed with the FDA's opening remarks from Dr. Robert Lim.

FDA Introductory Remarks - Robert Lim

DR. LIM: Good morning, Dr. Au, esteemed members of the committee, the Chiesi team, my FDA colleagues, members of the CF community, and other members of the audience, my name is Robert Lim. I'm a clinical team leader in the Division of Pulmonary Allergy and Rheumatology Products. I am also trained as a pediatric pulmonologist.

On behalf of the agency, I would like to welcome you all here to the FDA campus at White Oak to this very important advisory committee meeting, where we will discuss the NDA for dry powder mannitol, or DPM, for inhalation for cystic fibrosis. In my presentation this morning, I'll provide some brief background introductory remarks

and provide some context as we begin our discussion of this product.

The sponsor's probably going to go over this in greater detail, but briefly, cystic fibrosis is an autosomal recessive disorder caused by mutations in the CFTR gene. It affects approximately 30,000 patients in the U.S. and about twice that worldwide. It's a multisystem disorder affecting the airways, exocrine pancreas, GI tract, and reproductive tract.

There is no cure, and the majority of therapies are aimed at the symptoms and sequelae of disease. However, in 2012, the first drug targeting the underlying cause was approved, and since then, additional products have been approved which target the underlying cause of CF for patients with certain mutations.

These treatments have been referred to by some as CFTR modulators, and while these new therapies have been life-changing for some patients, there continues to be a continued need for additional therapies for all patients with

cystic fibrosis. It's also worth noting that the CF treatment landscape is rapidly evolving with many innovative products in the pipeline.

The product we're discussing today, dry powder mannitol, or DPM, is a sugar alcohol. It is generally recognized as safe by the enteral route and is approved as a bronchoprovocation agent by the inhaled route under the trade name Aridol.

The applicant's proposed indication is for the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. The proposed dose is 400 milligrams by inhalation twice daily.

This NDA was initially submitted in May of 2012. At that time, the product was not approved, and a complete response or CR action was issued. This current submission is the applicant's response to the CR action. In the next few slides, I will briefly review the regulatory history.

The original NDA was submitted in May of 2012, and at that time the development program

included one dose-ranging study, study 202, and two phase 3 studies in CF patients greater than 6 years of age. These were studies 301 and 302.

The primary endpoint for both these studies was FEV1 change from baseline in FEV1 over 26 weeks. Secondary endpoints included exacerbation as well as Cystic Fibrosis Questionnaire-Revised respiratory domain scores.

It is worth noting that in these two studies, if a patient was discontinued for treatment, there were no specific provisions to continue collecting data or follow these patients.

The key findings from the original NDA submission are summarized in this slide. With regard to efficacy data from study 301, while the results were positive in terms of the FEV1-based endpoint, the results were not considered to be statistically robust due to significant issues with differential dropout and missing data, which was potentially missing, not at random.

In study 301, 37 percent of DPM patients and 27 percent of control patients discontinued

treatment, and as there were no specific provisions to follow these patients, there was a significant amount of missing data. Study 302 did not demonstrate a statistically significant win on its primary endpoint.

Importantly, across both studies, secondary endpoints were also not supportive of efficacy. With regard to safety, there were concerns with hemoptysis, particularly in the pediatric population.

Given these issues, this NDA was discussed at a January 2013 Pulmonary Allergy Drug Advisory Committee or PADAC. At that time, the committee voted unanimously against approval in the 6-year and older population.

As a result of the committee input and agency review, DPM was not approved, and a complete response action was taken. Deficiencies included that efficacy was not adequately demonstrated and that there were safety concerns.

To address these deficiencies, the applicant was told to conduct at least one

additional clinical trial to show substantial evidence of efficacy and balance the safety findings. The expectation was that the trial would win on the FEV1 endpoint and have support from clinically meaningful secondary endpoints such as exacerbation and symptoms.

In the current submission, which is a response to this CR action, the applicant has limited the indication statement to include only adults, that is, patients greater than 18 years of age, and the contents of the current submission include a new 26-week phase 3 study in patients 18 years of age and older. That is study 303. The primary endpoint of the study was the same as 301 and 302. Secondary endpoints also included exacerbation and symptom-related outcomes.

This study was designed to address the concerns raised in 301 and 302 in the hopes that the same issues would not come up again. The current submission also includes a post hoc analysis of the 18-years-of-age and older subgroups from studies 301 and 302, so post hoc subgroup

analysis of a study whose results are not statistically robust, 301, and a study, subgroup analysis, of a study that did not win, study 302.

In the applicant's and the FDA's presentations that will come later, detailed discussions of the results will be presented. However, in order to provide some context for the issues that the agency would like the AC to consider, in this slide, high-level results for the 18-year-old-of-age-and-older population are summarized.

With regard to the primary endpoint for study 303, the results were statistically significant with a treatment effect of approximately 50 milliliters when comparing DPM to control.

In the post hoc analysis of the adult population in studies 301 and 302, point estimates were approximately 80 mLs in both studies. For exacerbation-related endpoints across all studies, there were no statistically significant differences between DPM and control. And in study 303, point

estimates for exacerbation rate favored control, and a similar observation was made in a post hoc analysis of study 302. In study 301, in contrast, post hoc analysis of exacerbation favored DPM.

With regard to symptom scores, as measured by CFQ-R, respiratory domain score, there were no statistically significant differences between DPM and control.

In considering the efficacy that is presented later this morning, keep in mind that only study 303 demonstrated clear statistically significant improvements in FEV1 in the adult population. While post hoc analysis of adults from studies 301 and 302 will be presented, it is important to note that these are post hoc subgroup analyses of a trial which was not considered to be statistically robust, 301, and a study that didn't win on its primary, study 302.

We also ask that you consider the magnitude of the FEV1 effect size point estimates, which are relatively small, and that the results have no support from secondary endpoints such as

exacerbation or symptoms.

In today's discussion, there are two primary topics, efficacy and safety. In the discussion of efficacy, we ask that you discuss whether there is substantial evidence to support efficacy in the proposed population, taking into consideration the effect size, the lack of secondary support, and statistical persuasiveness.

With regard to safety, we ask that you consider the overall safety as well as concerns regarding hemoptysis and numerical differences in exacerbations.

Thank you. That ends my presentation, and I'll hand it back over to the chair.

DR. AU: Thank you.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all

participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, interests in the sponsor, including equity interests, and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Chiesi's presentations.

Applicant Presentation - Mark Parry-Billings

DR. PARRY-BILLINGS: Good morning, Mr. Chairman, members of the advisory committee, and members of the FDA. I'm Mark Parry-Billings. I'm head of drug development at Chiesi. Thank you for the opportunity to present the data supporting

Bronchitol today.

Let me start with a brief overview of Bronchitol. Bronchitol acts effectively through a unique mechanism to improve lung function. It's a naturally occurring osmotic agent that is generally recognized as safe or GRAS by the enteral route.

The efficacy profile is based on improvements in lung function as measured by FEV1, which is a prognostic indicator of both morbidity and mortality in patients with CF. Moreover, Bronchitol has a generally well-tolerated safety profile.

Our data provides substantial evidence of efficacy with consistent FEV1 improvements across three phase 3 trials, as well as 8 years of worldwide post-approval clinical experience. Bronchitol is an easy-to-use inhaled dry powder form of mannitol.

Let me emphasize that we understand Bronchitol may not be appropriate for every patient, but we also know that patients with CF need options. There are clearly patients that will

gain clinically meaningful improvements in lung function and that will find Bronchitol easy and convenient to use. For these patients, Bronchitol can be a viable option.

Bronchitol effectively targets the lung. At its site of action, it first creates an osmotic gradient which facilitates efflux of water into the airway lumen. This increases airway clearance for two complementary mechanisms through enhanced mucociliary clearance and through cough clearance.

Thus, Bronchitol increases clearance of airways mucus, which is a key, indeed a central pathological feature of CF. This is somewhat different to COPD and asthma, for example, where bronchoconstriction and inflammation are central pathological features.

This targeted mechanism of action has been confirmed through a series of clinical studies, including this study, in patients with CF, where airway clearance was quantified by following a radio-labeled marker.

On the Y-axis, you see the percent of

radio-labeled marker where lower down on the axis represents improved clearance. On the X-axis, this is a time from inhalation of either mannitol or control. As you can see, mannitol in blue very clearly and effectively enhances airway clearance as compared to control in pink.

Now, let me show you how Bronchitol is delivered to the lungs. There are four simple steps. The process starts by removing the inhaler cap and simply twisting the top. Next, the patient places the capsule in the chamber and closes the inhaler.

After closing the inhaler, the patient presses the buttons on the side to puncture the capsule, and finally, the inhaler is placed in the mouth and the patient takes a deep breath, holding it for five seconds. This process is then repeated for the remaining capsules, which takes about 5 minutes overall.

In terms of global experience, Bronchitol was first approved in 2011 in Australia. It's now been approved in 35 countries for the treatment of

adult patients with CF, and markets include UK, Germany, Italy, and Spain.

In total, approximately 8,000 patients have been treated with no notable safety concerns. The proposed U.S. indication therefore follows this reassuring global experience. Here is the proposed indication for Bronchitol, indicated for the management of CF to improve pulmonary function in patients 18 years and older, in conjunction with standard therapies.

Next, I would like to summarize the U.S. regulatory history, very much in line with the presentation from Dr. Lim. The NDA was originally submitted in 2012 by Pharmaxis. The proposed indication was for patients with CF aged 6 years and older. You'll note this included pediatrics, which have now been removed from the proposed indication. This original submission included two phase 3 studies.

Then, in 2013, following an advisory committee, the conclusion of the FDA review was that the two phase 3 studies were not adequate,

particularly because one study missed the primary endpoint and the other study had a high level of patient dropouts, which were imbalanced across the treatment groups and which were not accounted for appropriately in the statistical analysis. Moreover, there were concerns regarding hemoptysis in the pediatric population.

Therefore, the agency recommended at least one additional phase 3 study with a similar design to the originals, using the same primary lung function endpoint and with proactive steps to minimize patient dropouts. This third study was also to be conducted in adult patients.

If we now fast-forward to 2018, in December of last year, the NDA was resubmitted, capturing key elements from the pre-submission meeting with the agency. The resubmission included and indeed focused on the new study, referred to as study 303, and focused on the adult population only. Moreover, dropouts were minimized and accounted for in the statistical analysis.

While study 303 is the primary dataset,

earlier studies were re-assessed using the prespecified statistical plan for study 303, and additionally, an integrated analysis of all three studies was also incorporated.

In summary, the primary evidence of Bronchitol benefit-risk comes from three similar randomized double-blind controlled phase 3 studies in a total of 789 adult patients with CF. The clinical data from these studies, which we'll share today, along with the global marketed experience, support a positive benefit-risk profile of Bronchitol in adult patients.

With this background in mind, here's the agenda for the remainder of our presentation. Dr. Scott Donaldson will describe the unmet need and disease background for adult patients with CF. The efficacy section will be presented by my colleague, Dr. Carmen Dell'Anna. Dr. James Alexander will review the safety data, and Dr. Patrick Flume will conclude with his clinical perspective.

We also have three additional experts with

us today to answer your questions. All outside experts have been compensated for their time and travel to today's meeting. Thank you very much, and Dr. Donaldson will now discuss the disease background and current treatment options for patients with CF.

Applicant Presentation - Scott Donaldson

DR. DONALDSON: Good morning, everyone. I'm Scott Donaldson. I'm a pulmonologist, and I direct the adult cystic fibrosis center at the University of North Carolina. I've been treating people with CF and working in CF research for more than 25 years. I really appreciate the opportunity to provide background on CF and to highlight the ongoing need for treatments that effectively improve lung function in our patients.

In the United States, cystic fibrosis is a disease affecting more than 30,000 patients, of whom 54 percent are now adults. This is a genetic disease caused by mutations in a single gene called CFTR, and most people with CF are Caucasian.

The median predicted survival in CF has

increased significantly over the years, and since 2002, we've seen a large improvement. However, patients with CF are still dying very young. In 2017, the average age of the time of death of patients with CF was approximately 30 years. Clearly, we still have a long way to go.

As you might expect, as a result of improved therapies, the number of adults with CF has increased and it will continue to do so going forward. CF is a disease that affects many organs, but progressive lung disease continues to be the major cause of morbidity and mortality.

People with CF develop bronchiectasis, which is defined as permanently thickened and dilated airways, and once this disease process is established, people with CF suffer from progressive loss of lung function and recurrent disease exacerbations until either premature death from respiratory failure or a lung transplant is performed.

Let me describe the pathophysiology in more detail. Mutations in the CFTR gene cause a cascade

of consequences. Reduced or absent CFTR activity results in depletion of that thin layer of fluid that lines airway surfaces and dehydration of airway secretions. This in turn causes airway mucus to become very thick and abnormally viscous and will stick to airway surfaces.

As a result, mucociliary clearance becomes impaired. Mucociliary clearance is a key lung defense mechanism, and when it fails, mucus begins to plug airways. This retained mucus in the lung creates an environment that's favorable for bacterial colonization that results in chronic airways infection, often with pseudomonas.

The inability to clear these infections results in a chronic intense neutrophilic inflammatory response. Once this process of chronic infection and inflammation is initiated, a vicious cycle further impairs airway function, including mucus clearance, and results in progressive injury and remodeling of the airways or bronchiectasis.

Now, it's well understood in the CF

community that treating CF should focus on mucus clearance. Improvements in mucus clearance lead to improvements in lung function, and improving lung function will inevitably reduce associated morbidity and mortality.

Let me explain further. The FEV1 is a widely accepted measure of lung function. We monitor lung disease status in a number of ways. The measurement of lung function through spirometry is our most reliable metric. Spirometry gives us an assessment of disease severity at that point in time, as well as allows us to assess the progression of lung disease over time. It's also an index of patient's response to therapies.

The spirometric parameter of interest in CF is FEV1, and this is really the gold standard. The FEV1 correlates with the extent of structural lung damage and is our strongest predictor of exercise capacity and survival.

It's long been known that when lung function declines to the point where severe impairment is present, the risk of death increases

substantially. FEV1 is not only the strongest predictor of mortality, but it's also a primary factor used to determine the need for lung transplantation.

As just noted, clearing mucus out of the airways is the most fundamental way that we treat our patients. This is a graphical description of the CF abnormalities in the airways. On the left is the normal airway, which has an intact airway surface liquid layer and normal hydration of mucus. This allows cilia to stand up, to beat rhythmically, and to clear mucus from the lung.

On the right is the CF airway where that thin layer of fluid is now very shallow, and this prevents the cilia from standing upright and moving mucus. In addition, the secreted mucus layer becomes very thickened and becomes non-transportable.

On the next slide, this is what CF lung disease actually looks like. On the left is a resected CF lung where you see a mucus plug that's being attempted to pull out of a very dilated

airway, and this is a prime environment for inflammation and infection. On the right is a photo micrograph of the CF airway. What we see is complete obstruction of the airway with mucus, infection, and inflammation.

Let me discuss how we currently treat our patients. Strategies for CF therapy have been outlined and treatment guidelines are evolving rapidly. Because mucus clearance is key, we use medications to change the properties of airway mucus, trying to make them easier to clear. However, all of these therapies are time and energy consuming and constrict patient mobility and lifestyle.

Nebulized hypertonic saline is an unapproved therapy that's used to hydrate airway secretions and to promote mucus clearance from the lung. Nebulized recombinant human DNase is used to enzymatically cleave extracellular DNA, which thickens inflamed secretions. Aerosolized antibiotics are used to suppress infection, and oral macrolides are used for their

anti-inflammatory properties.

These therapies are trying to treat, really, the downstream consequences of CFTR dysfunction, with a final option of lung transportation, which is a high-risk treatment option that's available when all other options have failed and lung disease is very severe.

We're now, however, in the era of CFTR modulators, which are oral drugs that can improve CFTR function and therefore are treating the upstream pathophysiology of this disease.

The relatively recent development of orally available small molecule CFTR modulators has been very impactful in CF. These drugs are useful for specific CFTR mutations, and highly effective modulators are currently available only for a relatively small proportion of our patients. However, even in those patients who are treated with CFTR modulators, we know that these medications slow, but do not stop, the progression of lung disease once it is established. There is going to be an ongoing need for downstream

treatments that focus on airway clearance.

The projected impact that highly effective CFTR modulators still in development may have for our patients has been included in a model developed by the CF foundation. As you can see, over the next 20 years, these medications will contribute toward a relatively large increase in the number of patients who are needing care, from the current approximately 18,000 patients to about 30,000 patients.

Not only are we expecting an increase in the total number of patients, but the number of patients with moderate to severe lung disease, as shown in the yellow, red, and black, is actually going to increase. And we know that these are the patients that are going to continue to need other treatments that improve lung function, so the need for new therapies is not going to go away.

The burden of lung disease is very high in CF. From the CF registry, we know that roughly half of adults with CF in their 20s and 30s are being prescribed all three of the major inhaled

CFTR treatment classes. That is inhaled antibiotics, recombinant human DNase, and hypertonic saline.

We also know from prior CF studies that while we may be writing a lot of prescriptions for these medications, adherence to these time-consuming treatments is quite low. Our best estimates of actual treatment adherence, using either electronic monitoring of nebulizer use or pharmacy refill data, range between 36 and 62 percent. Interestingly, the lowest adherence is for hypertonic saline, which is a somewhat more time-consuming treatment.

This failure to adhere to prescribed therapies is very important because reduced adherence is clearly associated with worse clinical outcomes, including important events such as hospitalization.

Patients are telling us that burden of treatment is one of the most important things to them. In the UK, a survey of CF patients, families, and healthcare providers list the

treatment burden as the number one research concern for them.

In the U.S., a separate survey of 135 patients, families, and an expert clinical research ward, treatment burden was ranked as the third most important research priority. So we are getting a consistent message, when surveying both patients are caregivers, that they want treatments that are less burdensome.

Finally, to crystallize an image of what our adults with CF go through, I want to present a typical patient example, and I'll refer to this patient by the name of Kim.

Kim is a 30-year-old woman with CF. She was diagnosed in the first year of life, and she's enjoyed reasonably good health. She's married. She has two kids. She's currently working full time and enjoys her work, but she has the usual complications seen in people with CF. Her airways are infected with Pseudomonas aeruginosa, the most common bacterium that we see in our adult patients, and she also suffers from pancreatic insufficiency.

I'll note that, although I describe her as relatively well, she has a lung function impairment that's about 50 percent of predicted FEV1, so she clearly has considerable lung disease.

To maintain her health, Kim is prescribed several medications. She has to get up very early in the day in order to get her CF treatments done, get her children up and to school, so that she can get to work on time. She follows a recommended order of treatment for bronchodilators, hypertonic saline, recombinant human DNase, inhaled antibiotics, and airway clearance. And of course, she tries to do all of these therapies before she eats in the morning.

After a full day of work, where she really avoids trying to take treatments in order to maintain some semblance of privacy and normalcy, she comes home. And after a busy day, she has to repeat all of these therapies all over again.

The constraints for treatment really compete with some of the fun and social activities she'd like to do more in her life. Finally, around

10:30, she's able to go to bed just to repeat this routine the next day, and day after day going forward.

So I don't know about you, but I would personally last about one day in this routine, yet we ask people with CF to do exactly this on a day-to-day basis throughout their life.

I'll close by simply reinforcing the idea that despite great progress in the treatment of CF, we've not solved the problem of progressive lung disease, even with intensive treatment regimens, including CFTR modulators. We therefore continue to need treatment options that are not only effective, but are feasible to use by our patients, because these easier-to-use treatments are much more likely to be actually used by people with CF, and they also will be more likely to achieve real-world efficacy.

The cornerstone of treating CF is to improve airway clearance using both mechanical devices and inhaled medications to improve lung function. This goal is not going to change going

forward. While hypertonic saline is our current approach of stimulating mucociliary clearance, not all patients will tolerate it, and many treatments will be skipped due to the significant treatment burden they entail.

An alternative agent that reduces treatment burden and increases portability would therefore be welcomed, and in fact is being demanded by our patients. Thank you very much. I'll now turn the presentation over to Dr. Dell'Anna.

Applicant Presentation - Carmen Dell'Anna

DR. DELL'ANNA: Thank you.

I'm Carmen Dell'Anna, vice-president of medical affairs at Chiesi. I will now share the Bronchitol efficacy data in adult patients with cystic fibrosis, which demonstrate consistent clinically meaningful improvement in lung function as measured by FEV1.

First, I will briefly discuss the three phase 3 trials included in the program. Next, I will present the primary endpoint results and the supportive sensitivity analyses. I'll then review

results from other measures of pulmonary function in two other clinical endpoints. Let me first turn to the overview of our three clinical studies.

As presented earlier, the clinical development program for Bronchitol include three randomized double-blind controlled phase 3 studies with 789 adults with cystic fibrosis, including 423 patients randomized in the most recent study, 303.

Overall, the design of study 303 was similar to 301 and 302. All included 26-week double-blind treatment periods, the same treatment arms, and a mannitol tolerance test to identify bronchial hyperresponsiveness. However, study 303 included additional measures to minimize patient dropout and missing data, such as encouraging patients to remain in study even if discontinuing from study treatment.

Patients who passed the MTT were randomized to either 400 milligrams of Bronchitol or control containing 50-milligram mannitol. In-office efficacy assessments, including spirometry,

occurred at week 6, 14, and 26. Patients completing studies 301 and 302 could elect to receive Bronchitol in an open-label extension for either 26 or 52 weeks.

Based on the need to meet the requirements of matching taste and appearance and the lack of response in phase 2 findings, we chose 50 milligrams inhaled mannitol, a twice-daily dose, as control for phase 3 studies. This selection was discussed with the FDA.

Moving to enrollment, all three studies had similar enrollment criteria. Patients were enrolled if they had a confirmed diagnosis of cystic fibrosis. Patients also had to have a percent of predicted FEV1 at screening, ranging between 40 and 90 percent, with values of greater than or equal to 30 percent allowed in study 301. Antibiotics and rhDNase treatments were also permitted.

Key exclusion criteria included the prohibition of nebulized hypertonic saline for maintenance treatment and failure to pass the

mannitol tolerance test at screening.

The endpoints were also similar. In all three phase 3 studies, the primary endpoint was the FEV1 change from baseline over 26 weeks. Other lung function endpoints evaluated were forced vital capacity and forced expiratory flow, 25 to 75 percent.

In addition, rate of protocol-defined pulmonary exacerbations, or PDPE, and change from baseline in CFQ-R, which is a measure of symptom severity, were evaluated in all studies. Additional endpoints assessed during the studies are included in our briefing book.

The statistical analysis accounted for missing data, and the prespecified methods from study 303 were applied to study 301-302, and integrated analysis. The ITT was defined as all randomized adult patients regardless of study drug intake.

Based on the assumption that the patients who withdrew from study due to an adverse event that lack of efficacy or physician decision do not

benefit from treatment, missing data were imputed with baseline value. On the other hand, no formal imputation was applied for patients who withdrew from study for other reasons.

The statistical method applied to the primary analysis was the Mixed Model Repeated Measures or MMRM. The analysis used all available data, including assessments measured after treatment discontinuation.

In order to assess the robustness of study results, preplanned sensitivity analysis, as discussed with the FDA, were performed under different assumptions, both for missing at random and not-at-random, and different statistical methods. These methods were pattern mixture modeling, MMRM without imputation, tipping point, and responder analysis using different thresholds.

We are presenting the efficacy data, focusing on study 303 to the left, followed by the adult data from the original studies, 301 and 302, and then the supportive integrated analysis.

In study 303, 88 percent of patients

completed the study, and reasons for study withdrawal were balanced between arms. Therefore, in study 303, the previous concerns for withdrawal and differential dropout rates were addressed.

All three studies reported similar demographics consistent with the adult patient population with cystic fibrosis. In study 303, the demographics were well balanced between arms, and as expected, the majority of patients were adult, young adult, and mostly Caucasian. U.S. sites were the largest contributor at 27 percent. In general, we see similarity across all three studies in baseline CF characteristics.

Focusing on study 303, the baseline FEV1 percent predicted in this population of adult cystic fibrosis patients was approximately 63 percent. More than one-third of the population had a baseline predicted FEV1 of greater than 70 percent.

The CFQ-R scores ranged from 0 to 100, where higher scores reflect less symptoms. Across all studies, 71 to 80 percent of patients had

baseline CFQ-R scores of greater than 50, attesting to a well-controlled patient population. About 43 percent of the patients had Pseudomonas aeruginosa infections at the time of screening.

In terms of exacerbations history, most patients in study 303 and 302 did not experience a pulmonary exacerbation requiring hospitalization or use of intravenous antibiotics within the last 12 months before enrollment. Data on exacerbations before enrollment were not collected in study 301.

Turning now to the primary results from the studies, the difference between treatments in FEV1 change from baseline over 26 weeks were significant in favor of Bronchitol compared to 50 milligrams control, with an adjusted mean difference of 0.054 liters in study 303 and a p-value of 0.02.

When identical statistical methods were applied post hoc to each study in the adult population, improvements were also observed in lung function over the 26-week treatment period.

Reassuringly, all three studies revealed

consistent findings. There was little effect on FEV1 from the control arms, with a majority of FEV1 gains driven by improvement in the Bronchitol arms. The integrated data demonstrated a 0.067-liter mean difference from control.

We also performed a multiple sensitivity analysis. All sensitivity analysis confirmed the primary results observed in study 303 and showed consistently favorable treatment difference supporting Bronchitol's efficacy. Highlighting represents a treatment difference in favor of Bronchitol.

The sensitivity analysis across the other two studies and the integrated analysis, again, supported the primary results. The entirety of this finding support the robustness of the dataset for improvement in pulmonary function.

An additional way to assess the FEV1 response to Bronchitol is to look at various response thresholds. In study 303, regardless of FEV1 threshold we apply, we see consistently more responders among patients treated with Bronchitol

at week 26 compared to the control group.

At the threshold of 0.1 liters, 34 percent of patients treated with Bronchitol were responders compared with 24 percent of patients in the control group. When, again, identical statistical methods were applied to study 301 and 302, similar responder benefits were observed across thresholds.

In this analysis, we see the impact of the effect of Bronchitol on lung function based on disease severity, as measured by percent predicted FEV1. It is notable that there is a consistent improvement with a greater effect observed in more severely affected patients.

Next, I will present results of other pulmonary function endpoints, starting with absolute change from baseline in forced vital capacity.

In study 303, as well as in study 301 and 302, FVC demonstrated the treatment difference in favor of Bronchitol compared to control, supporting the results of the primary endpoint or lung function. Similarly, FVF, 25 to 75 percent

calculation from the spirometry results supported the benefit of Bronchitol or lung function. We observed a positive treatment difference in all studies.

I will now discuss protocol-defined pulmonary exacerbations and the cystic fibrosis questionnaire. Several secondary endpoints were hierarchically tested, however, none met statistical significance.

Starting with the rate of pulmonary exacerbations, protocol-defined pulmonary exacerbations were defined as patients being treated with intravenous antibiotics because of 4 or more prespecified design and symptoms. These are reported PDPE experienced by the patients.

Only 13 and 14 percent of patients experienced a PDPE over the 26-week trial period in study 303. Moreover, it is notable that the number of events was very low. In the integrated population, the rate ratio was 1.0 between arms.

In study 303, there was no difference between arms in time to first PDPE, and as you can

see, very few patients experienced an event. Additionally, these curves look similar for the integrated analysis.

Next, looking at the CF questionnaire data, CFQ-R changes over 26 weeks were similar for both Bronchitol and control, which was not unexpected given the population was well-controlled at baseline.

Here, you see the CFQ-R results for the most symptomatic patients, who all had a baseline score less than or equal to 50. This is a post hoc small subset of patients and needs to be interpreted with caution.

In these more symptomatic groups, you can see that the changes from baseline were calculated within each treatment arm, and for these patients, the adjusted mean difference between treatment is about 4 units, in favor of Bronchitol and consistent with a clinically meaningful change. Studies 301 and 302 were also supportive.

To summarize, Bronchitol demonstrated consistent improvements in FEV1 across various

biometric measures, with greater improvements observed in patients with more severe lung disease. The results were confirmed in multiple sensitivity analysis and responder analyses, and were observed in a relatively stable CF population across the large phase 3 studies.

Secondary lung function endpoints support the primary results. The secondary endpoint of PDPE was comparable among treatments. In this relatively stable population, changes in CFQ-R were not noted overall. However, a clinically meaningful effect on non-symptoms was observed in more symptomatic patients.

Thank you. Dr. Alexander will now come to the podium to discuss the safety findings.

Applicant Presentation - James Alexander

DR. ALEXANDER: Good morning. I'm James Alexander. I'm representing the medical affairs division at Chiesi. It is my pleasure this morning to describe and discuss the safety data on the safety of Bronchitol in adult patients with cystic fibrosis. The safety profile of Bronchitol has

been well characterized in adult patients with CF. The data come from the three phase 3 studies, and because the designs were similar, we have pooled the events.

I'll first discuss the overall safety profile and then briefly summarize the safety profile for the open-label extension. Then I'll review the adverse events of special interest, including pulmonary exacerbations, looking specifically at the events in the U.S. and the non-U.S. subpopulations.

I want to mention now that the pulmonary exacerbations in the safety database represent a different dataset than that for the secondary efficacy endpoint of PDPE that was just discussed by Dr. Dell'Anna.

First, let me describe the patient exposure to Bronchitol across the phase 3 studies. 508 patients were treated with Bronchitol in the three phase 3 studies. Patients evaluated for randomization were required to pass the mannitol tolerance test to screen for hyper-responsiveness

to inhaled mannitol. 896 patients were tested; 824, or 92 percent, passed the MTT and were eligible for randomization.

The 508 patients exposed consist of the 414 randomized to Bronchitol in the double-blind period, 130 of whom entered the open-label period, and 94 patients who entered the open-label period, who had received control in the double-blind phase. In total, 62 percent of these 508 patients received Bronchitol for longer than 6 months.

Let's look at the overall safety profile during the double-blind period. Across the three studies in parallel with the 414 patients treated with Bronchitol, 347 received control. The percentages of patients with 1 or more adverse events, 1 or more severe adverse events, or 1 or more serious adverse events were very similar between the two treatment arms.

More patients receiving Bronchitol discontinued study drug due to an adverse event, and I will review the specific reasons in a later slide. Among adults in the phase 3 program, one

19-year-old male who received control in study 303 died following a pulmonary exacerbation.

Next, I'll show the more common adverse events that were reported. Pulmonary exacerbation was the most commonly reported adverse event, and it has the MedDRA code of condition aggravated. Cough, headache, and hemoptysis were the next most common events reported by 10 to 15 percent of patients.

Cough was more common with Bronchitol treatment, as would be expected based on the mechanism of action. Hemoptysis occurred in similar percentages of patients in both treatment groups. Among the less common events, pharyngolaryngeal pain, which is coded as oropharyngeal pain in MedDRA, was more common with Bronchitol treatment than with control.

Let's turn now to the more common serious adverse events. The percentages of patients with any of these individual SAEs were generally similar between the two treatment groups. For pulmonary exacerbations, 13 percent of patients in the

Bronchitol group and 11 percent of the control group experienced events meeting the definition of a serious adverse event.

Now, I'll review the adverse events that led to study drug discontinuation. We see that more patients on Bronchitol discontinued treatment due to an adverse event, and the two most common reasons were cough followed by pulmonary exacerbation.

While more Bronchitol patients discontinued due to cough compared to control, similar percentages of patients in both groups discontinued study drug due to pulmonary exacerbation. These data demonstrate that, overall, in the majority of patients, twice daily treatment with Bronchitol was well tolerated.

Let's look now at the safety profile for the 224 patients who entered the open-label extensions. In studies 301 and 302, patients could participate in open-label extensions and receive Bronchitol for up to 6 or 12 months. Among these patients, the adverse event profile was similar to

that for Bronchitol treatment during the double-blind treatment. These data support the long-term safety of daily treatment with Bronchitol.

I'll now review and discuss the adverse events of special interest, including pulmonary exacerbations. I will only briefly summarize the data for 4 of the 5 adverse events of special interest since our conclusions are consistent with the FDA's assessment of these events.

Cough and pharyngolaryngeal pain are expected with Bronchitol, and these events occurred more frequently than with control. The percentage of patients with hemoptysis was similar for Bronchitol and control, and the rate of this event aligns with expectations in the adult cystic fibrosis population.

Bronchospasm is a known risk, but this risk is mitigated by the use of the mannitol tolerance test. Consequently, the rate of bronchospasm was very low.

Finally, the overall event rate for pulmonary exacerbations was similar in both

treatment arms. However, I want to explore the exacerbation data in depth based on the observed imbalance in the U.S. patient subgroup.

As shown in table 33 of the FDA briefing document, among U.S. patients, there was a 2-fold difference in the number of patients with SAEs in the Bronchitol group compared to control, 21 percent versus 11 percent, or numerically, this is 23 patients versus 10.

In contrast, in the non-U.S. population, there was no difference. However, we need to understand that the U.S. patients randomly assigned to these two treatments were not comparable populations at baseline in a very important baseline characteristic.

More U.S. patients randomized to Bronchitol had a prior history of pulmonary exacerbations. Forty-five percent had experienced one or more exacerbations in the 12 months prior to screening compared to 38 percent with its history in the control group. An imbalance is also evident when looking at U.S. Bronchitol patients who had 2 or

more exacerbations in the past year, 20 percent versus 14 percent for the control group.

A similar imbalance was seen in the U.S. patients who had pulmonary exacerbation requiring IV antibiotics in the 12 months prior to screening. Consequently, comparative assessments should be viewed with caution since the U.S. subpopulation makes up only 27 percent of the total data. In contrast, the larger non-U.S. subpopulation was balanced for these key baseline characteristics.

It's commonly accepted that prior exacerbations are the number one predictor of future exacerbations in patients with cystic fibrosis. If you look across studies 302 and 303 by a subpopulation, most of the exacerbations SAEs on study occurred in patients with a prior history of pulmonary exacerbations.

With this in mind, I return to the display of the exacerbation SAEs in the U.S. shown on the first row of this slide. 21 out of 23 Bronchitol patients in the U.S. subpopulation who had an exacerbation SAE also had a prior history of

pulmonary exacerbation, and 6 out of 10 control patients in the U.S. had a similar history.

In contrast, we see a balance between treatments in the non-U.S. population. This emphasizes the importance of this baseline characteristic as a predictor of future exacerbation independent of treatment.

In conclusion, pulmonary exacerbations are not a Bronchitol-related risk that is specific to the U.S. population. In terms of the concern of pulmonary exacerbation in U.S. patients that has been raised by the FDA, Chiesi agrees that small subsets of data need to be cautiously interpreted. Moreover, since there were imbalances by treatment arm in the U.S. subpopulation for prior pulmonary exacerbations before study enrollment, caution is all the more warranted.

The overall safety population informs the risk for pulmonary exacerbations in the most reliable manner, and as I have shown, these data show no increase in risk.

In summary, Bronchitol treatment in adults

with cystic fibrosis was generally well tolerated. The adverse events of cough and pharyngolaryngeal pain are expected in this population due, respectively, to the mechanism of action of Bronchitol and the local effects of dry powder.

Hemoptysis was no more common with Bronchitol treatment than with control, and the occurrence of bronchospasm was infrequent and similar between arms. Pulmonary exacerbations were similar between treatment groups.

Finally, the Bronchitol safety profile is supported by eight years of post-marketing data and a five-year registry study conducted by the UK Cystic Fibrosis Trust. Thank you for your attention this morning. I'll now turn the podium over to Dr. Patrick Flume.

Applicant Presentation - Patrick Flume

DR. FLUME: Good morning, and thank you. I come to you as a clinician with considerable experience in treating patients with cystic fibrosis, more than 25 years of clinical experience, extensive participation in CF clinical

trials, and as a founding co-chair of the CF Pulmonary Guidelines Committee.

I believe that Bronchitol offers our patients an effective and safe choice, an option that they can consider for the routine management of their cystic fibrosis.

Here again is a slide demonstrating the pathophysiology of lung disease in cystic fibrosis and where we believe that current therapies have their function. I've placed Bronchitol in the same position as hypertonic saline, as its mechanism of action is to draw fluid into the airways to augment mucociliary clearance and help to clear the secretions.

I cannot stress enough the importance of clearance of airway secretions. It is the most fundamental aspect of disease management. Not only does this relieve some of the airway obstruction, but every drop of sputum contains millions of bacteria, so coughing up mucus, which we know that Bronchitol accomplishes, unloads a lot of infection as well as inflammation.

When I evaluate a medication for my patients, there are three questions that I ask: what is the evidence for efficacy, what's the safety and tolerability of the therapy, and when and how will I introduce this medication into their regimen? Let's look at Bronchitol with respect to these questions.

The results from the Bronchitol studies compared with the results from the hypertonic saline trial represent a clinically important treatment option for our CF patients. I have compared Bronchitol to hypertonic saline because it is the most relevant comparator. The CF Chronic Medication Guidelines recommend hypertonic saline based on its improvement in lung function, with a treatment effect that is similar to what has been shown with Bronchitol.

Hypertonic saline has become a major part of the CF treatment regimen. I know this to be true by looking at the CF patient registry data, which tracks prescription of therapies in the population. And as you can see, the use of

hypertonic saline has increased considerably, being prescribed for the majority of patients, and especially for adults.

I suggest to you that this demonstrates that the CF community perceives the effect of hypertonic saline on FEV1 to be clinically meaningful, and I would expect the same for their interpretation of the Bronchitol data.

This is the subgroup analysis of the impact of the effect on Bronchitol and lung function based on disease severity, as measured by FEV1, and I found this analysis revealing. It's notable that there is improvement in all subgroups, but a greater effect was demonstrated in more severely affected patients, and this may also provide a hint as to which patients may benefit the most. As Dr. Dell'Anna showed, the more symptomatic patients are also those that showed the greatest improvement in the CFQ-R.

Now, let's address the question of safety and tolerability in adults with CF. It is well known to us that some patients cannot tolerate the

introduction of inhaled medication, whether by nebulized solution or by dry powder. Cough is common. Some patients will experience bronchospasm with chest tightness or wheezing. Voice changes are also common.

But these are not all safety issues. Some are tolerability issues, and these can be easily mitigated by informing our patients about expectations. When they expect a cough, it is not as concerning to them. This is one reason why our center has had success in getting patients to adopt inhaled therapies.

Some patients will respond to teaching alone and perhaps some prevention in their technique. There will be others who cannot tolerate the therapy in spite of these efforts. But again, this is known for all of our aerosol therapies. The mannitol tolerance test provides clinicians a useful step to identify those patients who may not tolerate therapy. There is no such standard test for hypertonic saline.

It's notable to me that looking at

pulmonary exacerbations and serious exacerbations in the safety dataset, we see no clinically relevant differences between Bronchitol and control. In summary, the safety data reassure me that there are no major safety concerns.

Now that we find that Bronchitol may prove safe and effective, how do we think about introducing it to our patients? As Dr. Donaldson mentioned, we have enjoyed success in developing therapies for our CF patients. We are now in the era of CFTR modulators with even better results, so patients and clinicians have already begun to ask what therapies they might be able to stop, thinking about trading therapies rather than always adding on.

It's clear that novel therapies will not cure our patients nor will it repair established bronchiectasis, so we will not be able to stop all the other therapies. But if you ask patients, they are most interested in stopping those therapies that take the most time or require the most effort, such as in set-up and cleaning. In my practice, I

need options. I need options to individualize therapy and my patients want alternatives.

As should be readily apparent, our patients with cystic fibrosis have a significant burden of treatment. Bronchitol represents a therapeutic option with a lower treatment burden. It's portable. Treatment takes approximately 5 minutes. There is minimal set-up in cleaning. No refrigeration is required. So Bronchitol represents a convenient treatment choice and one that might fit into the lifestyle of many of our patients.

Going back to the patient example from Dr. Donaldson, recall that in order for Kim to complete all of her therapies, to get her kids off to school, and then get to work, she has to get up at 5:00 in the morning. What do you think her enthusiasm is to repeat that treatment cycle when she gets home after a long day?

For her, Bronchitol might actually offer a great option, to reduce the time in the morning and evening therapies, and perhaps even more relevant

is the freedom it offers, the portability. Maybe she chooses a dry powder inhalation with a hand-held therapy device, which would allow her to do her therapies discretely at work. She'd no longer have to decide whether she skips her children's activities or skips a treatment.

Having a portable treatment could have a significant impact on her life and perhaps being able to take that device and medication with her would allow her to take the therapy more effectively rather than choosing to not do the therapy at all.

In conclusion, Bronchitol is a viable treatment option with a positive benefit-risk profile. The cornerstone of CF treatment for adult patients is airway clearance. I cannot stress the importance of this enough, and this is how Bronchitol works.

Looking at the data, we see that treatment with Bronchitol consistently improves lung function. The efficacy was clearly established. Changes to FEV1 were clinically meaningful, even in

patients already treated with the best standard of care.

For me, the overall safety and tolerability profile appears acceptable. Bronchitol also offers additional benefits that may be important to people with CF, such as its ease of use, the short administration time, and the portability of the device. These benefits give the patients the freedom that they do not experience with many of their other therapies.

We do not expect Bronchitol to be the option for all patients, but that is what we already know for all of the other medications that we use to treat CF lung disease. This is about providing our patients with choices that offer benefits and fit into their lifestyle.

I thank you for your attention. Dr. Parry-Billings will now return to take your questions.

DR. AU: Thank you very much. Before we continue on with questions, Dr. Cataletto, will you please introduce yourself?

DR. CATALETTO: My name is Dr. Mary Cataletto. I'm from NYU Winthrop, and I'm a pediatric pulmonologist.

Clarifying Questions

DR. AU: Thank you very much.

Are there any clarifying questions for Chiesi? Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter.

Yes, Dr. Brittain? Sorry if I mispronounced that.

DR. BRITTAIN: Yes. I guess my first question is about slide CO-57. One thing I'm a little confused about, compared to results in the FDA briefing package, is in study 303, in their briefing package, they have a result that looks almost statistically significant in the wrong direction for what I think is this result.

Now, this one says "adjusted" and I don't know if that's the difference. Can someone explain? Am I comparing apples and oranges or is this just, this is adjusted and the other one

wasn't? And if it is adjusted, was it prespecified?

DR. PARRY-BILLINGS: Thank you for the question. If I may ask Dr. Day, our statistician, to talk to that point to explain the details.

Thank you.

DR. BRITTAIN: And I will have a follow-up.

DR. DAY: Thank you. I'm Simon Day, statistical consultant to Chiesi. The explanation is that in the original submission in the clinical study report, and as reported by the, the analysis was an adjusted analysis, including adjustment for missing values that were imputed based on the patient's historical p rate in the year prior to entry to the study.

Now, the problem was, in study 301, those historical rates were not collected. In this slide, what we wanted to present was the same method of analysis for each of the three studies and the integrated. So we had to come down to the lowest common denominator and use a method that did not impute the historical rate that patients had.

DR. BRITTAIN: I'm sorry. I'm still a little confused. For study 303, when you say adjusted, you've adjusted for what? I'm focusing on 303.

DR. DAY: The reason the result comes out differently in this slide, compared to the clinical study report and the FDA's presentation, is because this slide here does not use imputation for the historical rate of these in patients who had missing data.

DR. BRITTAIN: Okay. Secondly, in the pooled analyses that you present, also for exacerbations, in the safety presentation, when you're pooling, first of all, you're not doing it in a stratified way, I assume.

In the integrated analyses of efficacy, is that stratified by study, and in the safety pooling, you're not doing it in a stratified fashion; you're just lumping? Is that correct?

DR. PARRY-BILLINGS: Dr. Day again. Thank you.

DR. DAY: Yes, you're right. In the

efficacy analysis, there's a factor for study in the model. In the safety data, I believe it's just all pooled together.

DR. BRITTAIN: In fact, just to be clear, the pooled results say, for the exacerbations, we've understood in study 301, there was a lot of missing data. So you're only going to reflect exacerbations during the period when people were on drug.

DR. PARRY-BILLINGS: I'm sorry. Could you clarify your question?

DR. BRITTAIN: So in the pooled studies of exacerbations at all safety endpoints, we understood from before that there was a lot of missing data in study 301. Will you only be capturing the exacerbations and other events when people are on drug in those pooled analyses?

DR. PARRY-BILLINGS: Yes. In the earlier studies, when patients discontinued therapy, they discontinued the study. This was an enhancement of the design in the most recent 303 study, whereby for those patients who discontinued study

treatment, they were encouraged to stay in the study to complete the 26 weeks of treatment.

DR. AU: Dr. Emerson?

DR. EMERSON: Yes. On slide CO-74, where we're looking at the U.S. population in the pooled studies -- but those would actually just be two of them, I suppose -- you were making the point of an imbalance in terms of the history.

Now, as I look at the data that you also present on CO-73, but we can stay on this slide, where you said 45 percent of the Bronchitol patients had a prior history, whereas only 38 percent -- if I look stratified by that prior history -- and I'll note that, in any SAE, I'm always very, very worried about a treatment that magnifies an underlying risk -- I come up with that means that 42 percent of the patients with the prior history on Bronchitol went on and again had an SAE, whereas, on the control group, only 17 percent of the patients who had a prior history went on to have an SAE. And for what it's worth, in the non-prior history subgroup, it's 3 percent

and 7 percent for the mannitol and control groups, respectively.

I'd be interested in your comments on that. It looks like there's a great increased risk in that stratum of prior history.

DR. PARRY-BILLINGS: If we can have up again the CO-74, and I ask Dr. Alexander to come to the microphone to talk about that in more detail. The headline from our assessment of the data, and I think pretty well established in the literature, is that prior history of exacerbations drives future exacerbations, potentially with an independence from treatment.

But please, Dr. Alexander, if you can comment further.

DR. ALEXANDER: Jim Alexander from Chiesi medical affairs. Again, overall, we saw no difference. We looked very intensively at these 23 versus these 10 subjects for their history. I might mention that the history of previous exacerbation and previous IV antibiotic use was a male medical record determination look-back. This

was not something from memory. This was based on the records in the clinics.

There were actually more differences than I showed earlier because if you look at the 23, first of all, they both had the same disease severity, but then if you look at the number of hospitalizations, 21 of the 23 had 4, 11, 5, 1 versus lower numbers in the control groups.

This was an imbalance pretty obvious to look at. Also, the pseudomonas prevalence was also imbalanced.

DR. EMERSON: But again, if we're going to go on this, then I'm going to do a stratified analysis. I'm going to say, then, within each group, let's stratify by this prior history, and let's look at the rate of exacerbations within those groups. And I'm coming up with -- and the only data I have to do this on is the prior history of greater than or equal to 1. But I'm coming up with a difference of 42 percent versus 17 percent.

So if we're just pretending that for whatever reason, you did a -- well, I guess this

would be something like a 5 to 4 randomization ratio in that stratum, whatever it is. As I look at those statistics, I'm still seeing that there looks to be a greater tendency to magnify it.

I'll grant you, I do expect it to be predictive -- well, to be prognostic, but I'm afraid it's also predictive, is my problem. I'm afraid that there's also an increased chance that you are magnifying this tendency to have the exacerbations.

DR. PARRY-BILLINGS: If I may ask Dr. Alexander to comment further, and perhaps also we could explore the analysis that you proposed and perhaps come back to you after the break with further clarification because we appreciate, and indeed it was the reason we flagged this particular U.S. subpopulation in our core presentation.

Please, Dr. Alexander?

DR. ALEXANDER: Thank you again. Jim Alexander from Chiesi. I want to show you one analysis of subjects who had no history of previous exacerbations coming into the study. 351 of our

adult subjects in studies 302 and 303 answered no, and the medical records confirmed they had no history of previous exacerbations.

You see that, in that group, which represents over 50 percent of the subjects in both these studies, there was a 3-fold lower rate of pulmonary exacerbation in the Bronchitol-treated group, and these exacerbations were, as you may see, less severe than those in the control group.

These data and another subpopulation, albeit a very large subpopulation, show that we, again, don't see an effect of Bronchitol in increasing the risk of exacerbation.

DR. PARRY-BILLINGS: May I suggest, if I may --

DR. EMERSON: Just one comment, though, and then we can just go on to other things because I think the numbers speak for themselves. But this is not restricted to the U.S. population, and this is the opposite group that I was worried about, which is those patients who are at risk for an exacerbation because they have a history of an

exacerbation; is there a safety signal in that group?

Telling me that there isn't in a group that we have less statistical power because it's a lower rate doesn't answer that question.

DR. PARRY-BILLINGS: If I may, just to perhaps elaborate further and also to put some U.S. clinical context on these exacerbation findings, if I might ask Dr. Flume to comment because this is an area, I know, of his clinical expertise.

Thank you, Dr. Flume.

DR. FLUME: Yes. Thank you. Patrick Flume. I spent the last decade of my life focusing on pulmonary exacerbations in cystic fibrosis patients, and we have learned a lot about what predicts events, how they respond to events, and such.

If I could have the slide that shows the exacerbations with the pseudomonas that Dr. Alexander just had up. To make it more complex, since you're looking at a subgroup analysis, there are other risk factors that predict

events. So as has been stated, the history of events, and specifically IV events, are the strongest predictor of future events. Actually, if you design the study specifically looking at exacerbations as your primary endpoint, you really want to power your study for those patients who have a history of events, particularly those that have 2 or more events.

But the other highly predictive factor is also shown on this screen, and that's the prevalence of Pseudomonas aeruginosa. It was greater in the U.S. population, that had exacerbations had pseudomonas, because in order to meet the definition of the protocol-defined exacerbation, they had to get IV antibiotics.

We don't have many choices of oral antibiotics for pseudomonas. So if there is a situation in which the clinician has thought an intervention is warranted, it is much more likely to get IV therapy as opposed to oral antibiotics.

DR. AU: Great. Dr. Gillen?

DR. GILLEN: I have two actually. One is a

follow-up to what Dr. Emerson brought up just a moment ago. When you guys go back to look at that analysis, I was actually coming at this from a slightly different point of view, which is, when you look at the time to first exacerbation versus the rate which is going to allow people to have multiple exacerbations count, you see quite a bit of a difference, particularly in the analysis presented by the FDA.

So when you go back to re-examine those data and stratify on that, I would like to also see the time to first exacerbation versus the rate that's accounting for multiple events within side of a subject. It's a very similar concern in that if you are predisposed to a high risk of exacerbations, are we perpetuating that risk?

There's an attenuation when we only go to time to first, so I'd like to request that one when the sponsor goes back to that analysis.

My question that I was coming up with prior to Dr. Emerson's comment is much more broad, though. And I'm trying to get a feel for the study

design in 303 versus 301 and 302. Really, I'm trying to understand the rationale behind the sample size choice in those, and I'll tell you where I'm coming from.

We have almost a 2-fold increase in the sample size for 303, and my understanding of reading the briefing documents is there were questions at the previous advisory committee about the clinical relevance of the observed effect on FEV.

So given what was observed in those 301 and 302 studies, why are we powering a study for 303 to detect an even smaller minimally detectible difference? I'm just trying to get a feel for what was the rationale behind the choice of sample size; what were we looking to detect in terms of FEV; what was the clinical relevance thinking of what that minimum detectible difference would have been?

DR. PARRY-BILLINGS: If I take your comments in turn, if I may, you requested further analysis that we may provide after the break, evaluating both time to first as well as multiple.

So this is noted, and we'll try to come back to you after the break with that point.

In terms of the power calculation for 303 and to the specific question you've asked of the magnitude of effect size, in the power calculation, it was 80 mL.

DR. GILLEN: How did that change from 301 and 302? Those were much smaller studies.

DR. PARRY-BILLINGS: To address further details on the power calculation, I might ask my statistical colleague, Dr. Muraro, to come to the microphone. Thank you.

DR. MURARO: Annamaria Muraro, Chiesi statistician. You can see in this slide the assumptions that were used in 303 studies to define the number of patients to be randomized.

The treatment difference assumed was 80 mL, and this was based on the result of 301 and 302 studies in the adult population. We assume a standard deviation of 230 mL, a power of 90 percent, a two-sided alpha level of 5 percent, leading to 350 patients that had to be randomized.

Since there was uncertainty about the standard deviation, a blind sample size reassessed was also planned. The 80 mL was selected based on the result of previous studies, and there was no purpose to define with this 80 mL any link with the clinical relevance.

DR. GILLEN: My point here, though, is 301 and 302 started with some assumption about what the minimally clinically relevant difference would be to detect. How did that relate to this 80 mL that you're now pooling from 301 and 302?

I'm trying to get an idea for what the clinical relevance of this change in FEV is and what the original thinking on 301 and 302 was, and then that updated, if you will, prior, after you've seen the 301/302 data, to design the 303 study.

DR. PARRY-BILLINGS: Dr. Muraro, I don't know if you're able to comment further on the specifics of the power calculations, and then perhaps we can add a comment from the clinical experts on clinical relevance.

DR. MURARO: Annamaria Muraro, Chiesi

statistician. I could say again that the power calculation was based on results observed in previous studies. Indeed, there was no reference saying that this 80 mL is considered clinically relevant in the study protocol.

DR. PARRY-BILLINGS: You're pushing more specifically on clinical relevance, so if I may ask Dr. Flume to return to the microphone to talk to that.

While he does so, I should emphasize that, as you probably know, within the context of CF disease, there isn't a predefined numeric threshold for clinical relevance as is more typical, perhaps, in asthma, where we have an MCID of 100 that is commonly used in such trials.

DR. GILLEN: I understand, but I'm assuming there is some rationale for choosing the sample size in 301/302. I'm wondering what the rationale was behind the FEV difference that you were powering around in 301/302.

Now, I hear it's prior studies. That's fairly vague. And again, there must be some

thought to what the clinical relevance of that minimum detectible difference would have been. And I'm wondering why it changed when you went from 301/302 to 303.

DR. PARRY-BILLINGS: Perhaps we can come back after the break with the specifics on the numerics for you, but perhaps, Dr. Flume, since you're at the microphone, it may be helpful to put it into clinical context.

DR. FLUME: Yes. Thank you. Patrick Flume. This is a chronic progressive lung disease, and the natural history of lung disease in CF patients is loss of lung function. If I could have first the slide at the change in lung function from the population just to demonstrate what we see in our patients from the CF patient registry data.

When we're in the clinic with these patients, know that our patients are keenly aware of -- the patient registry data, please -- their FEV1. We teach it to them. We talk about it. They know these numbers. So when they come to clinic, they're really motivated to what the

changes might be. Actually, in the clinic, when lung function is stable, has not changed, that's a good day, and when it's gone up, that's a great day. So they get very depressed when those numbers come down.

What I am trying to show you is to look at that progressive loss of lung function in these patients; then if I could just jump to the hypertonic saline slide again. When we look at the basic mechanism of action in what we see with hypertonic saline -- and I use a lot of hypertonic saline. I prescribe it to my patients. We coach them, we teach them, and we encourage them to take this medication because we believe that it works.

What you see here is that change in lung function is comparable to what we see what has been reported with hypertonic saline. I would again state that I think the CF community has argued that that is a clinically relevant difference because they are also prescribing hypertonic saline to the majority of their patients. So in my view, this is a clinically meaningful difference.

DR. GILLEN: Since you brought that slide up, just for clarification, that's prescriptions, not use. Right? I mean, do we know that those patients were using?

DR. FLUME: [Inaudible - off mic].

DR. GILLEN: Sorry. So in terms of clinical relevance, we have a prescription, but whether patients are actually using that and adhering to that is slightly different, is it not?

DR. PARRY-BILLINGS: The confirmation from the experts was that, indeed, this is the correct interpretation of those data. Indeed, we know from adherence or compliance studies with hypertonic saline, this is not a therapy that is so readily adhered to. But nevertheless, there is an intention by the physician through the prescription to commit to that therapy.

DR. AU: Just for the committee, I just want to let you know that we've been taking notes about who's raised their hand, so we're just going in order, so just to let you know. Dr. Kelso?

DR. KELSO: I have, I guess, sort of three

sets of questions. While we're on the hypertonic saline, is it correct that use of hypertonic saline was an exclusion criteria because, in some respect, we're thinking of the mannitol as a substitute for hypertonic saline?

DR. PARRY-BILLINGS: Shall I take that first question? Sorry. You indicated you had a number of questions.

DR. KELSO: Yes, I do, but certainly, you can answer that, if you would.

DR. PARRY-BILLINGS: To this first part of your question, correct, the use of hypertonic saline for maintenance use of hypertonic saline was a prohibited medication on entry into the trial. However, the sporadic or periodic use of hypertonic saline was not excluded and did indeed occur during the trial.

In terms of your question on positioning, because I understood from your question that flows to how is the product positioned with respect to hypertonic saline, I can perhaps ask Dr. Schwarz to come to the microphone.

Dr. Schwarz is from Germany where Bronchitol is approved, so he can speak to the real-life clinical practice of prescribing both Bronchitol and hypertonic saline, and this might address your question on positioning.

Thank you, Dr. Schwarz.

DR. SCHWARZ: Thank you. My name is Carsten Schwarz from Berlin, Germany, and I'm the head of the Cystic Fibrosis Centre at the Charite University Hospital, and I'm also the chairman of the CF Conditions Council in Germany. Our center has more than 500 patients, so with this number, it's one of the biggest centers in Europe and the biggest one in Germany, and we are happy that we have Bronchitol now since 2012.

If I would try to reflect the use of Bronchitol, I mean, it's usually on an individual basis, where we try to implement new drugs and discuss those drugs with the patients. But regarding Bronchitol, I would say there might be three different groups.

One group is not tolerating hypertonic

saline, for example, so these patients need another option or an alternative. Then there are patients, although they are inhaling already Pulmozyme, hypertonic saline, and maybe other things, they still have a lot of mucus that they can't get rid of. So this is the second, maybe the biggest one, and so they're still suffering from this mucus.

The third one is that there are patients who want to have an easier way or a faster way to inhale drugs, therefore, they are using Bronchitol to get rid of their sputum a bit quicker, faster, and their clinic time is less.

These are, I would say, the three different groups we see in Germany.

DR. KELSO: The other question about saline, we saw that at least one prior study, the absolute increase in FEV1 with hypertonic saline and the mannitol is about the same. In the mannitol studies, there was no decrease in exacerbation rate and no improvement in the quality-of-life measures.

Do we have data on exacerbation rates and

quality-of-life measures from hypertonic saline studies?

DR. PARRY-BILLINGS: Yes. I can ask Dr. Flume to talk to that, but while he moves to the microphone, the short answer is yes. This study, which we refer to as the Elkins study, was a New England Journal paper, and they did measure exacerbations and showed an effect.

This was a 12-month study, a 12-month study, and also, very importantly, the event rate was around 0.9 exacerbations per year in the Elkins study, in the hypertonic saline study, as compared to 0.2, 0.2, in study 303; so coming back to the number of events being an element to allow us to measure a treatment benefit.

Please, Dr. Flume, if you could talk further.

DR. FLUME: Thank you. Patrick Flume. As was just stated, the Elkins study did actually show not just the changes in lung function, but in exacerbations. And when the pulmonary guidelines committee reviewed that, both of those factored

into the recommendation that it would become a routine therapy.

But there are striking differences between these studies that doesn't dissuade me from believing this is going to work as well, so if I could have the slide of the PDPE across all of the studies, not just looking at the event rate, but in the Elkins study, 40 percent of patients had an exacerbation during the study.

When you look at the proportion of patients who had an exacerbation in the 303 study, you see that's only 13 to 14 percent. And as we know, if you want to power a study to show a reduction in exacerbations, you need to demonstrate that you've got patients who are really at risk because you've got a different population here.

Similar numbers in 302, and we can look at study 301 where now the proportion of patients having events was starting to increase, you can see a nominal change in favor of Bronchitol. So those are some of the key differences between those studies.

DR. KELSO: Then finally, the results have been presented in absolute increase in FEV1, and I'm wondering if you have representations of the same data in percent predicted FEV1, and also if you have something akin to a scatter plot or dot plot comparing the group, so we can see, rather than just the mean values, what the spread is.

DR. PARRY-BILLINGS: To answer the last part of your question, I don't believe we have a scatter plot to show you instantly, but allow me to -- if we can have the slide of the FEV1 changes in the three studies as expressed by percent predicted, I understand that's the focus of the question.

This is the slide on the screen now. In terms of the key messages from this slide, the first is that there is a consistent therapeutic benefit of Bronchitol in blue versus control in pink across the three studies.

The second point, I think to your question, is that the magnitude of the treatment effect expressing FEV1 in this way is at or around

2 percent. The other aspect of the data that may be helpful, but sticking with the data expressed as FEV1 percent predicted, is a responder analysis.

In this presentation, as you can see in the title, this is in a responder analysis looking at the proportion of patients whose FEV1 as a percent predicted improved by 5 percent. You saw the mean change in the previous slide, which is 2 percent, but these are the responders above 5 percent.

You can see across the studies a similar message. The data is indicating a consistent therapeutic benefit of Bronchitol in blue versus control.

DR. KELSO: Thank you.

DR. AU: Dr. Parad?

DR. PARAD: I have three questions, hopefully short. One is, I'm wondering whether there are any sort of equivalent of wash-out data in 303, whether you did follow up on re-function testing after some period of time off the drug and/or whether any data are available from 301 or 302 on that, just to give a sense of whether there

was a return to baseline or worsening after coming off the drug.

The second question is regarding use of correctors. I'm wondering whether you have any stratification by patients who were on correctors, since that might affect pulmonary lung fluid and may also show some kind of responder difference.

Then thirdly, I'm interested a design question, how you improved your attention and what you had to do to keep those patients in the study that dropped out in the other studies.

DR. PARRY-BILLINGS: I take them in reverse order, if I may. In terms of measures taken from a clinical operations point of view at the sites, having been alerted that with the point of attention of dropouts in the previous trials, all the clinical investigators were encouraged to ask the patients.

Of course, it couldn't be mandated to stay with the study assessments, so it was a really practical measure taken at the sites. And indeed, we saw that that played out, so data were collected

for patients who discontinued study medication, but nevertheless, completed the 6-months assessment regimen.

The second question was about CFTR, and we appreciate that's a very important question. Dr. Donaldson talked about the era of CFTR modulators. Again, if I may ask Dr. Schwarz to speak to that since he is treating patients with both classes of therapeutics.

Whilst he's moving to the microphone, if I can just clarify, in the 301 and 302 study, there were no patients on CFTR modulators. This was a chronological consequence of the timing of those studies. In 303, there were, if I remember correctly, around 7 patients, so relatively a low number of patients who were on CFTR modulators.

Dr. Schwarz, if you can talk to your clinical experience, that might be helpful to address this point.

DR. SCHWARZ: Carsten Schwarz. Yes, Bronchitol is an important part of the therapy of our patients. We have more than 150 patients on

Bronchitol right now, and we have, I would say, 180 to 200 patients on modulator therapy, so including Kalydeco, Orkambi, and also Symkevi, that's called in German, tezacaftor/ivacaftor.

What we see is that there is an improvement, especially in the sinuses, where the fluid is not that thick anymore. But if it's in the bronchial system, we have the experience that the patients got rid of their sputum with CFTR modulators in the central airways, but not in the small airways.

So the patients are still using all their inhale therapy. We are not at the level where we can say you can stop any kind of their inhaled therapy. We would wish to do so, but with this treatment, what is on the market right now, there is no change in inhaled therapy.

DR. AU: Did you have a follow-up? Yes, go ahead.

DR. PARRY-BILLINGS: No, not a follow-up, but we didn't address the first question. We were working backwards.

DR. PARAD: The question was wash-out.

DR. PARRY-BILLINGS: Yes. The question was on washout. I'm not sure if we have the data to show you immediately, but in principle, since Bronchitol was evaluated in the studies as a chronic therapy, twice-daily therapy, and as you've heard, the central pathological role of mucus in the airway, we would anticipate that a change and improvement in lung function to be maintained would require the patient to continue treatment.

You were asking about the specifics, I think, of the time profile of change, and perhaps we can clarify that later. But the principle of the therapy is that it would need to be maintained to maintain the lung function benefit.

DR. PARAD: I was really asking more from the standpoint of additional reinforcement of your finding of a positive effect, that when you take the drug away, there's a change --

DR. PARRY-BILLINGS: I see. Sorry, yes.

DR. PARAD: -- back to baseline, and also in some cases, when some of these drugs are

removed, there may actually be an overreaction, and you'd drop below the original baseline.

DR. PARRY-BILLINGS: Yes. Sorry. I understand the point you are making. Again, if I may, in terms of stopping or not be able to use Bronchitol, Dr. Schwarz, if you could speak briefly to perhaps some experience you've had with patients who have initiated therapy, continued therapy, and then for whatever reason have not been able to maintain the regimen.

DR. SCHWARZ: Carsten Schwarz again. I think the main selection is done at the beginning when they do the mannitol tolerance test. And then, once on the treatment, usually they stay on the treatment.

So there might be some difficulties when patients experience an exacerbation because, then, it's sometimes a bit harder for them to inhale. But exactly at that moment, we motivate them to stay on the treatment because it's very useful in doing this phase of exacerbation, and we have experience that it gets through this exacerbation a

bit quicker and easier than without it.

During our experience over the 7 years, when looking back, there were only single patients who stopped the treatment regarding hyperactivity. I think the mannitol test is very important at the beginning, but we also use them for other drugs for inhaled antibiotics.

For example, with inhaled antibiotic, we sometimes have calls from patients because they get dyspnea at home, and we never saw such cases with Bronchitol.

DR. PARAD: So just to clarify just one more time, from a study design standpoint, you did not then collect pulmonary function data at some point in time after patients exited the study?

DR. PARRY-BILLINGS: Annamaria Muraro, my colleague statistician, can talk to the specifics of the data that we did collect because, as said, it was a feature of design enhancement of study 303 to continue assessments after termination of study indication.

DR. MURARO: Annamaria Muraro, Chiesi

statistician. We have summarized this in these slides, numbers to give you and the data about a patient who discontinued treatment, 37 patients in Bronchitol and 44 in control.

The majority of them continued in the study, 36 and 41 in the Bronchitol and control arm. We had 22 patients versus 31 in the control who had at least 1 FEV1 measurement during the off-treatment period or after-treatment discontinuation; 13 of them in the Bronchitol and 21 in the control completed this study while off treatment.

We can even show the trend in those 22 and 31 patients with data during the off-treatment period. In this slide, we have presented the data from those 22 patients randomized to Bronchitol. If we look at the line starting from the bottom, this is the line of patients who were treated for less than 6 weeks and all measurements were taken off treatment. We can see that the change from baseline in those patients is below zero or around zero or negative.

If you look at the curve on the top, this is representing patients who were treated for less than 14 weeks, so the first assessment taken off treatment was at week 14. In these patients, the effect was maintained until week 26.

Then we have the third group of patients, and I'm referring to the line in the middle. These represented patients who are treated for 14 weeks at least, but they perform the assessment at week 26 of treatment. In this case, we see that they returned to their baseline value.

DR. PARRY-BILLINGS: So small numbers, but I think it confirms the point that you were looking to address.

DR. AU: Great. Thank you. Dr. Schell?

DR. SCHELL: Thank you. Karen Schell, Kansas University. I just have a question, as a respiratory therapist treating patients with a variety of lung diseases over the years, compliance and instruction of delivery devices is so variable. I was curious to how the patients had consistency across in instruction or proper use of the dry

powdered inhaler versus the other possible ways they were taking medicine, and if that was re-evaluated throughout the study, because our patients, just because they've been taught once, doesn't mean that they still can do it properly throughout the study. And I was curious how that was handled during the study itself

DR. PARRY-BILLINGS: Of course at this initiation of the study, patients were trained on how to use the DPI, the 4 simple steps that I illustrated earlier. I'm looking for confirmation from my colleagues in terms of whether this assessment, whether correct inhaler technique was confirmed at the end of the study, which I understand is what you're looking to --

DR. SCHELL: Correct, not just at the end, but many times, while there are patients at the bedside, from one visit to the next, have developed habits that are not conducive to the equipment, and we have to reinstruct on a regular basis to make sure they're compliant and able to perform adequately.

I was curious if, during your pulmonary function or any time during the test, they were re-evaluated by observation, particularly, to see if their technique was proper because how we take a metered-dose inhaler, versus a dry powdered inhaler, versus an aerosol is completely different, and the medication delivery is susceptible to their technique. So I was just curious if this was monitored throughout the study.

DR. PARRY-BILLINGS: Yes. I can confirm that, indeed, as is routinely done, inhaler technique was re-confirmed at each visit. In terms of a specific assessment of correct technique -- and again, I'm just looking to my colleagues to make a confirmation.

Dr. Dell'Anna, if you could, talk to that, please?

DR. DELL'ANNA: Carmen Dell'Anna, Chiesi. Yes, compliance was monitored, and in particular, education was done at the beginning of the studies and during the visit. Additionally, if the patients missed some of the capsules, because

compliance was assessed by returned drug capsules, they were re-trained and they were re-educated to confirm that they understand the technique.

DR. SCHELL: Thank you.

DR. AU: Dr. Redlich?

DR. REDLICH: I had three questions since discussing the capsules. It's 10 capsules that are 40 milligrams each. Could you just clarify how that's actually administered?

DR. PARRY-BILLINGS: In terms of how the patients administers the 10 capsules, the simple graphics, the simple graphic that I showed earlier was the procedure for one capsule, if we could look at that slide again.

These are the four steps to deliver one capsule. Insert the capsule, puncture the capsule, inhale. This is the procedure for one capsule and this is essentially repeated 10 times.

DR. REDLICH: So how long would it take to do all 10 capsules?

DR. PARRY-BILLINGS: Around 5 minutes; so that would compare one of the points that our

clinical colleagues were making, was that this compares rather favorably to the duration for setting up, administering, and cleaning, et cetera, a nebulized therapy.

DR. REDLICH: That's the same dosage given for everybody, no matter their size or weight?

DR. PARRY-BILLINGS: Correct.

DR. REDLICH: Thank you. I believe the study was completed in early 2017. Has it been published in a peer-reviewed journal?

DR. PARRY-BILLINGS: Not yet.

DR. REDLICH: Has it been submitted for publication?

DR. PARRY-BILLINGS: No. It's not been submitted. The full manuscript has not yet been submitted.

DR. REDLICH: Then the third question, the last question, related to the durability of response. The table 17 from the FDA briefing document looked like over time, the magnitude of the difference in FEV1 had declined from 60 mLs down to 39 mLs.

Just related to the durability, you showed one slide that was looking at adverse events that showed the open-label extension. Do you have that data on the study 303? Did that one include an open-label extension for a year? And if so, is there data on the FEV1 endpoint?

DR. PARRY-BILLINGS: Yes. I can address both parts of your question, if I may by showing -- allow me 4 quick data slides. The first is you asked about the durability during the study, so if we can look at the 303 FEV1 profile on the same slide as the integrated analysis.

If we look at study 303, the effect size, you can see is the delta written across the top of the blue line there. Numerically, there's a small decline. I don't know if that's what you were referring to. However, if we look at the integrated analysis on the right-hand side, the effect size, as you can see, across the 6 months of the trial are rather well maintained.

The second set of data that I'd like to share --

DR. REDLICH: Could you just explain the integrated analysis?

DR. PARRY-BILLINGS: Yes. In short, the integrated analysis is the combination of the data and analyzed in a consistent manner across all three clinical studies.

DR. REDLICH: I'm not sure I understand that, but maybe others do.

DR. PARRY-BILLINGS: So we have the three phase 3 studies, and in all those, the FEV1 data from those three studies was essentially pooled and analyzed in a consistent manner. This is what we mean by the integrated analysis.

DR. REDLICH: Oh, okay. I understand.

DR. PARRY-BILLINGS: Focusing on study 303, the primary and most recent study -- sorry; if we could have the responder analysis -- this is a responder analysis looking at those patients who improved FEV1 by greater than 100 mLs, and along the bottom, you can see, we made this comparison of the two treatments at week 6, week 14, and week 26. So the difference, the therapeutic effect of

Bronchitol based on this highest predefined responder threshold is maintained throughout the trial.

The final set of data to address the durability of the response during the 26-week period is the completer analysis, if I might see the completer analysis. This, we think, can be justified like the graph of the completer analysis, FEV1 plotted against time. These are patients who completed the trial.

So if we're addressing the question, if patients continued treatment throughout the 6 months and all FEV1 measurements were taken to address your question on durability, there again you can see the FEV1 effect is maintained.

To the final part of your question, which was about the open-label extension, just recapping on the design study, 301 and 302 included an open-label extension. So of course, in looking at the data, we have to keep that design element in mind. This is open label and non-comparative.

Nevertheless, these are the FEV1 data. So

at the left, on the Y-axis is change from baseline in FEV1 expressed in liters. Week 26 refers to the end of the double-blind phase, and those 130 patients are the patients who agreed to continue in the open-label extension.

Those who completed the open-label extension to 52 weeks, that was 113 patients and that data is shown on the right-hand bar. So you can see that the treatment effect is maintained during that period.

If we look at 113 patients at week 52 and just look at those patients at week 26, the numbers are essentially the same at 84 mLs at week 26. I hope I addressed the question.

DR. REDLICH: Do you have a comparison to the control group at the 52?

DR. PARRY-BILLINGS: Again, in the open-label extension, this was not --

DR. REDLICH: You didn't follow the controls, obviously. Okay. Then just the final question was, in terms of how many people you needed to screen to get the 420 bigger number --

DR. PARRY-BILLINGS: Yes. I think the most useful slide, perhaps, is the slide that Dr. Alexander showed, showing the patient disposition.

This was a slide shown by Dr. Alexander. The number of patients treated in the double-blind phase or extension was 508 at the bottom row, and those that entered were 896. The percent of patients who passed the mannitol tolerance test in study 303 was 92 percent. So 92 percent of all patients screened by the MTT were able to move into the studies.

DR. REDLICH: It was actually a slightly different question, which was, there were exclusion criteria such that if you were on normal saline or some type of transplant -- so a certain number were screened that didn't meet the inclusion criteria. So related to that, if someone was on normal saline, were they offered participation to stop taking the normal saline or how did that work?

DR. PARRY-BILLINGS: As mentioned earlier, if a patient was on normal saline -- on hypertonic

saline, rather, they were not --

DR. REDLICH: That's what I meant.

DR. PARRY-BILLINGS: -- permitted to continue as a maintenance dose because, clearly, this would have confounded the analysis.

As Dr. Flume showed, Bronchitol and hypertonic saline are acting at a similar point in the pathological cascade. So maintenance dose of hypertonic saline was prohibited and not taken during the studies. However, if a patient needed a short burst, if you like, of hypertonic saline, that was permitted.

DR. REDLICH: But still in terms of how many were screened to get the 400 --

DR. PARRY-BILLINGS: Perhaps we can come back with the specifics on that point after the break.

DR. AU: Great. We have a number of questions. Right now, we have 1, 2, 3, 4, 5, 6, 7, 8; so just to put everyone that -- if I've seen you, I have your name down.

Why don't we go back to Dr. Emerson?

DR. EMERSON: Yes. I have some questions about the missing data analyses, and particularly the sensitivity analyses, which are crucial, but were presented in the briefing book, but were not presented in your presentation. I just would like some clarity on exactly what was done there.

The first question -- well, actually just a statement -- is I'm assuming the true estimand of greatest clinical interest is how would this drug work in chronic use among those patients who would be willing to keep taking it, that is to say, they could tolerate it, they seemed to respond to it, and they complied. But for regulatory and scientific reasons, we have to think about randomization, so there is this clash that we need to worry about.

As I understand it --and again, I am most interested in the tipping-point analyses, and I personally regard that your best missing data analysis would be the tipping-point analysis with 00 is the analysis that ideally you should have chosen.

I have great problems with baseline observation carried forward, and the panel on missing data in clinical trials was just unanimous, that that's a very, very bad thing to do. So that's not withstanding.

But the tipping-point analysis is useful, but if I understand, you centered that analysis on imagining that patients resumed to what their average effect was, and in the multiple imputation, you dealt with the variability. Is that correct?

DR. PARRY-BILLINGS: To explain the tipping-point analysis, if I may ask Dr. Muraro to move to the microphone, and perhaps we can share a summary slide to take you through the approach used in the findings.

DR. MURARO: Annamaria Muraro, Chiesi statistician. We performed a tipping-point analysis to evaluate the robustness of study results as recommended by the FDA. I would like to show you the result of this analysis applied on study 303.

After multiple imputation of missing data

in both treatment arms, we assign penalties, penalties to the control arm and penalties to the Bronchitol arm.

DR. EMERSON: Before I can understand this, I need to understand how you've done your multiple imputation. If I understand correctly, it seems that on those patients for whom you were missing data, you first imputed a baseline observation for them using the idea of what their baseline was, but trying to put some variability on that in your multiple imputations. Then your penalty was added to that in each of the -- I believe it was 2,000 imputations or 1,000 imputations you did, but again, it was centered on baseline.

DR. MURARO: No, this is not correct. The tipping point was performed following four different steps. The first step was to define a monotone pattern, so post-baseline, missing data on the terminated [indiscernible] visits were imputed to obtain the monotonal pattern, assuming missing at random. With this second step, multiple imputation, and we applied 1,000 imputation, was

applied using a regression-based model, regardless of reason of withdrawal, assuming missing at random.

After these steps, we assign to the imputed data for patients in the control and in the Bronchitol penalties, penalties from zero in the control arm, then 20 mL, 40 mL, 80 mL, et cetera. Then for all combination of penalties, statistical analysis was performed in order to evaluate the treatment.

DR. EMERSON: So can I ask for some clarification? There are roughly, just conservatively speaking, an infinite number of analyses that I could call missing at random. I need to understand missing at random based on what? What were you conditioning on as you went through and imputed the data, saying this was missing at random based on the data that you have. What was that?

DR. MURARO: Based on the data viable, meaning missing at random, based on patients who remain in the study, and then we applied the

penalties.

DR. EMERSON: So you imagined that the subjects who dropped out of the study were just like anybody who remained on the study, and you did not use the partial data you had on that subject so far to try to figure out whether they were the more responding or the less responding.

DR. MURARO: We did, but there are 2 steps in implementation of the tipping point. The first step is to apply the multiple imputation with missing not at random in order to have the pattern, and then to apply the penalties.

DR. EMERSON: So again, this is very, very important, and I'm still having trouble understanding this. Your primary analysis was baseline observation carried forward, which again I think was very bad, but that's okay. So now, this missing at random, you are imagining that the subjects who dropped out, because you were -- now, was this a mixed model? By the way, that was also recommended heavily against in the monograph, not using a mixed model.

But was this a mixed model? So then, when you were assuming missing at random, the patient was more or less continuing on their trajectory relative to the population of treated patients.

DR. MURARO: Yes. But this is an intermittent step of the tipping point, so then we have --

DR. EMERSON: Right. I'm trying to find out when delta is zero what you were doing.

DR. MURARO: So the delta of zero, if we describe in this table the first row, for example, in the first row is a description of penalty to control equal to zero. This is the assumption when patients in the control arm were dropped from the study are similar to the ones who remain in the study, missing at random, while we had to assign a penalty of 100 mL to patients who dropped from the Bronchitol arm, meaning that patients in the Bronchitol arm should be 100 mL worse than patients who remain into the study in the Bronchitol arm with similar characteristics.

DR. EMERSON: But here is the crucial point

that I need to make certain I understand. In the mixed model, more or less, you're imagining that every patient has their effect. So there are some patients who maybe were on a downward trend, some patients who were on an upward trend, although I bet you weren't modeling this as a trend for each patient, but just where they were in the population.

If you are then imputing under a missing at random model conditioning only on that, then your imputation will tend to follow that trend. That's very different from assuming the average for the entire treatment population. So which was it?

DR. MURARO: I have to verify. I think we applied the missing at random approach, meaning that patients who discontinued were multiple imputed with a regression model that included treatment and other characteristics, including the observed value during the study, if I understood correctly your question. But I think, as a tipping point, we should focus on the penalty assigned.

DR. EMERSON: Well, only if I know what the

penalty is measured relative to. This is my next question. This is what I'm trying to do, but let's move on to this penalty question.

In order to interpret what this penalty is, I need to know the distribution of changes. Do you have data, just among the completers, what the mean and standard deviation is on the change from baseline at each of the 6, 14, and 26 time points?

As I do a back-of-the-envelope calculation, I do find a standard deviation around 0.26, which is sort of similar to your standard deviation of 0.23. I don't know what the correlation is, but it's looking like there's not real good correlation in these measurements.

Do you have just those descriptor statistics? Because that 0.100 is interpretable as the average among the people who have dropped out. And if that 0.23 standard deviation is correct, we're saying, well, those are just people randomly selected from the lower 85 percent. So dropping off the study was, per chance, biased because they weren't doing as well, but it's the bottom

85 percent, which is not that implausible.

So can you provide me the descriptive statistics by time --

DR. MURARO: We can certainly --

DR. EMERSON: -- and all I want is just the change from baseline, the mean, and standard deviation for each treatment.

DR. MURARO: Yes. We can certainly provide.

DR. EMERSON: Thank you.

DR. MURARO: I would like to add, tipping point provides robust results, considering that we were focusing on only one of the scenarios presented in that table, the scenario where we are assigning no penalty to the control arm, meaning that we assume that patients in the control arm are similar; patients who drop in the control arm are similar to the ones who remain in the study, while in patients in the Bronchitol arm, we are saying that those patients who drop should be worse by 100 mL.

We can even consider the other scenarios,

where we consider that patients in both arms would drop out worse.

DR. EMERSON: Let me tell you my take-home message from this slide because this is one of the ones that concerns me very much. Number one, we have to recognize that the control arm did not have as much adverse effects -- or certainly in the other trials. It's not as clear here, so maybe I'm not as concerned, but the idea of the adverse effects. So there may be a greater tendency for them to drop off when they have slightly better effects than it is for the control group.

But what I was very interested in, in this, is that the difference that the FDA asked for and you did -- and this is the correct thing to do -- the 2-parameter tipping point. But what often you see when you do the 2-parameter tipping point is it wasn't all that necessary, that the difference is there.

But what we see here is the difference between the two penalties was negative 0.1 when its control was 0, but it drops down to 0.06 as you

start building up the difference in there. And some of this is going to be the uncertainty in the models and things like that, relative to what's potentially going on, but this tells us that there is something more going on than the very simple procedure.

Of course, there is nothing in our data, absolutely nothing in our data that tells us which of these are the correct penalties.

DR. AU: We are at 10:23. We were supposed to take a break at 10:15. I know there were a number of people who still had questions, and we're going to hopefully have an opportunity to come back to those questions during discussion.

Why don't we go ahead and take a break? We have 6 minutes now for a break in lieu of 15. Cindy just allowed me to make it to 10:35, so a little bit of reprieve from the FDA, so 10:35, back here, please. Thank you.

(Whereupon, at 10:23 a.m., a recess was taken .)

DR. AU: In the interest of time, I think

we're going to get going again. If I could have everyone take their seats, please. I think we're a little behind schedule, but we'll make it up with volume.

So we'll now hear from the FDA. We'll now proceed with FDA presentations.

FDA Presentation - Khalid Puthawala

DR. PUTHAWALA: Good morning, everyone. My name is Khalid Puthawala, and I'm a clinical reviewer in the Division of Pulmonary Allergy and Rheumatology Products. My training is as an adult pulmonologist and critical care physician.

I'd like to thank the panel members for coming out today and sharing their expertise with us. I'd like to thank the CF community for participating in clinical trials that really allow the agency to help it achieve its ultimate goal in furthering public health.

We've heard the sponsor's presentation and discussion on DPM, and the agency will now present its perspective on efficacy and safety of DPM.

This is an outline for the approximate

one-hour presentation by the FDA. I'll first begin by giving an overview of the clinical program for DPM. My colleague, Dr. Torres, will then provide the statistical review of efficacy in detail, and then I'll return to provide some clinical context for the efficacy, go over the safety, and wrap up with a benefit-risk discussion.

Let's start with the overview of the clinical program. As has been discussed, CF is a serious disease with considerable morbidity and mortality, and no cure. This table shows many of the common therapies used by CF patients. The top two-thirds of the table shows that the treatment landscape from a pulmonary standpoint, until fairly recent, has focused on treating symptoms and sequelae of the disease, which involved secretion management using mucolytics, bronchodilators, inhaled antibiotics, and other measures not shown.

More recently, some of the newer medications that have been approved for CF, sometimes referred to as CFTR modulators, focus on the more proximal cause of CF, the CFTR protein.

Those therapies are shown in the bottom one-third of the table.

I'll now discuss aspects of those recent approvals and the basis upon which those approvals were made. All of the recent approvals within the Division of Pulmonary Allergy and Rheumatology Products between 2012 and 2018 for CF have been the CFTR modulators. These recent approvals demonstrated FEV1 improvement within the approximate range as shown.

Studies used to support these approvals generally included exacerbations as a secondary endpoint along with other clinically meaningful measures, as shown, and had overall support from the secondary endpoints.

The general point to note here is effect size and the support from the secondary endpoints, and the agency will focus on this point repeatedly throughout the presentation for the advisory committee members to consider effect size and clinically meaningful endpoint support.

Let's focus our attention now on the DPM

program. I'll first start by going over the regulatory history. In 2012, the sponsor submitted their clinical development program that, at that time, included two phase 3 studies, 301 and 302, and we'll be discussing those in more detail further along.

Those were reviewed by the agency and several efficacy and safety concerns were noted. In light of these issues, an advisory committee panel was convened in January 2013, and the vote at that time was unanimous against approval.

The agency then took a CR action, stating that in order to move forward, an additional trial would be needed that demonstrated substantial evidence of efficacy and balanced safety. The sponsor then conducted study 303 and resubmitted their program in December 2018.

Let's look at some of these issues in a bit more detail. In the prior submission in 2012, there were two phase 3 studies. As I just noted, there were significant issues with efficacy. First of all, study 301 had significant statistical

issues, and these were mostly due to the large amount of missing data from study dropouts.

To give one a sense of this, 37 percent of DPM-treated patients in this study dropped out and 27 percent of control patients dropped out. For all of these dropouts, efficacy data was not collected, which led to major statistical problems that could not be overcome despite the multitude of sensitivity analyses that were conducted. For study 302, DPM did not show a statistically significant improvement over control.

Beyond these issues was the question that we will be raising for the panel to discuss today, which was raised in 2012 as well, which was whether the small treatment effect seen in the prior studies, albeit with statistical concerns, was clinically meaningful, especially in light of the lack of secondary endpoint support. From a safety perspective, there were concerns raised with hemoptysis, particularly in the younger population.

So with these problems with efficacy and safety, an advisory committee was convened. The

advisory committee reviewed the data and felt that overall DPM had not demonstrated an acceptable benefit-risk profile. They voted unanimously against approval.

For safety and efficacy, individually considered, the majority of the votes were still against DPM. However, several comments made by panel members at that time were directed at considering adults separately from the pediatric population.

In other words, many panel members, whether they voted for or against DPM in regards to safety or efficacy, made comments suggesting that the overall decision-making process for them was clouded due to some conflicts in the adult versus non-adult data.

Given the agency's review of the program at that time as well as the panel's decision, a CR action was taken in March 2013. In the CR letter, the deficiencies that I mentioned were outlined, specifically that substantial demonstration of efficacy was lacking because of treatment-related

dropouts, a lack of statistical significance, and a lack of secondary support.

From a safety perspective, the main deficiency was hemoptysis concerns in the younger age group, so overall, the benefit-to-risk ratio was not in favor of DPM. The agency recommended at least one future trial that demonstrated substantial efficacy and addressed safety concerns, specifically the hemoptysis concern. And related to this, the agency recommended that adults be the study population.

Shortly thereafter, a meeting with the sponsor occurred in May 2013. At that meeting, it was discussed that the most expedient path forward would be to adopt an identical trial design for study 303, but to minimize missing data and dropouts. It was recommended to exclude younger patients in light of the safety concerns that had been raised in 301 and 302.

The agency confirmed its agreement with the primary endpoint of FEV1 over 6 months, but it was noted that this primary endpoint would have to be

statistically significant and clinically convincing. Along with this, the new study 303 results would have to trend favorably for exacerbations.

This new study, which would be study 303, would be the tie breaker study, and the agency emphasized the importance that this study would have in a resubmission, given the problems with the prior studies and the post hoc nature of their analyses. As we move forward in the presentation, I'll remind the audience of this fact.

So study 303 was conducted, and a pre-NDA meeting occurred in November 2016. The agency at that time reiterated the importance of exacerbations as secondary endpoints, as well as the importance of the CFQ-RRD.

Also, the importance of assessing FEV1 at 26 weeks in addition to the primary endpoint, which is FEV1 over 26 weeks, was noted. Some of the necessary details to understand the difference between FEV1 at 26 weeks versus FEV1 over 26 weeks will be gone over by my colleague, Dr. Torres.

With this, study 303, was submitted as a completion to the clinical development program.

The sponsor's development program has already been described in detail, so my overview will be brief. There were 5 early-phase studies, most of which were open label. Dose determination was primarily based on study 202. Study 202 was also open label. It was a cross-over study over 2 weeks with 48 patients, and the results suggested the 400-milligram twice-a-day dose, the highest dose studied, to be the best candidate moving forward into phase 3.

Additionally, there was no effect with the 40-milligram dose, so 50 milligrams was chosen for control to match for mannitol's sweet taste.

The remainder of our talk will be on the three phase 3 studies, which constitute the focus of the current submission. Please note that studies 301 and 302 are from the original submission. However, as the target population has changed to adults only, the analysis of results from those studies is post hoc adults only. To

reiterate, this is one reason why study 303 is felt to be crucial.

Let's look at the three studies in a bit more detail. Here's a table showing the three phase 3 studies. The studies in blue were from the prior submission, and the most recent study, study 303, is shown in white. These were all randomized, double-blind, controlled parallel group studies of 26 weeks' duration comparing DPM 400 milligrams twice a day to control, which was DPM 50 milligrams twice a day.

In all three studies, patients continued their routine CF medications with the exception of hypertonic saline. CF patients with recent hemoptysis were excluded. Sample sizes shown on this table for studies 301 and 302 include all patients and not just the adult subgroup.

Next, we'll look at the important differences between the studies. Key differences are shown in this table, focusing on study design and study population differences. Again, blue shading represents the prior studies and the newest

study, study 303, is shown in white.

One very important difference between study 303 and the other studies was in its design in that study 303 had a specific provision to follow patients after treatment discontinuation. To clarify, in study 301 and 302, if a patient stopped study drug, they were withdrawn from the study and, importantly, no further data was collected.

As Dr. Torres will explain moving forward, this compromised the interpretability of these earlier studies considerably. In contrast, study 303 continued following patients who stopped study drug unless they withdrew entirely from the study.

Another important difference that has been mentioned was in regards to the study populations' ages. The earlier studies included patients 6 and older, whereas study 303 was patients 18 and older, and that is related to the prior hemoptysis concerns in the other population.

So the results we will be reviewing from

the prior studies are post hoc adult subgroup analyses, and thus carry less weight, and this will be touched on further by Dr. Torres. Also, it's important to highlight that study 301 did not include any U.S. patients. This also will be later reiterated in the study results that Dr. Torres will discuss.

Lastly, I'll mention what is fairly obvious, that study 303 was the most recent study. Note that a 4-year time span is present between the completion of study 302 and the start of study 303.

Based on these important differences, one can understand why study 303 plays a crucial role in the current benefit-risk assessment. Let's look at study 303 in a bit more detail.

I've shown diagrammatically the study design here. You'll see that patients were screened with the mannitol tolerance test initially and hyperresponsive patients were excluded. In other words, you had to pass the MTT and meet eligibility criteria to begin treatment.

The treatment period was 26 weeks, during

which there were 4 visits. The first post-treatment initiation visit was at week 6, the second at week 14, and the third at 26 weeks. Key efficacy and safety assessments are shown at the bottom. We'll focus in on efficacy.

The primary endpoint used, as I've mentioned before, was FEV1 over 26 weeks, and this was identical to the prior studies. The secondary endpoints in study 303 are listed here, and I'll remind the audience of the regulatory history I discussed a few slides back. The agency noted that exacerbation-related results and CFQ-RRD would be important considerations given their clinical relevance.

Next, let's look at the disposition of study 303's patients. In this table on the right, I show study 303 completers, non-completers, and early treatment discontinuations. I'll make a few points.

First of all, you'll note that there was no observed disproportionality between treatment arms in early study withdrawals, about 11 to 12 percent

in each arm. Next, you'll note that the treatment discontinuation rate is not the same as the study withdrawal rate due to the specific provision made in study 303's protocol to allow treatment discontinuation without study withdrawal, as I mentioned in the previous slides.

Lastly, overall, these rates of study withdrawal were lower than the prior studies, particularly study 301, in which early study withdrawal occurred in 37 percent of DPM patients and 27 percent of control patients. Note that these numbers are for the total study population, which include pediatric and adolescent patients.

Because of these disposition results showing less disproportionality and less dropout than the prior studies, the statistical results that Dr. Torres will be discussing will not have the same issues as the prior studies and will be more robust in that sense.

Next, we'll look at the demographics. The demographics of the patient populations studied in 303 were balanced and what one may expect from an

adult CF population. The mean age was about 27 to 29 years, and the majority of the population was Caucasian.

As noted before, study 303 did include U.S. patients, about a quarter of the study. And the baseline disease characteristics such as prior hemoptysis, lung function, mutational composition, and pseudomonal prevalence were also generally balanced between arms.

Although not an imbalance, it is worth mentioning that likely due to the timing of the study, there were no patients on CFTR modulators in study 303.

At this point, I think we're ready to go into the efficacy results for study 303, and I'd like to turn it over to Dr. Torres.

FDA Presentation - Cesar Torres

DR. TORRES: Thank you, Dr. Puthawala.

Hello. I am Cesar Torres, and I'm a statistical reviewer in the agency's Division of Biometrics II. As Dr. Puthawala noted, I will be presenting the review of efficacy. Dr. Puthawala

will then provide clinical context for efficacy before presenting the review of safety and discussing benefit-risk considerations.

Specifically, I will go over the endpoints and the planned analyses for these endpoints for study 303, and note some important differences from those of studies 301 and 302. I will then present results for the primary and key secondary efficacy endpoints, as well as for Cystic Fibrosis Questionnaire-Revised respiratory domain.

Finally, I will present some subgroup analysis results before summarizing the statistical efficacy findings and handing it back to Dr. Puthawala .

The primary endpoint for study 303, as well as for studies 301 and 302, was change from baseline in FEV1 over 26 weeks, not at 26 weeks. The primary analysis model included assessments at weeks 6, 14, and 26. Change from baseline to each visit was given equal weight.

For study 303, the primary analysis used a mixed effects model for repeated measures,

adjusting for treatment, rhDNase use, pooled country, visit, and interaction term between treatment and visits, baseline FEV1, and baseline percent predicted FEV1.

To target the treatment policy estimand for the primary analysis of this endpoint, all observed data were used, even those collected after treatment discontinuation. A modified baseline observation carried forward approach was used for patients with missing data for specific reasons.

In particular, for each patient who withdrew from the study due to adverse events, death, physician decision, or lack of efficacy, the baseline observation for that patient was carried forward. For patients who withdrew from the study for other reasons, missing data were not imputed and the primary analysis assumed that these data were missing at random.

In contrast, for the primary analysis for this endpoint in studies 301 and 302, post-baseline missing data were not imputed. In the primary analyses for the two prior studies, all post-

baseline missingness was assumed to be at random, even that resulting from patient withdrawal due to the reasons listed previously.

To control the family-wise type 1 error in study 303, a hierarchical testing procedure was used. If the primary analysis results from the primary efficacy endpoint were found to be statistically significant at the two-sided significance level of 0.05, then the first hierarchical endpoint, change from baseline over 26 weeks in forced vital capacity, was to be tested at the same significance level.

If the primary analysis results for this endpoint were also found to be statistically significant, then the next endpoint would be tested at the same significance level and so on. If at any point in the hierarchical testing procedure primary analysis results for a formal hypothesis test were found to not be statistically significant, formal hypothesis testing was not performed for any remaining endpoints in the analysis hierarchy.

Cystic Fibrosis Questionnaire-Revised respiratory domain was not in the analysis hierarchy, but I will also present results for this endpoint.

Change from baseline in forced vital capacity over 26 weeks was analyzed in the same manner as for the primary efficacy endpoint, including the handling of missing data. Time to first PDPE was analyzed using a Cox proportional hazards model that adjusted for treatment, pooled country, rhDNase use, and number of IV antibiotic-treated pulmonary exacerbations in the year prior to screening.

Key secondary efficacy endpoints related to antibiotics, hospitalizations, and PDPE rates were each analyzed using a negative binomial model that adjusted for the same covariates; that is, they adjusted for treatment, pooled country, rhDNase use, and number of IV antibiotic-treated, pulmonary exacerbations in the year prior to screening. For each of the antibiotics and hospitalizations endpoints, no imputation procedure was performed

for the primary analysis.

However, the statistical analysis plan for study 303 prespecified an imputation procedure for the primary analysis of the PDPE rate. Specifically, for each patient who withdrew before week 26 with no observed instances of a PDPE, the number of PDPEs was imputed using that patient's pulmonary exacerbation count in the previous 12 months. Further details regarding this imputation procedure are provided in the agency's briefing document for today's meeting.

Conversely, the statistical analysis plans for studies 301 and 302 did not prespecify any such imputation procedure for the primary analysis of this endpoint.

The following results are based on the analyses performed by the agency's statistical review team. In most instances, numerical differences between the agency review team's results and the applicant's results are small to the extent that the conclusions drawn are the same.

Recall that for the primary analysis for

FEV1, a modified baseline observation carried forward approach was used for the handling of missing data. With this approach, the adjusted mean change from baseline was 65 milliliters for the DPM arm and 10 milliliters for the control arm. The adjusted mean difference of 55 milliliters was statistically significant with a two-sided p-value of 0.018. The observed data are consistent with the adjusted mean difference being between 9 and 101 milliliters.

This analysis had the potential of being limited by the prespecified handling of missing data. One consideration regarding this approach was that for patients whose baseline observation was carried forward, the variability in measurements would be underestimated, potentially resulting in a confidence interval and a p-value that overestimated the precision in estimation of the treatment effect difference.

For this reason, the agency's statistical review team considered one of the prespecified sensitivity analyses for this endpoint to be

important. This sensitivity analysis used a pattern mixture model approach that incorporated multiple imputation.

This approach generally made similar assumptions as the modified baseline observation carried forward approach regarding the mean trajectory of the outcome for each patient who withdrew from the study.

However, the pattern mixture model approach more appropriately estimated the variability in measurements for patients who withdrew from the study. Details regarding this approach are provided in the agency's briefing package for today's meeting.

With this sensitivity analysis, the adjusted mean change from baseline was 63 milliliters for the DPM arm and 12 milliliters for the control arm. The adjusted mean difference of 51 milliliters was statistically significant with a two-sided p-value of 0.028. With this analysis, the observed data are consistent with the adjusted mean difference being between 6 and 97 milliliters.

How do these results compare to results from analogous analyses performed with data from adults in studies 301 and 302? From the perspective of the agency's review team, this comparison is difficult to make due to the concerns the agency had regarding 301 and 302 during the review of the original NDA submission.

Specifically, one, the protocols for studies 301 and 302 did not have provisions to continue following patients for regularly scheduled assessments after treatment discontinuation; two, the data missingness rates in study 301 were high; and, three, study 302 failed to meet its primary objective.

In this figure, the red dotted line indicates the missingness rate for the DPM group while the blue line indicates the missingness rate for the control group. As can be seen in this figure, in study 303, the missingness rates were at around 1 to 2 percent by week 6, 5 to 7 percent by week 14, and 9 to 12 percent by week 26.

Conversely, by week 26, according to the

solid lines, 301 adults had missingness rates of 35 to 41 percent, and according to the dashed lines, study 302 adults had missingness rates of 12 to 25 percent.

Again, given that the missingness rates in study 301 were high and study 302 was a failed study, the agency review team's position is that the following comparisons are limited.

This figure shows the treatment effect difference and corresponding 95 percent confidence interval for each of studies 301, 302, and 303. The dashed and solid black lines for the confidence intervals are to visually indicate that comparisons of results from study 303 to those of studies 301 and 302 are limited.

As shown previously, the treatment effect difference in study 303 was estimated to be 51 milliliters. Conversely, in each of studies 301 and 302, the estimated difference was 78 milliliters in adults.

The results of the pattern mixture model sensitivity analysis for study 303 along with other

sensitivity analysis results for this study suggest that the results for the primary analysis in study 303 appear to be statistically robust for the primary endpoint of change from baseline over 26 weeks in FEV1.

However, we found that this endpoint effectively puts more than two-thirds of the weight on change occurring during the first 54 percent of the 26-week period under consideration and less than one-third of the weight on change occurring between weeks 14 and 26.

Therefore, the analysis results could be largely driven by data collected in the first 14 weeks, leading to the analysis not estimating efficacy over the treatment duration period as intended.

Thus, a natural question arises that is important from a regulatory perspective. Is the treatment effect sustained through the end of the 26-week period? To help address this question, we also looked at change from baseline at each of weeks 6, 14, and 26 in FEV1.

Once more, the color red is for the DPM arm and the color blue is for the control arm. In this figure, the by-arm point estimates and 95 percent confidence intervals for the change from baseline to each of the 3 visits is presented.

The numbers at the top indicate the corresponding point estimates and 95 percent confidence intervals for the treatment effect difference. For example, the change from baseline at week 14 just past the halfway point of the 26-week period was estimated to be 56 milliliters higher in the DPM group than the control group with the observed data being consistent with the difference being between 2 and 109 milliliters higher.

However, the change from baseline at week 26 was estimated to be 39 milliliters higher in the DPM group than the control group, with the observed data being consistent with the difference being between 18 milliliters lower to 96 milliliters higher.

The point estimate of the difference here

was noticeably lower than those for change from baseline at week 6 and at week 14. Given the potential attenuation of the treatment effect by week 26, another question of interest from a regulatory perspective is, is there any support from the secondary efficacy endpoints?

The analysis results for the first key secondary efficacy endpoint in the analysis hierarchy were not statistically significant, with a two-sided p-value of 0.169. Therefore, all remaining endpoints in this hierarchy are not statistically significant and we do not report p-values for these endpoints.

Of the results presented in this table, those for PDPE rate are worth noting. For the PDPE rate per patient per year, the adjusted rate ratio was estimated to be 1.55, with the observed data being consistent with the adjusted rate ratio being between 0.99 to 2.41.

The results for the prespecified analysis for this last endpoint have raised some concerns within the agency's review team. Once more, we

recognize that there is some interest in comparing results from this study to those from studies 301 and 302 in adults only.

We remind everyone of comparisons across the studies being limited due to the reasons Dr. Puthawala and I have previously stated. The comparison of PDPE rate results specifically across studies is further limited by the fact that the statistical analysis plans for studies 301 and 302 did not prespecify any imputation procedure for the primary analysis of PDPE rates while the statistical analysis plan for study 303 did.

This figure shows the treatment effect ratio and corresponding 95 percent confidence interval for each of studies 301, 302, and 303. The dashed and solid black lines for the confidence intervals are to visually indicate that the comparisons of results from study 303 to those of studies 301 and 302 are limited.

As shown previously, in study 303, the adjusted rate ratio for this endpoint was estimated to be 1.55, with a 95 percent confidence interval

of 0.99 to 2.41. Conversely, for study 301, adults only, the adjusted rate ratio was estimated to be 0.77, and for study 302, adults only, the adjusted rate ratio was estimated to be 1.35.

Due to the importance of these comparisons being limited, we stress again that, one, the protocols in studies 301 and 302 did not have provisions for following patients after treatment discontinuation; two, the data missingness rate in study 301 was high; three, the statistical analysis plan for each of studies 301 and 302 did not prespecify an imputation procedure for the analysis of this endpoint; and four, the analyses using data from adult patients in studies 301 and 302 are post hoc.

Finally, the Cystic Fibrosis Questionnaire-Revised respiratory domain score was analyzed in the same manner as the primary efficacy endpoint. The treatment effect was estimated to be 0.87 when comparing DPM to control, and the observed data are consistent with the treatment effect difference between being 1.4 lower to 3.1

higher.

We do not present analysis results from adults in studies 301 and 302, but the results are generally consistent across the 3 studies.

There is some interest in comparing the effect of DPM on adult cystic fibrosis patients in the U.S. to the effect of DPM on patients not in the U.S. The following results comparing U.S. to non-U.S. patients are all from post hoc analyses.

In this figure, the color orange corresponds to U.S. patients while the color green corresponds to non-U.S. patients. The figure shows the by-region treatment effect difference and corresponding 95 percent confidence interval for each of studies 302 and 303.

The dashed and solid lines for the confidence intervals are to visually indicate that comparisons of results from study 303 to those of study 302 are limited. For change from baseline over 26 weeks in FEV1, the treatment effect comparing DPM to control in study 303 was observed to be slightly higher in U.S. patients with a point

estimate of 68 milliliters compared to non-U.S. patients with a point estimate of 50 milliliters.

The previous considerations apply regarding the comparison of results from study 303 to results of study 302, adults only. However, a similar trend, as in study 303, was observed in study 302, adults only, when comparing U.S. patient results to non-U.S. patient results.

As shown in the table here, the study 303 treatment effect difference between the DPM and control arms for each of number of days on antibiotics and number of days in hospital due to PDPE seemed to be similar between the U.S. and non-U.S. populations.

For time to first PDPE, the hazard ratio of 2.02 for the U.S. population was noticeably higher than that of 0.87 for the non-U.S. population. For this endpoint, it is not clear if the observed difference in hazard ratios between the regions is due to chance or if perhaps there is a concerning signal here.

Regardless, the numerical difference in

hazard ratios for this endpoint suggests that a difference between rate ratios for PDPE rate might have been observed as well.

In this figure, the color orange corresponds to U.S. patients while the color green corresponds to non-U.S. patients. The figure shows the by-region treatment effect adjusted rate ratio and corresponding 95 percent confidence interval for each of studies 302 and 303.

The dashed and solid lines for the confidence intervals are to visually indicate that comparisons of results from study 303 to those of study 302 are limited. As stated previously, the PDPE adjusted rate ratio in the overall study 303 population when comparing the DPM arm to the control arm was 1.55 with a 95 percent confidence interval of 0.99 to 2.41.

However, the adjusted rate ratio in study 303, U.S. patients, was estimated to be 2.93, with a 95 percent confidence interval of 1.36 to 6.32. Conversely, the adjusted rate ratio in study 303, non-U.S. patients, was 1.06 with a

95 percent confidence interval of 0.61 to 1.86.

The by-region results for this endpoint along with those for time to first PDPE suggest that DPM may have an undesirable effect on PDPE rate in U.S. patients. However, given that all of these analyses are post hoc, the ability to draw conclusions may be limited.

In summary, the primary analysis results for the primary efficacy endpoint of change from baseline over 26 weeks in FEV1 were statistically significant and appear to be statistically robust, given the results of sensitivity analyses for this endpoint. However, the observed effect size was marginal.

It is difficult to compare study 303 analysis results to results from study 301 and 302, adults only analyses because of the issues previously raised such as the protocols for studies 301 and 302 not having provisions for patients being followed after treatment discontinuation and the high amount of data missingness in study 301.

Furthermore, the analyses in studies 301

and 302, adult patients, were post hoc. Finally, there is no support from the secondary endpoints.

Thank you for your time. I'll hand it back to Dr. Puthawala for him to provide some clinical context for the efficacy discussed and to review safety before he wraps up with a benefit-risk discussion.

FDA Presentation - Khalid Puthawala

DR. PUTHAWALA: Thank you, Dr. Torres.

I will be delivering the last presentation for the FDA this morning. Here's the outline for my presentation. I'll review some of the key efficacy information that Dr. Torres discussed and add a clinical perspective. I'll then go into safety and the major safety categories listed here.

I'll then summarize the safety and provide a framework upon which a discussion of overall benefit versus risk can be initiated.

Let's start with the primary endpoint results for the three studies. This is the slide that Dr. Torres showed earlier. This shows the primary endpoint, FEV1, over 26 weeks for the three

phase 3 studies. The treatment effect size or the difference between arms is shown on the right with the confidence intervals

It should be noted, as he mentioned, that although these studies are shown together on the same diagram, there were some major statistical problems in the previous studies, as mentioned.

He visually indicated with the dashed lines, the studies that provide us limited information, and thus study 303 was the most statistically robust study. I'd like for us to again focus on the treatment effect size as shown on the right.

Next, we'll look at the durability of this treatment effect. This slide, which shows FEV1 over the treatment duration, was also shown to us by Dr. Torres, and I'll go over a few points.

Given the relevance of discussing durability in regards to a medication intended for chronic use, the agency had asked for an analysis of FEV1 at 26 weeks. The rightmost set of points represents that analysis. The main point is that

the magnitude of the treatment effect appears to attenuate over time.

Dr. Torres reviewed the findings of a treatment effect size, as shown at 26 weeks, observed to be lower than at earlier time points and that the confidence intervals shown at the top now included the value 0. Let's take a small step back and consider FEV1.

The issue is, in what context do we interpret these FEV1 treatment effects and how is FEV1 as an endpoint? In this program, FEV1 is being used as a measure for overall pulmonary function, and that is reasonable, as FEV1 has been used as a primary endpoint for many, if not all, of the recent CF drug development programs.

I had discussed earlier the range of FEV1 improvement seen in some of the more recent approvals, about 3 to 13 percent predicted. Although not presented as percent predicted, the observed treatment effect difference of approximately 50 milliliters is 1.2 percent predicted.

It's important to note that FEV1 does not directly measure how a patient functions, feels, or survives. DPM, which is not a bronchodilator, is expected to improve pulmonary toilet and secretion clearance. In that setting, we would look to other supportive measures as we have done for prior approvals.

One would expect that meaningful improvement in overall function would translate into meaningful improvement in other measures such as exacerbations, infections, hospitalizations, and/or symptoms.

So with those points in mind, the agency was concerned with the small treatment effect estimate that I showed you on the previous slide, and we will ask you to discuss this treatment effect size and consider it in your benefit-risk assessment.

The agency was also concerned with the potential treatment effect attenuation seen at week 26. This is important to consider as well, given that this would be a chronically administered

medication and could be, if approved, a medication that a CF patient may use for his or her lifetime.

Given these concerns, we would then naturally look to the secondary endpoints for support in more clinically meaningful measures.

Here are the secondary endpoints from study 303 that Dr. Torres discussed. We focused on exacerbation-related endpoints, shown in the red box, as they are the most clinically important of the secondary endpoints in the DPM phase 3 program. Those include time to first protocol-defined pulmonary exacerbation, PDPE, antibiotic usage due to PDPE, hospitalizations, due to PDPE, and the rate of PDPE.

You'll notice that 3 of the 4 secondary endpoints shown in the highlighted box are trending in favor of the control arm and not in favor of DPM, and the PDPE rate, arguably the most important of the exacerbation endpoints, suggests that exacerbations may be more common with DPM use.

Let's see how the PDPE rate compares across studies. Here's the slide that Dr. Torres showed

you comparing three studies for PDPE rates. Again, cross-study comparisons notwithstanding, the slide notes the PDPE rate in the phase 3 studies. The data for the prior studies is post hoc and thus limited in that respect and is shown with the dashed lines.

Remember that in the statistical analysis in the prior studies, there were no prespecified imputation procedures, as Dr. Torres went through in detail. What we see is that in studies 302 and 303, there were trends unfavorable for DPM. You'll remember that these were the two studies that included U.S. patients, so, understandably, the next step in our analysis was to look at the U.S. subpopulation.

Dr. Torres showed you this subgroup analysis for U.S. and non-U.S. patients in studies 302 and 303. Again, as he pointed out, the dashed lines are to visually indicate that results from 302 are limited.

What we see here is that the U.S. population shows numerically higher rates of

exacerbations than the non-U.S. population in studies 302 and 303. And remember, study 303 was a statistically more robust study overall for the reasons previously mentioned.

To clarify, the post hoc subgroup analysis of U.S. patients in study 303 suggests that DPM-treated CF patients have a numerically higher rate of exacerbations than controlled-treated U.S. patients. And the unfavorable trends seen in the overall population is accentuated in the U.S. population. So the rate ratio was quite concerning to the agency.

Let's discuss some of the implications of the secondary endpoint data that I just reviewed. It's clear that exacerbations are of significant clinical importance. They play a large role in the quality of life for CF patients, a large role in healthcare cost, and quality time lost.

Each exacerbation comes with considerable burden. Exacerbation measures have been used in all the recent approved therapies as secondary endpoints, so the emphasis that we are placing on

this is nothing new.

As I noted previously, we had discussed with the sponsor that a 26-week study may not be able to capture enough exacerbation data to reach statistical significance, so we would be looking for trends, and that the expectation was that trends would be in a favorable direction for DPM.

What I've shown you on the previous slide is that there are point estimates that do not favor DPM. There was a suggestion of an increased rate of exacerbations with DPM compared to control and with similar trends noted for time to first exacerbation.

Particularly concerning were the worsened trends in study 303 in the U.S. population, and that is of obvious interest, as we are a U.S. regulatory body. One additional important secondary endpoint that the agency had asked the sponsor to look at and that measures quality of life is the CFQ-RRD. You'll recall from Dr. Torres' presentation that there was no significant difference observed between arms in

study 303 and also for the other two studies as well.

So overall, in the entire phase 3 program, there were no secondary endpoints that provided significant report, and in fact, some concerning trends were seen.

To summarize the efficacy, let's first talk about the primary endpoint. We've discussed the problems with the prior studies and their post hoc adult analyses. It is likely that the treatment effect estimate, depending on the statistical analysis method used, lies somewhere between 50 and 80 mLs.

We would like the panel members to focus on the clinical relevance of this small treatment effect. Understanding that we are not assessing a bronchodilator, but rather a medication that by clearing airway secretions, should lead to clinical improvement in other clinically meaningful measures, we naturally look to the secondary endpoints. But there is no significant support from any secondary endpoint in any of the phase 3

studies.

In contrast, trends in 2 of the 3 studies are in the opposite direction, which raised concern. Those concerns are increased when we further look at the U.S. subpopulation, which is the main population for which the agency would focus on.

To summarize, a small treatment effect on the primary endpoint of FEV1 is likely present, but without clinically meaningful secondary endpoint support, and in fact, with concerning exacerbation trends.

I'll now go over safety results. I'll start with a brief mention of exposure and then go over the main safety categories as listed here. In general, the exposure for this orphan disease population was adequate, with a median exposure of around 6 months.

What I've highlighted in the red box is that more patients in the DPM group had a duration under 3 months, and this speaks to the tolerability of the medication, which we will discuss further in

the upcoming slides.

It's also worth noting that the safety data here and in the upcoming slides is only from the adults in the phase 3 studies, which for studies 301 and 302 was about half of the study population, whereas it would represent the entire study 303 population.

This safety overview shows the major safety categories for the phase 3 pooled adult subgroup. It shows that in all categories other than deaths, there were more DPM patients with the listed adverse event type than control.

For some of the categories, the differences between groups are small and for others, more noticeable. The difference between arms for the categories other than death ranges from 1 to 4 percent.

Let's focus on serious adverse events and look at the breakdown. This table shows SOC in preferred terms for SAEs with greater than or equal to 1 percent frequency from the phase 3 pooled adult subgroup. I'll also remind everyone that in

the original submission, there were concerns regarding hemoptysis, so you see I've highlighted that box in red.

I will continue to highlight hemoptysis as we move forward, and the difference between treatment arms for hemoptysis SAEs in phase 3 adults was minimal.

Also, I've highlighted the most common SAE in the phase 3 program, which was CF exacerbation coded as condition aggravated. This, too, I will continue to highlight as we move forward to help understand why the agency feels that this may be a safety concern.

It's important to note that CF exacerbations as reported from an adverse event standpoint were not the same as the protocol-defined pulmonary exacerbations that we discussed in the efficacy review. These were investigator determined without any prerequisites.

You'll note that there were slightly more serious CF exacerbations in the DPM patients than control overall. I will be returning to CF

exacerbations as an adverse event of special interest.

Next here, I have adverse events that led to treatment discontinuations, and this table shows results with a greater than or equal to 0.5 percent frequency. Here, I've highlighted a few things. On the top line, you can see that overall tolerability of DPM was an issue, with more adult DPM patients discontinuing treatment as a result of an adverse event as compared to adult control patients, and that mostly was driven by respiratory symptoms, the next row down, of which cough was the most frequent. This is understandable knowing DPM's action as an airway irritant.

Now, I've highlighted hemoptysis and CF exacerbations again. While slightly higher rates of DPM discontinuation due to hemoptysis and CF exacerbations were noted as compared to control, the differences between arms were small.

Let's look at the common AEs. On this table of all treatment-emergent adverse events, those with a greater than 5 percent frequency or

greater than 2 percent difference between arms are shown. You can see that, overall, more DPM patients had adverse events, the top row, and the most common adverse event was CF exacerbations, the second row. Cough was noticeably more common in DPM patients, and as I showed you before, led to treatment discontinuation more commonly as well.

I'd like to now focus on two adverse events of special interest, hemoptysis and CF exacerbation. As I mentioned earlier, hemoptysis was a concern raised, particularly in the pediatric population in the original submission, and therefore, exploring that further is important to ensure that a similar concern is not present in adults.

Exacerbations will then be discussed, not only for the reasons shown on the previous safety slides, but also to see if a safety signal is present that correlates with the efficacy concerns seen for higher PDPE rates, especially in the U.S. population.

Here, I've shown hemoptysis events in all

of the major safety categories, excluding deaths, but I've separated out the original submission, studies 301 and 302, the left two data columns and study 303, the middle two data columns, and then the pooled data for all 3 studies is the rightmost columns.

As I mentioned several times, the hemoptysis concern in the original submission studies was mostly in the pediatric subgroup. But what can be seen here in the leftmost part of the highlighted region is that even in adults, hemoptysis related to some of the important safety categories was still more common in the DPM patients in studies 301 and 302.

In contrast, study 303 results do not replicate those concerns -- you can see that in the middle two columns -- with the end result in the pooled adult subgroup for all 3 studies being such that the difference from the original studies are dampened.

I'd like to next move on to exacerbations. On this slide, I've consolidated information, most

of which I've already shown you. I've already shown you CF exacerbations that were SAEs, CF exacerbations that led to drug discontinuation, and a listing of all CF exacerbations.

The main purpose of this slide is to show that in most of the safety categories, CF exacerbations were more common in DPM patients than control, albeit with small differences between treatment arms.

While the differences were small, the consistency of these small differences across multiple important safety categories raised some concern, and given the PDPE efficacy data results showing concerning accentuation in U.S. patients, we decided to look at that type of regional breakdown for CF exacerbation in the safety data.

Here is that breakdown. This is from the pooled adult subgroup data across all phase 3 studies comparing the U.S. study population to the non-U.S. population. The highlighted box shows a strikingly higher percentage of U.S. adult CF patients in the DPM arm, nearly double, having

serious CF exacerbations.

I'll remind everyone that we saw a similar concerning increase in PDPE rates in the efficacy data that we reviewed when we narrowed down to the U.S. population. These subgroup safety results are consistent with the subgroup efficacy results seen earlier and raises the concern even further.

To summarize, we just reviewed CF exacerbations as an adverse event of concern. There were more serious CF exacerbations in DPM patients, and this difference was particularly concerning when looking at the U.S. subgroup. Also, there were more CF exacerbations leading to treatment discontinuation and study withdrawals.

The original submission in 2012, upon review, had raised concerns for hemoptysis, however, for adults, those concerns are lessened by the results from study 303.

Lastly, DPM-treated patients had more cough that led to treatment withdrawal as well as certain other adverse events related to the known airway irritant effect of DPM, and this may pose a

tolerability issue.

Let's quickly review the key efficacy points and then look at efficacy and safety together to frame a discussion of risk versus benefit.

Here's the key efficacy data for adults from the phase 3 studies. This slide summarizes what could be considered two of the most crucial endpoints, the primary endpoint of FEV1 and the clinically meaningful secondary endpoint, PDPE rate.

The treatment effect estimate is between 50 to 80 mLs for FEV1 on the left, and the PDPE rate favors control in both studies 302 and 303, two U.S. studies. We reviewed the efficacy focusing on the primary endpoint of FEV1 and its small treatment effect size.

We've looked at the results from the individual phase 3 studies with Dr. Torres providing us details on the multiple problems seen in the prior studies and the post hoc nature of their adult analyses. We noted that study 302 did

not achieve statistical significance on the primary endpoint and that study 303, for a variety of reasons, was the most robust study statistically speaking.

With this in mind, the treatment effect estimate remains in the range of 50 to 80 mLs. Because this was a small effect, we looked at the secondary endpoints that included clinically meaningful measures such as exacerbation-related endpoints and CFQ-RRD.

From those measures, there was no significant support, and of those measures, the exacerbation rate, arguably the most important measure, trended unfavorably for DPM. This unfavorable trend was further accentuated in the U.S. population. This raised concerns beyond just discussion of clinical significance of a small treatment effect. We also briefly discussed the lack of support from CFQ-RRD scores.

When we looked at safety, no large differences between treatment arms were noted in the major safety categories, but overall, a

consistent small increased frequency of adverse events in multiple important safety categories for DPM-treated patients was noted.

We focused on CF exacerbations where, again, a small increase in the frequency for DPM patients was seen in several safety categories. What was most concerning from a safety standpoint was that the U.S. subpopulation analysis, similar to what was done for exacerbation efficacy data, showed a striking increase for serious CF exacerbations, and the consistency of safety and efficacy results for increased CF exacerbations was of particular concern.

So I would ask for the panel members to carefully keep these points in mind as we enter the discussion. Thank you.

Clarifying Questions

DR. AU: Great. Are there any clarifying questions for the FDA? Let me actually see who didn't get to speak last time. We have Dr. Marshall as well as Dr. Blake. Why don't we go in that order?

DR. MARSHALL: It's Gailen Marshall, University of Mississippi. I actually have a question for both of the FDA speakers, and it relates to a non-statistician asking these question.

The question relates to the fact that it almost seems that one could suggest that you're selectively enforcing statistical significance, things that are not significant, but would speak against the product you're describing as concerning and trending; yet in one of Dr. Torres' slides, and because there was no statistical significance, they didn't even report the numbers, yet they use those to express concern.

I submit that if the sponsor were to say that those were trends that supported their argument, it would be rather heavily argued.

Could they comment about that, please, just from a procedural standpoint, how they do that?

DR. PUTHAWALA: I'll answer first from a non-statistician point of view. When we looked at PDPE rate, some of the things that we focus on are

what we have focused on in the past with prior approval, so I didn't think that we looked at things in a different fashion.

DR. LIM: This is Bob Lim, clinical team leader. I think what you're getting at is maybe we're looking at trends in PDPE rate being unfavorable for DPM versus placebo, and you're wondering perhaps we're unfairly bringing that up when it's not statistically significant.

I think that with these presentations, we're careful to note the limitations of the analyses, that some of these were post hoc, the previous ones didn't win, and then we had noted that there were certainly limitations to it.

We are not saying that DPM is causing exacerbations. We are simply raising that as a concern because of these trends that we have seen, so I don't think we are applying this in an uneven fashion, per se.

DR. MARSHALL: If I can just ask for clarification. I'm not really suggesting that you're attacking or not attacking. I'm trying to

understand your weighting of statistical significance because it does seem to be different depending upon what parameter you're talking about.

So is the standard different if you're raising a concern -- I'm not saying that's right or wrong; I'm just asking for clarification -- as opposed to saying there is a clear difference that is statistically significant?

DR. LIM: This is Bob Lim again. I think there is probably a difference. For just raising a concern, it's just a concern.

DR. MARSHALL: That's all I'm saying.

DR. LIM: That would be the answer, then.

DR. AU: Actually, Dr. Blake, and then Dr. Tracy?

DR. BLAKE: Thank you. Kathryn Blake. I'd kind of like to better understand the enrolled population a little bit better so we know who was in this trial. I know you didn't go over the inclusion/exclusion criteria, but previous use of hypertonic saline was an exclusion. Was that any use or was that that they had been prescribed it

before?

What I'm trying to get at is were the patients then who enrolled in this trial, given that one of the other slides showed prescriptions, percent of patients was about 60 percent at the time this trial would have been enrolling.

So would the patients who enrolled in this trial have been previous users of hypertonic saline at any point?

DR. PUTHAWALA: My understanding is hypertonic saline during the treatment period was not allowed, but previous use was not an exclusion criteria.

DR. BLAKE: So I'm just wondering what percent of patients have been previous users and maybe discontinued it because they had problem with hypertonic saline, and then enrolled in this trial and also had problems with mannitol.

DR. LIM: We don't actually have those numbers at our fingertips. I don't know if the sponsor would have that.

DR. BLAKE: Okay. I did have one other

question, which hopefully you can answer. It had to do with the durability of response.

When you're looking at -- it was slide 17, looking at the trend downward. I'm curious, though, what was the percent change from 6 to 14 weeks, and then 14 to 26 weeks, and then 6 to 26 weeks for DPM, and what was it for saline?

Saline also decreased, so I'm just wondering what that change was within the saline group versus the percent change within those patients in the DPM arm.

DR. PUTHAWALA: Sorry. Just to clarify, by saline, you mean the control group which was 50 milligrams?

DR. BLAKE: Control, excuse me. That's what I meant. I'm sorry, the control.

DR. PUTHAWALA: I would look to my statistical colleagues to see it.

DR. BLAKE: Because I'm just looking -- the trend is the same for both. I just wondered if the magnitude of the change was similar for the control in the DPM arm.

DR. TORRES: I'm sorry. Can you repeat that question?

DR. BLAKE: Certainly. So it's slide number 17. In the DPM arm, there was a decrease that started between weeks 6 and 14 and continued through 14 to 26, but also in the control arm, there was a decrease between week 6 and 14, and then 14 to 26.

So I'm wondering what the percent change was for both the DPM arm and the control arm to see is this change a 4 percent and 5 percent change in DPM and also a 4 and 5 percent change in the control arm.

DR. TORRES: We don't have those numbers right now, but maybe during the break, we can get them and get back to you.

DR. BLAKE: Thank you.

DR. LIM: This is Bob Lim again. In regard to that question, we don't have that percentage, but I believe table 17 of the FDA briefing document on page 47 has the change from baseline in terms of milliliters.

DR. AU: Great. I'm going to go to Dr. Tracy, and then we'll come to the side.

DR. TRACY: Dr. Tracy. I'd like to circle back a little bit on the hemoptysis question. It's actually fairly simple. It goes with the exclusion parameters for 303. You mentioned recent hemoptysis was an exclusion criteria, and then recognizing the differences of hemoptysis as a safety signal between 301 and 302 compared to 303, so it looked like it was better.

I just don't recall, with 301 and 302, whether that same parameter was part of the exclusion criteria.

DR. PUTHAWALA: It was. The exclusion criteria did not change.

DR. AU: Actually, Dr. Emerson first, and then Dr. Brittain?

DR. EMERSON: Just a question, again, about Dr. Torres' slide 17. As you computed that, what sort of imputation did you use? Also, you were using measurements that, by then, 20 percent of the subjects were off study.

Is that you were just using their follow-up? I mean, not off study, off drug?

DR. TORRES: For these analysis results, I did use all observed data, including data collected after treatment discontinuation, and I believe that for these numbers, I used a pattern mixture model approach with multiple imputation, but I'll double-check that and get back to you.

DR. EMERSON: Do you have any particular feel for the amount that potentially -- did you do any analyses to look to see whether the amount that this decrease might go with being off the study drug and that the patients who stayed on it might have descriptively stayed more constant?

DR. TORRES: I did not look at that.

DR. AU: Dr. Brittain?

DR. BRITTAIN: In terms of the U.S. population results, I wonder if you have any sense of whether the U.S. population could be different from the non-U.S. population at baseline in terms of previous exacerbation rates, et cetera.

I'm not taking about the difference between

arms, just overall, I'm trying to understand why the U.S. population might have a different outcome than the non-U.S. in terms of any baseline characteristics.

DR. PUTHAWALA: I'm not sure if what I'm going to say now is going to answer that question fully, but the U.S. population, in terms of medication usage; for example rhDNase use is significantly higher than it is in the rest of the world. There are mutational compositional differences in F508.

I don't know if these are playing a factor, but these are some of the differences between the U.S. population and the non-U.S. population.

DR. BRITTAIN: So potentially, the U.S. population results are more generalizable to the -- the U.S. population results in your study may potentially be more generalizable to the patients here in this, which you don't know.

DR. PUTHAWALA: That's the intention of the analysis. Yes.

DR. BRITTAIN: I just wondered if perhaps

they were sicker in some way like -- you don't seem to be thinking that.

DR. LIM: Yes. There might have been some differences, but it's really hard to attribute that to the difference that we see. I think, ultimately, it's hard to know exactly how real the difference is, and if it is real, then what the causes are. I think that's one of the things that -- that's why we brought it up at this committee, to get you guys' input as to what your thoughts were on that.

DR. BRITTAIN: Thank you. One other quick question. On slide 19, as an example, from the statistical set --

LCDR CHEE: Stats or which one?

DR. AU: Yes, stats.

DR. BRITTAIN: There you go. Just again, for this slide and in general, I just want to make sure I understood -- you emphasized how in the 301 and 302, they didn't have the plan, the provision in the study to follow people up once they were taking drug or withdrew in other ways.

Here, when you're doing these post hoc analyses, you use the same statistical approach in this post hoc analysis for 301 and 302 as had been prespecified in 303. Is that correct in terms of dealing with the missing data?

DR. TORRES: In study 303, they prespecified this imputation approach. For studies 301 and 302, that was not prespecified. There was a tricky situation where in study 301, the data was not collected that would allow for that imputation procedure, so we had a choice of either doing the imputation for studies 302 and 303 or just doing it for 303.

Given that we feel that studies 301 and 302 are more comparable to each other than they are to study 303, our perspective was that maybe it made more sense to just analyze 301 and 302 in the same way, which was no imputation.

DR. BRITTAIN: There's no imputation in 301 and 302.

DR. TORRES: Yes.

DR. BRITTAIN: Thank you.

DR. AU: Actually, does the sponsor have a comment about the previous discussion?

DR. PARRY-BILLINGS: Yes. We had a data slide that we could share very briefly to address Dr. Brittain's question about the difference in the U.S. population because we absolutely understand the focus on the pulmonary exacerbations and understand the focus in the U.S. population.

If I can share this slide with you, if you focus your attention in the middle of the slide, this shows the percentage of patients with PEs, exacerbations, treated with IV antibiotics in the last 12 months, and also in the row below, the percentage of patients with exacerbations requiring hospitalizations.

As we mentioned earlier, as you can see, by chance, those patients randomized to Bronchitol had a much more intense, if you like, exacerbation history based on those two key parameters. Thank you.

DR. AU: Thank you for clarifying that.

Dr. Gillen?

DR. BRITTAIN: Can I have a brief follow-up on that?

DR. AU: Dr. Brittain, did you want to follow up?

DR. BRITTAIN: I just wanted to say that it seems like this is relevant to the question that was brought up through here about getting results stratified by exacerbation history or hospitalization, which I can't remember how it was defined previously.

Is that going to be provided?

DR. AU: We'll see. I mean, the request has been made of the sponsor, so hopefully after lunch, we'll be able to see that in discussion.

Dr. Gillen?

DR. GILLEN: Thank you. This is a question on Dr. Torres' slide 18. I just want to make sure that I'm fully understanding what was done in the analysis to be able to compare this to what the sponsor has presented for the PDPE rates, at 18, one prior to this. There we go.

Just to make sure, individuals that stopped

study prior to week 26, you used their prior 12-month rate that was observed prior to this study to impute their PDPE rates if they had no observed PDPE events. Is that correct?

DR. TORRES: Yes, That's correct. Specifically, if we could pull up the backup slide number 3?

Here, we have that for each patient who withdrew before week 14 with no observed PDPEs, then the number of PDPEs imputed was using half of the patient's historical pulmonary exacerbation count, rounded upwards. However, for patients who withdrew after week 14, the number of PDPEs -- withdrew with no observed PDPEs, the number of PDPEs was imputed using one-fourth of the patient's historical pulmonary exacerbation count, rounded upwards, according to the prespecified analysis and the statistical analysis plan.

DR. GILLEN: Was there ever any analysis performed where you just used your best estimate of what that rate was relative to the amount of time that you had not followed them for? I mean, that

seems to be the most natural thing to do.

DR. TORRES: No.

DR. GILLEN: Was there any accounting for uncertainty in any of this? This was just a straight plug-in estimator?

DR. TORRES: Yes. We recognize that this is a single imputation approach, and we did not perform any sensitivity analyses that maybe more appropriately accounted for the uncertainty in parameter estimation.

DR. GILLEN: Just a final thing; for your confidence intervals, then, is this just based upon a Poisson model or is this counting for overdispersion at all?

DR. TORRES: This used a negative binomial regression model.

DR. GILLEN: Just as the sponsor did. Okay. Thank you.

DR. AU: Yes, a comment from the sponsor.

DR. PARRY-BILLINGS: A one-sentence clarification if I may. There were in fact multiple imputation methods prespecified in the

303 study protocol. I understand the focus on this specific data point and the rate ratio of around 1.5, but the other multiple imputation showed different rate ratios at around 1.2. These are data that we could share to put into context if that was helpful.

DR. GILLEN: I think it would be very helpful.

DR. AU: Yes. Why don't we share that after discussion?

Dr. Kelso?

DR. KELSO: If the possible explanation for the worst exacerbation rate in 303 is that the patients were more exacerbation prone to start with, is it also true that since there was a trend in 301 toward a lower exacerbation, that they were less sick, and in 302, they also had a worse exacerbation rate going into the study?

If that's going to be the explanation for 303, does that same pattern hold for 301 and 302?

DR. PARRY-BILLINGS: As mentioned also by the agency, the exacerbation history was not

recorded in study 301, so we don't have the ability to look backwards at 301.

In 302, as indicated by Dr. Flume in his presentation, the exacerbation rate during the studies were higher, and we accept the limitations as flagged by the agency in the analysis of those studies. But in 302, where the exacerbation rate was higher, the data were trending in favor of Bronchitol.

DR. AU: Great. Dr. Que?

DR. QUE: Hi. Loretta Que. A question for the sponsor. I could not find this information. Adherence is really important in any clinical trial, and usually, during the study, adherence is improved.

When you see the waning here of the effect over time, what was going on with adherence with these patients, starting out with 10 tablets and then maybe they started dropping tablets, or can you tell us what was going on?

DR. PARRY-BILLINGS: Because we have the capsule-based medication as opposed to, perhaps, I

don't know, a multi-dose, metered-dose inhaler, we're able to monitor adherence quite carefully. In fact, in 303, the adherence was extremely high. It's around 98 percent, if I remember correctly, and this was maintained throughout the study.

DR. AU: Thank you. Dr. Schell?

DR. SCHELL: Thank you. Karen Schell. I just have a question regarding the U.S. differences regarding the pulmonary function, the FEV1. What are the rates for the U.S.?

Since FEV1 is the amount of lung function the person came to, were they lower to begin with than the other countries, not so much through the aspirations, but what were the PFT functions? Were they comparable on both sides?

I don't know if that was looked at, and I think I read something during the studies about that, but I'm not quite sure if the PFTs were comparable.

DR. PUTHAWALA: Just to clarify, we're talking about the U.S. subpopulation?

DR. SCHELL: Yes.

DR. PUTHAWALA: I don't have that, but I can try to get that to you.

DR. AU: We may have follow-up from the sponsor. Yes.

DR. PARRY-BILLINGS: We can share those data. They're on the screen now. Perhaps the easiest way to look at it is FEV1 percent predicted at baseline. If you run your eyes along the second row of this table, there was consistency across the groups and across the U.S. and non-U.S. population.

DR. AU: Thank you for that.

Dr. Parad?

DR. PARAD: Richard Parad. This is a question from the briefing document, figure 1. I was wondering if Dr. Torres or one of the statisticians would like to comment on what could be a different effect between males and females.

DR. TORRES: As a clarification, you asked about figure 1, right?

DR. PARAD: Figure 1 from your briefing document.

DR. TORRES: Yes, we have that. When we

looked at different subpopulations, the treatment effect estimate was trending in the other direction for women as opposed to men.

DR. PARAD: Just from looking at the confidence intervals, it looks like a pretty big difference. Is this something you considered or looked into any further than that?

DR. TORRES: We're looking at a lot of different subgroups here. If there was truly no difference among the different subgroups, I think, by chance, you might have some random highs or random lows. So from our perspective, we didn't see this as something that was too concerning as opposed to something like U.S. or non-U.S., where, a priori, we were kind of interested in those differences.

DR. KIM: This is Yongman Kim. We looked at the study 301 and 302 for the general difference, but we didn't see any specific detected differences.

DR. PARAD: So it was only in 303 that --

DR. KIM: That's my finding.

DR. AU: Great. Thank you.

Dr. Lederer?

DR. LEDERER: Thanks. Dave Lederer. I just want to get back to the point the statisticians on the panel had brought up about the rate ratios for exacerbations in 303 and in the U.S. population.

Do you just have rate ratios, like plain old rate ratios for these events? This is from a negative binomial model where you're imputing events after 26 weeks. Do you just have rates per person over rate per person-year? Do you have that?

DR. TORRES: I'm not exactly sure I understand what you're asking. Are you asking for an unadjusted rate ratio?

DR. LEDERER: Yes. So you have randomized groups, and you can compare the rates in one group to the rates in the other group. Is there any barrier to doing that?

DR. TORRES: There is no barrier to doing that. We can certainly compute it. We did not

compute it.

DR. LEDERER: Okay. To me, it seems like a critical element here, is you're going to ask us about the safety of this, and these findings about exacerbations and exacerbations in the U.S. are a safety signal.

I certainly understand what was done, but I don't quite understand why we didn't see just unadjusted rate ratios in 303 for exacerbations when you have the data. And the sponsor presented adjusted rate ratios if I remember correctly.

I don't know. Maybe I'm not smart enough to understand. Maybe the statisticians on the panel can help me out.

DR. TORRES: The whole idea of the adjusted rate ratio, it's still clinically interpretable. For example, the adjusted rate ratio, one might say is that among those of the same region, having the same rhDNase use, and number of IV antibiotic treatment pulmonary exacerbations in the year prior to screening, when comparing the DPM to the control group, the rate ratio is 1.55. So it still has a

clinical interpretation.

DR. LEDERER: I understand the clinical implication. It's a randomized trial. We could look at rates in one group versus rates in the other group.

DR. EMERSON: Can I just comment on how I'm looking at this is we've got a problem; that this was a secondary endpoint for efficacy. It fails there, but had it never been a secondary endpoint for efficacy, we would have treated it only as a safety endpoint and we would have -- again, this goes to Dr. Marshall's question about p-values being reported or not. Efficacy; we need the p-value. Safety, we need what we're scared about, and that's really what it comes down to.

So there are some issues about how we would treat this for those two different issues. And again, we're sort of back to what's our estimand. At one level, you could say we only care about things that happened among those people who will take the treatment forever, but in the randomized comparison, we have to worry about the differential

dropouts. Even when the rates are the same, we have to worry about that the reasons for dropping out were differential, and we don't really know what that is. So these are the difficulties in judging these things.

DR. AU: Great. I just have -- go ahead, Dr. Brittain.

DR. BRITTAIN: I don't know if this is at all what you were talking about, but it appears that both the sponsor and the FDA are adjusting for the same covariates. The difference seems to be how they're handling the missing data.

DR. AU: Did you want to address that? Yes, the sponsor.

DR. PARRY-BILLINGS: If it's helpful, since there were questions about the rate ratios and adjusted rates, I wonder if we could see the slide which shows those data; and also to the question on clinical context, the number of events.

This was a slide that was shown earlier with a focus on the left-hand side of the slide, study 303. In terms of the second road, number of

events, as you can see, in the overall population, the actual number of events is really rather low.

You asked about the rate ratio. These are the adjusted rate ratios around 0.2. As you can see in the earlier study 303, we're acknowledging the limitations from the agency on those studies, but you can see there they're substantially higher.

When we were referring to the hypertonic saline study, the Elkins paper from the New England Journal, the annualized rate ratio is 0.9, so very similar to our first pivotal trial, but much higher than in the more recent 303 study.

DR. LEDERER: Sorry. I know we're running out of time, but I have to respond to that. My understanding on the Elkins 2006 study is that there was a significant reduction on the rate of acute exacerbation on the order of a 10 percent absolute risk reduction. Is that not correct?

DR. PARRY-BILLINGS: Yes. As mentioned, that study was a one-year study and did report a reduction in exacerbations, and this comparison, the positioning, if you like, versus hypertonic

saline, I appreciate it's rather important for the argument.

If I may ask Dr. Flume, since he is very familiar with exacerbations and indeed that study, to perhaps provide extra color for you.

Thank you, Dr. Flume.

DR. FLUME: Thank you. Patrick Flume. Yes, the study did show a reduction in exacerbations using a definition that was not unlike the definition used here for protocol determined. But they did have not just an increased event rate per patient, but 40 percent of the patients had exacerbations compared to just 13 percent here.

So again, if you're designing a study specifically looking for that, you'd like to enrich your sample with patients who are likely to exacerbate.

The way I look at it is if I think about the mechanisms of action, what we're trying to accomplish with our patients, I think of this product as very similar to hypertonic saline. We

see a comparable change in lung function. We see comparable issues of tolerability. It fits into our paradigm of treatment. So from that standpoint and the safety, I think we would expect similar results.

DR. PARRY-BILLINGS: If I may add -- and I appreciate we have to keep time short -- drilling down further on the clinical relevance, the difference we're seeing in between those two groups is in fact driven by one patient who had, if I remember correctly, 3 or 4 exacerbations. So it's one patient as well that's driving this difference in the number of events that I highlighted on the prior slide.

DR. TORRES: I would like to clarify, I believe it's the case that this patient that had 3 or 4 was not in the U.S.

DR. PUTHAWALA: I would also like to add -- if we could pull up my slide 15 from my second slide deck, and this is the safety data. You'll notice the SAEs for CF exacerbations. The numbers are similar to our understanding that

adverse event reporting is obviously different than PDPE. But generally, you've seen numbers that are not too far off from what we were just shown.

As soon as we have slide 15, this is showing the CF exacerbation SAEs, which the vast majority were deemed SAEs due to hospitalization and understanding that there's probably some crossover there between these SAEs reported in the PDPE, which was defined by standard criteria.

So this is one point. The second point that I want to make is if you could pull up backup slide 21, this is something that I think will add some element.

There's a lot going on, but I've tried to highlight the boxes. This is just showing some consistency in the safety data. This is study 302 and 303, and 301 is not present because there were no U.S. patients.

The pooled data that I showed you during my presentation is the rightmost highlighted box. That's the 23 and 10, and those are number of patients, and that's the difference. But you can

see the breakdown is seen in study 302 and 303.

I understand the sponsor's statement regarding their underlying history. I don't know if that same methodology goes for 302 as well, and if they have that, it would be interesting to see if that applies to 302. So that's it.

DR. AU: Please?

DR. PARRY-BILLINGS: I'm just responding to the question. We do have those data and would be very happy to provide it after the break.

DR. AU: Great. Yes, Robert?

DR. LIM: This is Bob Lim again. I just wanted to remind the committee, we're talking a lot about the exacerbation, and I think the reason we're talking a lot about it is because the FEV1 benefit is sort of numerically small, and that is really the only benefit we've consistently seen.

For a CF drug, primary endpoints, we measure FEV1. But even in a study that's not necessarily powered to show an exacerbation benefit, maybe even that's not long enough to show an exacerbation benefit statistically, our general

expectation is that in addition to showing an FEV1 benefit, that we would also want to see other things trending in the right direction.

What we have here is a relatively small treatment effect in terms of FEV1 and exacerbation results which, at best, are greater than 1, and at worse are -- are at best, greater than 1 and really don't support -- they're not trending in the right direction, which is something that we would expect and have seen previously, and that's really the concern here.

Regardless of what we talk about having the larger effect on the U.S. population versus the non-U.S. population, fundamentally, we have a small FEV1 effect and we do not have favorable trends in exacerbation, nor in CFQ-RRD.

That's the agency's dilemma in determining how clinically significant this FEV1 benefit is, and I do recognize that, in CF -- I took care of these patients -- on an individual-patient basis, any improvement is improvement, and you would want to take that. But I think that it's a pretty small

improvement. It wasn't directly expressed as percent predicted, but we're talking 1.2 percent improvement; 1.2 percent improvement in percent predicted, that's not huge.

DR. AU: Can I follow up on one question that I've had for a while now, that I thought I might take the prerogative to ask?

In the FDA document, it says study 302 did not win on FEV1. On slide number 46 from the sponsor, CO-46, study 302 notes an ADML benefit in drug with a p-value of 0.028. I was just asking for some reconciliation between these two pieces of information.

DR. LIM: That's adult only.

DR. AU: This is only adult.

DR. LIM: That's adult only.

DR. AU: And the non-win is for the primary trial --

DR. LIM: The primary trial, the primary endpoint of the trial in the population.

DR. AU: Great. I just wanted to clarify. Thank you.

It is 12:13. Why don't we give ourselves 45 minutes and come back at 1:00 p.m.? Again, we're going to adjourn for lunch. I'll remind the committee not to discuss any of these proceedings during their lunch break. I look forward to seeing everyone back at 1:00 p.m. Thank you.

(Whereupon, at 12:13 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. AU: I hope everyone enjoyed their lunch and their break. We will begin the open public hearing portion of the meeting, a little preamble.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee on any financial relationship that you have with the sponsor, its product, or if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel,

lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such conflicts. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson, and thank you for your cooperation.

I would like to call speaker number 1 to the podium, and please introduce yourself. Please state your name and any organization you are representing for the record.

MR. CALLANAN: Good afternoon. My name is Brian Callanan, and I am nearly 43 years old, living with the most common genetic form of cystic fibrosis, since my diagnosis at birth in 1976, when the average life expectancy at the time was that of 10 years

I'm here representing myself as an adult patient and do not have financial interest in Chiesi USA, aside from the accommodation and travel assistance for today's meeting.

I'm the founder and executive director of the Cystic Fibrosis Lifestyle Foundation of which Chiesi USA is one of more than a dozen corporate grantors. My organization provides recreation grants to patients in overcoming financial barriers to exercise as a supplemental means of airway clearance therapy and psychological and social strengthening. Since 2007, we have awarded more

than 1300 grants totaling more than $650,000 in assistance to the CF community.

I speak to you today with emphasis on, A, the importance of continued growth for treatment options, and B, considering treatment benefit in light of typically steady decline of lung function. I stand before you as somewhat of an anomaly in the CF community. I have been fortunate living with a mild to moderate form of cystic fibrosis, which has enabled me to maintain normal lung function in the mid 80th percentile.

I experience low levels of lung congestion on a daily basis, which is typically manageable with four different nebulized medications, roughly an hour of airway clearance, wearing a vest twice daily, consuming 5 to 7 enzymes with every meal and snack, and 7 to 9 additional medications and supplements in both the morning and evening. For the past 12 years, I've had to add both short-acting and long-acting insulin to manage CF related diabetes.

I've done the math, and since diagnosis,

I've swallowed more than 314,000 enzymes with meals, and I've had my chest clapped on or shaken more than 35,000 times.

I've consumed more than 5,000 pounds in supplements and vitamins, and additionally, I exercise 3 hours a day, 3 to 4 days a week to maintain my weight and lung function, and by maintain, I mean to slow the projected decline of lung function.

I've tried most new treatments that have come out. Some I've not been able to tolerate. My hearing is partially destroyed. I've had my throat burned for years. I had a bleeding ulcer that required 6 units of blood replacement and months of treating anemia. As my body has changed with age, I've also had to change between very similar medications. Without options, I would have been left to either suffer through the adverse effects or go without the treatment.

Diversification of treatments has enabled me to not only survive CF, but to thrive. It has enabled me to backpack across the Australian

outback, to ride my bicycle from Canada to Key West, and to sail from Miami to Cape Cod. Refrigeration hasn't always been possible on my travels, so an alternative treatment in powder form that does not require refrigeration would be welcomed.

With the progressive nature of cystic fibrosis, gradual decline of lung function is the expectation. Preventing loss of lung function is relevant in adding years on to lifespan trajectory. And any percentage gain in lung function is significant.

To illustrate what a small percentage of lung function improvement can feel like, please do me this favor. Please close your eyes for a moment. Imagine breathing through a snorkel with water trapped in the bottom of it. You feel the rattle and gurgle as you try to control your inhalation in fear of choking and coughing on the fluid. You also feel the difficulty of exhaling with the airway being partially blocked.

Now imagine the fluid is removed from the

snorkel and your breathing is unobstructed. While breathing through a snorkel is still restrictive, it is comparatively a literal breath of fresh air.

This difference is what just a 5 percent lung function improvement or loss feels like to me. What may look like modest benefits on paper feels like tremendous benefits in reality. In the context of a disease of typical steady decline in lung function, I ask that you consider the term "modest" as a patient would, and I ask you to also consider that this effective treatment also may provide the alternative to patients unable to tolerate other existing options, who are forced to currently go without tolerable access to treatment.

We are coming ever closer to a cure for cystic fibrosis, and we are all striving to see that cure in our lifetime. Please help us to have another powerful tool that will help us with this goal of maintaining our health long enough to see that happen. We need all the help we can get. I thank you for your consideration.

DR. AU: Thank you. Will speaker number 2

step to the podium and you introduce yourself? Please state your name and any organizations you're representing for the record.

MS. WETMORE: Good afternoon. My name is Ronnie Wetmore. I'm a registered nurse with a bachelor of science degree in public health and a master of science in health care policy administration. In full disclosure, Chiesi is reimbursing me for my travel here today.

For the last half of my professional nursing career, I specialized in adult cystic fibrosis as coordinator of three adult CF centers, Albany, New York; Jacksonville, Florida; and Stanford in California. I'm also the sister of two now deceased brothers who had cystic fibrosis.

My first brother passed away at the age of 3, over 60 years ago, and the second brother at the age of 40, 15 years ago. I also have a second cousin who is currently post-bilateral lung transplant at the age of 35 who required a transplant, as his CF had progressed to the end-of-life diagnosis.

In addition to my first personal family history and career work, I've made myself available for research trials requiring family members of CF patients, as I myself am a carrier of delta F508. I've been able to participate in several research trials over the course of my career, assisting in recruitment of patients to participate as subjects in studies and with the collection and entry of data as required by specific studies. I was fortunate to be involved in the initial phases of the inhaled mannitol trial several years ago while still in Florida.

As we all know, there's no cure for cystic fibrosis. It's a progressive and debilitating disease. Patients with cystic fibrosis face a lifetime of intensive therapies, which includes multiple medications.

In addition to those medications, it's extremely important for this patient population to exercise and practice aggressive airway clearance routine, lasting at least 20 to 30 minutes each time and at least twice daily. This airway

clearance aids in maintaining optimal FEV1, which measures lung function, which is a strong determinant in the health of the cystic fibrosis patient.

My argument for the approval of inhaled mannitol is this; adherence, underlined. According to the WHO, the World Health Organization, non-adherence is a major obstacle to effective delivery of healthcare. WHO estimates that only 50 percent of patients with a chronic disease follows recommended treatment.

Adherence to a demanding medication and therapy routine for patients with this chronic progressive and debilitating disease is difficult. Multiple medications and therapies require an average of 2 to 3 hours daily, 7 days a week, no vacations, no exception.

How many in this room can say that we have a minimum of 2 hours every day just for ourselves for medication and therapy? This doesn't include routine things like breakfast, a shower, going to work, or reading, or emails.

I believe, along with scientific data showing improvement in FEV1m with the use of Bronchitol, along with other prescribed therapies, this will have a side effect and benefit of contributing to adherence. Whatever can be done to maintain or slow the progressive inevitable decline of this disease is a benefit and may just contribute to the adherence.

No medication can be effective if it's not administered as prescribed. And if a medication or therapy is time consuming or difficult to administer, that medication may be one of the most likely to not be adhered to by 100 percent.

In the life of cystic fibrosis where time and multiple medications and therapies are required daily simply to maintain the status quo, or at best, to slow the progression, any medication that can be offered in a simple and easy to administer manner is needed, welcomed, and necessary. Thank you.

DR. AU: Thank you very much. Will speaker number 3 step up to the podium introduce yourself?

Please state your name and any organization you are representing for the record.

MS. KELLY: Hello. My name is Nicholas Kelly. I'm a dietitian. I have my master's in food nutrition. I'm an artist, a patient advocate, and I am a CF fighter. I have not been paid by any entity to be here, however, my travel has been covered.

First, take a breath in. Now take another breath. Now imagine taking that breath through a straw. Difficult right? Now imagine if I squeeze the bottom of that straw and you tried to take that same breath. That's what it's like living with cystic fibrosis for so many patients.

Cystic fibrosis primarily affects the lungs, pancreas, and stomach, but what they don't tell you when you sign up for this disease is that it has the ability to affect everything else.

Now, I could give you a bunch of stats and statistics about CF, but the one that I find most important is that 50 percent of the patient population is over the age of 18 years old. Now

this is a far cry from where we've come, and it's a testament to where we can go.

This is also a direct byproduct of the strides research physicians and healthcare professionals have made. The research is a vital and pivotal part in this conversation because in many ways, it is the backbone that contributes to help individuals like myself and so many others that look nothing like me excel.

As a patient, we rely on hard work and dedication that researchers, and the companies, who provide these medication therapies to create, innovate, and understand our needs. Sometimes these needs are very simple, just like everyone else's. But other times these needs are extremely complex with so many layers.

As medication and therapies, they literally treat a litany of the part of the healing process. And for that reason, it is important to understand that variance, variety, and options are a crucial part of that healing process.

My doctors once told me the unique thing

that she loves about treating CF is that if you treat one CF patient, then you've only treated one CF patient. That sentiment really speaks to the unique nature of this disease, while also speaking to how we can be similar, and why the need for those variances.

Now understand, me as a patient, I've had numerous ups and downs with this disease. On average, I spend a third of my year in the hospital, but that has not stopped me from living because I take a large part in taking my health into consideration as my priority by committing.

This is an example I've seen by being a part of research studies because my mother once told me what's good for the few is good for the many. That's actually one of the main reasons I'm here today, to speak for the individuals without a voice who could not be here today, that rely on policy makers to consider all areas of this conversation, a conversation that is fueled by science, statistics, information, but most importantly that human element, because that's the

factor that that must be considered.

Look, I'm not asking you to approve every medicine and therapy that comes across your desk, or minimize the process or due diligence that you go through. But what I am saying is you're in an amazing and a unique position to provide hope, and more importantly, opportunity to patients by offering them medications that will improve their quality of life.

Understand, for a CF patient that could be as big as walking down the aisle without oxygen, or it could be as simple as going to the ballpark and catching a Nationals game with their friends. But the thing that is most important, regardless of activity, is the thing to remember is you have a chance to affect people that before today you may have never known existed. But now you can apply faces to fighters who look or sound something like me, nothing like me, or something like you. Thank you.

Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state

your name and any organization you're representing for the record.

DR. WOJTCZAK: Good afternoon. It's a pleasure to be here to address this committee today. My name is Henry Wojtczak, and I am a board certified pediatric pulmonologist. I've had the privilege

over the last 20 years to direct the CF care team that's positioned within the Department of Defense medical healthcare system, and I've had the opportunity to provide care for hundreds of pediatric as well as adult CF patients. I wish to disclose that the sponsor Chiesi is providing funding for my travel here today.

I'm here today to ask you to consider approving Bronchitol and to talk about how Bronchitol can have a positive impact on the life of adults with cystic fibrosis.

As mentioned by several previous speakers in this forum, back in September of 2014, we crossed an amazing milestone. When I first started practicing CF care, we had about 3,000 CF patients

in the United States older than 18. In September 2014, I have about 15,000. We're now at about 54-55 percent of our total U.S. CF population, enjoying adulthood.

You can see how quickly CF is emerging from a pediatric disease to an adult disease. We also believe we're changing CF from a symptom based to a disease-modifying based model, i.e., going from a progressive lung disease to a chronic lung disease. This may be due to the development of a CFTR modulators. However, there will still be a large portion of the population who will require symptom-based treatments such as mucolytics to clear their airways from mucus plugging.

Several previous speakers mentioned the treatment burden. The treatment burden in CF is what really drives poor adherence, and poor adherence is what results in poor outcomes. The end result with poor adherence -- a typical daily treatment routine, you've heard described, can be up to 2 and a half hours a day, dedicated to treatment, and oftentimes that's not accomplished

successfully. It leads to morbidity such as pulmonary exacerbation, IV antibiotics, and a need for prolonged hospitalization.

Among the various treatments we ask our CF population to perform each day, mucolytics and airway clearance requires the greatest amount of time, and it's frequently neglected. The approval of a novel mucolytic agent, which is safe and effective that can thin mucus and hydrate CF airways, especially one that requires less time in is highly portable, should improve airway clearance adherence and ultimately outcomes.

We know that with poor adherence we go from proactive care to reactive care and higher resource utilization. Now, it's been 25 years since the FDA approved the only other approved mucolytic in our toolbox, and that would be Pulmozyme in 1994 to address the issue of mucus plugging.

About 15 years ago, 7 percent hypertonic saline started being used routinely in a population of CF patients who could tolerate it. However, in my population, 40 to 50 percent of my patients do

not tolerate hypertonic saline. Additionally, Pulmozyme and hypertonic saline are very cumbersome to administer. They're both delivered by nebulization, and they're two of the least favorite treatments when I poll my CF patients.

The average CF patient, we believe, doing as best as they can with adherence loses 1 to 3 percent of their FEV1 every year. Agents that are available for approval that have any positive impact on FEV1, whether it be slowing or reversing this ongoing process, are essential. Drugs such as Bronchitol offer the potential to improve adherence and attenuate loss of lung function.

Approval of Bronchitol with a unique mechanism of action would empower both our patients and care teams to individualize airway clearance treatment plans based on each patient's needs and tolerability.

With those, there are going to be a subset of patients who are intolerant of Bronchitol, however, the same could be said for other

respiratory medications. Providers will identify those patients with tolerability issues through standardized testing and symptom history, and avoid use of the drug in those patients. But by adding Bronchitol to our options to maximize airway clearance, we can have the ability to improve mucus clearance and increase it here.

So in summary, CF outlook for both patients, families, and care teams are certainly brightened. According to the 2017 CF Foundation registry, patients born in the 2013-17 birth cohort are expected to live to 47 years of age. When I started my career in CF, it was 20 years of age. And infants born this year with CF, estimates are will live into their early 50s.

So certainly we've increased the quantity of CF patients' lives, however many still suffer poor quality of life. The approval of Bronchitol will allow our CF patients to continue their quest for a better and longer life. Thank you for the opportunity to be part of these important proceedings today.

Thank you. Will speaker number 5 step up to the podium and introduce yourself? Please state your name in any organization you are representing for the record. Thank you.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and medical data to provide objective health information to patients, health providers, professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no of interests.

We all agree that new treatments to improve lung function and quality of life for patients with cystic fibrosis are needed. It's equally important that the new treatments should have a clear benefit and a well-defined risk profile. Mannitol was not approved during its first application due to concerns about safety and efficacy, and even though the new clinical trial addresses some of the issues with your original clinical trials, there are still

central questions that haven't been answered about both safety and efficacy.

The new clinical trial found that patients taking the 400 milligrams had statistically significant improvement in FEV1 compared to patients taking a subtherapeutic dose. However, this improvement was modest and was similar to the improvements seen in previous trials. It is unclear if this translates into a meaningful outcome for patients.

In addition, secondary efficacy endpoints related to exacerbations and respiratory symptoms did not support efficacy. Since there was no improvement in the functional outcomes, it seems that the small changes in FEV1 may not be meaningful for patients' lives. Furthermore, FDA raised concerns that this modest improvement may decline over time.

In addition to questionable efficacy, the mannitol may also increase the risk for serious exacerbations particularly in U.S. patients since 21 percent of U.S. patients taking mannitol had a

serious exacerbation compared to 11 percent of U.S. controls, or either of the treatment arms outside the U.S.

At least part of this difference could be due to differences in patients and medical practices between the U.S. and other countries. Unfortunately, that means that including the rates of adverse events from all countries may underestimate the risk of patients in the U.S.

We are concerned that if subtherapeutic doses of mannitol used by the controlled group had an increased risk for adverse advents, in the control group, it could also bias the results to make the risks of the drug seemed lower than it really is.

In summary, it is uncertain if the benefits outweigh the risks based on the data discuss today, however, there should be sufficient evidence for both safety and efficacy before approval. Post-approval regulatory methods would be insufficient to determine if the benefits outweigh the risks.

Perhaps this is a good treatment option for some patients, but if so, this should be determined prior to approval and specified in the indication on the label. Finally, if mannitol is eventually approved, we agree that the label should require a mannitol tolerance test prior to starting treatment. Thank you for your time.

DR. AU: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record. Thank you.

MS. HURLEY: [Inaudible - mic fades] -- a new -- should I restart?

My name is Zoe Hurley, and I would like to think Chiesi for reimbursing my travel here today. I have CF, but I'm relatively new to this diagnosis. It wasn't until I started attending Michigan State and contracted pneumonia at the age of 20 that I was first diagnosed. I had a lot to get used to in the year and a half since, and here's a day in my life.

I spend an hour in the morning and an hour

at night on breathing treatments. I fill my lungs with medications to help me breathe. These treatments include bronchodilators to open my lungs, hypertonic saline to produce mucus, Pulmozyme to break down sticky mucus, and finally an antibiotic that is used to treat and prevent infections.

I have to do this each morning and each night so that I can clear out mucus from my lungs and to prevent infections. As part of my treatments, I also wear a vest that shakes me to help get mucus out of my lungs. This takes approximately 15 minutes in the morning and 15 minutes again each night after each treatment.

After this, I must disassemble and hand wash my nebulizers with soapy water, let them soak for at least 15 minutes, then rinse them again with tap water.

After this, I soak them in distilled water for another 10 minutes to make sure all germs are gone, and then place the parts of the nebulizer on a special mat to air dry, and every 3 days, I have

to sanitize them in a baby bottle cleaner. I do the same cleaning routine after my night treatment.

This adds about an hour daily to my routine, and in order to get these treatments done, I have to wake up an extra hour and a half early every day, and this is all while in college.

I also have to take several pills a day, and these include 2 specific multivitamins, and I also take up to 3 enzyme pills with every meal. I have to take these because my body doesn't absorb nutrients naturally. This is possibly the most uncomfortable part of my treatment and the part I struggle with the most because it causes me a great deal of discomfort and bloating.

I also take a gene therapy drug called Symdeko, designed to help slow the progression of my disease.

If I travel, for instance like coming here, I have to take a portable nebulizer and its attachments with me to do my treatments. I also have to purchase dish soap to clean them, distilled water to soak them, and just something to hold them

in, along with the water and distilled water. And I have to clean them while I'm away, just like I do while at home.

When I travel or when I'm away from home, I use a device called an Aerobika in place of a vest. This is a small plastic device that I have to forcibly breathe into, and this is meant to simulate the effects of the vest. This takes approximately 15 minutes in the morning and 15 minutes again at night. Sometimes I will combine with my nebulizer to be more efficient.

I have to be extremely careful in my everyday life to protect my health, as catching a cold can put me in the hospital and further complicate my life. I wear masks in public places, such as in planes when I travel, and sometimes at school, and especially at the doctor. And I'm very careful to keep my hands clean, and I'm always cautious of my surroundings. On a daily basis, I struggle with feeling well, and I don't remember the last time I didn't cough or have stomach pain.

For those of us dealing with this disease

every day, finding a cure would obviously be ideal, and I do believe that this will happen. But until then, having medications that are less time intensive while keeping our FEV1 numbers stable or better, would be greatly appreciated. Thank you, and thank you to the FDA for providing me this platform to share my story.

DR. AU: Great. Thank you very much. Will speaker number 7 step up to the podium and introduce yourself? I believe it's a video, so will you introduce the --

MS. HURLEY: Hi. I'm back. Okay. So I'm Zoe, and I'm introducing a video testimony from Emily Grumbine. She's a CF patient, and she is one of only two people in the U.S. who is on Bronchitol through compassionate use. If you could please start the video.

(Video played and transcribed.)

MS. GRUMBINE: "I'm excited to tell you about my experience with inhaled mannitol. Health stability is not something anyone wants to let go of, but when you live with cystic fibrosis and you

find something that gives you health stability, it's better than winning the lottery [indiscernible - audio interference].

"My name is Emily, and I'm 38 years old, and I was born with cystic fibrosis. About three and a half years ago, I asked my CF doctor about the possibility of applying for compassionate use of inhaled mannitol. I had been in a clinical trial for the potential treatment and experienced a significant increase in my lung function during the study. I would granted compassionate use of inhaled mannitol.

"So for three years now, I've been religiously taking inhaled mannitol twice a day, every day. I've never missed a dose in three years. I believe this treatment has been the reason I've experienced stability in my lung function and overall health. It's been a very effective tool for me. It helps me clear my lungs morning and night. I don't cough as much throughout the day because I'm able to clear more out of my lungs during my treatment time.

"Not having to constantly cough throughout the day gives me more energy to invest in other important things like work, volunteering, the lives of my family and friends, and exercise. In the three years that I've been taking inhaled mannitol, I have not experienced any negative side effects, and I've only needed IV antibiotics once a year.

"I'm convinced that without inhaled mannitol, I would have more mucus plugs and infections, which would lead to more IV antibiotics and hospitalizations because I wouldn't be able to clear my lungs like I'm able to now.

"I realize that inhaled mannitol might not be the right treatment option for all cystic fibrosis patients, but it's been a great option for me for three years now, and I'm convinced that it is an effective treatment option for many more people living with cystic fibrosis, and the cystic fibrosis community desperately needs more effective treatment options. Thank you."

DR. AU: Thank you very much. Will speaker number 8 step up to the podium and

introduce yourself? Please state your name and any organization you're representing for the record.

DR. BOYLE: Great. Thanks. Good afternoon, everybody. My name is Dr. Michael Boyle. I'm the senior vice president of therapeutics development at the Cystic Fibrosis Foundation, as well as an adjunct professor of medicine at Johns Hopkins.

Prior to joining the foundation in 2015, I founded the Johns Hopkins adult CF program, served as its director for 15 years. I still see patients at Hopkins, which cares for over 300 adults making it one of the largest CF care programs in the country. I don't have any conflicts of interest to declare.

I'm here today, really, on behalf of the CF foundation, and more importantly, on behalf of people with CF and their families, really to talk about my perspective or the impact that inhaled Mannitol or Bronchitol could have on the cystic fibrosis community.

I'd really like to focus my comments around two main points. First, Bronchitol has the

potential to address an important need for those people with CF who can't take hypertonic saline. As a physician, I would just love to have another option for those patients to help really optimize their health and to maintain their lung function, and give them the best health possible.

Second, Bronchitol is a great option for people who struggle with treatment adherence due to the substantial time burden of the treatments. Bronchitol we know is both more convenient. It's easier to use in the current available treatments. And because of this, it has a power to really alleviate some of the barriers that prevent some patients with CF from achieving optimal health outcomes.

Now, as we all know, clearance of mucus from the airways is essential for individuals with CF, but unfortunately there've been relatively few advances in this area in the recent years. The main advancement has been introduction of inhaled hypertonic saline, which is actually, if you look at the CF registry, prescribed over 70 percent of

patients with CF over the age of 6 because it's been shown to help maintain lung function as measured by FEV1.

However, there is a significant problem with hypertonic saline. It's often our patients' least favorite drug. This is due to a combination of tolerance and time issues.

We know from clinical trials that hypertonic saline can be effective. In fact, one of the key trials demonstrating this was conducted by Dr. Scott Donaldson, who we heard from earlier. While the good news is that this clinical trial showed how hypertonic saline can be effective, the not so good news is that in real life, we know that the effectiveness of hypertonic saline can be limited by tolerance and adherence issues.

Several studies have described the low prescription refill rates and adherence for hypertonic saline, including in this study by Lin and group in 2017, where the self-reported adherence for hypertonic saline among participating patients was only 47 percent.

Treatment adherence we know is impacted by the fact that some patients find hypertonic saline irritating and have difficulty tolerating the long treatment durations required to administer a meaningful dose. I have a few patients that have given basically unrepeatable nicknames to their hypertonic saline for this exact reason.

We know that treatment adherence, as well, is integral for improving health outcomes in people with CF. The poor adherence has been linked to increased need for IV antibiotics and worsening lung function. For these individuals having an alternative treatment available like Bronchitol would be a key advance and optimize their maintenance regimens, and then ultimately increasing their chances of achieving their best health.

Based on the data presented, Bronchitol appears to be safe, and the totality of the data suggest effectiveness as an alternative therapy, particularly for patients who can't tolerate hypertonic saline. The totality of this data

supports the efficacy that both clinical studies and use by patients in the real world have demonstrated a good safety profile.

We know since its approval in 2001 in Australia, it's been approved in 35 countries. Making an additional therapy like Bronchitol available would help enable patients with CF and their physicians to make the best care decisions based on individual needs.

We also know the duration of time taken for treatment can have a substantial impact on patients' adherence. A typical prescription for hypertonic saline is 20 minutes per administration twice a day. The 40 minutes of treatment time comes on top of an already very lengthy and burdensome regimen that we've heard quite a bit about earlier.

In contrast to hypertonic saline, Bronchitol takes only about 5 minutes to administer, uses a disposable inhaler that doesn't require all the maintenance and cleaning. Because the burden of care is so high in CF, patients

balancing daily therapies with their school, with work, with other life circumstances, often compromise in the amount of time they spend on disease management. For these individuals, reducing treatment time for 40 minutes to 10 minutes for Bronchitol can make the difference in finding time to actually maintain their daily regimen.

In summary, I ask the members of the advisory committee to consider these two important factors during the committee's review of Bronchitol; one that we know some patients are going to be unable to tolerate hypertonic saline; the other is there are individuals in the community who will greatly benefit from reduced treatment burden.

So making Bronchitol available could give back a sense of agency and empowerment to adults with CF who are struggling with available therapies. Thank you very much in advance for your consideration.

DR. AU: Thank you. Will speakers number 9

step up to the podium and introduce yourselves? Please state your name and any organization you are representing for the record. Thank you.

MS. A. ROCK: Good afternoon. My name is Angelica Rock. I'm 18 years old, and I have cystic fibrosis. My travel is being reimbursed by Chiesi so I can be here today.

I look just like any other 18 year old and can fix every problem I encounter, except for cystic fibrosis. My CF is omnipresent. I cannot wish it away, cure it with a few pills like a common cold, or pretend it does not exist, but I don't let it define me.

When people hear cystic fibrosis, they think death, sickness, and struggles, especially since the median age for living with CF is early 40s. But I don't think of it as any handicap or any kind of prison. I think life, opportunities, perseverance, and the freedom to be myself.

A disease that can cut the average human life expectancy in half has allowed me to live my life to the fullest for valor, optimism, and

curiosity. My day starts with 2 puffs of an inhaler 10 minutes before my therapy. While waiting the 10 minutes, I get dressed for school, and before I know it, I end up rushing downstairs to start my therapy.

I lug the 15-pound vest machine over to the couch and go in and grab my nebulizer so I can complete them at the same time. It takes me 20 minutes to finish the vest and nebulizers, and I still have to sterilize my equipment. Thirty minutes later, I finally complete my therapy, and it's not even 7:00 a.m.

My pulmonologist recommends that I complete my therapy twice a day, but due to time constraints in my schedule, I confess that I only do my therapy once. I know my therapy is required, but the mentality of doing therapy for 2 hours a day is tough. On top of managing the disease, I have to set aside time for therapy while sometimes fitting in school, running practice, work, family meals, and time to sleep.

Completing a task so time consuming and

mundane for 18 years of my life is not motivating. Next year, I'll be moving 2,600 miles away to the University of California, San Diego. With no family over there, I'll be completely responsible for adhering to my therapy; no one to remind me to complete it after a long day and no one telling me I need to do my therapy when I don't feel like doing it. With Bronchitol approved, I can be able to prioritize my therapy to complete it twice a day because it only takes about 5 minutes.

For 18 years, I've been told, no, you can't and you won't. Most people would succumb to these comments and accept failure. I will not. People have told me that my lung function is declining, and I can't fix that because it just happens with age. But I raised my FEV1 by 10 points, and I'm very proud of that. I was told I'd most likely have a lung infection for the rest of my life, but I got rid of it 2 months later.

A social worker refused to believe that I could be a fast runner just because I had CF, but I won states, went to nationals, and I am one of the

top runners on my team. My neighbor told me I would never get accepted into a college in California, but I was accepted at UC San Diego, one of the top 15 colleges in the country.

After all these times I've been told no, I hope you can say yes to Bronchitol. I know I need help prioritizing my therapy to consistently complete it twice a day. With Bronchitol approved, it could give me an option I've been looking forward to talk with my doctor about. I am hoping you can help me by voting to approve Bronchitol. Thank you.

MS. M. ROCK: Good afternoon. My name is Mary Beth Rock, and I'm here to share my story as a CF parent. My travel is being reimbursed by Chiesi so I can be here. My time is not being reimbursed, and I have no financial stake in the company.

You've heard from my daughter Angelica and what she goes through as someone living with CF. So that's the patient's perspective. Now I want to share with you a parent's perspective.

My husband Mike and I learned of Angelica's

CF diagnosis at birth when she was born with an obstruction of her small bowel. Hours later, she was operated, so I was not able to see her right after her birth.

Fast forward to today. You can see Angelica looks like any other healthy 18-year-old young woman, and despite her having CF, Angelica has been living a very healthy life; that is thanks to the treatments that are available for people with cystic fibrosis. What you don't see are the lungs of a person with CF. They can lose up to 2 percent of their lung function every year of their lives.

Angelica is one of the few that has been able to maintain her lung function primarily due to her running and of course the treatments that she does every day. Many are not so lucky. As you know, the median age for living with CF is in the mid 40s. Although this has come a long way since Angelica's birth, this badge is unacceptable to me as a parent of my beautiful daughter. If you have children, you would agree.

People with CF are at a greater risk of getting lung infections because thick, sticky mucus builds up in their lungs, allowing germs thrive and multiply. Despite significant progress for treating CF, infections remain a serious problem and can lead to worsening lung functions and even death. Bronchitol is a treatment that will help with this.

Data shows that when young people 18 and older enter college or the workplace, there tends to be a decline in therapy adherence, and consequently lung function and overall health. Angelica will be attending college in California in September, and my biggest worry is her adherence. I feel confident if Bronchitol was an option, this would cut her therapy down substantially and allow her to do her recommended therapy twice a day.

It's great that Bronchitol is inhaled using a small hand-held device that is convenient and portable. This is just what a college student needs. Having good options for treatments that serve a patient's time schedules, living

arrangements, and personal style, and reducing the burden of care of this very difficult disease is important to the person who is living with CF and their families.

How effective is a treatment if it's too challenging to use consistently? Good options are important, and CF patients need options that will make their therapy shorter, so they will adhere to their therapy. You can make this happen with your vote today. I know that Angelica and the 30,000 people living with CF in the United States would love the opportunity of using Bronchitol.

Another fun fact of people with CF you may not know is that the guidelines from the CF Foundation advises that if they are attending an indoor function like the one here today, no two people with CF should be in the same room. If they are attending and outside function, a 6-foot distance should be maintained at all times. Can you imagine being told this?

This morning, Angelica and I have been in a holding room. She has the chance to be infected by

another CF patient here today. The CF Foundation advises we should not attend this hearing, but we are here because it's important to us, and we were taking this risk.

Every day, people with CF and their families, healthcare professionals, researchers, donors, and volunteers work together to advance the search for a cure and improve the quality of life for those with cystic fibrosis. If Bronchitol gets approved in the U.S., I feel confident this will increase Angelica's lung function. My hope is that this will increase her lifespan of living past the median age of 40.

Do the right thing and vote yes today to approve Bronchitol, this much needed therapy for CF patients. Thank you for letting me speak with you today.

DR. AU: Thank you very much. Will speaker number 11 step up to the podium and introduce yourself? I'm sorry, 10. I apologize, 10. Please state your name and any organization you're representing for the record.

MS. A. ROCK: Hi. I'm Angelica. I'm introducing the video for Tess Dunn. She's a CF patient who wanted to participate, and opted to do so with a video.

(Video played and transcribed.)

"MS. DUNN: Hello, members of the FDA Pulmonary Allergy Drugs Advisory Committee. My name is Tess Dunn, and I thank you for this opportunity to speak and share my views on Bronchitol via video and for providing time for the patient voice to be shared on this issue. I'm sure I do not need to give you the scientific breakdown of how mutated CFTR devastates my body and those of my CF peers.

"What I do want to emphasize is that there are many, many CF mutations, and a therapy that works for one person with CF may not work for me. We need new therapies and we need options. You are in the position to make this possible.

"I am 24 and live in California. I was diagnosed with cystic fibrosis when I was 5 months old. At the time, I weighed less than 10 pounds,

had pneumonia, and had already endured numerous invasive and painful tests. Since then, it has been a daily battle to stay healthy in the face of CF, which is a bit of a misnomer, as healthy for me means that I'm spending only 3 hours a day doing my respiratory therapy instead of 5; that I can speak for more than a few minutes without coughing; that I am not in the hospital; and that I do not have a PICC line in my arm.

"I'm stating the obvious when I say that cystic fibrosis is a capricious disease and that it has managed to impact nearly every part of my body. Before I talk about the respiratory issues, I will share that I am pancreatic insufficient due to my disease, meaning that I must take 8 capsules of replacement enzymes every time I eat, which adds up to nearly 10,000 pills per year. Even with enzymes, by absorption of nutrients is compromised, and while only 24, I already have been diagnosed with osteopenia.

"My pancreas is damaged, and I was diagnosed with cystic fibrosis related diabetes

when I was 11 years old, which requires regular blood testing and insulin injection. My sinuses are also impacted, and I have had 5 surgeries to remove recurring polyps. And it is no surprise that my mental health suffers because the impact of my own disease, coupled with the death of friends with CF, causes depression and anxiety.

"All this, and I haven't even begun to mention the respiratory challenges, the reason we are here today. I have battled lung infection since my diagnosis. My lungs are filled with thick, sticky mucus and provide a perfect breeding ground for infection. Collectively, I have spent months in the hospital to treat these exacerbations and many more months doing IVs at home.

"These infections happen no matter what I do. I am extremely adherent to my medical regimen and spend at least 3 hours a day doing my respiratory therapy. Very little has changed with the drugs that I nebulize and inhale each day. There has been no exciting breakthrough for airway clearance since hypertonic saline became part of

the standard protocol years ago.

"I know many people with CF who are desperate for new therapies to thin and clear mucus. For many of us, hypertonic saline can be irritating and cause bronchospasms. For many people, they have no alternative drug to use to help clear their lungs.

"Bronchitol is exciting for all of us in the CF community. The safety of the drug has been proven, and it has been shown to improve FEV1 during the phase 3 trials. I know there are some people who may say that the increase in FEV1 was not very significant. To those people, I say look at the charts. My friends and I are going to have a decline in lung function no matter what. To stop the decline is a win. To actually show improvement is a big victory.

"I am one of the lucky ones. Because my mutations, I am able to use the new CFTR modulator drugs. Even with these drugs, I have experienced a significant lung exacerbation. My heart aches from my CF peers who feel like they are out in the cold,

still waiting for new drugs that can improve their health and quality of life.

"Many people talk about the increases in life expectancy for those with CF. I wanted to clarify that these numbers are based on those who are born in recent years. The sad truth is that last year the median age of death was only 30. I am 24 and acutely aware of my mortality. I am a writer, a musician, a friend, a daughter. I want to live.

"I implore you to please advance Bronchitol through the approval process. We are a very diverse community, and there is no one-size-fits-all therapy. Our community is suffering, and we need new options. Please help us make this a possibility. Thank you."

DR. AU: Thank you. Will speaker number 11 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record. Thank you.

MS. M. ROCK: Good afternoon. I'm introducing a patient video who decided to

participate in this important meeting via recorded video. I'm Mary Beth Rock, and the video I'm introducing is from Emily Schaller. Thank you.

(Video played and transcribed.)

"MS. SCHALLER: Good afternoon. My name is Emily Schaller. I'm a resident of Grosse Pointe Woods, Michigan, and I'd like to thank the FDA for letting me speak today in support of Bronchitol. I was born on February 21, 1982, the third of three children to my awesome parents.

"This was 1982 in the '80s before we had any form of newborn screening or anything, and when my mom held me for the first time, she knew something just wasn't quite right, but I appeared to be healthy. I was a 6 pound 10 ounce cute baby, and I was sent home with no diagnosis.

"For the first few months of my life, I had chronic ear infections, runny nose, and failure to thrive, so my pediatrician sent me for a sweat test for cystic fibrosis. My parents really didn't know what cystic fibrosis was because we had no family history and nobody really talked about it or knew

about it.

"The first test came back negative, so my parents were super relieved that their cute baby didn't have CF. But as much months progressed, I began to develop more symptoms and more severe symptoms. So they tested me again at the age of 18 months, and this time, the test came back positive for cystic fibrosis. Again, this is 1983 at the time, and there were just not a lot of treatments for my parents. So the prognosis was that I probably wouldn't live long enough to graduate from high school.

"Today it's a different story. I'm 37 years old and doing great and thriving, but it's because of those medications that we have available today. In the '80s, they told my parents to pound on my chest and my back and my side several times a day to loosen that mucus up in my lungs because the mucus is what holds bacteria and causes lung infection and loss of lung function.

"I was started immediately on digestive enzymes, which I still take today and most of my

friends with CF also take, and vitamins. Those are the only three options we had in 1983, frankly, to 1993 or so. So now I'm 37 years old, and I've lived through three decades with cystic fibrosis. I've been in the dark ages when our treatments were incredibly minimal and barely touched our symptoms, to now the side where we are treating CF at the underlying cause.

"I'm fortunate enough to benefit from some of these new medical advancements that treat the underlying cause, which has allowed me to have high lung function, have a new look on life, a new lease on life, buy a house, set up a retirement fund, and work full-time, run marathons, and love my life.

"But I still have cystic fibrosis, and my burden of care is still there. Each day I wake up and put on a vest that shakes up the mucus in my lungs. So my parents used to have to pound me, but now I have this vest that can do it for me, so that's a great medical advancement. I have to inhale medication to thin the mucus in my lungs. I have to inhale antibiotics to treat the

Pseudomonas aeruginosa in my lungs. I have to take digestive enzymes and take probably 40 or 50 pills a day when I eat right.

"So the burden of care is still there, even though the median age of survival has increased, and my quality of life has increased beyond something that I could ever imagine. But we still have this enormous burden of care. These inhaled antibiotics can take 20 minutes or longer. Sterilizing the nebulizers for those can take just as long, and you're doing those a few times a day.

"So we need more tools in our toolbox. I'm an advocate for CF with my Rock CF Foundation. When I speak around the country, I hear from parents that the burden of care is one of the hardest things about living with CF. And as somebody who has CF, I agree. We spend hours a day on these treatments to stay alive.

"So if there's anything that can help ease that burden with a dry powder such as mannitol, something that's Bronchitol, something that's easy to use, it doesn't take the time to disinfect after

but it's effective, we need that. CF patients still have a slow rate of decline, so a drug like Bronchitol would help potentially decrease that decline.

"Things are really changing in the world of CF, but we still need drugs everyday to help us stay alive, and live, and run marathons, and work full-time. So I'm here today to advocate for Bronchitol as someone with CF who still uses all the treatments but has lived through three decades of CF, where we've gone from nothing to my second decade, where all these drugs started to come out, to now this third decade where we have medications to treat the underlying cause. We need to all of it."

DR. AU: Thank you. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee now will turn to its attention to the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Dr. Lim will now provide us with a charge to the committee.

Charge to the Committee - Robert Lim

DR. LIM: Good afternoon. It's me again. I'd like to thank all of you for the very fruitful discussion this morning. As well, I would like to specifically thank those who spoke at the open public hearing and who submitted comment, public comments, with regard to this advisory committee.

As we move into the next part of this meeting and prepare for further discussion and voting, I would like to use the next few minutes to provide a brief reminder and overview of the issues of the regulatory framework upon which our decision-making is based and the questions to be discussed and voted on.

Now that you've heard all the presentations and have had an opportunity to ask clarifying questions, we ask that you carefully consider whether the efficacy results are robust. In your assessment, we ask that you consider that only one study demonstrated a clear statistically

significant improvement in FEV1 in the adult population, and while subgroup analyses of adult patients from studies 301 and 302 also suggested a positive benefit on FEV1, these were post hoc analyses of a trial that failed and one that had statistical issues.

Additionally, taking the FEV1 point estimates in the adults at face value, the effect size was also consistently relatively modest and were small. And for clearly clinically meaningful secondary endpoints such as exacerbations, across all studies, the results were not supportive of efficacy with some concerning trends, which were somewhat accentuated in the U.S. population.

With regard to safety considerations, there were some numerical imbalances in adverse events as reviewed by Dr. Puthawala. The two major safety concerns were the historical concern for hemoptysis events. The second concern, newly raised in this review cycle, was for the numerical differences noted for exacerbation that were accentuated in the U.S. subpopulation and also consistent with the

exacerbation related endpoint trends observed in 302 and 303.

With that brief review to frame this discussion, the next few slides will provide an overview of the governing regulations. FDA's decision to approve an application depends on the determination that the drug meets the statutory standards for safety and effectiveness, manufacturing controls, and labeling. The focus of today's meeting is on the safety and effectiveness piece of this application.

In the questions that follow, you'll see that you'll have the opportunity to vote on the adequacy of the efficacy and safety data separately. For the risk-benefit assessment and approval question, your vote should reflect your assessment of both safety and efficacy together for the proposed indication.

The efficacy standard describes the need for substantial evidence from adequate and well-controlled investigation supporting the language in the labeling. The relevant regulation

is quoted in this slide, but I won't read that word for word.

There are also a number of safety reasons I could underlie a refusal to approve an application, and these are summarized on this slide. These could include (b)(2), a lack of adequate tested document safety; (b)(3) that results show the product is outright unsafe, or that results simply do not show that the product is safe for the proposed use, or finally, (b)(4) that there's insufficient information to determine whether the product is safe for the proposed use.

So this brings us to our questions. The first question to put forth to the AC panel members is a discussion question, and is as follows. Question 1. Discuss the efficacy of dry powder mannitol, or DPM, for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients aged 18 years and older in conjunction with standard of care, and include in your discussion the following topics: effect on FEV1, including effect size and

durability; secondary endpoints, particularly exacerbations and CFQ-RRD; and statistical persuasiveness.

The second discussion question gets into the safety and is as follows. Discuss the safety data for dry powder mannitol for the proposed use in patients with cystic fibrosis age 18 years and older, particularly including exacerbation and hemoptysis.

The remaining three questions are voting. Question 3, the first voting question is, do the data provide substantial evidence of efficacy for dry powder mannitol 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-of-care therapies? If no, what further data are needed?

Question 4, also voting, is, are the safety data adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with

standard therapies? If no, what further data are needed?

Question 5, and the final question to the AC committee, is where you're asked to bring together both the safety and efficacy data, and the question is as follows.

Does the benefit-risk profile support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies? If no, what further data are needed?

Thank you. That ends the FDA presentation, and we really look forward to your thoughts and discussion of these questions.

Questions to the Committee and Discussion

DR. AU: Thank you.

We will now proceed with questions to the committee and panel discussions. I'd like to remind the public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request

of the panel.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start to flash and will continue to flash even after you've entered your vote.

Please press the button friendly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue the same until all questions have been answered or discussed.

I'd like to take this opportunity right now to -- there were a number of questions that came up

previously, and the sponsor has taken the time to address the questions on behalf of the committee. So I wanted to present an opportunity for the sponsor to discuss some of the questions at hand.

DR. PARRY-BILLINGS: Thank you. We will try to go as fast as possible in the interest of time.

One of the first questions was initiated I think by a question from Dr. Emerson around focusing on us exacerbations. There was a question relating to stratification, and I'd like to ask Dr. Flume to address that particular point. Thank you.

DR. FLUME: Thank you. Patrick Flume. Essentially, Dr. Emerson had suggested whether there was stratification in the group based upon that increased risk of SAEs. Without going through all the math, I'd say your math was pretty good. But your question was really directed towards, is there increased risk of those patients who already have a higher risk; is the Bronchitol magnifying that risk? The short answer to that I believe is

no, and I wanted to provide some perspective regarding this, so I've merged some data from slides.

The first is that second line, which is the SAEs. These are serious adverse events for pulmonary exacerbation in which it was raised that the U.S. group had a higher rate at 21 percent versus the 11 percent.

We have to be cautious because this is actually a small number of events which is driving this difference in the SAE rates. So I point to the first line, that any adverse event listed as a pulmonary exacerbation, as you can see between -- the Bronchitol and control groups, are essentially similar.

So the issue is about what makes it an SAE, and essentially that's hospitalization. What's the difference between these groups we've talked about, and the past history of events, but also the pseudomonas rate.

In patients who had a history of prior hospitalization, they're more likely to get IV

antibiotics in the hospital in future settings. That's the way we provide care. And as I mentioned earlier today, the prevalence of pseudomonas, if you have pseudomonas presence, you don't have many drug options. Most of which we have our intravenous only, and our practice is generally to begin to initiate that therapy in the hospital setting. So hospitalization makes those adverse events suddenly become a serious adverse event.

I also want to make sure people understand an SAE is not necessarily a severe event, and when we look at those events, the majority of these events were reported to be mild or moderate. So in my view, we have explanations for why we're seeing that imbalance of SAEs for that particular exacerbation, that adverse event, and I don't think it actually is provoked by Bronchitol.

DR. PARRY-BILLINGS: As a follow-up to that and to further elaborate on the discussion this morning in relation to the sensitivity analysis, if we could have a look at the forest plot of the ratio as presented this morning with the value at

the top, which has been the focus of attention at around 1.5. But below it, you'll see the series of sensitivity analyses conducted, which present a rather consistent and slightly different rate ratio closer to unity.

The third point that we'd like to cover, if there's time, there were a series of questions and discussions in relation to hypertonic saline, the number of patients on hypertonic saline before, and the switches and non-switches, et cetera.

More than 50 percent of patients coming into the trial -- and this was balanced between the two arms -- used hypertonic saline. If we look at the FEV1 response between users and non-users in the trial, there isn't really a difference.

To put the hypertonic saline point into some clinical context for the committee, if I may, I'd like to ask Dr. Schwarz to speak to that. As you heard this morning, he has now seven years of experience of treating patients with these two agents together.

Dr. Schwarz, thank you.

DR. SCHWARZ: Carsten Schwarz. Thank you. So as mentioned, I think we always look on an individual base to the patients. In our experience, there are patients tolerating Bronchitol but not tolerating hypertonic saline. Then there are patients who are tolerating hypertonic saline and not tolerating Bronchitol. Then there are patients, they are taking both, so they're tolerating Bronchitol and hypertonic saline.

We have patients, for example, who inhale both therapies only 2 or 3 days per week, and then they have no expectoration anymore, so that shows that we, I think, need more therapeutics, make available for the patients. I think it's very important, so I think it's saying this. It's logic to have more opportunities, as the patients also said. Thank you.

DR. PARRY-BILLINGS: Thank you.

DR. AU: Thank you very much.

DR. EMERSON: I'd also ask for data on the standard deviations of the change from baseline.

Do we have that per chance by day? And this, again, is important for judging the importance of the magnitude of the 0.1 tipping point.

DR. AU: Sure. We'll ask that of the sponsor.

DR. PARRY-BILLINGS: I apologize. We didn't have time to collect those data for you.

DR. MARSHALL: There were a couple of us that had questions this morning that you were deferring to this afternoon.

DR. AU: Yes. We'll start getting into them I think now.

The questions for discussion are discuss the efficacy of dry powder mannitol for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. Include the following topics in your discussion: the effect of FEV1, including effect size and durability; secondary endpoints, particularly exacerbations; the Cystic Fibrosis Questionnaire-Revised respiratory domain score; and

statistical persuasiveness.

I don't know what the questions were from this morning, so if your question's actually pertaining to this topic, now is the time to raise them.

DR. MARSHALL: Gillen Marshall. It's a background question that speaks to this, a very straight-up background question.

That's fine.

DR. MARSHALL: The question is for Drs. Donaldson and Flume. The FDA appropriately makes a concern about splitting the U.S. and non-U.S. data because of their charge to take care of the U.S. component, and I fully appreciate that. But in your roles as acknowledged international experts in cystic fibrosis, your pedigrees and your credentials speak for themselves.

Do either or both of you believe that there are any fundamental differences in pathophysiology, clinical course, or approach to medical management, generally speaking, between the CF community in the United States and other parts of the world?

DR. FLUME: Patrick Flume. I thank you for that question. With respect to pathophysiology, I don't think there are any differences between our patients and those around the world. In terms of different approaches to treatment, we have worked very hard with the CF Foundation, the European CF Society, CF Australia, CF Canada, to continue to work together to develop standards of care that would be used across the world. I would say the only differences are really just about how well resourced a country might be.

DR. PARRY-BILLINGS: Dr. Donaldson?

DR. DONALDSON: Scott Donaldson. Very briefly, I would concur with what's been said already. I do not see differences in populations that would explain the observed differences in exacerbation; rather, in my opinion, seeing the data, the imbalanced randomization within the U.S. population explains what we saw.

DR. AU: Dr. Brittain?

DR. BRITTAIN: I have a question I guess either for the FDA, or the sponsor, or both. One

of the questions I keep thinking is, since the observed treatment effect is pretty small, or at least I don't really understand -- I don't know that it's small because I'm not a clinician in this area, but that's what I keep hearing.

Could it be that there are some people who benefit a lot and some people who don't benefit at all? We haven't really seen anything -- distribution of the benefits, I can't really tell if there are clusters or what's happening. But I'm wondering is it possible to identify a subgroup that does benefit more?

We heard about a group that had I think a difference in a 5 percent predicted. Is it possible to identify a group that's more likely to observe a substantial treatment effect and also has favorable results on the exacerbation? I know that would be hard to do in a study this size, but I'm just wondering has that been anything that anyone has you considered.

DR. LIM: This is a Bob from the FDA. To your point, I think with regard to FEV1, there were

probably some subgroups of people that potentially might have a larger effect size with regard to the exacerbation. I don't think we looked at that specifically for every subgroup, but just given the number of events, I don't think we would probably see too much.

I also want to remind the committee, you're getting hung up on the U.S. versus non-U.S., and it is a concern because we are a U.S. regulatory body. But even when you look at the entire population, the effect on exacerbation, even in the slide, they showed where they had multiple sensitivity analysis.

The point estimates are never on the right side of 1. Those confidence intervals are wide, but typically, and as we told the sponsor before, if we were going to see -- we wanted to see a big effect on FEV1, and we wanted to see secondaries trending. And what we're seeing now is a small effect on FEV1, although as the patients have said during the open public hearing, some of them feel like that really does make a difference. But we're

not seeing the needle really move at all on exacerbation.

So that is one of the concerns where we're coming back and -- we can slice and dice that stuff up as much as we want to, but it's kind of getting into small numbers if we're trying to identify those groups.

DR. AU: Is your point along this point or --

DR. EMERSON: [Inaudible - off mic].

DR. AU: Okay. Why don't you go ahead, and then I'm going to move on.

DR. EMERSON: I have the same problem always. I advise everybody, yes, use means because that's the best thing to look for in an effect in an omnibus sense, and I hate the term "personalized medicine," but I'm going to use it right now. We've always done personalized medicine -- in the sense that we always entertain that a treatment doesn't work for everybody; it's really a mixture, and the idea is how many people can potentially benefit.

So I always think about that. And the responder analysis is the best measure, to me, as a general rule, and the continuous responder analysis presented by the FDA was extremely helpful along those regards.

I still don't know how to interpret it entirely because of the different patterns we see and because of the problems with the 301 study can be substantially biasing. But it was of interest to me that if we seized on that 0.1 threshold, which the sponsor didn't seize on, the idea is that we saw very similar results across the three studies. Again, one of them might be biasing.

That is roughly a 4 percent improvement with roughly an estimated 10 percent additional part of the population that achieved that on treatment rather than on the control. That's a number needed to treat of 10. We do that all the time. That's something that makes it hard, is the fact that, yes, people can do this.

The other problem that I have in all of this is there are so many ways we could have done

this study. You could have restricted the population, if we knew it in advance, to just those people who absolutely would have gained this benefit, and we would have seen a larger effect across the board, and we might not have these concerns.

So there's the difficulty between the clinical estimand, as I stated earlier. I definitely believe we're interested in how does this treatment work in those people who are most prone to take it for a long time, but that's a very difficult clinical trial to do, and we have to deal with the regulatory and the scientific aspects of it must be a per-randomization analysis.

But again, to some extent, the responder analysis helps us there. I don't totally agree with the idea of saying everybody who stopped taking therapy obviously didn't respond because the control group had a 25 percent response rate. But when you say it's not going to be differential, well, that sort of comes out in the wash.

So just from the efficacy side and just on

the FEV1, I think there's a very plausible idea that this treatment is helping a respectable portion of the population, again, on FEV1. But then going to these other points of saying, but why can't we see this on all the secondary outcomes, and why have we turned one of the secondary efficacy outcomes into a safety outcome? And that then detracts.

Now, the tipping point analysis, that 0.1 is not that big of a delta. I'm forced to just come up with my own back -- calling it a back-of-the-envelope analysis is giving too much credit to it. But just as I can try to guess, based on the estimates, and the confidence intervals, and what the correlation might be, roughly, if you believe that the patients' missing data were randomly selected from -- and my latest calculation says 65 percent; other ones I came up with 85 percent. But the bottom 65 percent or the bottom 85 percent of the distribution of patients, that's not that hard to believe.

It's not that hard to believe that patients

who -- if they were doing better, they would have stayed on the treatment, but if they weren't doing well, they didn't. Arguing against that is the fact that the patients couldn't tell they were doing better based on the respiratory quality-of-life thing. But that's not much of a reach to say there might be that much bias, in which case the statistical persuasiveness is problematic, to say that that missing data is there.

DR. AU: Actually, this is a great conversation, but there are a lot of people who have questions, so I'm going to continue to move on if that's okay.

Loretta?

DR. QUE: Thank you. Loretta Que. Going back to slide 17, which shows the change from baseline and FEV1 over time for study 303, can the sponsor just clarify, in the beginning of the slide at 0.0, you have 209 on DPM and you have 214 on control.

When you look at 614 and 26 weeks, does

this include patients that may have dropped out the FEV1 scores in that?

I'm trying to look at the durability of the effect over time, and I want to make sure I understand whether or not, when you go from 209 to 183 for the DPM, if these values here are including those patients that might have dropped out and their numbers are still being included.

DR. PARRY-BILLINGS: May we see the slide just so we are sure that we're addressing exactly the question.

DR. AU: I actually think it's in the FDA book. Is that the FDA book?

DR. QUE: Yes, FDA book, slide 17, change from baseline in FEV1 over time, study 303.

DR. AU: Sorry. We're trying to figure out what section.

DR. TORRES: I think it's slide 17.

DR. QUE: Yes.

DR. PARRY-BILLINGS: While we're waiting, I'll ask my colleague Dr. Muraro to address this just to make sure we are clear for you.

DR. MURARO: Annamaria Muraro, Chiesi statistician. Indeed, this analysis is based on the ITT that includes all patients so they are then evaluated during the 26 weeks; for patients who drop from this study due to reason related to treatment meaning lack of efficacy, adverse event, physician decision, and imputation as being done; while for patients who discontinued for other reasons are considered related to treatment like relocation or lost to follow-up, a formal imputation was not done, meaning that we are assuming that those patients had the same behavior than a patient who remained in the study.

In all sensitivity analyses, all patients are included. We have sensitivity analysis -- maybe we can even show the slides -- with multiple imputation and several different methods and assumptions that provide very consistent results, as shown in this slide.

DR. AU: Did that adequately address your question?

DR. QUE: To clarify then, subjects that

were enrolled, if they dropped out and they still had data, that data was included in this or the data was imputed in this?

DR. MURARO: For any patient who dropped, data were used until evaluable, and then was in the primary analysis imputed with the baseline values. Then are other statistical analyses that use different assumptions and different imputation methods.

DR. PARRY-BILLINGS: But I think, if I may, the message from the data analysis is that, independently of the imputation method used, the last graphic shown in the forest plot, the effect size was rather consistent.

DR. AU: Dr. Redlich, did you have a question?

DR. REDLICH: Well, I had a similar question -- I had a related question. Maybe it would help clarification with slide 16. There were 26 people that had early study withdrawal. Were most of those complications that you said you were included or the ones that you imputed? Which group

did those 26 fall into?

DR. AU: I'm sorry. Can you clarify what you're looking at?

DR. REDLICH: Oh, sorry. It was slide 16 that just gave the number that were early study withdrawal and the number that were early treatment discontinuation.

DR. AU: That's in the FDA book.

DR. REDLICH: Yes, FDA book, slide 16, page 8 of the handout, of the booklet, page 8 and slide 16. Again, this relates to the question of the durability of the effect and trying to understand what impact either study withdrawal or early treatment discontinuation might have had on those results. Maybe the stats people could help me with this.

DR. LIM: This is Bob Lim again. I think to understand the missing data and how it was imputed, I think it's probably best to have Dr. Torres respond to that.

Doctor, when you were referring to slide 17 regarding the effect over time, you were referring

to the FDA slide and not the slide that was brought up by the sponsor, correct?

DR. REDLICH: Yes.

DR. LIM: Were your answers [sic] regarding that slide answered? Were your questions regarding that slide answered? I wasn't clear if they were.

DR. REDLICH: I could use further clarification.

DR. AU: So why don't we go to this one, and then we'll go over to the next slide as well. Thank you.

DR. PUTHAWALA: So this was my slide. This is Khalid Puthawala. I guess there may be some confusion, but the middle two rows add up to a hundred percent. I'm not sure if some of that confusion was there. The bottom row is simply to show treatment discontinuation and how -- it's sitting around 20 percent, and this is study 303, and the early study withdrawal was around 10, 11, 12 percent.

So that difference is what I was highlighting. This difference did not exist in the

older studies where treatment discontinued.

DR. REDLICH: So is that there a total of 30 percent of people that did not complete the study either because they dropped out or discontinued, or is there some overlap between those last two?

DR. LIM: Those are sort of separate groups. You could discontinue from treatment but still continue in study. Like 18 percent of patients discontinued treatment in the DPM arm, whereas only 12 percent withdrew from the study early. So you have 37 patients who discontinued treatment, but 26 still continued through despite being off treatment.

Does that make sense?

DR. REDLICH: Yes. So I guess at the final time point of that 6 months -- at the 26 weeks, do you have just 30 percent of the original cohort that started or is it actually somewhere less? You have a higher number, I mean, because that would be the most --

DR. PUTHAWALA: I mean, 88 percent is --

DR. REDLICH: The completed, that completed the study, and you have data that they had their FEV1.

DR. LIM: I'm going to defer that question to Dr. Torres.

DR. REDLICH: I'm just wondering how much data is missing at that final time point, and how that might impact the longer term efficacy.

DR. TORRES: So we have 88 percent 89 percent in the arms, respectively, that completed the study. That means that we have data on 88 percent and 89 percent of the patients through week 26.

DR. REDLICH: But not all of them took the medication.

DR. TORRES: Yes. Some of them withdrew from the treatment. Yes, they discontinued treatment prematurely. We don't have the exact breakdowns as to how many stayed on treatment and how many discontinued early.

DR. REDLICH: So I guess simplistically putting it, and I defer also to the statistician,

how much confidence do people have in the last time point? Because this is a chronic medication that someone might -- a chronic disease.

DR. TORRES: This is Cesar. When we were evaluating this application, we were interested in the treatment policy estimand. So the question we were trying to address is, with respect to the primary endpoint, what is the treatment effect difference of prescribing DPM to them as opposed to prescribing control to them? And in that regard, we have the data -- well, we have most of the data, about 88 to 89 percent.

So with regard to that, I think we have fairly good confidence when targeting the treatment policy estimand.

DR. REDLICH: Just so I understand this, if you were to do the analysis and look at the effect at the last time point, that would not be statistically significant, but it is when you take into account all of the time points. Is that --

DR. TORRES: If the primary endpoint had been changed from baseline at week 26, then we

would see -- and we had formerly done a hypothesis test for that, that would have failed to reject the null hypothesis.

As I noted in my presentation, the primary endpoint in this study, and in studies 301 and 302, gave over two-thirds weight to change occurring during the first 14 weeks of the 26-week period, and less than one-third weight to the last 12 weeks of the 26-week period.

DR. AU: Great.

DR. REDLICH: Thank you.

DR. AU: I think I saw Dr. Emerson's hand go first.

DR. BRITTAIN: Maybe not. I just want to make sure we're clear on what -- well, going back to page 17, slide 17 -- I want to remember, though, those numbers. It was 12 percent and 11 percent in those two groups that had missing data at week 26.

So just to be clear, about 90 percent in both groups have their data that are represented there. Some of them might not be on treatment anymore, but that's still the intent-to-treat

estimate that we're interested in.

So of that roughly 11 percent in each arm, some of them -- and make sure I have it right. Some of them, the ones you had bad outcomes, are basically being imputed roughly by their baseline value. Is that correct? And the ones that didn't have bad outcomes, they moved or whatever, they're being imputed based on the whole population.

Am I correct about that? There are a lot of different imputation rules going around here. I'm hoping to make it really concrete to see, of those 12 percent, what's happening there. You have data on most -- most of the people have data here, so most of it is real data.

DR. TORRES: This is Cesar. The results on this slide reflect those using the pattern mixture model approach. Per our briefing package, once we did the imputation to have monotone missingness, then we did two separate sets of multiple imputation where patients who withdrew to adverse events, physician decision or lack of efficacy were imputed using a regression model for the baseline

FEV1, including covariates, rhDnase use, pooled country, and FEV1 at screening, estimated on data from patients with non-missing baseline FEV1 values.

So the trajectory was going to go kind of to like a baseline level, while still having some uncertainty in the imputation process.

For everyone else, they were imputed using a regression model, including rhDnase use, pooled country, FEV1 at screening, baseline, and at weeks 6, 14, and 26 using data from patients in the same treatment group who completed the study.

DR. BRITTAIN: Again, I'm trying to make it simple, although it isn't simple.

(Laughter.)

DR. BRITTAIN: Of the 11 percent who don't have data, who data are being imputed here at week 26, can you tell us what proportion are in that category that are essentially being imputed by their baseline or an estimate of their baseline, and what -- is it like half-half roughly, in that ballpark?

DR. TORRES: I don't have those numbers.

DR. BRITTAIN: You don't know. Okay.

DR. EMERSON: I did look at what those numbers would break down to, and it is the half-half. Of the patients -- again, we saw that there were patients who stopped therapy, so this is a simplistic view. But if you believed the treatment worked, and then they stopped taking the treatment, in essence, by going to an intent to treat, those patients' measurements that we do have would tend to go back towards the null group, and that's how they're being measured. They're being measured that way.

The patients that we don't have data for fell in two camps, and they were roughly equal of those that arbitrarily was decided that if it was loss of efficacy, adverse events, position, decision, you would presume that they would go back down to not having data. And the other ones, you presumed that if they had stayed on, they would have stayed on taking the treatment and having whatever benefit they were having at the time.

So that's the one that's biasing, and the other ones, we can say, well, that that's attenuating any effects that there really was. But it is just that the -- I'm always most concerned about pretending that people will continue on their same course when they stop therapy and stop getting their measurements, and that's a relatively small amount in this thing; that that we've imputed them as if they would continue on what could be a good trajectory or could be a bad trajectory. We don't know. They didn't tell us that.

DR. BRITTAIN: So it seems like -- one of the bottom lines --

DR. AU: I'm going to let you make this point, and then I'm going to move on.

DR. BRITTAIN: Okay. One of the bottom lines, again to answer the question from the panel, is that if you're worried that a lot of that data were imputed at week 26, it's a relatively modest proportion, 10 percent.

DR. KIM: This is Yongman. I just found from the briefing document that about 60 percent

discontinued due to adverse event or low efficacy, so a little more than half.

DR. AU: Okay. If I could get the summary of this particular discussion, just because I think it's complicated for the clinicians, the non-statisticians in the room, is there a summary of the discussion that you could make for us, for the non-statisticians in the room, of this kind of conclusion, of this discussion that we've just participated in?

What is the effect? What is the magnitude effect that we might anticipate on FEV1?

DR. EMERSON: So one answer to that question is we don't know because we don't have enough of the breakdown about what happens. Then, even if we did have the breakdown, we'd just have to go with some subjective feel about what's there.

But again, I'm feeling -- and my esteemed colleagues to my right might be way, way smarter than me in this. But there are enough questions about what the pattern of missingness was and what the impact was.

I do trust the tipping-point analysis the most, so then that just boils it down to, do you believe that 0.1 difference describes what the average effect would have been in those people? And if you felt that that's implausible, well then, we don't have to worry about it.

DR. AU: Great. I'm going to move on if that's okay with the group. Dr. Kelso has been waiting for a long time.

DR. TORRES: I know we're trying to move on, but I just wanted to put it out there that the FDA has a backup slide with that table for the two-dimensional tipping point analysis, if you guys would find that helpful, if we have time.

DR. BRITTAIN: I would really like to see that.

MALE VOICE: We'd really like to [inaudible - off mic].

DR. AU: Yes. I'll let you find that document. Let's move on to Dr. Kelso, and then we'll come back and show that slide.

Go, Dr. Kelso.

DR. KELSO: I have a question and a comment. The question is, I understand the intention to treat and the importance of that. Do we have a per-protocol analysis of that same slide?

DR. AU: Are you asking that of the sponsor?

DR. KELSO: I'm asking of the sponsor. Do you have a per-protocol analysis of that same change in FEV1 slide that we've all been talking about?

DR. PARRY-BILLINGS: We don't have a per-protocol slide to show you. We can show a completer's analysis, but not the per protocol.

DR. KELSO: Okay. Then the comment is I absolutely appreciate, particularly from the folks who gave public comment, the seriousness of this disease and the burden of treatment. And it seems like, both from clinicians and patients, people are thinking of this as sort of a substitute for hypertonic saline or a drug that can be used in people who don't tolerate that, but that would somehow do the same thing with much less burden on

the patients. And if that were the case, I think that would be wonderful.

But we're being asked did this thing increase people's lung function? I mean, we're really on the edge of that. It's a tiny little increase. We're not sure it's durable over time. I'm not convinced that we've stopped somebody's decline in lung function or certainly not that we're improving it, compared to the control group.

So you say, well, gee, if that's not so good, what else you got? Well, we'd like to decrease exacerbations. Even if we say, well, there are reasons to explain the possible increase in exacerbations, and that's not real -- we certainly haven't shown any decrease in exacerbations. Well, gee, what else you've got? Well, we'd like people to feel better. The patients were absolutely compelling. We want people's quality of life to be improved, but that wasn't shown either.

MALE VOICE: Although maybe it was.

DR. KELSO: I think the reason we're all

struggling with this is we need -- I agree with the patients that there's a need, but I don't think we've seen that met.

DR. AU: I'm going to take control of this, so we'll put you on the list. Dr. Lederer?

DR. LEDERER: Thanks. Actually, I want to build on what Dr. Kelso was saying, and maybe direct this at the FDA. The proposed indication is to improve pulmonary function, yet we're also asked to look at the secondary endpoints in which probably they were grossly underpowered with very low event rates for exacerbation in the control arm and relatively high CRQ -- I think it's the CRQ, CFQ -- scores. So there's kind of a ceiling effect.

If you're asking us, does this improve FEV1, I think we can all decide for ourselves if the evidence strongly supports that or supports that. And I know you always include the word "substantial" in your voting, which I struggle with.

I guess back when you were having the

conversations about the design of 303, was the indication to improve pulmonary function part of that discussion or did that come later?

DR. LIM: This is Bob Lim. I wasn't here during those discussions or I was not involved in those discussions. But typically, when we're talking about how you design the trial, we're not necessarily having the exact indication in mind, and that's something we often will talk about or negotiate once it comes in.

I think that while the indication here may say improvement in pulmonary function -- and this is just my opinion -- sometimes because of the size of the effect, then whether or not that's a real or clinically meaningful endpoint, a clinically meaningful improvement, it almost forces you to look at the secondaries.

DR. LEDERER: But that's a matter of opinion, right? I mean, that's why we're here.

DR. LIM: Yes, that is why we're here, and that's why

we're here to seek you guys' advice because

FDA can get

mine whenever they want.

DR. LEDERER: Okay. And I don't disagree. I think you guys have done a great job. But maybe can I just follow up with one?

DR. AU: Sure.

DR. LEDERER: If the original charge or recommendations from the FDA were FEV1's primary endpoint, we'd like to see trends in the secondary endpoints, and the sponsor has this data and come back to you and they say, I just want the indication for pulmonary function, from my perspective, I feel like I should be looking at pulmonary function to drive my vote on the efficacy question.

Am I misguided in that thinking or is that also a matter of opinion?

DR. SEYMOUR: Hi. This is Dr. Seymour. I think it depends, right? If we saw a tremendous FEV1 treatment effect, we may not be here. But we have something that's on the cusp, or the edge I think are the words that you used. So in that

case, when we're looking at an effect size that is much lower than some of the other drugs that we've approved, we're going to be looking at some of those secondary endpoints.

We look at the totality of data regardless, but in some respect, it depends upon the effect size that program would have shown. If it had had a big treatment effect, we may not be here.

DR. LEDERER: Thank you.

DR. AU: Thank you. Dr. Blake?

DR. BLAKE: Thank you. As a pharmacist, I'm just surprised that FEV1 is the primary endpoint for a drug that's not a bronchodilator. But given that I heard someone say that the rate of decline of pulmonary function is 1 to 3 percent per year, and this drug at least maintained that over the 6-month period, that to me speaks that it does have some clinical efficacy.

It would have been nice to have seen some dispersion of the responses with means and standard deviations as been described before.

But we do have your responder rate

analysis -- and this is on your slides CO-50 -- and I'm interested in knowing how many, the number of patients who actually did have an increase of 0.1 liters.

Yes, so that's slide. What is the number that's associated with that 34 percent, the number of patients in the trial?

DR. PARRY-BILLINGS: That's 34 percent of the patients randomized in study 303.

DR. BLAKE: But if you -- okay. Alright. So it also includes those who had greater than 0.75 and 0.5, so it's not like a range.

DR. PARRY-BILLINGS: The higher cut, the greater or equal to 100, is quite discrete from the lower cuts.

DR. BLAKE: Right. So that 34 --

DR. PARRY-BILLINGS: Sorry. Let me -- I'm sorry to interject. The 34 percent of patients who had an improvement greater than a hundred mLs would also be included in the lower cuts because they're greater than or equal to.

Sorry --

DR. BLAKE: No --

DR. PARRY-BILLINGS: I apologize. I'm confusing --

DR. BLAKE: That would be if we said less than.

DR. PARRY-BILLINGS: Yes. I'm sorry.

DR. BLAKE: So what's the number for those that had -- I'm really interested in those who do respond well. So how many were in that final column?

DR. PARRY-BILLINGS: Thirty-four percent of patients randomized to Bronchitol had an improvement equal to or greater than a hundred mLs. That's the take-home message from the right-hand set of data here, as compared to only 24 in the controls.

DR. BLAKE: So I've forgotten how many were randomized to each arm. So what number is that?

DR. PARRY-BILLINGS: I'll just check with my colleague, so I give you the precise number.

DR. LIM: I'll just interject --

DR. GILLEN: It should be the 183, the

completed study. It was 34 percent of the 183, the completed study.

DR. BLAKE: Thirty-four percent of 183. Okay.

DR. GILLEN: 183 completed studies. That's what this has got to be on, correct? That week 26.

(Crosstalk.)

DR. BRITTAIN: They said non-responders. Patients with that data are non-responders.

(Crosstalk.)

DR. LIM: Dr. Au?

DR. AU: Sorry about that. I kept on pressing it.

DR. TORRES: We have the count from our analyses with regard to the responder analyses for these three different thresholds, and we had backup slides prepared, slide number 15 from the slides that we prepared previously.

DR. BLAKE: So it's 72 patients.

DR. PARRY-BILLINGS: Thank you.

DR. BLAKE: Is that what I'm looking at?

DR. PARRY-BILLINGS: Yes, and thank you.

Thank you very much for clarifying.

DR. BLAKE: Thank you.

FEMALE VOICE: [Inaudible - off mic].

DR. BLAKE: Right.

DR. AU: Just let me clarify. This gets back to Dr. Emerson's point earlier of the NNT of 10, to get to 100, to get to 100 mL effect.

Okay. Dr. Parad, you had a comment earlier. I'm sorry to interrupt you.

DR. PARAD: Getting back to Dr. Kelso and Dr. Lederer, I think pulling out that group that had -- it seems like there's a hidden group in there, and it is what it is. We can't go back and do it over again, and figure out who they are. But it seems like a substantial number did have a response, and I think we saw some extra data before from the sponsor that said that the CFQ-R scores were higher in a subgroup of patients that seemed to have response.

So again, that may be diluted out by this other two-thirds that maybe aren't having such a big response and have hit the ceiling on their

score.

I wish there was a way to make the indication more specific, that we had data to say, okay, if your percent predicted FEV1 started at 40 percent, and you were a male and whatever, that this drug is going to really get you up there, but we're kind of stuck spinning our wheels with these data. But that doesn't mean that it might not be hidden in these numbers somewhere, that some patients actually are feeling better after getting the drug, and we just can't see it the way the data are being presented to us.

DR. AU: Dr. Tracy?

DR. TRACY: Dr. Tracy. I'll kind of follow up on that a little bit, along with Dr. Kelso. This is my third CF meeting for the FDA, and one of the questions that continuously comes up is both the relevance of FEV1 as a measure and the clinical significance of whatever number that is. It seems to be fairly universal.

So when we looked at the CFTR modifiers, a few years back, we had a very similar conversation,

and then obviously it moved forward, and ultimately got approved.

I went back and I actually talked to some of my patients about this. I'm not a statistician, thank God.

(Laughter.)

DR. TRACY: But I really asked this; what does a 2 percent improvement in year FEV1 mean? And I asked this of three, and they all happened to be 30-year-old-ish mothers of at least one or two kids. And they all basically mentioned it's the difference between walking upstairs or not, sometimes, depending on where they are in their disease process.

So 50, 60, 2-mL change in your FEV1, for most of us, it wouldn't measure at all, but for these people, this is a big deal. Absolutely, this is not a drug for everybody, but it certainly sounds to me like it's a drug for somebody. Speaking as a clinician, I'd like to have that chance to make that call myself.

These cystic fibrosis patients are followed

by doctors and staff that do this all the time. That's just what they do. I think trying to slice and dice an FEV1 of 50 mLs doesn't really get to the heart of why we do this.

I mean, ultimately, we have to make that decision. Actually, ultimately, the FDA has to make that decision. But I do think we need to remember that we're dealing with -- we study populations, but we really take care of people. And if you can't remember that at the end of the day, then I think we kind of get lost in some of the numbers. So you just do the best you can, and maybe the data's not perfect, but so far it looks not too bad for me, at least for some people. Thank you.

DR. AU: Dr. Schell?

DR. SCHELL: Thank you, Dr. Tracy. I was just going to say, working with patients and doing daily PFTs on them, they may not have significant number changes, but how they feel from one moment to the next, after they've improved their numbers, is what we have to consider. To me, as you stated,

small numbers won't make that much difference, but for them can really make a difference in their day. I just wanted to thank you for bringing it up.

DR. AU: Great. I had one other point that I was going to follow up with Dr. Kelso. I agreed with everything you said. I heard that the -- and this is going to express concern, which is that we've heard that hypertonic saline is a burden to patients in that the regimens are burdensome to them.

We've heard, I think, that loud and clear. In contrast, though, there's a robust evidence base that shows that hypertonic saline actually reduces exacerbation rates and improves FEV1 at a magnitude that's greater than what's been described.

There's no direct head-to-head comparison. There's no comparative effectiveness directly to it, but I do have some concerns that we're going to start substituting therapy with this substance, for another substance that actually may have better efficacy. It may not be better effective, maybe not more effective, but certainly has better

efficacy data. So I just wanted to put that out.

Are there any other comments about these? Otherwise, I will do my best to summarize this very difficult conversation.

(No response.)

DR. AU: Great. Yes?

DR. BRITTAIN: We were interested, though, in seeing that tipping point; at least I was. Thank you.

DR. TORRES: Sure. So we have a backup slide previous to today that we prepared, slide 14; backup slides previous to today.

DR. AU: Would the FDA mind walking us through this?

DR. TORRES: Sure. This is Cesar. This table displays estimated differences between DPM and control, and the mean change from baseline of FEV over 26 weeks, regardless of adherence, with varying assumptions about data missingness.

Because in the majority of the scenarios considered on the table, the lower bound of the 95 percent confidence interval is greater than or

close to zero, the tipping point sensitivity analysis largely supports the finding of the primary efficacy analysis for this endpoint in study 303.

For example, if FEV1 values, after study discontinuation in the control arm, follow the same trend as those of comparable control patients who remained in the study through week 26 -- in other words, if the shift for control was zero milliliters, then in order to tip to a lack of statistical significance, FEV1 values, after study discontinuation in the DPM arm, on average would have had to be 100 milliliters lower than those of comparable DPM patients who remained in the study through week 26.

DR. MARSHALL: Gailen Marshall. I simply would point out that the number 100 mLs is the cutpoint that we use in asthma responsiveness, where numbers are clearly established. So this issue of trivial changes, maybe not.

DR. AU: I'm sorry. Can you clarify that one more time?

DR. MARSHALL: The point that was just made about the 100 mLS necessary for the tipping point to be there, that 100 mLs in FEV1, that becomes very significant because it's the number we use as a cutpoint for responsiveness is asthma, and no one argues that a 100 mLs is trivial.

DR. AU: Any other discussion? Dr. Redlich?

DR. REDLICH: This is a question for the FDA -- [Off mic].

DR. AU: Could you turn on your mic, please?

DR. REDLICH: When you had mentioned that other studies have found a 3 to 13 percent improvement in FEV1, in that setting, what effects have you seen in terms of the secondary questionnaire, symptoms, exacerbations, in terms of how those two relate?

DR. PUTHAWALA: Generally, they had secondary endpoints support, exacerbations -- and this is really referring to the CFTR modulators. They had trends in the right direction from an

exacerbation standpoint, so they had secondary support. They also looked at BMI. They also looked at CFQ-R.

What we're asking for today is not too different than what we have asked for before.

DR. GILLEN: This is outside of the --

DR. AU: Could you introduce yourself for the record?

DR. GILLEN: -- oh, sorry; Dan Gillen -- outside of the technical aspects. But one thing that wasn't really discussed a lot, and I realize we focused a lot on 303 and for very good reasons, but 301 and 302 had an open-label extension and I wanted to ask this earlier when you did your presentation.

What was that open-label extension open to? Was that open to everyone, and people could self-select back into it? Because as I look at the numbers -- and I'm trying to get a gauge for how enthusiastic people were to stay on this therapy after they had finished the blinded portion of the study.

My numbers, anyways, that I've kind of taken from the document are that there were about 221 people that were previously treated with Bronchitol; 130 of those elected to stay in and go into the open-label portion of those studies. So that's about 59 percent.

Do I have those numbers correct, that about 60 percent of patients -- and I realize that's a biased sample. Those are people that made it to 26 weeks that were still on therapy that went through, but is that correct? I'm trying to, again, gauge enthusiasm for people using this drug after they've been on it for six months.

DR. PARRY-BILLINGS: Yes. The proportion of patients in the Bronchitol arm, the Bronchitol arm, who elected to continue therapy was -- I'm sorry. I don't have the number immediately at hand, but it was between 30 to 40 percent. I think the larger percentage you've calculated may include those patients who are on placebo who elected to continue.

DR. GILLEN: I don't think so, no. On

placebo, you had 145 and you had 94 that went on to the open label. That's 65 percent of those.

DR. PARRY-BILLINGS: I'll ask my colleague, Dr. Alexander, to clarify that point. Nevertheless, if I may just make the general point that cystic fibrosis patients, as I'm sure you'll appreciate from some of the discussions today, are invited, and indeed encouraged perhaps, to take part in many trials with many emerging new therapies.

So this type of percentage -- we'll clarify the numbers for the committee -- whether it's 30 to 40 or 60, is not untypical for these patients who tend to switch between trials.

But, Dr. Alexander, please, we should clarify the specifics. Thank you.

DR. ALEXANDER: Thank you. This is Jim Alexander from Chiesi medical affairs. In study 301 plus 302, those are the studies that had the open label, there were 70 patients in each of those studies who had been on Bronchitol and completed the study. That's 140; 130 of those, or 93

percent, entered the open-label study.

In those two studies, there were 102 patients who had been on the control group. Of the 102, 94, or 92 percent, entered the open-label study, 301, 302.

DR. GILLEN: In 301, 302, how many subjects completed 26 weeks in that study that were on control, combined 301 and 302?

DR. PARRY-BILLINGS: Dr. Alexander, please?

DR. ALEXANDER: Jim Alexander, Chiesi. I have 102, one-hundred-and-two. There were 52 patients in one study and 50 in the other.

DR. PARRY-BILLINGS: If I may offer another comment, which may help this discussion that the panel's having with regard to longevity and there was reference earlier to FEV1 decline --

DR. AU: I'm sorry. Can I interrupt you for a moment, please?

DR. PARRY-BILLINGS: Certainly.

DR. AU: I'm going to request that the sponsor wait until we make formal requests for more information. Thank you.

Dr. Gillen, are you satisfied? You seem to be digging in.

(Laughter.)

DR. GILLEN: Yes, because the numbers aren't jiving with what is reported in the sponsor's document, and multiple different places about controls that have completed the 301-302.

To be honest, those numbers, those percentages that you just quoted at 40 percent are worse than the 60 percent that I'd come up with from your briefing document numbers. What you are saying is about 40 percent of individuals that completed the 26 week endpoint, that were still on treatment at that time, in 301 and 302, and on Bronchitol, chose to go into the open-label study; 40 percent.

Is that what I heard?

DR. PARRY-BILLINGS: I confirm.

DR. AU: Great. Any other discussion?

(No response.)

DR. AU: Great. Let me first try to summarize the discussion. The questions that we

were asked to really focus on were what is the effect on FEV1, including the effect size and durability.

What I heard was a little bit of competing issues around the size of the total effect size, on an average basis as being quite small, 50 mLs, but there was approximately a number needed to treat of 10 that would receive a benefit of 100 mLs. We heard that perhaps those kind of decisions might be best led to clinicians to make decisions about whether or not to use a medication or not.

Around secondary endpoints, I think the data is relatively robust that we did not see effects that were in general support of the secondary endpoints around exacerbations and the CF questionnaire, the revised version.

In comment to that, though, there were questions about whether or not there could have been ceiling effects applied to that, and whether or not the city population was designed to actually be able to adequately address it, given the overall low rates of events.

In terms of persuasiveness, including the long, drawn-out discussion that we had around the missingness of data, at least to my ears, it seems like there is a preponderance of data to support the overall idea of statistical persuasiveness in terms of the FEV1 effect size, but there I think there still remains questions around the issues of how missing data were addressed and the -- well, I'll leave it at that.

The last part of the discussion was really around this open-label issue and some ambiguity in differences between data that was being presented in terms of our information book as well as what was presented to us verbally today.

Does everyone feel like I gave a reasonable summary? Okay.

We're due for a break in 4 minutes. The advice I was just given is that we should probably just go ahead and take a break now, which I think is a good idea.

Why don't we go ahead and take a 15-minute break. We'll come back, and we'll do some voting,

and then we'll continue on with the next set of questions. Thank you very much. Remember, no discussion, about these very interesting points, outside the committee.

(Whereupon, at 3:09 p.m., a recess was taken.)

DR. AU: Why don't we go ahead and get started again? Just to follow up at one point, that Dr. Gillen had some questions about open-label follow-up, and the sponsor has that information.

Do you mind just presenting that quickly?

DR. PARRY-BILLINGS: Dr. Gillen, thank you again for the question. Your question was, for those patients who completed 6 months of treatment in 301 and 302 -- and you emphasized, and we agree this is a selected population because we had the high dropout, et cetera, that's been much discussed.

The number of patients that completed 301 and 302 on Bronchitol was 141; 1-4-1 got through those two studies, completing treatments for 6 months; 130 went on.

So the message is that 92 percent of those that made it through those first two studies, 92 percent, actually were -- yes. were, I apologize, again, for mixing the numbers, but I was thinking peds. Anyway, the number is 92 percent, so thanks for the question.

DR. AU: Great. So it turns out statisticians can count. Right?

(Laughter.)

DR. AU: Is that the message we should take?

With that little bit of humor, I think we're ready to go on to discuss question number 2. I'll read question number 2. Discuss the safety data for DPM for the proposed use in patients with cystic fibrosis, 18 years of age or older, particularly exacerbation and hemoptysis; so discuss the safety data.

I'm sorry.

DR. MARSHALL: No problem. Gailen Marshall. I would like to ask a question.

Maybe, Dr. Lim, if you could comment on

this? The message I got from you all in your presentations is related to the safety issue, and as we talked about, the p-values also, was that there was a signal there, and the signal was of concern as a possible safety issue. But yet, you also acknowledge that the numbers were small, so it was one of those gray areas; what do you do?

Correct my thinking if it's wrong, but it is my sense that in other situations that I'm aware of other drug developments in the past, the FDA has indicated that there would be things such as postmarketing studies that would address these concerns, or black-box labels, or other things that would acknowledge the concern without clear evidence to confirm what that concern is.

Is my thinking completely off on that or is that a correct assessment of potentials that can be done when a concern exists, but the evidence is in the gray area?

DR. LIM: So there are multiple ways that a safety concern that's raised during the review cycle can be addressed. It can be resolved, and we

believe that there's not really an issue, so it doesn't require anything additional. Depending on the level of concern, there can be warnings and precautions, box warnings and things of that nature.

So it really depends. There are a variety of things, but it usually depends on the level of concern with the potential safety issue.

DR. AU: Dr. Lederer?

DR. LEDERER: Thanks. My take on safety -- and it builds a little bit off of what you're bringing up, Dr. Marshall -- is that statistical and trends testing may not be as important. The burden here is to convince ourselves that we have enough data, there's adequate data and adequate testing, and that there is enough reassurance and confirmation that it's safe regardless of any statistical hypothesis testing. At least that's my take on it, and I think that's the burden of proof. It's not did you show harm; it's are we concerned there may be harm?

DR. AU: I don't know which one of you two

were first. You can choose.

DR. BRITTAIN: I have a question rather than an answer here. I guess I'm a little confused about the exacerbation that's on the efficacy side and then the exacerbation data that you analyze as AEs. Obviously, they're linked, and I'm a little confused about how to think about that.

DR. PUTHAWALA: This is Khalid Puthawala. On the safety side, this was investigator determined. This is simply recorded in the database. There's no prerequisites. On the efficacy side, PDPE, protocol-defined pulmonary exacerbations, the patient had to be on IV antibiotics and meet 4 of 12 criteria.

I'm not sure if that answers your question.

DR. BRITTAIN: At least in study 303, there was some concern about imbalance that you've seen somewhat in 302 on the efficacy version of exacerbation. Now I can't remember if in the safety slide, were we only seeing the pooled data -- is that correct -- where it didn't look terribly different on exacerbation?

DR. PUTHAWALA: The difference was about 2 percent difference overall. The numbers are very similar, though. So the consistency of the signal is there, or rather, the concern is there. I would say it's corroborating information.

DR. BRITTAIN: Finally, the final question, the efficacy version of the exacerbation, is that a small subset of the AE or not? How do they relate?

DR. LIM: I think there are probably patients who had investigator reported CF exacerbations who probably had events that would fall into the PDPE definition. We haven't had a breakdown of what that overlap was. I think exacerbation is one of those endpoints where we can view it, and it's often viewed, as an efficacy endpoint. But if we see something concerning going in the other direction, it can kind of become a safety concern.

So it's a little bit of both -- it can be both safety and efficacy driven. However, when we're thinking about it to demonstrate efficacy, we usually use the protocol-defined exacerbation

rather than the investigative reported.

DR. PUTHAWALA: Sorry. Let me just add one thing. If you look at table 24 on the briefing document, that's the essay that I also showed on my slides, the numbers for the DPM arm of 55 patients and then the control having 39, they don't match up, obviously, entirely, and they're not going to because we're talking about two different methods in which exacerbation was determined. But there are some similarities there between the increase. You wouldn't come up with a rate ratio based on that, but you can look at it and see that it's generally consistent.

DR. AU: Dr. Emerson?

DR. EMERSON: I'd just like to add a comment to Dr. Marshall's and Dr. Lederer's. Not only on safety do we not act on we've proven harm. It's just that this is a concern. But in clinical practice, and for the labeling, and as I look at it from the regulatory standpoint, if we can label correctly to say this is something to watch out for, that's the most we can ever do, because every

clinician has to -- we don't necessarily have in this clinical trial the entire patient population that the people would be considering on.

So this is something that I don't really know how to judge. And to Dr. Au's comment early, one of the major ways a treatment can be harmful or non-effective is if you shift people away from effective therapies into something that turns out to be ineffective. It's sort of like if you promise me that -- I have no knowledge, but if hypertonic saline truly is effective in some people, and if you promise me that those people will keep using that, and the only people we'll go to is the people that couldn't do that, well then, I will react differently than if I think there can be some swap.

But this is where I have trouble with this exacerbation and hemoptysis. I'm going to say I'm underwhelmed by the hemoptysis in the adult population. I look at it as this is a confirmatory study that's not really too much of a concern.

I consider it quite plausible that there

can be potentiation of an underlying exacerbation risk from this treatment, and it might be a misdiagnosis of the exacerbation. It might be something about the treatment in some people that's being called an exacerbation, but is really, if we'll say, getting used to the treatment.

I have no idea, but if you put something solid in my lungs, I'm going to cough, and maybe not cough it all out, and I can imagine that. But I think it is something of concern, and I'm going to do the very bad thing here, the very, very bad thing on subgroups of subgroups, and stratifications and unplanned analysis. I'm going to tell you what a p-value is if it were a legitimate p-value.

It isn't, but if we had done a clinical trial in those people who had a prior history of an exacerbation within the past 12 months, and we randomized them roughly in the 4 to 5, it would have ended up with what was the imbalance in this study, and we looked at those results where there were of the 50 people that we put on

Bronchitol -- and this, by the way, is also just the U.S. population.

If we looked at the 21 people out of the 50 versus the 6 out of 35 -- and I computed a p-value, so Drs. Brittain and Gillen are taking away my union card -- it's 0.078. The trouble is the multiple comparison here. We're looking at that, and I'm doing this p-value precisely because I looked at the data, and it's surprising, but the idea of calling it a randomized comparison apart from the multiple comparison is correct.

So that's what I'm concerned at, and I don't know whether there's a possibility of misdiagnosis. I don't know how well this could be handled by saying watch out for this and getting it in the labeling, but I think something needs to be thought about.

DR. AU: Great. Let me just get a point clear.

Dr. Lederer to respond, and then Dr. Kelso.

DR. LEDERER: So that's very helpful. Can I ask maybe either the sponsor or the FDA, was

there a test for interaction between U.S. and times treatment done for that subgroup analysis? Because that p-value I think would be really helpful for me rather than the p-value for the subgroup.

DR. LIM: I don't think we did that.

DR. LEDERER: Okay.

DR. TORRES: I think, in general, such a test would not have been very informative since the power to detect such a difference would be very low.

DR. LEDERER: And I agree it would be low, but I really would still like to see it.

DR. EMERSON: You're right that looking for that p-value in the presence of me going after so many multiple comparisons is correcting, but rather than testing for interactions, if you have pre-identified the groups, it's better to just do the subgroup analysis and not demand significance on the interaction.

DR. AU: Great. Dr. Kelso?

DR. KELSO: This thought that if there's a potential bad thing here and we're going to in some

way describe to clinicians that it's something they need to watch out for, I think what we're talking about here is not easily addressed by that because if what you're saying is that with some drug, there's this very rare but unusual thing that might happen, so just keep it in mind, and when it happens, somebody can notice it; what we're talking about here is something that happens to these patients all the time anyway.

So we're telling them they might have more exacerbations. Well, they have exacerbations anyway, and if they only have one or two a year or whatever, it's going to be hard to describe that in a way to say watch out for exacerbations when it's something that happens to the patients anyway.

We kind of got a little better handle on the FEV1 thing when we finally clung on to the 100-mL increase and the number needed to treat of 10 to get that. That is a little reassuring in some way. Is there a same way to apply some other crude logic like number needed to harm to this bad thing that we're talking about, to get a little

better handle on that, or is that not doable or not appropriate statistically?

DR. EMERSON: Well, the number needed to harm would be the natural thing, except for into such of a subgroup of a subgroup that I don't know how many -- to talk about what will be the prevalence of that among the population.

To me, and who knows, maybe this is this thing that, yes, it's only the people who are at risk, and if we were to treat a bunch of people and prevented their tendency to have exacerbations, they'd never have the problem. I don't know. I just don't know how to come up with a number needed to harm that factors in that there may be differing numbers of people that are being treated.

DR. GILLEN: I think there's that. And to go with your point earlier about the multiple comparisons, it's a biased estimate likely that you have anyway. After you've gone digging through all of the subgroups of subgroups, you've found this high rate.

DR. AU: Dr. Parad?

DR. PARAD: Could we just be reminded of what the phase 4 rules are for -- if the FDA approves this, is it automatic that there's a postmarketing process or does it have to be -- does the opinion

of the committee direct the FDA to say, okay, now you've got to collect some data on SAEs, AEs, pulmonary function tests?

DR. AU: Would FDA like to comment?

DR. SEYMOUR: Sure. This is Dr. Seymour. We have options for phase 4 postmarketing type data. It's something we can request. It's something we can require, too. We can require it if we think there's a safety issue that's serious that needs to be evaluated that's a postmarketing requirement.

In these meetings, if there is concern about a safety issue, or the community thinks there's a need for a postmarketing study, it is something that can be brought up in the discussion, and we'll take that back and deliberate about that. But there are options to get postmarketing data.

DR. PARAD: It just seems to me with 8,000 patients having been treated outside of the United States, that there were opportunities already missed to try to answer some of these questions, and it might make sense to think about this going forward.

DR. AU: Dr. Brittain?

DR. BRITTAIN: If you're talking about the exacerbation, I think it would be awfully hard to evaluate that outside of a randomized study. I think it would be pretty tough to do that in a postmarketing setting. Maybe I'm wrong.

DR. AU: My apologies. Any other discussions from the group?

(No response.)

DR. AU: Okay. No other discussion about safety? Let me see if I can summarize what we talked about. I think it might be a little easier discussion.

In terms of specifically around exacerbations and hemoptysis, there is some potential safety concern in the U.S. population

that there was an increased risk of exacerbation in the AE reporting, and that the AE reporting and the primary efficacy endpoints of exacerbation were measured slightly differently. But nonetheless, there is general agreement that on the overall population, there was a small signal, or if not balanced, around exacerbations. The hemoptysis question seems like it was resolved with this.

In terms of other discussion points, there was some concern that had been raised previously about whether or not a drug that is easier to use but is less efficacious would then be substituted for a medication that was more efficacious.

There were also discussions around postmarketing surveillance and whether or not that was possible. There was no specific recommendations to FDA about if this drug were approved, what postmarketing surveillance would be required. One point that was made was that any comparison of exacerbations would be challenging to measure over time.

Were there any other points that the panel

felt like I missed or would like to further clarify? Scott?

DR. EMERSON: This is just a procedural thing. I'll note that it's not uncommon in clinical trials where you have really an efficacy endpoint that's been protocolized, and it could be listed as an AE, but it's not really supposed to be. This is like progression in cancer.

It's not uncommon that there are bizarre patterns in the way people do that, and that adds a little bit more noise to this AE in the presence of a protocolized collection of the data, that just people reporting it will be very bad. I've many times seen them go in opposite directions.

DR. AU: Right. Okay. That's very good. So there are issues around potential measurements of AE events that were less well protocolized than the primary efficacy data of exacerbations.

Any other discussions?

(No response.)

DR. AU: We're moving to the voting phase. We will have three votes. Question 3 is a vote,

and I will read it out loud. Do the data provide substantial evidence of efficacy for DPM 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? If no, what further data are needed?

I think we're ready to vote on question 3. Are we ready to vote? There we go. Okay, now it's flashing. So everyone vote their conscience.

(Voting.)

LCDR CHEE: For question number 3, we have 10 yeses; 6 nos; and zero abstain.

DR. AU: Why don't we start on this side of the room?

DR. GILLEN: Sure. I voted no for a couple of reasons. One is obviously the small effect that we're observing on FEV. I was struck by the 1.2 percent-predicted difference and the fact that recently approved drugs, as noted by the FDA, are in the 3 to 13 range.

Also, the lack of sustained effect truly

bothered me over the 26-point time range, and if you looked at truly the zero to 26, it's a question of how much that's really going to move the needle, given that there is no effect, at least that's been observed on exacerbations or other key more clinical endpoints.

So to me, it comes down to the clinical relevance. I understand that statistically we have significance in testing the FEV level, but it's not clear to me that that's the clinically relevant difference that we would be looking for here.

DR. BRITTAIN: Erica Brittain. I voted no. I do think there's a statistically significant difference on the FEV1, but the effect size, my colleagues tell me is modest, and we see some indication that it wanes over time.

To be substantial evidence, it sounded like with a modest treatment effects, you needed some support from those secondary endpoints. We didn't see that. In fact, the FDA study 30-3 exacerbation analysis was particularly concerning. So it just did not seem to pass the threshold that the FDA

established, which it sounded like they established at the time the study was designed.

I feel bad voting this way after hearing the public open session because I feel great sympathy for the hardships of these patients. Perhaps the way out of this is finding -- if there is some way to identify the subgroup that benefits most from this therapy, that might be a way forward.

Normally, we wouldn't say, oh, just look at a subgroup, and that's okay, but here's a scenario where we have a significant result on the primary endpoint, so that feels better than the normal case when we don't have a significant result overall and we'd find a subgroup. That's not okay. This is sort of different from that.

DR. EMERSON: This is Scott Emerson. I voted no. It was a hard decision because of the way things were phrased. I do think there's a very good chance that there's an effect on FEV. I'm not convinced that it's of the magnitude that's commensurate with what we've done with other

treatments.

I am more inclined to go with responder analyses, but I'm worried about something that's quite chronic treatment, but that we started with a large population of people who would never go on to this chronic treatment as evidenced by the fact that they stopped the treatment. I don't know how much of the waning of the effect is due to the drop out of that, but there are other trial designs that might be able to sort this out better.

In that inclusion of lots of different populations that maybe aren't getting the benefit, that that's exactly the case where you could say, well, the secondary endpoints won't shine through, but let's design a study where they will shine through, whether it's by a randomized withdrawal or something like that to enrich the population with the people who are really going to benefit over a long period of time.

As I say, I came close to voting yes, and I would have said all of these same comments that I was worried about it. But I really came down on

the side of the lack of the secondary endpoints that would support it, and that's just increasing the chance that this is a false positive. That's the problem that we have to face.

DR. PARAD: Richard Parad. I voted yes. I think the FDA set the primary outcome, and statistically that was passed. So the effect size, in my own mind, is small, but I believe if a third of the patients really were in the range of 100 mLs, then that's a lot of patients who will benefit. I think we have to put some faith in the CF clinicians that they will figure out how to appropriately use this.

Having said that, it would be really nice to have more information and drill down on the best patients to give this to, and I certainly wouldn't want to interfere with another drug that works better. So if there's some way that the FDA can approve this but look into things more, maybe through phase 4 data and warn the clinician appropriately, then I think, yes, it's the right decision.

MS. MOORE: This is Erin Moore. I voted yes. I think 1.2 percent increase in lung function is showing us that we're actually decreasing the rate of decline, which can mean years to some of these patients. Like Dr. Tracy had said earlier, it's the difference between being able to go up a flight of steps or go to your child's soccer game.

I did consider the challenge of folks wanting to substitute this type of treatment for something like hypertonic saline. In the personalized medicine space, a patient who is only doing her medication treatments one time a day because of the burden of it may actually increase her adherence if she's given this as an alternative and can do both.

I think we're making an assumption about it being a replacement for hypertonic, and a concern that I did have is that it adds to the burden. As a parent of somebody with cystic fibrosis, thinking about adding something else to our plate is daunting, but if I can do hypertonic once a day and this once a day, that already saves me 25 minutes.

So I think I think that there is enough data to show efficacy for this.

DR. SCHELL: Hi. Karen Schell. I voted yes. As a clinician and seeing the difference in patients in their pulmonary function, how they feel afterwards and an improvement in the study showed that FEV is improved. I had to vote yes because those patients are the ones that I care for and how they feel is part of it.

DR. WEBER: Richard Weber. I voted yes, although I had concerns about the other direction of the secondary endpoints. But it may well be that there is a subgroup that we haven't cleanly identified, which may be more responsive to this. The question is also how much of an effect is really clinically helpful. I'm used to dealing with asthma, where I expect that you need -- I'd like to see a much bigger effect, but here we're dealing with a different disease that may not have that much variability. So therefore, small amount of improvement may be a good thing.

The other issue is patient adherence. I

think we heard from some of the tapes that the hypertonic saline is probably fairly obnoxious, and probably many patients avoid taking it as often as they should because of that, whereas this appears to be very easy to use. Ease of use I think has a big impact on patient adherence, so therefore, again, that's why I voted yes.

DR. REDLICH: Carrie Redlich. I voted no, also with some angst for the reasons that have already been stated: the duration of effect, the magnitude, concern about diversion from a potentially more efficacious treatment, and also that this was a larger study but showed a smaller effect than the prior studies.

DR. QUE: Loretta Que. I voted yes for some of the reasons stated earlier, improved -- there is an effect size, albeit small. But for reasons stated earlier, adherence is a huge factor for these patients, and if we can at least get them to use a medication, I think they're going to see benefit.

DR. KELSO: John Kelso, and I voted yes. I

also struggled. It sounds like everybody's right on the line, and I'm right there as well. I focused in, I guess, on was there a difference in FEV1 because that's kind of the primary question, and, yes, there is a difference in FEV1.

I don't know where that fits in the big scheme of taking care of patients with CF. The secondary endpoints were not there. But just in answering and focusing in on that one question, there is a difference, and for some subset of patients, it's a larger difference. I'm really counting on the CF clinicians who do this for a living to figure out where do you use this in their armamentarium, with good reason, I think; that people who do this will in fact find a place, the patients for whom this is appropriate.

DR. AU: This is David Au. I voted no for a number of the reasons that are similar that have been previously stated. In addition to those, the effect size was, in my view, very small and likely not clinically meaningful for a number of patients, which was then also supported by the preponderance

of data across the other outcome measures they had.

DR. AU: If I were to ask to see additional studies done, I'd like to see this done on patients who were either non-adherent to hypertonic saline or inability to take hypertonic saline. Then also, I'd be interested in seeing it in patients with more severe FEV1 because think a 50 mL difference in someone who's percent predicted is around 60 percent is going to have small, if any, clinical effect, and I think that might be what we're seeing here.

Yeah.

DR. LEDERER: Hi. David Lederer. I voted yes. Actually, Dr. Kelso, you were speaking the words I was thinking, so I won't repeat what you said, and I agree with that. If I were able to suggest if there were a future study, I agree people with more advanced disease, people with more symptoms, people at higher risk for exacerbation so that we could effects on these other endpoints would be helpful.

DR. MARSHALL: Gailen Marshall, and I voted

yes. I wasn't anywhere near the line. It was clearly yes for me. The yes for me relates to the idea of the potential use for this. The people taking care of these patients are not generalists; they're very sub-sub specialists, very focused, very well defined in what they do.

I'm incredibly impressed with the sophistication of the cystic fibrosis patient community, including their support groups.

The word's going to get out there very quickly, here's this new opportunity for them to treat, and if there is a significant adverse effect that's there, it will be picked up probably in the community about as quick as it will be by the clinicians themselves. It will get to the meetings that they speak at. It will be in refereed, peer-reviewed publications, and the drug will be altered in terms of its utility, accordingly.

I won't belabor it, but I think all of us that have practiced medicine for any period of time know of drugs that were approved, they got into practice, and they really didn't have a use, and

they died off.

In terms of the next question that we'll ask about the safety benefit ratio, but in terms of the absolute parameter that was met, the primary endpoint that was met, it's a clear yes for me in terms of its potential to be effective.

DR. BLAKE: Kathryn Blake. I voted yes. Again, I come down to that this is not a bronchodilator, so I was impressed that the FEV1 was maintained and slightly higher over the 26-week period. Also, when I looked at about 22 to 24 percent of the population enrolled in 303 had an FEV one less than 50 percent, and that was the group that had the greatest response rate with an estimate of 0.13 liters.

So there's clearly, to me, a population that would respond, and I think that these are the sickest patients and they should be given the opportunity t have the drug.

DR. TRACY: Jim Tracy. I also voted yes. I do believe quite strongly that the primary endpoint was met. Obviously, it would have been

nice to see better results on the secondary endpoints. I've kind of reflected on the change in therapy and the issues with hypertonic saline, but I kind of reconciled that under the general heading of shared decision-making at the clinical level.

I'm like Dr. Marshall and Kelso. The amount of clinical oversight for this group of individuals in this disease state is just amazing. I have great confidence that this will help a significant number of individuals. Thank you.

DR. CATALETTO: I voted no, and the reason I did so I had to do with the way the question was formatted. Substantial evidence, statistically significant, borderline yes, but also saying in conjunction with standard therapies.

As I listened to the experts that are here, there were a number of comments that some patients may do better with one choice of hypertonic saline or with the Bronchitol, and sometimes with both. I hear patients and people on the committee who were saying, well, I could cut time back if I gave one of these in the morning and one of those at night.

There's a lot of flexibility in this, and I understand that that's what we do in practice, and that may be the way this goes, in which case maybe we should be talking about a noninferiority trial, or we should be talking about an open label with multiple arms. But I don't think the way the question is written that I was comfortable with a yes.

DR. AU: Thank you very much.

It was a very productive discussion. I will now read the second voting question or the fourth question overall. Are the safety data adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies? If no, what further data are needed?

I think we're ready to vote, please. Thank you.

(Voting.)

LCDR CHEE: Question 4, you have 10 yeses;

6 nos; and zero abstain.

DR. AU: We're nothing if not consistent.

(Laughter.)

DR. AU: Why don't we start on this side of the room?

DR. CATALETTO: I actually switched and said yes for this one.

(Laughter.)

DR. CATALETTO: And I did so --

DR. AU: I'm sorry. Could you say your name for the record?

DR. CATALETTO: Oh, sorry. Mary Cataletto. And I did so because of the issue of exacerbation, and I think that's part and parcel of advanced disease, and unless you're doing a comparison in a static disease, that's a hard marker to use. So I said yes.

DR. AU: Thank you. Dr. Tracy?

DR. TRACY: Jim Tracy. I also said yes. Once I went through this and in my own mind cleared the hemoptysis issue out of my out of my head, I looked at the exacerbations. And like the previous

speaker, I think this is, a bit, part of the natural history of this disease. I do think there is a place here for some postmarketing surveillance, and I have no doubt that that will happen informally. It would be nice to see it formally.

DR. BLAKE: So I switched, and I voted no for this one, and mainly because I didn't feel like I had enough information to know who would be at risk of exacerbations with this treatment. So I would have liked to have had more information to know who those people might be to aid in the clinical use of the drug.

DR. MARSHALL: Gailen Marshall. I voted yes for three reasons. Number one, absolutely respecting the FDA's responsibility to be concerned of these signals, there's clearly no statistically significant increase in adverse effects, and yet that was put in a different context when it related to the primary endpoint.

The second point is that, as was mentioned previously, the major one that people seem to be

most concerned about is increase in exacerbations, and this is a disease that's characterized by exacerbations. It's hard for me to imagine that a clinician is going to put this into practice with his or her patient, and over a 6-month period of time, their clear perception, and the patient and family perception, is that they're having more exacerbations, and that would be fed back.

Number three is that I'm quite comforted, particularly in the words of the experts that I asked specific questions, that an 8,000-patient world experience with no clear safety signals reassures me that this is safe. It doesn't prove it; I recognize that. But it reassures me and helped dictate my decision to vote yes.

DR. LEDERER: Hi. Dave Lederer. I voted no. I feel very strongly about this. We have a drug that is modestly effective. Remember, I voted yes for efficacy, but I am not reassured about safety at all based on the data that was presented regarding exacerbations. In good conscience, I can't vote anything other than no as a person. If

there were more studies, I think this is a critical, critical measure, and that it be carefully thought out how it's measured and how long patients are followed.

DR. AU: This is David Au. I voted no for the same reasons that Dr. Lederer did, but also for the fact that the U.S. population I think is actually different than other populations. The pathophysiology may be the same, but I think treatment patterns and treatment adoption within the U.S. is different.

I think the foundation is incredibly strong here and deserves a huge amount of applause for the efforts that they champion for individuals with cystic fibrosis, but on the other hand, I actually do think that care is very different in other countries, not just Europe, but eastern Europe and the like.

So I have concern about safety signals. I think it befalls us to consider not only the potential benefits, but the potential harms, especially in a medication that I think is of

limited efficacy.

DR. KELSO: John Kelso, and I voted yes. Again, just as with the effectiveness, I think there probably is a subset of people where this is going to be effective, and clearly there's potential harm, the signal, if it's real, there are some subset of those patients that we also can't identify or know about.

For the same reason on the upside, I'm counting on the clinicians who take care of these patients to recognize that this is not necessarily causing more exacerbations, since that's what they're already seeing anyway, and it would be hard to pick out an exacerbation that was due to the drug versus one that was going to happen anyway, but that would be seen as a lack of effectiveness. Once the patient gets put on the drug and keeps having exacerbations, that a clinical decision would be made, this drug isn't for you. We need to go back to the hypertonic saline or do something different. So I think that for most patients, this would not cause harm.

DR. QUE: Loretta Que. I switched here as well. I just need to see more data. There was a clear consistent signal showing that there might be harm, and I wanted to make sure that before moving forward, I would see that we knew more about which patient population might be affected. And I agree with Dr. Au. I think that we do have different practice patterns within the United States.

DR. REDLICH: Carrie Redlich. I also voted no for the reasons stated, a concern about the U.S. population, the challenge of doing any sort of postmarketing analysis to figure out side effects. Also, there were a reasonable number of people that stopped taking the medication or dropped out that I didn't really fully understand.

DR. WEBER: Richard Weber. I voted yes. Although, again, the exacerbation rate is a little bothersome, the question is how much of this is natural history of the disease? How much of this is not so much that the drug is bad, but that it's ineffective in some? So I strongly feel that what's going to happen is we're going to see a

subset of patients who are more responsive to this and some that are distinctly less responsive. But in any case, I did vote yes.

DR. SCHELL: Karen Schell, and I voted yes for all the reasons stated by previous yeses.

MS. MOORE: This is Erin Moore. I voted yes. I think one of the challenges that I had is about exacerbation equaling harm when exacerbation for me is a natural part of the disease progression, so similar to what Dr. Marshall was stating. And the question asked if it's adequate to support approval, and I believe that it's adequate to support approval.

DR. PARAD: I said yes. I think the hemoptysis issue was related to the pediatric group that was treated before, where I think there was a 2- or 3-fold greater risk in that group. That doesn't seem to be the case anymore in the older patients.

I am concerned about the issues of exacerbation, but because of the skewing of the randomization, the bad luck of that, and maybe just

a little bit too much smoke and mirrors for me in terms of trying to manipulate the data into an answer, I wasn't completely convinced that I knew what the right answer was to that. So I remain concerned and do feel that more information needs to be collected if this drug is made available.

DR. EMERSON: This is Scott Emerson. I voted no. I am unashamed in my focus on clinical trials because that's where I get to answer questions such as when does a treatment cause a risk by potentiating an underlying risk, and it happens with great regularity. So therefore, if you're depressed, the worst case is suicide. So take this drug; warning, may cause suicide.

There are so many situations like that; the same with cancers. Cancer is a fatal condition, yet I've worked on many clinical trials where death, well, that's a natural part of the cancer progression, but why should it be higher on the treatment group?

So I always consider the fact that the hardest thing to find out about a drug is when it

does not act in the expected manner and actually makes it worse, because there's too great of a tendency for everybody to say, well, yes, you had a heart attack, but then you were male, and, again, it's well known that males are at higher risk. No. It's the question of has it made it worse?

So it's just uncertain in my mind. If I had to bet, I don't think it is that magnitude, but I say, well, what if there is a group that exacerbations are worse, was that enough to explain why an apparent effect on FEV was not shining through on the secondary outcomes that should have moved in that same direction? I don't know, but on safety, I don't have to prove harm. All I have to do is prove that I'm not sure, and that's easy.

DR. BRITTAIN: Erica Brittain. I voted yes, maybe for a funny reason. I was already using exacerbation in my previous vote. When I wasn't comfortable with the efficacy, a lot of it was about the exacerbation. So I decided, okay, I'm going to ignore exacerbation for this question to make the two questions independent, and I wasn't

concerned about anything else, particularly on the safety. But to be clear, I do think we do not know if there is a subgroup for which there is harm with respect to exacerbation. It definitely could be.

DR. GILLEN: Dan Gillen. I voted yes for a couple of reasons. One is I think that the concerns on the exacerbation are being driven by the protocol-defined efficacy definition of exacerbation. When we look at the AEs and SAEs, we see balanced there. I do agree that we don't have to prove harm, absolutely, for safety signals, but I also think that we never are certain that we don't have safety signals either, but we look at the preponderance of evidence, as we've seen.

I think that what we have seen to this point are multiple data-driven analyses around an event that is likely going to be very closely monitored through regular care as well, so to me that's less of a concern.

DR. AU: Thank you very much. We are now two our fifth question and third voting question, and this is one where we integrate efficacy and

risk.

Does the benefit-risk profile support the approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years and older in conjunction with standard therapies? If no, what further data are needed?

(Voting.)

DR. AU: Anyone left to vote? It looks like everyone's voted. There we go; locked in.

LCDR CHEE: Question 5, we have 9 yeses; 7 nos; and zero abstain.

DR. AU: Why don't we start back on the right? Dr. Gillen?

DR. GILLEN: Sure. I voted no on substantial evidence of efficacy. I voted yes on adequate safety data. For me, thinking about the benefit-risk profile and going back to my previous statement about me never being absolutely certain that something is totally safe, I need to know that it's certainly going to be efficacious to outweigh any kind of doubt or uncertainty, realizing that

we're dealing with finite samples in a controlled clinical trial setting.

So for me, it's really the lack of substantial evidence of efficacy in terms of clinical impact on patients as we're going through; drove my answer here, if the numerator is zero.

DR. AU: I understand.

DR. BRITTAIN Erica Brittain. I voted no, again, primarily because of the seemingly inadequate efficacy data, or disappointing efficacy results. However, it's a difficult no. I want to vote yes, and I do wonder if -- I keep wondering if A, as I said before, is there some subgroup that makes this a better risk-benefit profile that could be identified, and maybe the data could be re-examined for that? Also, at patient level, is it also possible for patients to be given the drug and then see if they are the patient who really does respond.

One thing that we didn't actually hear anything about is if there's any relationship between a change in FEV1 and people who get

exacerbations. I think that might also be something interesting to look at.

DR. AU: Thank you.

DR. EMERSON: Scott Emerson. I voted no. In addition to the things that I've said before, I'll note that on this, there have been times that drugs that I thought maybe had a safety problem, but I thought that labeling could handle it -- but I will say that I'm going somewhat on Dr. Kelso's testimony to say that this would be a hard thing to label where the uncertainty is.

The additional data that I would really love to see is I would love to see a randomized withdrawal in which you treated people for 6 months, and the people who were still on the trial at 6 months, that then you randomized withdrawal, so that we got some measure of whether there was continued efficacy and what the longer term effects were. I usually go with randomizing the first 6 months, too, but I don't know that that's as crucial on this.

We're talking about taking this hopefully

for 50 years, and we're acting right now on 6 months worth of data and don't really know whether the effect is there. So this would go a long way of having a 6-month trial on a randomized withdrawal and would help me a whole lot.

DR. PARAD: Richard Parad. I voted yes. Again, primary endpoint was met. I'm not happy there wasn't more secondary support, but we've already talked about that. I really find it hard to believe that the biology of this disease is any different in Germany or Australia than it is in the United States. I would have a little difficulty in believing that the treatment approaches differ. So that makes me feel a little -- maybe makes me feel better inappropriately, but I'm hoping that if it's something different about the way we treat patients here, that we're going to figure that out quickly.

MS. MOORE: This is Erin Moore. I voted yes. I think the one outstanding thing that I think is important to see, as Dr. Emerson had stated, is a longer term look at this because we saw an improvement and then a slight decline. So I

think I'd like to see that over the long run, especially because something that struck me was the idea that this is put into a class with other drugs designed for airway clearance of which coughing is a critical component. When you're defining an exacerbation, cough is one of the indicators for that.

So perhaps exacerbation isn't being appropriately defined in these patients to say, is it decreasing the rate of exacerbation? Is it slowing the rate of FEV1 decline instead of just looking at it at those points in time?

DR. SCHELL: Karen Schell, and I voted yes as well or with the increase of the FEV1 indicated. Also, as people are living longer with this disease, the longevity and the progression of the disease, I think we're not only responsible for the improvement of the symptoms, but I was particularly moved by the patient's voice and their quality of life and how we can improve their quality of life. And if they're willing to take the risk with the benefits, I think we have to give them a chance to

do that.

DR. WEBER: Richard Weber. I voted yes, and the prime reason was internal consistency with my previous responses --

(Laughter.)

DR. WEBER: -- to be honest. But it also struck me that in some cases in the past, adverse effects or some undesirable side effects have come to light only through postmarketing data. So it will certainly be interesting to see what U.S. postmarketing data does show us, if any adverse signals show up.

DR. REDLICH: Carrie Redlich. I voted no, also for internal consistency. I previously expressed concerns about both efficacy and safety. The key question in terms of what data would be useful, I think that's probably a little bit complicated and maybe beyond this meeting, thinking about what really would be the best study design to address.

I think all of us feel that there probably is a subgroup that would benefit and how to

identify that, and/or how to identify if there really is a problem with exacerbations or other adverse events. Usually a more severely affected group gives you greater opportunity to identify both improvement and adverse effects, but I would defer, really, on that question; especially, I think people who have a lot of experience managing these patients, because of all these other issues of hypertonic saline, and who's included, and those sort of factors, and the duration is obviously another issue in terms of wanting a treatment that will last.

DR. QUE: Loretta Que. I voted yes. I think there is a subset of patients that will benefit from this, and I'm hoping that our CF clinicians will figure that out.

DR. KELSO: John Kelso, and I voted yes. I'm hoping that the FDA, if they approve this drug, has some way to transmit, both in the labeling and advertising of this drug, the ambivalence, personal and collective of this group that has been expressed in terms of it's a very tiny effect size;

is it durable; is there a signal about exacerbations?

I don't know how you do that, but somehow that needs to be communicated either in the labeling or advertising of this to reflect the struggle that we have all had here today.

Finally, I hope the next time you have us come to town, you can ask easier questions.

(Laughter.)

DR. AU: David Au. I voted no. It was challenging. It was a challenging vote, I have to say, overall. I'm impressed with an NNT of 10, but I agree with this issue of durability and overall effect. I'm pretty unsatisfied with the idea of unintended consequences of drug, And I was very impressed by the conversations that we heard from the community about how this is going to be viewed as a substituted drug.

As I mentioned before, I think we have a responsibility to do our best for the public good. I have concerns when I hear that one approach to this agent will be as a simpler agent, but it will

lead to potentially greater exacerbations, less FEV1, which actually is associated with mortality. So before we make the leap of faith on 50 mLs and an NNT of 10, I think we have to better understand how it's going to be used.

The other thing I'll comment on is I actually do think that I don't have the same degree of faith in terms of heterogeneity and practice patterns across providers. I think there's huge practice variation. I'd be surprised if you don't see it very much in the cystic fibrosis. Even in the cystic fibrosis registry, that should be examined because I would bet that you'd see large practice variation within that group.

DR. LEDERER: Hi. Dave Lederer. I voted no. I really, really hope that this drug is safe, and I hope that if it is not approved, I hope there is more work done to show us that it's safe with regard to exacerbations because I do think we need more drugs in our armamentarium for these patients. So my vote really all revolves around unresolved or uncertainty about safety.

DR. MARSHALL: Gailen Marshall, and I voted yes. I guess, to me, one of the words that I've heard others speak about is "effectiveness" as opposed to efficacy, and the idea that this agent, as it's been presented today, is going to clearly be easier to use. Whether it's used complementary in an augmented way or whether it's used in substitutionary way, I think is going to be a decision between the patient and family and the provider.

I guess with Dr. Au, I have a little bit more faith in the homogeneity of how the experts, the cystic fibrosis experts, several which are in this room, practice with consistency.

Yes, obviously all of us, we could all talk about a fever of 101, and however many physicians there are in here, there would be that plus one different opinion on how to deal with it. But there would be a certain consistency of that as well. The world experience to me is very much a tipping point, and the idea that these are experts, both in our country and others, that get together

on a regular basis is reassuring.

Having said all that, I fully support that the FDA would do some sort of continued surveillance of this to help guide the use of it in the United States, which is their responsibility and ours, as to what is the right population to use it in and how to use it in the best way, whether it's similar or different than what's done worldwide.

DR. BLAKE: This is Kathryn Blake. I voted yes, and again, I voted yes because I feel like there is going to be a population of patients that this benefits, and I think that the ease of use is quite important. I was concerned about the risk of pulmonary exacerbations, but I was also reassured by the fact that it's available in these other countries and has been used in over 8,000 patients.

I, too, would like to see some additional long-term data on exacerbations for the population in the U.S. to try and better understand those at risk, but I do also think that this is a population of patients that are carefully monitored by their

physicians, and if there's a change in their exacerbation frequency, I would expect that those physicians and the patients themselves would pick up on that fairly quickly, and then decide maybe at that point to discontinue this particular treatment.

DR. TRACY: Jim Tracy. I always struggle with balancing the regulatory component along with the human piece, but I voted yes. I think this is going to be help to a significant number of individuals. I'm not sure exactly who they are yet. I do believe that surveillance postmarketing is a necessity.

DR. CATALETTO: Mary Cataletto. I voted no. I think we've covered a good number of those topics. But I think when all is said and done, we're going to need to look to our colleagues abroad and see how do you choose -- whether using hypertonic saline or the mannitol, how do you decide when you're going to make a switch? How do you decide when you're going to stop? What number of exacerbations is too much? There are a lot of

things that were not in this protocol that I think we need to look at, and that's why I voted no. Thank you.

DR. AU: Does the FDA have any comments?

DR. SEYMOUR: I just wanted to thank the committee for your discussion on today's topic. It was certainly a good discussion for us and a challenging application for us, and I think it also, based upon the discussion, was challenging for you. We don't bring the easy questions to you, so don't count on that in the future --

(Laughter.)

DR. SEYMOUR: -- but we appreciate the time and input on this application.

Adjournment

DR. AU: Thank you. I'll take the chair's prerogative by saying thank you to the discussants and the panel members. It was a fantastic discussion. I respect everyone's opinions here and value them all. I think we all kind of expressed different opinions and were able to incorporate them in a thoughtful, meaningful way.

I'd like to also thank the sponsor. I thought they worked very well with us today, and I appreciate their efforts at this meeting.

If there are no other order to business, just as a reminder, once we're done and we all leave, everything in this room will be cleaned up and thrown away, or recycled, so please make sure that you take the stuff that you want to take, and everything else will be dealt with appropriately.

I wanted to thank everyone for their time and energy, and safe travels on the way home. Thank you so much.

(Whereupon, at 4:33 p.m., the meeting was adjourned.)