UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

+ + +

June 14, 2018
8:00 a.m.

Gaithersburg Holiday Inn
2 Montgomery Village Ave., Grand Ballroom
Gaithersburg, MD 20879

PANEL MEMBERS:

STEVEN D. NATHAN, M.D.	Chair
HUGH A. CASSIERE, M.D.	Panel Member
JEFFREY R. KIRSCH, M.D.	Panel Member
ANDREA M. KLINE, CPNP-AC/PC, FCCM	Panel Member
LONNY YARMUS, M.D.	Panel Member
KARLA V. BALLMAN, Ph.D.	Panel Member
PAULA CARVALHO, M.D., FCCP	Temporary Panel Member
ALEXANDER CHEN, M.D.	Panel Member
LORI DODD, Ph.D.	Panel Member
JESSICA S. WANG MEMOLI, M.D.	Panel Member
BOHDAN PICHURKO, M.D.	Panel Member
DAVID SCHOENFELD, Ph.D.	Panel Member
VICTOR H. VAN BERKEL, M.D., Ph.D.	Panel Member
RANDY HAWKINS, M.D.	Consumer Representative
DEBBIE BROWN	Industry Representative
THERESA BARNES	Patient Representative
EVELLA F. WASHINGTON	Designated Federal Officer

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

MICHAEL J. RYAN
Associate Director, Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
Office of Device Evaluation

TINA KIANG, Ph.D.
Acting Director, Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
Office of Device Evaluation

YANPING QU, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics

STEPHANIE CACCOMO
Press Contact

FDA PRESENTERS:

DERYA COURSEY, Ph.D.
Lead Reviewer
Respiratory Devices Branch
Office of Device Evaluation

LILA BAHADORI, M.D.
Respiratory Devices Branch
Office of Device Evaluation

HEATHER BENZ, Ph.D.
Division of Biomedical Physics
Office of Science and Engineering Laboratories

SPONSOR PRESENTERS:

JULIA ANASTAS, M.P.H.
Vice President, Regulatory Affairs
PneumRx, Inc., a BTG International group company

JAMES DONOHUE, M.D.
Professor
UNC School of Medicine

CLAIRE DAUGHERTY, M.S.
Director, Biostatistics
BTG International, Inc.

GERARD J. CRINER, M.D.
Professor and Founding Chair
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University

DAVID HAHN, M.D.
Head of PneumRx, Inc., a BTG International group company
University of Chicago, Pritzker School of Medicine

BRETT HAUBER, Ph.D.
Senior Economist and VP, Health Preference Assessment
RTI Health Solutions
Affiliate Associate Professor
University of Washington School of Pharmacy

FRANK SCIURBA, M.D.
Professor of Medicine and Education
University of Pittsburgh Medical Center

ASHLEY BURNS
Clinical Development
PneumRx, Inc., a BTG International group company

SCOTT BERRY, Ph.D.
Biostatistician

OPEN PUBLIC HEARING SPEAKERS:

EILEEN WILSON

JAMIE SULLIVAN
COPD Foundation

KATHLEEN ESCHENBURG
Patient

STEPHANIE FOX-RAWLINGS, Ph.D.
National Center for Health Research

CINDY GASPARO
Patient

INDEX

PAGE

CALL TO ORDER - Steven D. Nathan, M.D. 7

PANEL INTRODUCTIONS 7

CONFLICT OF INTEREST STATEMENT - Evella F. Washington 9

SPONSOR PRESENTATION

Introduction - Julia Anastas, M.P.H. 14

Emphysema Disease Background - James Donohue, M.D. 17

RENEW Trial Design - Claire Daugherty, M.S. 23

Development and Effectiveness - Gerard J. Criner, M.D. 28

Safety Profile - David Hahn, M.D. 37

Post-Market Plan - Julia Anastas, M.P.H. 43

Patient Preference - Brett Hauber, Ph.D. 46

Clinical Context and Sponsor Summation - Frank Sciurba, M.D. 49

SPONSOR Q&A 53

FDA PRESENTATION

Study Overview - Derya Coursey, Ph.D. 62

Clinical Review - Lila Bahadori, M.D. 66

Patient Preference Information (PPI) Study - Heather Benz, Ph.D. 86

Applicant Proposed Future Post-Market Study - Lila Bahadori, M.D. 89

FDA Q&A 90

INDEX

	PAGE
OPEN PUBLIC HEARING	
Eileen Wilson	106
Jamie Sullivan	107
Kathleen Eschenburg	110
Stephanie Fox-Rawlings, Ph.D.	113
Cindy Gasparo	116
PANEL DELIBERATIONS	121
FDA QUESTIONS TO THE PANEL	
Question 1	165
Question 2	178
Question 3	186
Question 4	189
Future Post-Market Study	202
SUMMATIONS	
FDA - Lila Bahadori, M.D.	206
Sponsor - Frank Sciurba, M.D.	209
PANEL VOTE	217
ADJOURNMENT	227

M E E T I N G

(8:00 a.m.)

DR. NATHAN: I would like to call this meeting of the Anesthesiology and Respiratory Therapy Devices Panel to order. I am Dr. Steven Nathan. I'm the Chairperson of this Panel. I'm a pulmonary critical care physician, and I'm the Medical Director of the Advanced Lung Disease and Lung Transplant Program at Inova Fairfax Hospital, which is in Falls Church, Virginia.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the ELEVAIR Endobronchial Coil System sponsored by PneumRx, Incorporated.

Before we begin, I would like to ask our distinguished Panel Members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. We'll go in counterclockwise order and start with Ms. Barnes.

Thank you.

MS. BARNES: Hi. My name is Theresa Barnes. I am a patient advocate in pulmonary. And I am an independent advocate.

MS. BROWN: My name is Debbie Brown. I am a consultant in regulatory affairs for medical device companies. And I've been -- this is the second time I'm sitting on a panel. I've been doing regulatory affairs for a long time. The last time I was here talking about an emphysema product was in 2003, so it's been 15 years.

MS. KLINE: My name is Andrea Kline. Excuse me. I'm a nurse practitioner. I work in

cardiovascular surgery at Children's Hospital in Michigan, in Detroit.

DR. VAN BERKEL: Hi. My name is Victor Van Berkel. I'm a thoracic surgeon. I'm the Division Chief of Thoracic Surgery at University of Louisville in Kentucky. I'm also the director of the transplant program there and do the majority of the lung volume reduction surgeries there.

DR. SCHOENFELD: My name is David Schoenfeld. I'm a biostatistician. I'm at the Harvard T.H. Chan School of Public Health and the Harvard Medical School.

DR. YARMUS: Good morning. My name is Lonny Yarmus. I'm the Clinical Chief in Pulmonary Critical Care and an interventional pulmonologist at Johns Hopkins.

DR. KIRSCH: My name is Jeff Kirsch. I'm an anesthesiologist and neurointensivist currently at Oregon Health Science University, chair of the department there and previously for Hopkins.

DR. CASSIERE: Good morning. I'm Hugh Cassiere. I'm the Chief of Cardiovascular and Thoracic Surgery Critical Care. I'm also Medical Director of Respiratory Services at North Shore University Hospital in New York.

DR. NATHAN: Evella, if you can introduce yourself.

MS. WASHINGTON: My name is Evella Washington. I'm the DFO.

DR. BALLMAN: Hi. I'm Karla Ballman. I'm the Division Chief of Biostatistics and Epidemiology at Weill Cornell Medicine in New York City, and obviously I'm a statistician.

DR. PICHURKO: Hello. My name is Bohdan Pichurko. I'm a pulmonary physician at the Cleveland Clinic Respiratory Institute, and I'm Director of Pulmonary Function Laboratories for the Cleveland Clinic Health System.

DR. WANG MEMOLI: I'm Jessica S. Wang Memoli. I'm Director of Bronchoscopy and Interventional Pulmonology at MedStar Washington Hospital Center in Washington, D.C.

DR. DODD: I'm Lori Dodd. I'm a biostatistician at the National Institute of Allergy

and Infectious Diseases.

DR. CHEN: Good morning. I'm Alexander Chen. I'm the Director of Interventional Pulmonology at Washington University in St. Louis.

DR. CARVALHO: Good morning. I'm Paula Carvalho. I do pulmonary critical care, University of Washington. I'm also the head of bronchoscopy and critical care at the Boise VA.

MR. RYAN: Good morning. I'm Mike Ryan. I am the FDA representative. I'm the Associate Director for the Division of Anesthesiology, General Hospital, Respiratory and Infection Control and Dental Devices. I'm with the division at the respiratory branches.

DR. NATHAN: Thank you, everyone. And for everyone else, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Evella Washington, the Designated Federal Officer for the Anesthesiology and Respiratory Therapy Devices Panel, will make some introductory remarks.

MS. WASHINGTON: Thank you. Good morning. I will now read the Conflict of Interest statement.

The Food and Drug Administration (FDA) is convening today's meeting of the Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel 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 Panel'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 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel 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 financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees 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.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application for the PneumRx ELEVAIR Endobronchial Coil System, which is a first-of-a-kind implantable lung reduction coil. The coil system is indicated for use in patients with homogenous and/or heterogenous severe emphysema, to improve quality of life, lung function, and exercise capacity.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Steven Nathan and Dr. Bohdan Pichurko.

Dr. Nathan's waiver addresses his personal investment in the health sector fund that contain underlying asset shares in the parent company of a firm that makes a product that competes with the Sponsor's device. The total magnitude of the fund is between $50,001 and $100,000.

Dr. Pichurko's waiver addresses his institution's interest as an ongoing clinical site for the PneumRx ELEVAIR Endobronchial Coil System clinical trial in which he is not

personally involved. His institution is awarded between $200,001 to $700,000 for the entirety of the study.

The waivers allow these individuals to participate fully in the panel deliberations. FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov/advisorycommittees. Copies of the waivers may also be obtained by submitting a written request to the Agency's Division of Freedom of Information located at 5630 Fishers Lane, Room 1035, in Rockville, Maryland 20857.

Deborah Brown is serving as the Industry Representative, acting on behalf of all related industry, and is employed by D. Brown Consulting Services, LLC.

We would like to remind members and consultants that if the discussion involves 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 Panel of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript.

Thank you.

I will now read the appointments to a temporary voting status statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter of the Center for Devices and Radiological Health, dated October the 27th, 1990, and as amended August the 18th of 2006, I appoint the following individuals as voting members of the Anesthesiology and Respiratory Therapy Devices Panel for the duration of this meeting on June the 14th of 2018:

Drs. Karla Ballman, Alexander Chen, Lori Dodd, Jessica Wang Memoli, Steven Nathan,

Bohdan Pichurko, David Schoenfeld, and Victor Van Berkel.

For the record, these individuals are special Government employees or regular Federal employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. In addition, I appoint Dr. Steven Nathan to act as a temporary chairperson for the duration of this meeting.

This was signed by Dr. Jeffrey Shuren, the Director in the Center for Devices and Radiological Health, on June the 8th of 2018.

For the duration of the Anesthesiology and Respiratory Therapy Devices Panel meeting on June the 14th, 2018, Dr. Paula Carvalho has been appointed to serve as a temporary voting member, and Ms. Theresa Barnes and Dr. Randy Hawkins have been appointed to serve as temporary non-voting members.

For the record, Dr. Paula Carvalho serves as a regular Government employee to the Antimicrobial Drugs Advisory Committee in the Center for Drug Evaluation and Research. Ms. Theresa Barnes serves as a Patient Representative to the Pulmonary Allergy Drug Advisory Committee in CDER. Dr. Randy Hawkins serves as a member to the Cellular Tissue and Gene Therapy Advisory Committee in the Center for Biologics Evaluation and Research.

These individuals are special Government employees or regular Federal employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Their appointments were authorized by Dr. Rachel Sherman, Principal Deputy Commissioner, on the May the 25th of 2018.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Thank you.

Before I turn the meeting back over to the Chair, I would like to make a few general announcements.

Transcripts of today's meetings will be available from Free State Court Reporting.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Ms. Stephanie Caccomo. If anyone from the press desires to speak with her, please see Ms. AnnMarie Williams at the desk outside the meeting room to obtain her contact information.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing sessions today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence all your cell phones and other electronic devices at this time.

Thank you.

Dr. Nathan.

DR. NATHAN: Thank you very much.

For the record, we've been joined by our final panelist.

Dr. Hawkins, if you can just introduce yourself very briefly. Thank you.

DR. HAWKINS: Dr. Randy Hawkins, pulmonary and critical care medicine, Inglewood, California, Consumer Representative.

DR. NATHAN: Thank you.

We'll now proceed to the Sponsor's presentation. I would like to invite the Sponsor to approach the podium. I'll remind public observers at this meeting that while this

meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair. The Sponsor will have 90 minutes to present.

You may now begin your presentation.

MS. ANASTAS: Good morning, Chairman Nathan, Advisory Committee members, and FDA staff. I'm Julia Anastas, Vice President of Regulatory Affairs for PneumRx, a BTG International group company.

We're very happy to speak with you today about the ELEVAIR Endobronchial Coil System, a device intended for the treatment of severe emphysema in patients with severe hyperinflation. I'll start by presenting some background information on the clinical development of the ELEVAIR system and then outline the agenda for the remainder of our presentation.

The ELEVAIR system was granted priority review by the FDA as a result of the unmet need for management of severe emphysema. Emphysema affects approximately 3.5 million adults in the U.S., and of these, 1.2 million are estimated to have severe emphysema. It's a progressive disease that causes significant debilitation, and there's no cure and no way to halt disease progression. These patients are often too sick to work or to care for others. Their activities of daily living are severely affected. In many cases they are not able to care for themselves, and simple activities such as taking a shower or getting dressed may require assistance from others. The ELEVAIR system is intended for those patients with severe emphysema, that is, those that continue to have a significant symptom burden despite optimal medical therapy.

ELEVAIR coils are designed to compress diseased tissues, which reduces lung hyperinflation, relieving patient breathlessness and improving quality of life. The system has two main components, the coil and the delivery system. The coil is shown here. It is a nitinol-shaped memory coil, intended as a permanent implant. The delivery system is used

to place the coils, in a minimally invasive procedure, through a bronchoscope.

Our presentation today is the culmination of more than 10 years of benchtop and clinical development. As shown here, PneumRx conducted a number of feasibility and multi-center studies in Europe starting in 2008. These were the basis of our CE mark, granted in October of 2010. Since then, we've accumulated more than 7 years of postmarket clinical and commercial experience in an estimated 4,000 patients in 19 countries. Today we'll focus on PneumRx's IDE clinical studies performed in the U.S., Europe, and Canada.

Our IDE program consists of two clinical protocols. The first protocol is RENEW, the pivotal randomized trial of the ELEVAIR system plus optimal medical therapy versus optimal medical therapy alone. RENEW enrolled a population of subjects with severe emphysema, with roughly three-quarters of subjects having the most severe categorization of emphysema, GOLD 4. RENEW also had a single-arm roll-in phase and rolling up to two patients at those investigational sites that did not have prior coil experience.

The second protocol, crossover, was a smaller, single-arm observational study. It was intended to help reduce loss to follow-up in RENEW by making ELEVAIR treatment available to control subjects who chose to have coil treatment who completed the randomized trial and who met eligibility requirements. Each of these studies had a 1-year primary endpoint and a 5-year follow-up period.

Our interactions with the FDA began with our pre-IDE meeting in March of 2010. Enrollment in RENEW trial began at the end of 2012 and concluded in October 2014. Throughout the period shown, we've had a number of meetings with FDA to discuss aspects of the clinical program and progress of the PMA.

I'd like to highlight an important aspect of the RENEW enrollment, resulting from a protocol amendment made midway through the trial. The original entry criteria in RENEW

required subject residual volume greater than or equal to 225% predicted. This requirement was based on an early dataset of 23 subjects which suggested that subjects with RV above 225 had increased benefit compared to lower RV subjects. Fifty-four percent of trial enrollment was completed using this entry criterion.

When additional European data became available, a combined analysis of 140 subjects from several small studies suggested that in addition to the subjects with RV above 225, subjects with RV above 175 were also likely to receive benefit. And as a result, the RENEW protocol was amended in July 2014 to use an RV baseline threshold of 175% predicted. Enrollment continued using this entry criterion through the remainder of the trial.

It is important to note that 75% of the subjects enrolled in RENEW met the original criterion of RV greater than or equal to 225% predicted. As you'll hear today, RENEW met all primary and secondary endpoints based on the ITT population. However, greater clinical improvement was observed across all endpoints in the originally defined population with RV greater than 225.

Our presentation will demonstrate that the totality of evidence from the RENEW pivotal trial provides reasonable assurance of the safety and effectiveness of the ELEVAIR system. Specifically, coil treatment demonstrated a clinically meaningful improvement in quality of life, exercise capacity, and lung function in patients with severe emphysema and severe hyperinflation. This is demonstrated by our analysis of the originally defined population with RV greater than or equal to 225% predicted.

Coil treatment also demonstrated a manageable safety profile through 24 months after implantation, in both ITT and in the subjects with RV above 225. These data support a favorable benefit-risk profile in conjunction with standard of care medical therapy in patients with severe hyperinflation. They demonstrate that the ELEVAIR system represents

a compelling alternative to the limited treatment options available for patients with severe emphysema.

Based on these data, we've proposed the following indications for use. The ELEVAIR system is indicated for bronchoscopic placement of ELEVAIR coils in patients with severe emphysema, either homogenous or heterogenous, and severe hyperinflation, to improve quality of life, lung function, and exercise capacity. As noted earlier, in the analysis of the RENEW trial data, we have defined severe hyperinflation as the population with RV above 225.

In clinical practice, we believe that clinicians should target this population but should also have flexibility to exercise discretion to incorporate overall patient health status into clinical decision-making.

In the remaining portion of our presentation, you'll hear from Dr. James Donohue, who will discuss the severe emphysema disease state and current treatments. Then Claire Daugherty will present the RENEW trial data and statistical analysis plan. Dr. Gerard Criner will share the clinical data supporting effectiveness of the ELEVAIR system, and Dr. David Hahn will review the system's safety profile. After Dr. Hahn, I'll come back and discuss our postmarket plans. Then Dr. Brett Hauber will discuss a patient preference study that we conducted as part of our PMA program. And, finally, Dr. Frank Sciurba will share his perspective on the use of the ELEVAIR system in clinical practice.

In addition to our presenters, we've been joined by these advisers, who are available to help answer your questions. And so with that, let me turn the microphone over to Dr. James Donohue.

Dr. Donohue.

DR. DONOHUE: Thank you, Julia.

Chairman Nathan, members of the Advisory Board, members of the FDA, ladies and

gentlemen, good morning. My name is Dr. Jim Donohue from the UNC School of Medicine, and I'll be presenting the emphysema disease background.

I was a member of the data monitoring board for PneumRx during the conduct of the study, and I am a paid consultant to the Sponsor, but I have no financial interest in the outcome of the meeting.

Emphysema is a chronic and irreversibly debilitating disease that affects approximately 3.5 million Americans. It's characterized by a loss of the lung's natural elastic properties, leading to permanent enlargement of lung air spaces, as shown here in the cartoon. This is caused by the irreversible destruction of alveolar walls, which in turn results in air trapping and hyperinflation. The air simply can't get out.

Here is the clinical picture of a typical patient suffering from severe emphysema. The patient is breathless, which is the most common complaint of emphysema patients. He's using oxygen, and he has a big barrel chest, which is the hallmark of hyperinflation. Additional symptoms would be cough -- could be cough, wheezing and weight loss. These patients also have sleep problems and often suffer from lung infections, leading to progressive and irreversible decline in their health.

Shown here is the classic chest x-ray of a patient suffering from severe emphysema. First, note how large the lungs are. There is simply too much air trapped in the chest. If you look at the lower lobes of the lung, there are hardly any markings. This means that the emphysema has replaced normal lung tissue. The diaphragm is almost flat and scalloped. It is pushed way down into the abdomen, which impairs breathing mechanics and also can affect eating and gastric filling.

Progressive air trapping and hyperinflation in emphysema leads to major problems with what is called the inspiratory capacity. This illustration shows total lung capacity. The top brackets on the left indicate the inspiratory capacity or the air that is available to

breathe. In a normal lung, inspiratory capacity is about half of a total lung capacity. Below this is the functional residual capacity and the residual volume, which is the air that stays in the chest and does not contribute to respiration.

Now, over time, we begin to see hyperinflation develop in the emphysema patient as more air is trapped in the lungs. At the end of a breath, they do not return to the normal resting position, and the air available to breathe is diminished. We see a reduced inspiratory capacity and an increased residual volume.

In this next panel, the patient has progressed to the point of hyperinflation even at rest. We call this static hyperinflation. Residual volume has increased and inspiratory capacity has further diminished. This is the new normal for this hyperinflated emphysema patient.

Now look what happens when the patient has to do something that involves a moderate activity such as walking. They suffer from what is called dynamic hyperinflation. The residual volume is further increased, and the inspiratory capacity is now much smaller, as shown by the brackets on the right. What this means is that the patient is breathless, even with the simplest activities of daily living.

Emphysema is marked by a progressive decline in lung function, exercise capacity, and quality of life. We often refer to this as the downward spiral. The patient with shortness of breath decreases their exercise. This leads to weakness of respiratory muscles and chest wall mechanics, which lead to worsening of breathlessness. This downward spiral ultimately leads to severe impaired quality of life, and it may eventually lead to respiratory failure and death.

These data from a study of over 600 COPD patients reported by Casanova and colleagues clearly show that patients with more hyperinflation -- that's the purple curve -- have worse survival outcomes compared to patients with less hyperinflation.

Now I'd like to discuss emphysema staging and prognosis. The Global Initiative for Chronic Obstructive Lung Disease, or GOLD, has created a strategy for the diagnosis, management, and prevention of COPD. GOLD staging uses the measure of forced expiratory volume in one second, or FEV_1, as a means of benchmarking against normal lung function. The most severely diseased patients are in GOLD stages 3 and 4. This group represents approximately 1.2 million Americans, and it is a relatively unstudied patient population.

Shown here are data from NHANES III showing that overall survival correlates with GOLD stages. Let me draw your attention to GOLD stage 3 and 4 patients whose mortality, if you look at it here at 5 years, is approximately 50%. In fact, patients enrolled in the RENEW trial were all stage 3 and 4 and predominantly stage 4, so even further down on this curve, the bottom curve.

When we discuss long-term benefits in these patients, many are at a stage where the benefits seen at 1 to 2 years represent a substantial portion of their remaining lives. Their lives at this stage, quite frankly, are pretty miserable, so improvement in breathlessness for 1 to 2 years is very meaningful for these patients.

In addition to GOLD stage, we look at the chest x-ray and CT scans to see where the lung is diseased. On the left, we have heterogeneous disease, which means part of the lung has emphysema, those areas shaded in blue, and other parts do not. On the right, we see homogenous disease, where the emphysema is more evenly distributed in the lung or exhibits a patchy pattern. This type of emphysema is more difficult to treat and generally less responsive to maximum medical therapy than the heterogeneous disease.

It is worth noting that the profile of response in homogenous patients is different from heterogeneous patients across all types of lung volume reduction therapy. In addition to these disease patterns, it's also important to assess whether the fissures between the

lobes are intact. In most patients with severe emphysema, they are not, which leads to collateral ventilation, meaning that air is able to pass between the lobes, as we see up here. These disease characteristics are important factors when considering treatment options for severe emphysema patients.

Now I'd like to turn your attention to the measures we assess when caring for patients and also when developing emphysema trials. For any study in this patient population, we need to consider the totality of evidence across multiple endpoints. First, of course, are the measures of lung function. Typically, we look at forced expiratory volume in one second and residual volume. An intervention that reduces residual volume and increases FEV_1 should result in improvement of quality of life.

The instrument used to measure quality of life is the St. George's Respiratory Questionnaire, or SGRQ. The SGRQ captures symptoms, activity, and impact on the patient's daily life. The SGRQ is also accepted by FDA as a patient-reported outcome assessment tool in trials in patients with COPD. And then, finally, the 6-minute walk test measures exercise capacity.

This slide shows the impact of emphysema disease progression on the clinical measures outlined in the previous slide. These data are from the National Emphysema Treatment Trial, or NETT, which was a randomized trial comparing lung volume reduction surgery with medical therapy alone for the treatment of severe emphysema. It is worth noting that the patient population enrolled in NETT was similar to the RENEW study population. These graphs show changes from baseline in FEV_1, St. George's, and 6-minute walk over 2 years in the NETT control group that received medical therapy only. Please note, for SGRQ, an increase in the score represents worsening, in the middle panel, worsening quality of life.

These data highlight the rapid disease progression one typically sees in the patient

population with severe emphysema. To demonstrate with a specific example, here is a pictorial representation of question 11 from the SGRQ, which you'll see today. This question, posed to the patient, assesses breathlessness with activity. The patient does not feel out of breath when sitting or lying -- that's the green on the extreme left -- but does feel out of breath doing any of the other activities pictured here. This is typical of what we see with GOLD stage 3 and 4 patients.

There is no cure for emphysema, and patients will continue to decline even after treatment. Pharmacotherapy is the backbone of treatment across all forms of COPD, but the benefit in severe emphysema patients is somewhat limited. In fact, medical therapy has shown very limited ability to improve quality of life, and no single drug trial has demonstrated an improvement of the 6-minute walk test.

Lung volume reduction surgery, of course, does improve survival, quality of life, and functional capacity, but it's limited to patients with upper lobe heterogeneous disease and is further limited by morbidity and mortality risk. In practice, very few patients undergo the surgery, just a couple of hundred per year in the U.S. Lung transplant is really not as widely used and is offered only to a few selected patients with emphysema. So there's clearly a high unmet need for patients with severe emphysema.

Showing here are the current GOLD guidelines for advanced COPD. Let me focus your attention on the last row, where we see the recommended treatment approaches for patients with heterogeneous or homogenous emphysema. For patients with heterogeneous disease, lung volume reduction surgery is an option, in practice, as we said, used very sparingly because of associated risk. The GOLD guidelines recommend that bronchoscopic lung volume reduction is an option for some patients. Endobronchial valves, which are not yet approved in the U.S., could be an option but only in the subpopulation of patients without collateral ventilation. The one bronchoscopic approach that could

potentially be employed across the broad population of severe emphysema is the coils. That's why we're here today.

In summary, severe emphysema represents a substantial unmet need. Lung hyperinflation is strongly associated with patient-centered outcomes. Reducing hyperinflation improves lung function, quality of life, and improves exercise capacity. Unfortunately, available treatment options for severe emphysema patients are limited. Surgical options are limited by patient eligibility, high procedural risk, and high morbidity and mortality.

The pharmacologic options in this population have limited benefit. It is clear that a non-surgical lung volume reduction therapy, effective in both heterogeneous and homogenous disease, is needed for severe emphysema patients. This is the rationale for development of the ELEVAIR Coil System.

And now I'd like to introduce Claire Daugherty, who will represent -- present the design of the RENEW trial.

Thank you very much.

MS. DAUGHERTY: Thanks very much, Jim, and good morning, everyone. My name is Claire Daugherty. I am the Director of Biostatistics at BTG International.

My focus today will be on the RENEW study design, including entry criteria, effectiveness endpoints, statistical methodology, and analysis of subpopulations. I'll briefly touch on the crossover protocol as well.

The RENEW pivotal trial was an assessor-blinded randomized controlled trial. Patients were randomized one-to-one to treatment with the ELEVAIR system and optimal medical therapy, or to a control arm treated with optimal medical therapy alone. A sham bronchoscopy was performed for this study -- was proposed for this study, but the FDA deemed that due to the high likelihood of the treatment group to become unblinded, the

risk of AEs and SAEs associated with sham bronchoscopy could not be justified. Control patients participated in all study visits that were not specific to coil treatment.

RENEW incorporated a primary safety and effectiveness evaluation at 12 months. After the 12-month visit, the control patients exited from RENEW and had the option to enter into screening for the crossover study. Coil-treated patients remained in RENEW for long-term annual follow-up out to 5 years post-treatment. The long-term follow-up phase is currently ongoing.

The key original entry criteria for RENEW are shown on this slide. Importantly, they were GOLD stage 3 and 4 patients who were significantly symptomatic despite optimal medical therapy, including smoking cessation and pulmonary rehabilitation. Of note, RENEW was originally designed to include patients with baseline residual volume greater than or equal to 225% predicted. As Ms. Anastas mentioned in the introduction, the RENEW RV entry criteria was amended while enrollment was in progress, to include subjects with RV of 175 or above.

This CONSORT diagram shows how subjects were screened, enrolled, and followed in the study. For sites with no prior coil experience, the first two eligible subjects were treated with coils in a single-arm roll-in phase and not randomized. Subsequent eligible subjects were then enrolled into the pivotal randomized phase, which was conducted with high rates of subject completion through 12 months in both study arms. After completion of the 12-month visit, control subjects had the option to screen for the crossover study, and those eligible were enrolled.

The primary endpoint for RENEW was the change in 6-minute walk distance. Secondary endpoints included percent change in FEV_1 and change in SGRQ. Additional effectiveness endpoints included change in residual volume and ratio of residual volume to total lung capacity. RENEW also included responder endpoints for 6-minute walk and SGRQ.

A patient is defined as a responder if they experience an improvement at or above the minimum clinically important difference, or MCID. For 6-minute walk, this was an improvement of 25 meters or more, and for SGRQ, an improvement of 4 points or more. Recall that for SGRQ, a decrease in score indicates a better outcome.

RENEW incorporated an alpha controlling strategy for the primary and secondary endpoints. First, the primary endpoint was evaluated, and if statistically significant, the secondary endpoints were tested. Since the p-values for the additional effectiveness endpoints were not included as part of the alpha control, they are denoted through Dr. Criner's presentation as nominal p-values, to indicate that they have not been adjusted for multiple testing.

This next slide summarizes the RENEW primary and secondary analysis method based on the final statistical analysis plan. It is appropriate to compare treatment and control arms using a nonparametric test when the data come from a significantly skewed or asymmetric distribution. Since the data were significantly skewed for both 6-minute walk and FEV_1, a nonparametric analysis was done and medians reported. However, when the data come from a normal or symmetric distribution, it is appropriate to compare means using a parametric test. Since the data were normally distributed for SGRQ, a parametric analysis was done.

The rate of 6-minute walk test responders was compared using logistic regression. Rates of missing data were low and comparable across treatment arms and were estimated using multiple imputation.

A responder rate analysis compares the percentage of patients achieving a response at or above the MCID. In this way, it directly evaluates the clinical meaningful benefit to each patient. Therefore, it is a more direct measure of the clinical significance of treatment benefit than a mean or a median, which may not reflect a typical patient's experience.

Consider, for example, a hypothetical case where 50% of patients in the treatment arm have a 25 m improvement and are therefore responders, while the other half have no improvement. Also in this example, none of the patients in the control arm have any improvement. This would be considered a highly clinically significant treatment benefit. However, the mean change in the treatment arm would be 12.5 meters or one-half the MCID.

The subpopulations listed here were predefined and were assessed for consistency or poolability of treatment effect. They were not alpha controlled, so reported p-values from these analyses are nominal.

I would like to focus now on the relationship between two of these subpopulations' baseline RV status and region.

The timing of the RV entry criteria protocol amendment led to an imbalance in the enrollment across regions by baseline RV status. This graph depicts the enrollment in RENEW over time by region. The cumulative number of patients enrolled is shown on the y-axis. The outside-U.S. sites are shown in purple and began enrollment before the U.S. sites. The U.S. sites, shown in green, started enrollment later and had more opportunity to enroll patients with RV below 225, subsequent to the protocol amendment, as depicted in dark green.

This imbalance by baseline RV status across regions was substantial. Thirty-six percent of U.S. patients had RV below 225, while 6% of OUS patients had a RV below 225. As you will see in Dr. Criner's presentation, the effectiveness results were less favorable in the RV below 225 subpopulation. Therefore, the imbalance or overrepresentation of the RV below 225 patients in the U.S. drives the regional differences in effectiveness results seen in the ITT population. In the RV above 225 subpopulation, effectiveness results are comparable and remain poolable across regions.

As Dr. Criner will present next in more detail, it is important to consider a few points when evaluating the RENEW pivotal trial results in relation to the RV above 225 subpopulation.

The trial met all primary and secondary endpoints for the entire ITT population. Residual volume reduction is the mechanism of action for the coils and therefore the clinical basis to expect increasing effectiveness in patients with increased residual volume at baseline. The group of patients with RV above 225 was the original population, the only population for more than half of the RENEW trial, and 75% of subjects enrolled overall were in this subpopulation. Lastly, the empirical evidence supports an increasing differential benefit with coil treatment for patients with higher residual volume at baseline.

Before I turn it over to Dr. Criner, I would like to discuss the crossover study. This study was designed to offer coil treatment to RENEW control patients and to promote study retention. Control patients wanting treatment were rescreened prior to entry into crossover. This resulted in a single-arm observational study cohort with no concurrent control, consisting of self-selected patients who had progressed 1 year further in their disease.

You will see the results from this study appear worse than the randomized coil-treated group; however, these two groups are not directly comparable. You will see that the subjects that crossed over were the best performers on the 6-minute walk test from the control group. For a group of self-selected, positive performers, we expect, as a result of inherent natural variability, to observe a trend over time toward the population average. Mathematically, we call this phenomenon "regression to the mean."

We also expect that these subjects will experience progression in their disease throughout the year. As noted in the published FDA guidance for industry E10 on control groups in clinical trial design, when there is a lack of a concurrent control arm, it is not

possible to separately attribute the change due to treatment from spontaneous change due to disease progression or regression to the mean. Thus, it is inappropriate to directly compare this single-arm study to the randomized controlled trial results and inappropriate to view these results with equal weight.

With that, I would like to turn it over to Dr. Criner to walk you through the device procedure and the effectiveness results.

DR. CRINER: Thanks very much, Ms. Daugherty.

And good morning, everyone. My name is Gerry Criner. I'm a professor and founding chair of the Department of Thoracic Medicine and Surgery at the Lewis Katz School of Medicine at Temple University in Philadelphia.

It's my pleasure to talk to you today about the development and effectiveness of the ELEVAIR Endobronchial Coil System. I was principal investigator for the RENEW study at Temple, and I am a paid consultant for the Sponsor; however I have no financial interest in the outcomes of this meeting.

During this presentation, I will start by giving you an overview of the ELEVAIR procedure and then present the RENEW effectiveness results, first in the overall intent-to-treat population and then in the proposed indicated population of patients with residual volume greater than or equal to 225% of predicted. I will then present the subgroup analyses, the long-term durability results, and then I'll touch on other studies.

To begin, let's review the ELEVAIR procedure and the lobe selection process. The objective is to reduce hyperinflation in severe emphysema patients who remain symptomatic despite optimal medical management, regardless of disease distribution or the presence of collateral ventilation. By reducing hyperinflation, we can achieve clinical improvements in lung function, exercise capacity, and quality of life.

The ELEVAIR coil system is designed to be a minimally invasive bronchoscopic lung

volume reduction procedure. The most emphysematous lobes are treated with 10 to 14 coils per lobe. The procedure is bilateral, and it's performed over two separate treatments.

To choose the correct coil size, we measure airways using a flexible guidewire with radiopaque markers. Then we choose corresponding coil lengths of 100, 125, or 150 mm. We use the longest coil that allows the distal portion of the coil to be no less than 4 cm from the pleura but without the proximal end producing into the airway lumen. The catheter is then threaded over the guidewire, and subsequently, the coil is loaded into the catheter. Finally, the catheter is slowly withdrawn proximally, while the coil is deployed into its preformed shape. This then allows the coil to compress lung tissue.

Coils can be retrieved and repositioned during the procedure by using forceps if positioning is not optimal at the initial deployment. Multiple coils are placed into upper or lower lobes to reduce lung volume, as shown on these two x-rays.

In RENEW, the lobe with the highest emphysema score was treated, according to a visual CT scoring method. For each patient, we acquired high resolution CT scans at baseline. A radiology core lab scored the size of emphysema defects in each lobe from 0 denoting small tissue defects to 5 for exceedingly large defects. Patients with exceedingly large tissue defects were excluded from the study to ensure that there was sufficient parenchyma in a targeted areas for treatment to allow the coils to work effectively.

Let's now look at the baseline characteristics and the results of RENEW. RENEW patients were on maximal medical therapy at baseline. The treatment and control arms were well balanced with no meaningful clinical differences in baseline characteristic in the intention-to-treat population. Virtually all patients were on combinations of long-acting and short-acting bronchodilators, with or without inhaled glucocorticosteroids, and most, over 70% were prescribed supplemental oxygen.

All patients in both groups had stopped smoking and had completed a pulmonary

rehabilitation program at baseline. Importantly, per protocol, patients in both groups were encouraged to continue physical activity by discussing pulmonary rehab maintenance at each study visit.

The RENEW study cohort had severe emphysema and severe hyperinflation with a significant symptom burden despite optimal medical management. Seventy-seven percent of the study cohort had homogenous emphysema. To date, medical therapy and lung transplantation are the only therapies available to this population. As Dr. Donohue mentioned, medical therapy is not particular effective, and lung transplantation is not readily available.

Approximately 75% of patients in each study arm were GOLD stage 4, very severe airflow obstruction. Given the severity of this disease, these patients are typically excluded from clinical trials.

Now let's turn to the results. In the intention-to-treat population, all pre-specified endpoints were met. There was statistically significant improvement in all these endpoints. For the primary endpoint, 6-minute walk distance, the between-group difference was 14.6 m, significantly favoring treatment. For the secondary endpoints, the responder rate for 6-minute walk was significantly in favor of treatment over control. SGRQ showed an improvement of -8.9 points, and FEV_1 showed a 7% improvement over control. The other exploratory endpoints show improvements in SGRQ responder rate and reduction in hyperinflation, measured as RV and RV/TLC.

However, while we observed significant improvements in the ITT population, we also saw greater improvements across the three clinical endpoints as baseline RV increased. Patients with baseline RV greater than 225 or equal to 225% of predicted, shown on the right in beige, had consistent improvements in all effectiveness outcomes. This observation is understandable given the mechanism of action for lung volume reduction. It's reasonable

to expect that patient with higher degrees of air trapping derive greater benefit with any lung volume reduction procedure.

Earlier we stated that the original entry criteria required patients to have a baseline RV greater than or equal to 225% and that about 75% of the patients enrolled into RENEW had met this original entry criteria. Patients with RV greater than or equal to 225% showed substantial improvements across the clinical endpoints, as shown here in orange. In contrast, patients with RV less than 225% showed inconsistent improvements in their clinical endpoints.

As shown in the bar graph to the right, patients with RV greater than or equal to 225% achieved substantially greater lung volume reduction. Therefore, patients with greater degrees of hyperinflation had larger reductions in air trapping with coil treatment, thus leading to greater clinical benefit.

Looking at baseline characteristics for patients with RV greater than or equal to 225%, the treatment and control arms were well balanced, with no differences in clinical meaningful baseline characteristics. This confirms that the results for patients with RV greater than or equal to 225% are not affected by imbalances in baseline characteristics.

For the next portion of this presentation, I will focus on the proposed patient population for the indicated treatment, advanced emphysema patients with severe hyperinflation, defined as patients with RV greater than or equal to 225%.

Effectiveness benefit in this population is consistent over 12 months. Here, treatment is shown in blue and control is shown in red for all visits between baseline and a 12-month follow-up. Coil-treated patients demonstrate improvement in exercise tolerance, compared to control patients, shown here by increased 6-minute walk distances across all time points. Importantly, coil-treated patients also had substantial improvements in quality of life across all time points, shown by a between-group difference of nearly 11 points.

Remember that a reduction corresponds to improvement in quality of life when viewing the SGRQ. This sustained reduction in SGRQ exceeds two times the minimal clinical important difference.

Coil-treated patients also experienced improved lung function as demonstrated by improvement in FEV_1. The reduction in hyperinflation was maximal after the second treatment. The bar chart on the right shows that a large proportion of treated patients had a reduction in air trapping greater than 350 mm of residual volume, compared to medical care alone. These data further demonstrate that coil treatment reduces hyperinflation, which can then translate to clinical improvements.

Consistent with a reduction in hyperinflation, we see substantial differences in responder rates between coil-treated patients and control for 6-minute walk distance, SGRQ, and FEV_1. All nominal p-values are less than 0.01. The bar charts show the percentage of patients that met or exceeded the minimal clinically important difference for each of these measured endpoints.

All responder rates favored treatment. There was an 18% differential for 6-minute walk distance, a 43% differential for SGRQ, and a 30% differential for FEV_1. These data show that coil-treated patients with baseline greater than or equal to 225% had substantial clinical benefit across all measured clinical outcomes.

The clinical benefit seen in 6-minute walk distance, SGRQ, and FEV_1 are also reflected in patient-reported measures of breathlessness. Here we see that dyspnea, measured by the modified Medical Research Council (mMRC) dyspnea scale, is substantially reduced in a treatment arm compared to control. Fifty-one percent of the treatment group improved one or more full points on the mMRC scale compared to 28% of control. Twenty-seven percent of treated patients improved two or even three points.

Dr. Donohue noted that breathlessness is the most debilitating complaint that

patients with severe COPD have, and it is the complaint that is most difficult to treat for patients with COPD. By treating hyperinflation with coils, we see that functional dyspnea burden has substantially and significantly improved in these patients.

In addition, question 11 of the SGRQ provides supportive evidence of the impact of breathlessness on the activities of daily living in this patient population. Here we show a substantial improvement in coil-treated patients over medical care that is optimal, alone. At 12 months post-treatment, 47% of treated patients had a one or more category important in question 11 in the SGRQ, compared to 24% of control patients, and 29% of patients experienced a two or three category improvement. These data reinforce that patients with RV greater than or equal to 225% had a meaningful and sustained reduction in dyspnea during performance of their daily activities at 1 year post-intervention.

So what does a one- or two-point improvement in SGRQ question 11 mean to patients? For example, if we think about a patient, like most RENEW patients who feel breathless doing any activity more than washing or dressing themselves, a one category improvement means that they are now able to walk around the house without feeling breathless. And a two or more category improvement means they are now able to walk outside on level ground or even up one flight of stairs without feeling breathless. In this severely impaired patient population, optimally medically managed, these changes are clinically meaningful.

I will now turn to the ITT population to review some of the relevant subgroup data and present the 24-month outcomes.

In the ITT population, subgroup analyses showed that the effectiveness outcomes were inconsistent between the U.S. and outside-U.S. populations. Although both U.S. and outside-U.S. populations showed benefit from coil treatment, the between-group differences across all endpoints were greater in the outside-U.S. population, especially in

the 6-minute walk distance, and the results may not be poolable. But it's important here to recall, from Ms. Daugherty's presentation, that 36% of the U.S. patients had RV below 225%. It's the difference in baseline RV level in this population, rather than the geographic differences, that appears to be the driving the differences in outcomes.

In fact, if we look at U.S. outcomes by baseline RV, we see a substantial differential benefit in patients in the U.S. with RV above 225% across all endpoints, just as we saw in the entire population above 225%. While 6-minute walk distance is negative for patients with RV below 225%, there is a positive 17.4 m improvement in the U.S. patients with RV equal to or above 25%. This finding is consistent with findings in the entire ITT population and is again driven by the larger reduction in hyperinflation from baseline, shown here for the U.S. patients with an RV equal to or greater than 225%.

Now, when we compare the outside-U.S. versus U.S. group, in patients with RV above 225, we see comparable improvements across all endpoints, regardless of whether patients were treated in the U.S. or outside the U.S. Now we find that the U.S. and outside-U.S. results are poolable. In fact, when we look at what this means in terms of clinical benefit, we see a 20% differential benefit in the 6-minute walk distance in the U.S. patients and an 18% differential benefit in the outside-U.S. group. Thus, similar clinical benefit was achieved in both U.S. and outside-U.S. population for patients with RV greater than or equal to 225%, and seemingly apparent regional differences in effectiveness outcomes were driven by differences in baseline RV.

As you can see in the between-group analyses, patients with homogenous disease have substantial improvements above optimal medical care alone. Patients with heterogeneous disease had greater improvements in 6-minute walk distance and FEV_1, but homogenous patients had the same substantial improvements in SGRQ that were observed in heterogeneous patients. Both of these findings are consistent across all other lung

volume reduction therapies, as discussed by Dr. Donohue. Importantly, there was clinical benefit in both groups, both heterogeneous and homogenous patients, as shown by the responder rates.

This slide shows the 24-month durability of coil treatment. As discussed, the control patients exited the study at 12 months, so we don't have a comparative control arm at 24 months. However, for 6-minute walk tests, the treatment group benefit at 24 months is comparable to the control group at 12 months. We see a delayed decline due to disease progression in exercise tolerance. As you remember, Dr. Donohue mentioned that in the NETT study, they observed an annual rate of decline of 40 m in the control arm at 1 year, and 65 m at 2 years.

For other endpoints, the treatment arm also shows sustained benefits at 24 months over the 12-month control arm data. For instance, while the control patients' SGRQ had begun to worsen at 12 months, the treatment arm shows an SGRQ that remains below the minimum clinical important difference of -4 points at 24 months.

Now I'll discuss the crossover study, which was a separate, single-arm study. This study was primarily used as a retention tool for RENEW control patients. They could be screened for crossover only if they completed the RENEW study through 12 months as a control patient.

Here we show the results of the crossover study. Without a control arm, we report only the change from baseline and not a between-group difference. These data can be used to provide supportive evidence, but to be clear, they are not the same level as the pivotal trial data.

Coil treatment reduced hyperinflation from baseline, shown by a reduction in residual volume. However, the crossover study shows a decline in 6-minute walk distance from baseline. Given the limitations of measuring clinical endpoints in a progressive disease

without a control arm, these results must be interpreted with caution.

When we compare the patients that enrolled in the crossover to those who did not, we see different 6-minute walk test performances. Among the patients who enrolled in crossover, shown in red, we see almost no decline in 6-minute walk distance during the RENEW trial. In fact, their 6-minute walk distance at baseline of crossover is virtually identical to their 6-minute walk distance at baseline of RENEW. This is uncharacteristic and unexpected in this patient population, as we previously discussed. From other bronchoscopic studies, as we previously mentioned, a 26-meter reduction in 6-minute walk distance has been recently reported in a control arm of LIBERATE, and in NETT we saw a 40 m reduction, as previously mentioned.

In contrast, in the RENEW control patients who did not cross over, shown in green, we see an immediate decline in 6-minute walk distance, which is what we would expect from disease progression alone, as we saw in Dr. Donohue's previous slide, in the NETT population. These two subgroups, who both were randomized in the RENEW control arm, diverged an additional 30 m in their 6-minute walk distance at 12 months. Thus, the crossover study enrolled only the positive performers from RENEW. Selection bias, as we see here, is one of the several reasons why non-randomized, single-arm studies cannot be compared to randomized controlled trials, especially in a very severe patient population.

So recognizing the limitations of crossover, we can perhaps put the RENEW results into some better context by comparing them to other randomized controlled trials for ELEVAIR.

The findings from RENEW, in a proposed indicated population, are consistent with previous ELEVAIR RCTs. Here we see the REVOLENS trial. It was a randomized controlled study sponsored by the French government. It enrolled 100 patients. It had a comparable patient population to RENEW, with 66% of patients having homogenous emphysema.

REVOLENS restricted enrollment to those with severe hyperinflation with RV greater than or equal to 220%. These similarities allow for a comparison of outcomes between REVOLENS and RENEW.

REVOLENS met its primary endpoint at 6 months and at 12 months. The results are consistent with RENEW in terms of both the magnitude of reduction in residual volume and the related improvements in FEV_1, SGRQ, and 6-minute walk distance. The consistency between these two independent RCTs on the ELEVAIR system further exemplifies the robustness of the RENEW pivotal trial.

So to summarize the effectiveness results we've presented today, all effectiveness endpoints in the RENEW trial were met. The RENEW study shows clinically meaningful benefit in very severe emphysema patients with severe hyperinflation, regardless of their disease distribution or geographic region. These are patients that would otherwise remain symptomatic despite optimal medical treatment.

Eligible patients for coil treatment can be identified based on standard pulmonary function testing and CT scanning of the chest. Therefore, the ELEVAIR Coil System provides an effective, minimally invasive, bronchoscopic lung volume reduction therapy that improves lung function, exercise capacity, and quality of life.

I would now like to introduce Dr. David Hahn, who will present the safety data.

David.

DR. HAHN: Thank you, Dr. Criner.

Good morning. My name is David Hahn. I'm the head of PneumRx and a practicing interventional radiologist. I'll be presenting the safety profile of the ELEVAIR system.

The IDE clinical program consisted of the RENEW randomized controlled trial, the roll-in phase, and the crossover from RENEW study. The population I'm going to focus on today is from the randomized phase of RENEW, which included 155 coil patients and 157

control patients. Long-term follow-up is ongoing and includes a safety analysis for up to 5 years post coil treatment. All treated patients in RENEW have completed 2 years of follow-up.

Here is an overview of the safety presentation. And I'd like to begin by discussing the adverse and serious adverse events. This is a high-level summary of the number of adverse events reported in the RENEW study. Every treated patient had an adverse event versus 88% of control patients, demonstrating the high morbidity associated with this patient population. However, the treated population had significantly more serious adverse events compared to the control group. The mortality rate between treatment and control groups was comparable, reflects the disease severity, and is consistent with published literature and GOLD stage 3 and 4 patients.

This slide shows the most frequently reported adverse events, which are known risks in severe emphysema patients undergoing bronchoscopic intervention. Now we show the next five most frequently reported adverse events, and with the exception of bronchitis, all occurred more frequently in the control group -- sorry, the treatment group.

This slide presents the most frequently reported serious adverse events through 12 months. I'll start with the four most frequent events seen here on the left. I will focus on these as events of interest because they occurred at a significantly higher frequency in the treatment group for both AEs and SAEs. Here are the remainder of the most frequently reported SAEs, reported by greater than or equal to 2.5% of patients.

This graph compares the rates of SAEs in the entire RENEW safety population, shown in dark blue, and the population with an RV greater than 225% predicted, as shown in light blue. As you can see, the incidence and types of SAEs reported most frequently in the RV greater than 225 population were similar to those reported in the overall safety population. Therefore, for the remainder of this presentation, we will focus on the entire randomized

population in order to take a comprehensive look at all safety events in the study.

To be comprehensive, this graph shows the safety profile in the single-arm studies of roll-in in gray and crossover in green. You can see types and rates of serious adverse events that are similar to the RENEW safety results.

Now, on to major complications: The primary safety endpoint in RENEW was the difference between treatment and control groups in the proportion of patients who experienced one or more major complications within 12 months of the first coil procedure. Major complications were specifically defined in the protocol and were potential adverse events of special interest known to occur with bronchoscopic intervention.

For example, a pneumothorax requiring chest tube drainage for 8 days would be considered a major complication, but a pneumothorax requiring a chest tube for 2 days would not be considered a major complication. Both of these events would be considered an SAE. A complete definition of major complications is provided in the panel packet. All potential major complications were adjudicated by an independent clinical events committee. Additionally, all safety data was reviewed on an ongoing basis by an independent data monitoring committee.

Overall, these protocol-defined major complications occurred in 35% of patients in the treatment group, compared with 19% of patients in the control group. The mortality rate between treatment and control groups was comparable. The overall between-group difference in major complications was driven by lower respiratory infections. All other major complications were experienced at a similar rate in the treatment and control groups. Importantly, no major complications were related to device malfunction.

Shown here are the number of fatal events through 12 months in the treatment and control groups, which are comparable between the two groups. In the events denoted by the asterisks, there were seven fatal adverse events that were considered at least possibly

related to the device or procedure. None of the fatal adverse events in the control group were considered related to the device or procedure; however, this would be expected in an unblinded study.

Now I will describe the data regarding lower respiratory infections. This slide shows the occurrence of pneumonia adverse events over time. One can see that the treatment-related SAEs were highest in the periprocedural period, around treatments 1 and 2. The rate of pneumonia SAEs was higher in the treatment group than control, and pneumonia rates for treated patients were similar across the IDE studies.

Prior to RENEW, a local, noninfectious inflammatory response around the coil was identified in the European commercial and clinical experience, but the characterization of this process was not well understood as it resembled pneumonia on radiographic imaging. As our understanding of this process has evolved, we now call this coil-associated opacity, or CAO.

Within RENEW, there were a total of 28 events that we have come to consider CAO. Fourteen of these events were identified during a post hoc evaluation of pneumonia performed by the clinical events committee. However, the events were not reclassified and remained pneumonia for the analysis in RENEW. The remaining 14 of the 28 were not reported as pneumonia but rather identified as a noninfectious inflammatory reaction by the investigator and coded as such throughout the trial. These events were not reclassified either. Out of these 28 events, 14 of them were serious and 14 were non-serious.

Distinguishing between pneumonia and CAO is important. There was one death in the pneumonia group, which was later evaluated to be a possible CAO event. These events should be diagnosed and managed appropriately, are described in the IFU, and have been incorporated into physician training. Here on the left we see a patient that was diagnosed with pneumonia, and on the right, a different patient with CAO. As you can see, the CT

findings are similar in both, with opacity and consolidation surrounding the coils.

At the time of the event, most were classified as pneumonia, since the understanding of this clinical finding developed over the course of the trial. Despite radiographic similarities, patients with pneumonia tend to present with symptoms and findings suggestive of an infectious etiology. These patients tend to respond to antibiotics with steroids administered at the discretion of the treating physician. In contrast, patients with CAO tend to present with more inflammatory type symptoms, without the typical findings associated with bacteremia. Because CAO events can range in severity from mild to severe, early diagnosis and treatment is important to post-procedural management.

In this next series of slides, we've graphed out the occurrence of the most common adverse event of interest over time to show you the trends. Shown here is the occurrence of COPD exacerbations over time. Exacerbations were common in both the treatment and control group, and it is clear that the treated patients experienced exacerbations at a higher rate than control and notably during each periprocedural period. When we add in the SAEs of COPD exacerbation, one can appreciate that the majority of the exacerbations were non-serious and resolved with medical therapy. After treatment number 2, the incidence of serious COPD exacerbation events in the treatment group approached the level observed in the control group.

This slide shows pneumothorax serious adverse events over time. There were only three non-serious adverse events, so only SAEs are shown here. Pneumothorax SAEs were experienced by 9.7% of treatment group patients. The majority of these events resolve with chest tube insertion. They typically occurred during the first 30 days post coil treatment. There were no deaths due to pneumothorax in the RENEW study, although there was one death in the crossover study due to complications from a recurrent pneumothorax. This was the only death due to pneumothorax in the IDE studies.

Shown here is the occurrence of all bleeding events over time in the treatment group, which includes both hemoptysis and hemorrhage. There were no bleeding events in the control group. Over half of treated patients had a bleeding event, and they typically occurred within the first 30 days after treatment and resolved, which produces the two peaks around treatment 1 and 2. Ninety-four percent of these events were non-serious and resolved without intervention; however, 6% of patients in the RENEW treatment group had a serious bleeding event. There was one death in RENEW and two deaths in the crossover study, which represents 1% of total treated patients. The majority of serious bleeding events resolved with medical treatment.

On to long-term follow-up safety data from RENEW: The RENEW study is designed to follow patients in the treatment group for up to 5 years. All treated patients have reached the 2-year follow-up visit. The summary of our 24-month long-term follow-up data in RENEW shows the decline in adverse events over time. The overall AE and SAE rates remain elevated, as would be expected due to the overall morbidity of this population. However, you can see the event rate in the treated patients in the second year approaches that of the control group in the first year.

Deaths occurred at a similar rate in the first and second year. After 12 months, one death was determined by the investigator to be probably related to the device. Noticeably, there is a decline in the rate of SAEs that were possibly or probably related to the device from 45.8 to 9.9% of patients.

Finally, let me close with a few words about our postmarket safety experience and our overall safety conclusions. Over 7 years of commercial experience and approximately 5,700 treatments, the top five most frequently reported complaints in postmarket surveillance are shown here. Each of these events were reported in less than 1% of patient treatments. No harms were reported to be related to device failure, and no unanticipated

harms were identified.

In summary, the safety profile is well characterized, and with the exception of CAO, the event types are known in patients undergoing bronchoscopic intervention. The most frequently reported SAEs are COPD exacerbation, pneumonia, and pneumothorax, and as previously discussed, some of the pneumonia events were determined to be CAO events. The safety profile was consistent with both the overall RENEW population and RV greater than 225% predicted. Coil-associated opacity was determined to be a noninfectious inflammatory event, distinct from pneumonia, and these learnings have been incorporated into physician training.

Device and procedure-related complications decreased over time, and they approached that of the control group at 12 months and beyond. While there are a greater number of adverse events in the treatment versus the control group, as Dr. Criner's presentation, the benefits of treatment outweigh the risks.

And now Ms. Anastas will speak about the postmarket plan.

MS. ANASTAS: Thank you, David.

Now I'd like to discuss the comprehensive postmarket plan we have proposed for the ELEVAIR system. Our launch will be based on a centers of excellence model, that is, that the ELEVAIR will only be offered at a select group of medical facilities based on specific acceptance criteria. A subset of these centers, referred to as model treatment centers, will not only offer the therapy but will also work with PneumRx to host a peer-to-peer portion of our physician training program.

The postmarket plan incorporates both a comprehensive physician training program and U.S.-focused post-approval study. Data collected through these two mechanisms will be monitored, along with data from our other ongoing clinical studies and our postmarket surveillance system.

To be selected as a treatment center, a hospital must have appropriate infrastructure, equipment, and personnel. They must be experienced with interventional therapeutic procedures, committed to completing the training curriculum, and participating in the post-approval study. PneumRx will be looking for sites that follow a multidisciplinary approach, incorporating input from pulmonologists, thoracic surgeons, radiologists, and others required for successful treatment of severe emphysema.

This slide depicts our multi-phase physician training program. First we'll select the treatment centers and the model treatment centers. Then qualified physicians at the selected sites can participate in online training, including documentation of relevant experience, required reading, and verification of therapy knowledge. Upon completion of the online training, physicians may participate in peer-to-peer training at the model treatment centers.

This training, conducted by PneumRx employees and supporting external physicians, will include lectures covering topics such as CT evaluation, patient selection and consultation, and periprocedural care. Case reviews will be presented, along with case observations when possible. Hands-on benchtop testing will be conducted with a custom bronchial model developed by PneumRx, and technical competence must be demonstrated on the model by participants.

The fourth phase of the training program is onsite proctoring, conducted at the physician's hospital by PneumRx-authorized trainers. This team-based training includes both the physician and the support personnel that will participate in patient care. A minimum of five cases will be supported by the PneumRx-approved proctor, but there may be more, if required. At the conclusion of this phase, there'll be an assessment of key skills and documentation that the physician and the team are able to operate independently without a proctor.

The fifth stage of the training program is PneumRx monitoring and maintenance of training records along with assessment of ongoing site performance data.

As part of our PMA submission, PneumRx has submitted a proposed study design for a post-approval study. PneumRx's goal for the proposed study is to capture a majority of patients treated in the U.S. in the first years following approval. All participating sites will be required to offer study participation to all patients.

A basic outline of the study is shown here. We expect to enroll a minimum of 300 subjects to be treated bilaterally, with 1 to 3 months between treatments. There'll be scheduled follow-up visits at 6 and 12 months after the first procedure and annually thereafter for up to 3 years.

Effectiveness endpoints and clinical data similar to those in RENEW will be evaluated at 12 months. The proposed primary safety endpoint is the composite rate of device- or procedure-related respiratory SAEs of interest. Additional safety endpoints include the frequency of individual device- or procedure-related respiratory AEs, including CAO. The primary safety and effectiveness endpoints are based upon the performance seen in the RENEW trial. The objective is to determine whether the results observed in RENEW are representative of those seen in commercial use.

In addition to the U.S. post-approval study, PneumRx is continuing to collect longer term data through the ongoing RENEW IDE studies listed here. And we're also conducting two postmarket European studies, which will result in a total of more than 2,000 subjects followed through long-term follow-up in clinical studies. Data from our U.S. post-approval study and our other studies will be included in an ongoing postmarket surveillance program. This program has been in place since initiation of commercial activity in Europe more than 7 years ago.

A cross-functional vigilance team regularly reviews the data collected through a

variety of sources, including clinical studies and commercial use of the product. We share what we learn with the medical community to assist in the development of clinical practice guidelines for coil therapy. Results of the postmarket review will also be provided to the PneumRx Medical Education Department, which will consider if there are elements of the training program that may require enhancement. This feedback process will enable PneumRx to continuously improve the training program and provide the latest knowledge to customers.

And with that, I'd like to introduce Dr. Hauber, who will present results from our patient preference study.

Dr. Hauber?

DR. HAUBER: Thank you, Julia, and good morning.

I'm Brett Hauber from RTI Health Solutions and the University of Washington. I'm an economist by training and an expert in patient preference analysis. I was part of the team that conducted the CDRH-sponsored study on benefit-risk preferences and obesity. I led the development of guidance for the analysis of discrete choice experiments for the International Society of Pharmacoeconomics and Outcomes Research.

The study that I will describe today was funded by PneumRx and conducted by my team at RTI Health Solutions. I am a paid consultant to the Sponsor, but I have no financial interest in the outcome of this meeting.

Patient preference testing is a rigorous approach to incorporating the patient's perspective into benefit-risk decisions. This type of study provides systematic evidence to support the personal stories you may hear from individual patients at an open public hearing like the one scheduled for this afternoon.

In 2016 CDRH issued guidance for the voluntary submission of patient preference information and stated that this information may help identify groups of patients who may

consider the benefit-risk profile of a medical intervention favorable. FDA can consider this information in its benefit-risk determinations.

In this study we developed a patient preference survey following CDRH guidance and established good research practices. We interacted with FDA early in the process to discuss this study, and this is one of the first such studies to be presented to an advisory panel.

The study suggests that there is a group of patients in the target population for whom the benefits of a coil-like profile likely outweighs the risks when compared with the outcomes of maximum medical therapy-like profile. Maximum medical therapy offers patients with severe emphysema limited benefit with relatively low risk.

Currently, there was only one realistic alternative, which is LVRS, that may provide substantial benefit but is associated with substantial risk and is only appropriate for a subset of patients. Endobronchial coils provide additional benefit relative to maximum medical therapy but also pose additional risks. So this treatment lies somewhere between maximum medical therapy and LVRS on this graph. The CDRH guidance refers to a decision like this, in which multiple treatment options exist and none is clearly superior for all patients, as a scenario for which patient preference testing may be helpful.

The key endpoint of this study was the proportion of patients with severe emphysema who likely would consider the benefits of a treatment like endobronchial coils to outweigh the risks based on the results of the RENEW trial. The patients in this study did not participate in RENEW, but they met enrollment criteria similar to those in RENEW; 202 patients were recruited through eight sites across the United States, and seven of those sites had participated in RENEW.

The CDRH guidance states that the benefit in a patient preference study must be meaningful to patients. Some trial endpoints, such as the FEV_1, are not particularly meaningful to patients and may not be correlated with meaningful outcomes. So during

survey development, the patients we interviewed told us that breathlessness with activity was the primary goal for them, of any emphysema treatment.

The benefit described in a patient preference study must also correspond to an outcome that's measured in the trial. Improvements in quality of life were demonstrated in RENEW using the SGRQ. Capturing all domains of the SGRQ in the survey was not methodologically feasible; however, question 11 of the SGRQ directly captures a patient's self-reported breathlessness with activity. In fact, more than 90% of RENEW participants who had an improvement in question 11 also achieved an MCID in overall SGRQ score. Based on these relationships, we used an improvement in breathlessness as the benefit in the patient preference survey.

To capture a patient's level of breathlessness, we used a pictorial adaption of SGRQ item 11, which you have seen previously, and we described the benefit as the probability of achieving a one-level improvement in breathlessness with activity, so that we could tie this meaningful benefit directly to the response rate on SGRQ item 11 in RENEW. We used a discrete choice experiment, which is the same method that was used in the CDRH-sponsored obesity study. Using this method, we break treatments down into the attributes that differ among individual treatment options.

Methodologically, we are limited in the number of attributes that we can include in a study, and in this case, we included the type of treatment, the treatment benefit, increases in the risks of the three most frequently reported SAEs, including COPD exacerbations, pneumothorax, and pneumonia. We also included the risk of death. We used an experimental design to create hypothetical treatment profiles, defined by different levels of each attribute. We then asked patients to choose between two different hypothetical options in each of a series of questions. By modeling the pattern of responses, we quantified the tradeoff the patients were willing to make between benefits and risks. We

then applied the model results to the clinical data to estimate patients' preferences for specific treatment profiles.

When we apply the results of the patient preference model to the data from RENEW, we predict that a substantial proportion of patients with severe emphysema would likely choose a coil-like profile if it were available. Thirty-two percent of patients with severe emphysema would likely perceive the benefits of a coil profile to exceed the risks when compared with maximum medical therapy alone. When we look at the subset of patients with RV greater than 225% predicted, this proportion increases to 51%. In other words, the study demonstrates that there is a group of patients with severe emphysema that would perceive the benefits of a coil-like profile to outweigh the risks.

Now I would like to introduce Dr. Frank Sciurba to discuss the clinical context of the treatment.

DR. SCIURBA: Thank you, Brett, and good morning.

I'd like to take this opportunity to offer my perspective on the clinical context of the RENEW data. I'm Frank Sciurba, Professor of Medicine at the University of Pittsburgh, Director of the Emphysema-COPD Research Center. I was an investigator in the RENEW study and the lead enroller and corresponding author on the *JAMA* article. I'm an unpaid consultant to the Sponsor but was reimbursed for my travel for this meeting. I have no financial interest in the outcome of this meeting.

Today I would like to put the data from RENEW into clinical context and explain why we need this therapy and why it is meaningful for me as a treating physician and to my patients with severe emphysema.

These are my patients. They have GOLD stage 3 or 4 emphysema and severe hyperinflation. They're very ill people. They have come to me on guideline-based maximum bronchodilators, usually inhaled corticosteroids. Most of my patients participate

in pulmonary rehabilitation, and yet their shortness of breath continues to have a dramatic negative impact on their daily activities and quality of life.

They're proud people. They can no longer actively play with their grandchildren, and further, a common concern that I hear from my patients is that they cannot even engage in a full conversation with their loved ones. These patients have been told by many physicians, there's nothing that can be done. This is an irreversible disease. They come to us, often as a last resort, because they want a chance at some relief. They ask if there's anything available that offers a meaningful chance of improvement, and they're willing to take some risks of adverse events to achieve a benefit. Mr. Wilson will be speaking with you later today.

There's, in fact, a significant unmet need. The ELEVAIR system is the first new device alternative to come to the FDA in a decade, and we need these options for our patients. I firmly believe these data presented today from the RENEW study clearly outline the benefits and risks of the ELEVAIR Coil System and show a clinically meaningful benefit in patients with hypertension. As Dr. Criner previously described, the study met the primary outcome in the overall randomized population based on the 6-minute walk test. And it demonstrated statistically significant and clinically meaningful improvement in SGRQ and FEV_1.

Later this morning, the FDA will comment on a *JAMA* article which described the results of RENEW. As the lead author and corresponding author, I believe it's important that despite the standard language used by *JAMA* article describing the modest clinical importance, to rather consider the responder rate based on the proportion of patients achieving that minimal important difference. Furthermore, the greater benefits seen in the proposed indicated population today of severely hyperinflated patients is now the most relevant statistic for the proposed indication.

Shown here are these data from the study population with an RV greater than 225, which was the original defined RENEW study population. As you can see, a substantial proportion of those patients, 42%, had a meaningful 6-minute walk response, and fully two-thirds had a meaningful improvement in their quality of life. I believe these data offer me the tools to have the appropriate evidence-based discussion with my patients in offering ELEVAIR coils as a realistic treatment option.

We also heard from Dr. Hahn about the risks associated with ELEVAIR coils. The safety profile is well understood, and we can explain this to the patients when they are making their choice. The observed adverse events are what pulmonologists would expect with any bronchoscopic device intervention in this group of fragile patients. And they most often resolve and decrease in frequency over time after treatment. Most importantly, similar mortality rates were observed between the treatment and control groups in RENEW, and further, the safety profile was similar in the overall randomized population and those with the severe hyperinflation that are being proposed to move forward.

So that brings me to the benefit-risk profile to the ELEVAIR system. On the left, we have the demonstrated benefits that you saw in the RENEW trial. These include improvement in lung function, quality of life, which includes less breathlessness, and increased exercise capacity, all of which are very important to my patients.

On the right, we have the well-characterized risks, which include an increased risk of COPD exacerbation, pneumonia, pneumothorax, and bleeding. And from a clinician's perspective, all these are generally transient and manageable risks. So when I have a conversation with my patients with severe emphysema who have no other options, this is essentially what I would present to them. These are well-defined outcomes and allow me to have an evidence-based discussion with them.

So when I evaluate the benefits and risks demonstrated in the RENEW trial, I believe,

and many of my own patients would agree, that the potential benefits outweigh the risks. And I consider the patient preference study results, as described by Dr. Hauber, to be consistent with the decision process my patients would go through when making their decision. The study showed that a substantial proportion of severe emphysema patients with severe hyperinflation believe, and would choose, that the potential benefits of this type of treatment do outweigh the risks. They would be willing to accept this treatment to potentially improve their quality of life. They have no other options.

That brings me back to the severe emphysema patients I see in clinic who have extremely poor quality of life and limited available treatment options. There's no cure for emphysema, and patients will continue to decline even after treatment. But for these patients, the ELEVAIR system offers the potential for a better life, and for me as a clinician, it's a meaningful clinical tool that will allow me to offer a realistic hope to many more of my severe emphysema patients who are desperately seeking options.

Finally, as a physician, it's also important to know that the Sponsor has a responsible, well-planned roll-out strategy based on their extensive clinical experience in Europe, and they will ensure that physicians are well trained and that only centers offering comprehensive care using all available options have access to this technology, and that the procedure and device are used appropriately in patients with severe emphysema.

So thank you for the opportunity to speak to you today, and now I'll turn it back to the Sponsor to address your questions.

DR. NATHAN: Thank you. I'd like to thank the Sponsor's representatives for their presentation. Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberation session. So anyone from the Panel have any questions you would like to ask at this time?

Yes. Please identify yourselves as you ask the questions, just for the transcript. Thank you.

DR. KIRSCH: Jeff Kirsch from Oregon.

I have, I guess, three questions. The first question relates to slide CD-32. Are you going to be able to pull that up?

I'm concerned about the presentation of the data from 12 to 24 months. It gives one the impression that it's a smooth transition from the benefit to returning to control. Do you have any data at all between 12 months and 24 months to suggest that that line that's drawn between the 12-month and 24-month period is actually smooth? In other words, what evidence do you have that maybe the effect goes away at 13 months or 12 months and 1 day versus 24 months?

MS. ANASTAS: There was only the -- after the 12-month visit, there was only a 24-month visit. There were no scheduled visits in between 12 and 24 months.

DR. KIRSCH: So I think a better presentation of the data may be without a line between those two points.

My second question relates to CD-21. Do you have data that could show us the range of responses? This is -- these are bar graphs without any standard error, standard deviation, or individual points. It'd be nice to see whether there was overlap and how much overlap between the blue bar and the red bar.

MS. ANASTAS: We do have those analyses, and I would ask Claire Daugherty to come to the podium to show those.

MS. DAUGHERTY: Claire Daugherty, BTG.

We have the confidence intervals for the odds ratio, not in this slide at this moment, which we could have for you after the break. If you'd like to see a histogram or a waterfall plot of the individual responses, we could show you that as well.

DR. KIRSCH: Thank you. My last question relates to what happens for -- there are going to be some patients, despite their horrible disease, who will return to smoking. What happened within the study and in your postmarket roll-out for patients who returned to smoking despite not having smoked in order to get into the study?

MS. ANASTAS: We did not collect data on return to smoking. We don't have that information.

DR. KIRSCH: Moving forward in the roll-out, you know, the postmarket study that you plan to do, will patients continue -- what will happen if the patient returns to smoking as you move forward, if this product is actually released in the United States?

MS. ANASTAS: We're still developing a protocol, and so that is information that we could collect as part of the protocol.

DR. KIRSCH: Thank you.

DR. NATHAN: Dr. Hawkins.

DR. HAWKINS: Randy Hawkins, Inglewood, California.

So my question had to do with implementation, and you helped me with that because I was concerned about the technique implementation. It appeared that there was a required online assessment or program that the physician had to go through. But it almost seemed like the -- was any part of this optional? I saw the mandatory online, and there was an option to go and get training, or that was -- you could skip that part and just have a proctor, because I have concerns about what seemed to be a somewhat technical procedure. And also did it have anything to do with the evaluation by CT scanners? How does that -- how does this evolve?

MS. ANASTAS: I believe you're speaking about the portion of the program where I outlined our postmarket plan for training.

DR. HAWKINS: Correct. Implementation if it's approved.

MS. ANASTAS: So our plan is to -- we would have online training initially. And then after a person finishes that, then they can go forward to peer-to-peer training. They can't just go to proctor training. They must attend -- it's a multi-phased approach, and you must go through the phases.

DR. HAWKINS: So peer-to-peer is required?

MS. ANASTAS: Peer-to-peer is required.

DR. HAWKINS: Okay.

DR. NATHAN: Dr. Ballman, you had a question?

DR. BALLMAN: Just a couple of quick questions. First of all, was there a test for interaction done between the less than or equal to 25% and greater than in the treatment?

And then the second question is, in the crossover study, was there a new baseline value, which was what their value was at 12 months, and then that was used for the crossover?

MS. ANASTAS: Can you clarify the first part of the question?

DR. BALLMAN: I want to know -- and I'm sorry, I'm Karla Ballman. I forgot to say that, from Weill Cornell.

I want to know whether or not there was a test for interaction done between the variables of the RV being less than or equal to 225% versus greater, and the treatment, you know, treatment versus control?

MS. ANASTAS: I would -- we've done that in the office. I'd ask Claire Daugherty to come to the podium, please.

MS. DAUGHERTY: Claire Daugherty, BTG.

Yes. We did a test for interaction between high and low RV, and that was statistically significant at the 0.15 level. If you'd like to see the specific p-values, I can put that up.

DR. BALLMAN: 0.15?

MS. DAUGHERTY: So we tested for an interaction term. I'll put the slide up so you can see. So this is my understanding of what you're asking, is was there an interaction between high and low RV and the treatment effect? And so we performed this for all the endpoints, for 6-minute walk test, rank-transformed 6-minute walk, responder percent change in FEV_1, rank-transformed percent change in FEV_1, and SGRQ. Those are the results. They're statistically significant if we use a significance level of 0.6 or below.

DR. NATHAN: So I was going to ask the same question, but from a clinician's standpoint, I believe. And that is you show a nice decrease in the RV and then patient-friendly outcomes in terms of the St. George's and the 6-minute walk distance. Do you have -- is there -- can you show a correlation between change in the RV and some of these outcome measures? Do you have any graph like that? Is the RV a good biomarker for subsequent improvement?

MS. DAUGHERTY: Yes, we have that information.

DR. NATHAN: Okay. Maybe you can show that this -- oh, you've got it right here. Good. While you're getting that up, I'll fire with my second question, and that pertains to I believe it was just in excess of 70% of the patients enrolled were on oxygen, supplemental oxygen, and I didn't see any change in this during the course of the study and specifically how that relates to the 6-minute walk test. How did you control for oxygen use for the baseline and subsequent 6-minute walk test?

MS. DAUGHERTY: I want to ask a clarifying question on the first question, which was looking for the association -- were you asking for the association between change in residual volume and -- okay. Then I'll show this slide.

So this shows the association between the percent change in FEV and the change in residual volume. And you can see that these are highly correlated at about 0.5 for the

correlation coefficient.

DR. NATHAN: Do you have the same for the St. George's and the 6-minute walk test?

MS. DAUGHERTY: Yes. Here's St. George. Again, it's positively correlated, not as strong as the FEV_1. As we would expect, this is further away from the mechanism of action and a little bit more variable endpoint. I believe we also have this for 6-minute walk.

DR. NATHAN: Sorry. Not quite yet. He's looking now for the 6-minute walk? Okay.

MS. DAUGHERTY: Yes. Sorry for the delay. Here's the correlation between 6-minute walk and percent change in FEV_1.

DR. NATHAN: All right, thank you. Dr. Kirsch had another question, and then we'll get to Dr. Hawkins.

Sorry, Dr. Kirsch -- Dr. Kirsch first.

DR. HAWKINS: I'm sorry.

DR. NATHAN: And then Dr. Hawkins.

DR. KIRSCH: Jeff Kirsch from Oregon.

I wrote two questions related to device removal. Maybe that was in the presentation and I missed, but what are the typical indications for device removal? And when you say that there's device removal, is that removal of all the coils or coils in one region of the lung, one coil? What does that mean for device removal?

MS. ANASTAS: First, I'd like to clarify. When you're speaking of removal, whether you're speaking of removal during the procedure to reposition or removal of a coil in a second procedure?

DR. KIRSCH: The latter. The latter, second procedure.

MS. ANASTAS: So the device is intended as a permanent implant and is only recommended for removal as a medical indication. It's not recommended to remove if in

the event of no responsiveness. And --

DR. KIRSCH: What are those medical indications?

MS. ANASTAS: I would ask Dr. Hahn to speak to the types of events we've seen.

DR. HAHN: David Hahn, BTG.

The typical indication would be something like pleuritic chest pain or pneumothorax. And so the removal of the coils would typically be the coil or two that were felt to be the cause of the symptom.

DR. KIRSCH: Thank you.

DR. NATHAN: Okay. Dr. Hawkins, please.

DR. HAWKINS: Thank you. So we are aware these patients are quite ill. And you have more experience with the use of this technique and procedure outside of the U.S., not related to this study. Just curious, what have you learned with those other large numbers of patients that help us with adverse event mitigation? What reduces these serious complications related to this procedure?

MS. ANASTAS: Dr. Criner?

DR. CRINER: Yes. Gerry Criner.

There has been over 850 patients that have been treated outside the U.S. since it's approved for the CE mark. And from the registry data overall, it shows that the event rate is about the same in terms of complications of pneumothorax and the minor hemoptysis, pneumonia, as well as COPD exacerbations. What it does show also is that a patient who has a greater than or equal to 225% of predicted has a better response in RV reduction and improvement in FEV_1 as well as an improvement in 6-minute walk distance. So it kind of confirms what was shown in RENEW, in that patient group.

This is a slide that shows the registry safety data, if you're shown here. So the postmarketing plan that was put into place took the registry data in trying to formulate a

plan that would have systematic education and training, both training by the individual taking a baseline didactic course then the patient also -- or the clinician also going to a clinical center where they would have didactic lectures, interpretation of CT scan, interpretation of lung volumes and PFT measurement, and actually see a case at those training centers, and then when they would have patients available, then be proctored at those sites that have care. So a lot of the registry data was used to project that.

The other thing that was shown from registry data that was a learning is that the patients who have a baseline, in terms of a marker for patients that have a better outcome, shows that the patients that have an RV greater than 225% of predicted are the ones that have a stronger improvement in RV. So it was helpful in trying to get this targeted patient population that would most likely have benefit and construct a postmarketing plan that would have patient safety and effectiveness at the forefront.

DR. NATHAN: Thank you. I'd like to get back to the one question I posed, which wasn't addressed, I believe, and that was oxygen use.

MS. ANASTAS: First to clarify, did you mean oxygen use specifically with respect to the 6-minute walk testing?

DR. NATHAN: Yeah. Did -- and well, really, it's two-pronged. How many more patients needed oxygen after the therapy, or did some patients come off versus the control group? And then how was a consistent supply of oxygen managed, to compare 6-minute walk tests serially?

MS. ANASTAS: So we had a standard methodology for conducting the 6-minute walk test.

Ashley Burns, come to speak to that.

MS. BURNS: Ashley Burns, Clinical Development, BTG.

During the course of the RENEW trial, the 6-minute walk test was performed after a

titration of oxygen at the baseline level. And at each subsequent walk during the study, they were walked on the same liter flow of oxygen.

DR. NATHAN: Okay. Thank you.

And we're running short of time. We perhaps have time for two more questions.

Dr. Dodd, you had one.

DR. DODD: Yes. Lori Dodd.

I have a question for Dr. Hahn about the adverse events. Just to clarify, you were saying that some of the pneumonia events appeared to be CAO events. And so since I'm not a clinician, can you help me understand if you were trying to say that those were not clinically meaningful, or how do I interpret those, if they were indeed CAO events?

And I also thought you -- in that same discussion, you mentioned that one of those did lead to death; is that correct? Or was associated with death.

DR. HAHN: David Hahn, BTG.

Yes. So the CAO events, as we described, represented a local inflammatory process around the coil, and the evolution of the event has been understanding -- evolving over time. The majority of these events were recognized as pneumonia, typically because they presented as such, without the understanding of CAO. And so with a reevaluation of these events post hoc, they were determined by a clinical events committee to be not so much an infectious response but really more of an inflammatory response.

DR. DODD: But is the morbidity the same? I mean, in terms of the patient's perspective.

DR. HAHN: Well we have not separated out CAO from pneumonia in terms of that type of analysis. But what we do see is that all the pneumonia events that contained CAO were not worse than the people, the patients that were treated that had had pneumonia without CAO.

DR. NATHAN: Okay. Dr. Carvalho, we'll give you the last question for the session.

DR. PICHURKO: Bohdan Pichurko, Cleveland, Ohio.

Also a complication question for Dr. Hahn: You listed the comparisons of adverse events and serious adverse events, control versus treated group. If you were to look at it in terms of sick days or days of hospitalization, that of course could be very impactful on this debilitated population. Have you looked at those numbers? And did the presence of the coils impact the rate of resolution, let's say within each diagnostic group, COPD exacerbation control versus treated, pneumonia control versus treated? Was there a delay in resolution, any impression on the impact of coils on these clinical diagnoses?

DR. HAHN: Just to clarify, is your question specifically about hospital days and CAO and pneumonia or all of the adverse effects?

DR. PICHURKO: Most importantly, hospital days, but sick days in general, if you had a chance to look at those days under treatment.

DR. HAHN: Yes. We have that slide for you. The slide slows healthcare utilization in the randomized controlled. And from the left to right, we have 12 months prior to baseline, and on the right side, we have 12 months. And so we have hospitalization on the first line, showing treatment versus control in both categories.

DR. NATHAN: Okay, thanks. In the interest of time, we'll take a 10-minute break. Let's try and reconvene at 10:15. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. Thank you very much.

(Off the record at 10:05 a.m.)

(On the record at 10:19 a.m.)

DR. NATHAN: All right. We're going to get going, in the interest of time. It is now 10:20, and I'd like to call this meeting back to order. The FDA will now give their

presentation. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair. FDA will have 90 minutes to present.

FDA, you may now begin your presentation.

DR. COURSEY: Thank you.

So good morning, everyone. My name is Derya Coursey. I am the lead reviewer for the subject device, and I am a member of the Respiratory Devices Branch in Office of Device Evaluation at FDA.

This is the current review team; however, there have been many more reviewers who have provided support throughout the course of the review of this device.

The Agency wishes to obtain feedback regarding the clinical aspects of the data provided, specifically if the study population supports the proposed indications for use and if the study outcomes are clinically significant. The Agency also wishes to obtain Panel's recommendation regarding the benefit-risk profile of the coil system.

To provide a brief outline, we are going to start our presentation with the study overview. This will be followed by the safety and effectiveness results of the clinical review for the overall population. Afterwards, we will have a short presentation on the patient preference study, and we will finalize our presentation with the applicant proposed future postmarket study plan. The afternoon session will include the Panel questions. Also, key points in FDA's presentation regarding the Panel questions will be highlighted in the orange boxes on the bottom of the relevant slides.

We are going to start our presentation with the study overview.

ELEVAIR Endobronchial Coil System is a Class III device. What it means, that it is a high-risk device. And the Agency is looking for adequate data that will provide reasonable assurance of safety and effectiveness. Some of the relevant factors that should be

considered are intended patient population; conditions of use, including recommended or suggested in the labeling; probable benefit to health versus probable injury.

The following is the applicant-proposed indications for use. The coil system is indicated for homogenous and heterogeneous emphysema patients with severe hyperinflation. And it is also intended to improve quality of life, lung function, and exercise capacity. The Panel will be asked to make a recommendation on the benefit-risk profile of the coil system based on the proposed indications for use by considering the overall effectiveness results, not for the subpopulation only.

Today we will be presenting two clinical studies. One is the RENEW pivotal study, and the other one is the crossover study.

RENEW pivotal study, as explained in detail by the applicant, it was a multi-centered, one-to-one randomized, assessor-blinded study. However, subjects and investigators were not blinded. It was also stratified based on the emphysema type. Both treatment and control received optimal medical therapy and also completed their pulmonary rehab before enrollment. There was no sham control. The sample size for the pivotal study was powered by the secondary endpoint of FEV_1, not the primary endpoint of 6-minute walk test.

Second study that we are going to present the results are for the crossover study. Crossover study included subjects who were the control arm in the previous 12 months. And these subjects had the option of receiving the treatment if they are eligible and they passed the inclusion/exclusion criteria. This was a single-arm observational study. And the inclusion/exclusion criteria was similar to the pivotal study treatment arm, except the requirement of completion of the pulmonary rehab before receiving the coil treatment. However, these subjects were the control group in the previous 12 months, and they had completed the pulmonary rehab before enrolling as a control group in the pivotal study.

These are the primary and secondary effectiveness endpoints that was pre-specified,

with multiplicity adjustment in the pivotal trial. They were explained in detail by the applicant. There were also many exploratory endpoints such as residual volume, SGRQ responder rate, or various subgroup analyses, such as U.S. versus out-of-U.S. or various RV cutoffs. However, all these exploratory endpoints were only exploratory without multiplicity adjustment. And for the safety, major complications were the primary safety analysis; however, we will be presenting data for all adverse events for benefit-risk determination.

There are two major changes to the protocol. The first one is the removal of cap on homogeneous emphysema patient enrollment. Initially, the cap was limited to 150 subjects. There were 75 in coil and 75 in control. Later in the study, this cap was removed based on early feasibility studies showing that patients with homogenous emphysema may also benefit from the coil treatment.

The second change is the change of inclusion criteria for the baseline residual volume. It was changed from residual volume greater than 225% predicted to residual volume greater than 175 % predicted. The justification provided for this change was that European studies showed that subjects with residual volume greater than 175% predicted also showed some benefit with the coil treatment. When this change happened, 169 out of 315 subjects had been already enrolled. The importance of this cutoff value is that after evaluation of the overall results, the applicant is basing the effectiveness on residual volume greater than 225 %.

As mentioned previously, this was a multi-centered study. There were U.S. and out-of-U.S. data. Pooling of U.S. and out-of-U.S. data assumes that treatment effect is comparable across the region such that out-of-U.S. data can be used for effectiveness results for the U.S. population. However, when they looked at U.S. and out-of-U.S. data separately, the treatment effect was consistently smaller in the U.S. compared to

out-of-U.S. Additionally, the treatment by region interaction effects are statistically significant for all continuous variables, 6-minute walk test, FEV_1, and SGRQ, at 0.15 significance level. What it implies, that it may not be appropriate to use the pooled data for treatment effect assessment for the U.S. population.

Also, the Panel will be asked to discuss the pooling U.S. and out-of-U.S. data for overall assessment for U.S. population in the afternoon session.

After the evaluation of the overall results, the applicant is focusing on the effectiveness results on residual volume greater than 225% predicted. So the diagram here shows the patient population who has this baseline. We can see that 75% of the population has residual volume greater than 225% predicted. The applicant is not including 25% of the data. And when we look at closely to this 25%, we can see that 91% of the data is from U.S. population. Also, there is no pre-specified hypothesis testing for this subpopulation with multiplicity adjustment.

The Panel again will be asked to discuss this proposed data cutoff for overall effectiveness.

The original pre-specified primary statistical plan was parametric ANCOVA. And results are not statistically significant with this method. What it implies is that basically none of the secondary endpoints should be formally tested. However, this final pre-specified primary method was changed to nonparametric ANCOVA, and results are statistically significant with this method.

Then in the next presentation, we are going to present effectiveness and safety results for the pivotal study and effectiveness results for the crossover. We will be presenting the results for the overall population. And for the effectiveness, ITT population will be presented. Basically, it will include all randomized patients in the control and treatment arm.

For the safety, we will be presenting data, again for the pivotal, for the modified ITT. It will basically include all randomized patients for control or for the treatment who entered the procedure room. For the crossover, we will be only presenting the descriptive statistics.

Now Dr. Bahadori will provide the effectiveness and safety results of the overall study.

DR. BAHADORI: Good morning. Good morning to members of the Panel and the public. I am Lila Bahadori, and I am a pulmonologist and critical care medical officer in the Respiratory Branch in the Center for Devices and Radiological Health.

Now I will be providing you with the clinical review for the total study for the ELEVAIR Endobronchial Coil System.

Now, and just to give a quick outline, you've heard about most of the procedure overview, and I'll touch on a couple of points, and then we will go through the study results with the safety and effectiveness for the total study in the RENEW. We'll cover a couple of the publications since then, and then finally, we'll talk about some of the clinical uncertainties that we have seen while we have been going through our review. And, of course, we will be asking for Panel feedback on some of these.

Now, briefly, you have heard about the procedure overview. This is a nitinol coil that is placed bronchoscopically. This is placed in two separate bronchoscopic procedures, anywhere from 1 to 4 months apart. And it is recommended to place 10 to 12 coils for the upper lobes and anywhere from 10 to 14 coils for the lower lobes.

Now, the decision of where to treat was based on a central core laboratory that assessed the lung parenchyma damage per a CT scoring plan that's then transmitted to the centers. And then there is the recommendations for the bilateral lobe treatments. And so the Panel will be also asked to discuss the applicability of the centralized scoring and treatment recommendations to real-world views.

When we looked at the treatment planning, this is a CAT-scan-based method of patient selection that was developed by the applicant. It is based on lobar damage and visual assessment and scoring that's not based on densitometry or other analytic metrics. This is a scoring system of 0 to 5 that's based on the extent of lung parenchymal tissue defects and then the amount of the interstitium that's actually intact.

Now, the other thing to just keep in mind is that this is a different scoring system than what was used in the National Emphysema Treatment Trial. That was a multi-center trial that evaluated patients for lung volume reduction surgery. And so we really have no way of comparing the -- there's really no publications to compare these two methods of visual scoring.

Now I just wanted to turn to some of the pivotal key inclusion/exclusion criteria for the study. And when we look at the major inclusion criteria, these are consistent with patients who have severe COPD. Part of the inclusion criteria, patients also had to complete a pulmonary rehabilitation program prior to enrollment.

When we look at the major exclusion criteria, this excluded patients with very severe homogenous emphysema, based on the scoring plan, and so this was subjects that had a score of 5. It also excluded patients that had a bronchodilator response with possible asthma. And part of the exclusion criteria was also any comorbidities that may impact exercise capacity in the subjects.

So when we looked at the highlights of the inclusion criteria, the study did initially enroll subjects with a residual volume of greater than 225%. And this was changed after almost 54% of the subjects had been enrolled, from 225% to 175%. Now, the residual volume is a measure for air trapping and hyperinflation, and one of the things that we do need to keep in mind is that all these patients are severely hyperinflated and have severe lung disease, severe COPD.

Based on also the National Emphysema Treatment Trial results that was conducted in the 1990s to evaluate lung volume reduction surgery, it was determined that mainly subjects, patients that have severe upper lobe heterogeneous emphysema with a low exercise tolerance are the patients that would benefit from this type of surgery. Based on early feasibility studies that had been done in Europe with the coil, it was found that also patients with homogeneous emphysema might benefit from this procedure as well, and so this study enrolled about 77% of homogenous patients.

The other thing that we looked at, as far as the inclusion criteria, was what would be the effect of pulmonary rehabilitation? And one of the major differences between the pivotal trial for the RENEW, and then the single observational study for the crossover, was the requirement for pulmonary rehabilitation. And so one of the questions that will come up is that whether maintenance pulmonary rehabilitation program during the RENEW trial and then subsequently the lack of the pulmonary rehabilitation requirement prior to the crossover study, whether this may have impacted some of the results or not.

Now, when we looked at the study population and baseline characteristics, we looked at this for both the coil and control group in the pivotal study and then separately for the observational arm in the crossover. And based on the global obstructive lung disease criteria, most of the patients that were enrolled in the study were patients that had stage 4 GOLD emphysema, and these are patients that have very severe emphysema with an FEV_1 of less than 30%.

Also, most of the patients in the study were subjects that had homogenous emphysema. Baseline characteristics, including the 6-minute walk test and the pulmonary function test, were very similar. And so because there was similarities across all these groups, we also expect that the treatment effect between the pivotal and crossover most likely should not be confounded by these baseline characteristics.

Now, what I'm going to do is first present you the effectiveness results, and these are going to be for the overall study population. And just to give a brief outline for the effectiveness, we'll go through the pre-specified endpoints, the primary and secondary endpoints. And then we're going to look at some of the subsequent subgroup analyses that were done for the U.S. versus OUS, the type of emphysema and the RV cutoff. And then I will talk about some of the results beyond 12-month to look at the durability of effect. And then before going on to discuss the safety results, I will also discuss the conclusion from the effectiveness results.

So we'll first look at the primary endpoint at 12 months, which was the 6-minute walk test change, between the control and the treatment arm at 12 months. Now, the 6-minute walk test has been the surrogate that has been used for exercise capacity. And when we look at some of the studies that have identified the minimal clinical important difference, the difference of 25 m that has been reported is based on anchoring to perceptions of dyspnea and activity.

Now, to just give you also a perspective on what can happen with the 6-minute walk test, pulmonary rehabilitation can also give you up to a 44 m improvement in the 6-minute walk test. When we looked at the pooled study results for the U.S. and OUS, there was a median change of 14.6 m. And this was statistically significant with the nonparametric ANCOVA. And so the Panel will be asked this afternoon to discuss the clinical significance of the change in 6-minute walk test of 14.6 m.

Now, when we look at this primary endpoint, this graph shows that there is a median difference of 14.6 m between the coil treatment and the control group. And just to keep in mind, this median difference is not a simple difference between the two numbers.

The other thing that we looked at was the single observational study with the crossover. And just to remind you, the crossover is the control group that went in, and so

their baseline is just prior to the treatment period. And when we looked at the crossover results, there was a reduction of 15 m in the 6-minute walk test at 12 months.

When we look at this graph on the right side, this is a graph that shows the 6-minute walk test for the subjects in both the coil and the treatment arm of the study. And you see both the improvement and the worsening at 25 m. And this graph just shows a lot of variability in both arms of the study.

Now, we also looked at the clinical significance of the 6-minute walk test over time. And when we look at this treatment effect, there is a modest improvement in the first month in the circle. And then there is a progressive decline that starts at 4 to 6 months and persists out to 12 months.

Now we're going to look at some of the secondary endpoints for this study. There was a modest difference in the 6-minute walk test responder rate. The responder rate is the 25 m improvement for the subjects in the treatment arm. And there was almost a 12% improvement. In this study, the subjects were encouraged to continue with a maintenance pulmonary rehabilitation program. However, the information and data was not collected on who actually continued, and therefore it's unknown if that may have impacted some of the responder rates that we saw.

Of note, when we looked at the crossover responder rate, this was identical to what was seen in the control arm of the pivotal study. And so the Panel will also be asked to discuss the clinical significance of the 6-minute walk responder rate of almost 12% that we saw in the study.

We also then did some further evaluations to look at some of the variability in the 6-minute walk test results. We do know that pulmonary rehabilitation can improve the 6-minute walk test anywhere up to close to 50 m. And so we wanted to see whether there could have been other variabilities and impacts on some of the results we were seeing.

Now, when we look at some of the time points beyond 25 m, such as the 50 m, there's a 4% difference between the treatment and control arm. And then when we also look at the declines, the decline seems to be comparable between the treatment and the control arms as well. And these results indicate that there's quite a bit of a variability between both the improvement and decline in the treatment subjects.

Now, the next secondary endpoint was the FEV_1 percent change, and this was the surrogate for lung function. And you've heard a little bit more about it from the applicant, and the minimal clinical important difference that has been reported in the studies is about 10%, or for an FEV_1 of 100 mL. Now, when we looked at the FEV_1 percent change at 12 months between the treatment and control arm, there was about a 7% difference. And the crossover declined about 1.3% at 12 months.

We additionally looked at the effect over 12 months, and again, there was an initial improvement, and then at 4 to 6 months after treatment, there was a progressive decline that was seen through 12 months. And the Panel will be asked to discuss the clinical significance of the FEV_1 change of 7%.

We also looked at the St. George's Respiratory Questionnaire changes that was reported. This is the patient-reported outcome that has been used in COPD studies. And as you have been already told, a decrease in the number is actually a positive outcome. The St. George's Respiratory Questionnaire difference was clinically and statistically significant. And there was almost a 9 m reduction in the points between the treatment and control arm. Also, the crossover group also had a reduction that also met the minimal clinical important difference.

When we also looked at the St. George's Respiratory Questionnaire over time, there was also an improvement that was initially seen, which also continued with minimal loss and still persisted at 12 months, meeting the minimal clinical important difference.

Now, this study was unblinded for both the investigators and the study subjects. And so we looked at the St. George's Respiratory Questionnaire a little bit closely. When we looked at the various domains, the main improvement that we saw in the domains was in the psychosocial domain in the St. George's Respiratory Questionnaire.

The other thing that we wanted to see was if there was a clinical correlation between the results of the St. George's Respiratory Questionnaire and some of the objective endpoints that were studied in the study. And so if you look at the lower left quadrant that's in gray, what you will see is these are the subjects that had worsening in their 6-minute walk test and had an improvement in their St. George's Respiratory Questionnaire. And if you look at the green area, this is the subjects that also had an improvement in their St. George's Respiratory Questionnaire and had an improvement in their 6-minute walk test. And we could not see a clinical correlation between the 6-minute walk test and the St. George's Respiratory Questionnaire.

We additionally did this evaluation in comparison to FEV_1 percent as a surrogate for the lung function. And also similarly, the area in the gray are subjects that had worsening in their FEV_1 and an improvement in their St. George's Respiratory Questionnaire. And then on the other side, in the green, is the patients that had improvement in both their St. George's Respiratory Questionnaire and their FEV_1. And, again, we had difficulty in seeing a correlation between the FEV_1 and the improvement in the St. George's Respiratory Questionnaire.

Now what I'm going to talk about is some of the subgroup analyses. And we'll start out with the U.S. versus OUS, because one of the things that we want to see is whether the effects are generalizable to the U.S. population.

So when we looked at the U.S. and OUS results, this was a pivotal study that was conducted both in the United States and OUS. There were 20 sites in the United States, and

there were six sites OUS that had subjects enrolling. There was comparable FEV_1 percent and predicted residual volume to total lung capacity ratio. But then there were substantial imbalances in the U.S. versus the OUS for certain baseline characteristics, and these included things like 6-minute walk tests, age, incidence of several comorbidities, their St. George's Respiratory Questionnaire scores, and RV percent predicted. And so this brings up whether these pooled results might not be generalizable to the U.S. population.

One of the things that was interesting was that when we looked at the control population in the U.S. versus the OUS, most of the decline was actually 22 m in the OUS population in the control group as opposed to almost a 1 m decline in the U.S. population. When we also looked at the crossover single-arm observational group separately, there was a 19 m decline in comparison to their previous 12 months in the crossover group in the U.S., in comparison to a 1 m improvement in the OUS group. And, of course, these were much smaller numbers in the crossover.

Now, when we looked at some of these results for the treatment minus the control -- and, again, these are the overall results for the total study population, and we're comparing the U.S. versus OUS. When we look at the various clinical endpoints that had been identified, for the 6-minute walk test, this was 6 m in the U.S. versus almost 32 m OUS. The percent change in the FEV_1 was a modest change of almost 5% versus almost 11%. There was an improvement in the St. George's Respiratory Questionnaire in both groups that was -- that did meet the minimal clinical important difference. And then when we looked at the responder rate, there was a difference between the U.S. and OUS of about 8% versus 17%.

Now we're going to look at some of these, another subgroup analysis based on the emphysema type. And the Panel will be asked to weigh in and discuss the effectiveness results for the homogenous and heterogeneous emphysema population.

Now, this study did enroll 77% with homogenous emphysema and 23% with heterogeneous emphysema. And as we know is that this study population is different than the population that was identified by the National Emphysema Treatment Trial to benefit from this type of treatment.

When we look at these results -- at this group of patients, there is really no differences in their baseline except some differences in the St. George's Respiratory Questionnaire. And when we looked at the results, the difference between the homogenous and heterogeneous group was 9 meters in the homogenous improvement versus 21 in the heterogeneous.

And then when we looked at the results separately in the single-arm observational study with the crossover, there was a 20 m reduction in the homogenous group in comparison to their previous 12 months. And the numbers in the heterogeneous group are much smaller, just because of the number of patients that were initially enrolled, but there was an improvement of 25 m in that small group of patients.

And, again, when we looked the treatment minus control for the homogenous versus heterogeneous for all our clinical endpoints, for the 6-minute walk test, there was a change of 11 meters in the homogenous versus a little over 27 m in the heterogeneous. For the other endpoints, for the $FEV_{1\%}$ change, 7% versus 9%. The St. George's Respiratory Questionnaire did meet the minimal clinical important difference for both subgroups. And then when we looked at the 6-minute walk test responder rate, this was 9% versus 13%.

And then what we'll do is next discuss the effectiveness results based on the residual volume cutoff. And, again, the Panel will be asked to discuss the analysis change for this group of patients and the impact of evaluating patients with residual volume of greater than 225 and then also the impact of excluding 25% of the study results.

Now, when we look at the residual volume cutoff, the residual volume has been

commonly used to evaluate for both air trapping and for hyperinflation. And this RV cutoff was changed from 225 to 175 after 54% of the subjects were enrolled. Again, these are all subjects that are very hyperinflated. They all have severe COPD. These patients all had similar baseline FEV_1. And for this RV cutoff, there was also no pre-specified hypothesis testing for this subpopulation with a multiplicity adjustment.

When we look inside this circle here, there is a -- this a graph, first, that is a cumulative between the group difference at 12 months. And it looks at the baseline residual volume versus the change in 6 months at 12 months -- 6-minute walk test at 12 months. And we were trying to see if we can see an area where you actually see a correlation between the RV baseline and where the 6-minute walk test can happen.

And when we looked at this circle, there's really no obvious change or an inflection point to really suggest that this is the point that we're going to see an improvement, and this is the point that we should be enrolling patients and so whether this is the cutoff that's actually clinically relevant.

We looked at the residual volume cutoff 6-minute walk test results, and as we looked at these effectiveness analyses, there's a lot of clinical uncertainties. When we look at the group with the residual volume of less than 225% -- again, these are subjects that are very hyperinflated. And one of the things that we saw was there was almost a 10 m decline in the treatment arm in comparison to the controls that did not change. And it was not clear why patients that are hyperinflated should actually worsen with this type of treatment within this subgroup.

When we look at the residual volume of greater than 225% separately in the crossover group, what we saw was that the subjects that had a residual volume of greater than 225% in the crossover actually had close to a 19 m decline, as opposed to the residual volume of less than 225 in the crossover that had a decline of 10 m. And this just added a

little bit more to our uncertainty based on these differences.

Now, when we look at the residual volume cutoffs for the coil minus control, and we look at the results for the clinical endpoints, for the residual volume of less than 225 versus the residual volume of greater than 225, there was a 13 m decline versus almost a 24 m improvement, and this is for the pivotal trial. For the $FEV_{1\%}$, there was a modest change of almost 3% versus 9%. The St. George's Respiratory Questionnaire did meet the minimal clinical important difference again. And when looked at the 6-minute walk test responder rate, actually the treatment arm did worse than the control arm. And the control arm did better than the treatment arm for the residual volume of less than 225% by 8% versus the responder rate in the residual volume of greater than 225% was 18%.

And now what I'm going to do is turn to some of the results beyond 12 months, just so we can look at the durability of effect beyond 12 months, since this is considered a high-risk device.

When we looked at the long-term effectiveness results, the data cutoff for what I will be presenting was July 17, 2017. And as has been previously mentioned, all the subjects exited the study -- all the control subjects exited the study at 12 months. The data that was available at 24 months was for 114 in the coil group and 26 in the crossover. And at 36 months, there was 49 in the coil group and 5 in the crossover, and as expected, not a lot of patients at 36 months.

When we looked at these longitudinal changes, there is no control beyond 12 months, and so which we have is the two lines here is the red is the coil and the green is the crossover. And so after 12 months, we're only looking at the coil treatment groups with the crossover and the subjects that were followed from the pivotal trial. And what we do see is a progressive decline in the 6-minute walk test at 24 months and 36 months. And so it's not clear that there is a durability of effect.

We also looked similarly at the $FEV_{1\%}$ change, and again, there's no control after 12 months, and what we're looking at is the coil treatment group and the crossover group. And, again, there's a progressive decline for these results at 24 and 36 months. And just to keep in mind, there's not a lot of patients yet at 36 months.

The St. George's Respiratory Questionnaire change, which was the other secondary endpoint, was also looked at. And there was a persistent effect at 24 months that still met the MCID. And then there was a slow worsening between 24 to 36 months.

So just to conclude on our effectiveness results, this pivotal study was powered based on the secondary endpoints, and so the primary endpoint should achieve both statistical and clinical significance. Some of the factors that might impact the estimation of the treatment effect may be the lack of blinding. The patients may be susceptible to the placebo effect, and investigators may exhibit treatment bias. Maintenance of pulmonary rehabilitation was encouraged and was asked at each visit, but we do not have the data on that, and so we do not know if maintenance of pulmonary rehabilitation had an impact on some of the treatment results in the first 12 months.

The applicant is basing the effectiveness analysis on the residual volume of greater than 225%, and so 25% of the data is excluded, and this is mostly in the United States. And then when we looked at the crossover results separately, we found that these results are not consistent with what was seen in the pivotal results, especially for the residual volume cutoff.

The pooled study results are statistically significant with uncertain clinical significance. And so these pooled results may not be generalizable to the U.S. population. And statistical significance was achieved for the primary endpoint in the ITT population with a nonparametric ANCOVA analysis.

And now what I'm going to do is present the safety results for the pivotal study. The

safety results in the crossover study were very similar to what was seen in the pivotal study. And when we look at the safety results, we're also looking at it in the context of what the benefit of the device is.

So when we look at the safety results outline, we'll be presenting the adverse events. The adverse events includes all events, and all subjects are counted at most for each event. So, for example, if a subject has recurrent COPD exacerbations, this will be counted as one.

The serious adverse events, and we're going to be focusing on the thoracic adverse events, are a subcategory of the adverse events. And then the major complications, which was the primary safety analysis but did not have a pre-specified hypothesis, is then a subcategory of the serious adverse events. Deaths are part of the major complication, but I will be talking about some of these deaths separately. And then we will talk about some of the other events, including things like hospitalization, emergency room visits, and unscheduled physician visits.

Now, when we look at the overall safety results, and this is for adverse events, serious adverse events, major complications for the percent of subjects, and the percent of events in the study, what we found was that these were all increased in the treatment arm in comparison to the control arm.

And when we look at the adverse events through 12 months -- again, all the subjects are counted at most once for each event -- adverse events that are relevant to COPD patients are things like COPD exacerbation, lower respiratory tract infections, which does include pneumonias, and hemoptysis were increased in the treatment arm. Also, some of the other adverse events, which are disease-related adverse events and related to quality of life issues such as cough and dyspnea, were also increased in the treatment arm in comparison to the controls.

And so these -- it's based on longitudinal studies for COPD. We also know that some of these adverse events are things that can contribute to worsening progression of the underlying disease. And some of these adverse events do not necessarily correlate with some of the results that we saw also in the St. George's Respiratory Questionnaire.

Now, when we look at mainly the serious adverse events through 12 months, the ones that were increased were COPD exacerbation, especially lower respiratory tract infections, with 24% versus 6%, and pneumothorax in the coil-treated group as opposed to control.

And then when we looked at the major complications -- and these have already been defined by the applicant, and I have listed them on the right side of the slide just for reference. And when we looked at these major complications, the mortality rate was comparable in both the control and the treatment arm. But I will go through some of the death reports a little bit separately. And, most notably, there was an increase in the lower respiratory tract infections between the treatment group and the control arm of the study.

Now, when we look at some of the mortality data a little bit closely through the first 12 months, the mortality rate was comparable between the treatment arm and the control group. And I will talk about the crossover group a little bit separately. But then when we looked at these deaths a little bit more closely, the deaths that were seen in the coil treatment group were reported by the investigators as being potentially or possibly related to the device or the procedure, whereas half of the deaths that were seen in the control group, as expected, were related to COPD exacerbations.

Separately, in the crossover study, we also looked at some of the deaths there, and two of these deaths were related or possibly related as reported by the investigators to the procedure or device. And then I'll go through some of the other deaths that were also reported as possibly related.

When we look at the pivotal treatment arm mortality details, what's in the red box are the subjects that died with possibly related to procedure or device. The first is a subject that had a intra -- a procedural pulmonary hemorrhage. Another subject died within a week that developed progressive right upper lobe opacification respiratory failure. The next one died a little bit after a month, after complications of a pneumothorax and subsequent respiratory failure. There was another subject that died a little after 2 months with progressive right upper lobe infiltrates that started about a month after the procedure. And then there were the three others that had complications of pneumonias and COPD exacerbations.

The other three that was reported as unrelated, one was a subject that had subacute endocarditis and died under 3 months after the procedure. Another had sigmoid perforation, and this subject had been treated with steroids prior to coil implantation. And then another subject that had a much later death related to metastatic bone cancer that was definitely unrelated.

And when we look at the crossover device-related mortality, two of these deaths occurred under 30 days, which actually triggered the stopping rules for the study for the DSMB to review before the study could be resumed again. And one was a massive hemoptysis that occurred about 10 days later, and another patient that had a post-procedural pneumothorax and then had complications and died about 17 days later. And then some of the other causes of deaths that were reported as possibly related included a subject with COPD exacerbation and then a couple of pneumonias.

We have some limited autopsy results based on some of the deaths that we have seen. And one of these autopsy results was on a subject that had progressive right upper lobe infiltrates that started 30 days after the procedure. And this autopsy did show extensive fibrosis of varying age and architecture at the sites of the coils in the right upper

lobe.

One of the crossover deaths that happened with massive hemoptysis, and the patient, the subject died about 2 months later, also showed extensive fibrosis with the right lung that was completely fused to the apical chest wall, and there was necrosis at the site of the coils.

Another crossover death with a massive hemoptysis showed diffuse hemorrhage and coil hematomas, and a second opinion had been requested on this, but the gross specimens were not available. And so these limited autopsy results indicate that the local reaction may still be a serious adverse event.

There is one case here, and this was a crossover death that was a complication of the post-procedural pneumothorax, and just, as you have briefly heard, the applicant has said that these coils can be removed up to 2 months after the procedure if medically indicated. These recommendations for coil removal are based on animal studies. And during the clinical trial, there was no actual coil removal in any of these subjects with severe emphysema. And so the Panel will be asked to discuss the safety of coil removal in subjects that have, patients that have severe emphysema, since there's been no coil removal during the study.

Now, after the study was completed, the clinical events committee, the CEC, went back and adjudicated some of the pneumonias as this new entity called coil-associated opacities. And they also provided definitions that the applicant has already reviewed, and it's on the right side of the screen, with the definitions of a pneumonia versus the definition of a coil-associated opacity.

After the study was completed, 14 out 40, 35%, of these events in the treatment group were adjudicated as a coil-associated opacity by the CEC. And we do need to keep in mind that whatever, whether it's pneumonia or a coil-associated opacity, these are still

serious adverse events.

And some of the concerns, as we looked at the adjudications was -- with the retrospective adjudication was that in some of these there was insufficient clinical details. Subjects had been treated with antibiotics. The chest x-ray results were not provided, and so you do need some chest x-ray results for some of these diagnoses. And based on some of the adjudications we reviewed, these were sometimes difficult to distinguish. And I will be providing some examples of these adjudications.

When we looked at some of the pneumonias that were readjudicated as CAO, and based on what has been provided as a definition, this included subjects with purulent sputum that would be defined as a pneumonia, sputum cultures that were positive. And then there were other subjects that had left-sided coil implants but had right-sided infiltrates that were said to have a coil-associated opacity. And then the coil-associated opacity supposedly happens within the first couple of months, and then there was a patient with fever, chest pain, and that was also readjudicated as having a CAO at 240 days post-procedure.

There were also some examples of cases that could not be adjudicated. And these included subjects that had positive blood culture and sputum cultures that would have met the definition of a pneumonia. These were again patients that had purulent positive cultures. There was a patient that had increased sputum production and a change in the sputum.

And so essentially what this means is that we're really not sure what the true definition is at this point. The other is, is that this coil-associated opacity is a serious complication. We had one patient that was adjudicated as having a coil-associated opacity that died 6 days after the second procedure, with right upper lobe opacification, another subject that received 5 weeks of IV and oral antibiotics with 3 weeks of IV antibiotics and

was also adjudicated as having a coil-associated opacity.

We also looked at hospitalizations, emergency room visits at 12 months, and unscheduled physician visits. There was really no difference in the unscheduled physician visits. When we looked at the hospitalizations and emergency room visits for the coil-treated group in comparison to the control, these were all increased, as far as the hospitalization and the emergency room visits, in comparison to the control.

We separately looked at the crossover group, and for the crossover group, what we did was we compared this to the prior 12 months, so essentially when they were in the study as a control prior to coil implantation. And, again, the hospitalization and the emergency room visits were increased in comparison to their prior 12 months.

What we need to keep in mind also is that things like -- events like COPD exacerbations, pneumonias, these are all things that can lead to frequent hospitalizations with a downward spiral for these patients with the progression of their disease and then worsening quality of life.

We also separately looked at oxygen use that we had available for some of the complete cases. And we looked at the coils in comparison to their baseline, the controls and the crossover, again, in comparison to baseline, and we did not see a difference in the total oxygen utilization for the total use, for the at rest and during exercise.

So when we look at the safety conclusion, the mortality rate was comparable between the treatment and the control arm. However, the treatment deaths were potentially related to device complications. We also saw increased COPD -- increased serious adverse events that were higher in the treatment arm, and these included events such as COPD exacerbations, pneumonia, pneumothorax. The coil-associated opacity is not well characterized, and this can be a serious complication. There was increased hospitalization and unexpected emergency room visits in the treatment arm.

Also, what we found was that the St. George's Respiratory Questionnaires really did not correlate with the reported COPD adverse events, such as cough, dyspnea, COPD exacerbations, pneumonia, in the study. And, conversely, we also did not see a decrease in COPD exacerbation with treatment.

Briefly, I'm going to just go over some of the published literature. The RENEW study publication was actually published by the investigators in *JAMA*, and their conclusion was that the use of the endobronchial coils, compared with usual care, resulted in an improvement in median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications, and further follow-up is needed to assess long-term effects on health outcomes.

Additionally, there has been another randomized controlled trial that was conducted in France, and this was conducted by one of the original investigators in the RENEW trial. And in their conclusions, what they stated was that in this preliminary study of patients with severe emphysema, followed up for 6 months, the bronchoscopic treatment with nitinol coils compared with usual care resulted in improved exercise capacity, and then further investigation is needed to assess durability of effect.

We did look at the REVOLENS study as well, and the data that we had for review was based on publication only. And so we had no case reports or line data. In this study there was a lack of blinding, so we don't know what the effects on the 6-minute walk test and St. George's Respiratory Questionnaire were. The crossover results were not provided. There were unknown differences in the treatment decisions. There were unknown protocol and statistical analysis plan modifications.

There was conflicting information about the handling of missing data between the published SAP and the main body at the publication. And in this study, the secondary endpoints were all exploratory, with no pre-specified multiplicity adjustment. Some of

these endpoints were a little bit different. There was a different randomization scheme, with a ratio of one-to-one in blocks of four, with a potential bias to the fixed block size.

And so, in conclusion, this is why we're here, and we are going to be asking the Panel input about some of the clinical issues that we had as we went through our reviews. And some of these included what's the significance of the safety data in a risk-benefit analysis, what are some of the factors that may impact the estimation of the treatment effect? Since we did not have data on the maintenance pulmonary rehabilitation, and it was encouraged during the study, did this have any effect on any of the results that we saw?

There were some differences in the results that we saw between the pivotal trial and the crossover trial. Did the prerequisite for pulmonary rehabilitation before the pivotal trial but not the crossover have an impact on the results? Then there was the effect of the lack of study blinding on the SGRQ results. These results did not correlate with the increased dyspnea, COPD exacerbations, cough, pneumonias, and hospitalization.

One of the treatment decisions was target lobe selections. That has not been tested outside of a central core laboratory assessment, and so how will this translate into real world use?

Some of the other clinical issues included that there were clinical uncertainties in the study results. There were exploratory endpoints that were looked at, including the residual volume reduction, and there's really limited data on the clinical significance and what level of reduction would correlate with meaningful anchoring for patients. The endpoints did meet statistical significance, with uncertain clinical significance.

Based on the comparison to controls, the OUS controls did worse than the U.S. controls. There was no improvement in the 6-minute walk test in the crossover, and then the crossover subjects that had a residual volume of greater than 225% actually did worse than the subjects that had less than 225%. Some of these pooled results may not be

generalizable to the U.S. population.

Then what's the effect of the emphysema heterogeneity on the study outcome? The study population that was looked at here was different than the population that was identified by the National Emphysema Treatment Trial to benefit from lung volume reduction. What's the impact of the data cutoff? And the observational crossover study results were not consistent with what we saw in the pivotal study.

Thank you.

And now I will turn this to Dr. Heather Benz, who will be talking about the patient preference study.

DR. BENZ: Good morning. My name is Heather Benz. I'm a patient preference reviewer at the FDA and an investigator on patient preference studies led by the FDA.

The FDA has released guidance about patient preference information and how these studies can be submitted to the FDA to inform a benefit-risk assessment. Well-designed patient preference studies can provide valid scientific evidence about patients' risk tolerance and perspective on benefit. The guidance included a variety of recommended qualities of patient preference studies, and today we'll focus on those that go into good study design, including effective benefit-risk communication, minimal cognitive bias, and relevance to the benefit-risk assessment. In the guidance, the Agency encouraged early interactions in order to receive feedback about these good study qualities.

The applicant already showed you what the patient preference study looked like. You'll recall that different attributes were shown to the patients responding to the survey, so we'll compare those to the RENEW clinical trial experiences. You'll recall that in the clinical trial there were two arms. One received optimal medical care; the other received optimal medical care plus the coil.

In the patient preference survey, respondents were presented with three treatment

options that were one of the attributes they looked at. These were medicines, implantable lung device, and lung surgery. There were descriptions about all of these treatments prior to the preference survey. And the implantable lung device description did include the mention of medication, continued medication; however, these were the labels that respondents saw during the survey, and respondents may have incorrectly assumed that implantable lung device included a potential decrease in the amount of medication they were taking.

In the RENEW clinical trial, you've heard that one of the secondary outcomes was the St. George's Respiratory Questionnaire. This has 3 domains over 16 questions, including symptom frequency and severity, activities and breathlessness, and impact. Section 2, part 2, one question is shown in the bottom of this left-hand blue box, and that was used to represent the treatment benefit to respondents of the patient preference survey. In the clinical trial, 45% of the treatment group experienced the one-step improvement in this section in this part that was represented as the benefit in the patient preference survey.

You saw that the patient preference survey included a variety of risks that were presented to patients, including pneumonia. In the clinical trial, a 17½ percent additional risk of pneumonia requiring hospitalization through 12 months was reported, and there was also a 21% additional risk of lower respiratory tract infections, including pneumonia, through 12 months. In the patient preference study, the additional risk of pneumonia that was presented to respondents was from 0 to 15%, and there was not information presented on other pneumonia adverse events.

So to summarize the study design concerns, there may have been a misalignment between patient preference study benefits and risks and what was seen in the clinical trial. So respondents may have assumed fewer medications were required with the lung device. One question from the overall SGRQ was used to represent the coil benefit, and the risks

presented in the patient preference study do not map directly to the clinical risks. Pneumonia requiring hospitalization in the clinical trial was greater than the risk of pneumonia requiring hospitalization that was presented to the patient preference survey respondents, and additional risks, such as overall risk of lower respiratory infection and risks of serious flare-ups, weren't presented in the patient preference survey.

When we look at the results, we see that there were differences in preferences between respondents recruited from the RENEW trial sites and respondents recruited from one non-RENEW trial site. None of these respondents had had a coil procedure, lung procedure, lung surgery or lung transplant, so all were naive. However, they were recruited from different sites, and 165 patients were recruited from a variety of RENEW trial sites, and 37 patient preference study respondents were recruited from a non-RENEW site.

You see in this plot one set of preference weights for one attribute in the preference study. The preferences between the two groups for all the rest of the benefits and risks that were discussed were very similar. However, for the type of treatment, non-RENEW site respondents had preference weight that was highest for medicine, so most preferred medicine. Next was implantable lung device, and the least preferred would be lung surgery.

For respondents from RENEW sites, we see that implantable lung device is the most preferred, and medicines are preferred at the same amount as lung surgery.

Because it's unclear what was driving these differences in preferences between these two groups, and it's unclear whether the relative proportion of these two groups is generalizable to the patient population for this device. If these two groups' preferences are pooled without weighting, the preferences may not be generalizable to the overall patient population for this device.

Finally, we looked at the results from the clinical study to better understand this single benefit attribute that was used in the preference survey. So in this correlation plot,

you'll see the change in SGRQ question 11, that's the question that was used in the preference study, compared to the change in FEV_1 at 12 months. And there's a Spearman correlation of less than 0.2 between those two outcomes.

So we conclude that the results of the preference study are intended to show that a substantial proportion of well-informed representative patients would accept the probable risks in exchange for the probable benefits of the device. A patient preference study for regulatory applications includes the benefits and risks that will be relevant to the benefit-risk assessment. So when the patient preference study benefits and risks do not map to the clinical trial outcomes, the patient preference study has limited application to the specific device. Therefore, the applicant's patient preference study results may not be relevant to this benefit-risk assessment.

Now Dr. Bahadori will briefly describe the proposed future postmarket study.

DR. BAHADORI: Thank you.

Just as a reminder, the discussion of a postmarket study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective. The plan to conduct a postmarket study does not decrease the threshold of evidence that will be required by the FDA for device approval. The premarket data that is submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit-risk balance.

You've already heard about the applicant's proposed postmarket study. This is a new enrollment with 300 subjects, and they are proposing to look at a primary effectiveness endpoint of a change in St. George's Respiratory Questionnaire at 12 months, and then to look at the composite respiratory-related adverse events. And so the Panel will be asked to discuss what type of a postmarket study may be appropriate, including that whether a

registry would be the way to go to be looking at this type of a device. And so that's what the Panel will be asked to weigh in as far as post-approval.

Thank you. And thank you for your time.

DR. NATHAN: Okay. I'd like to thank the FDA speakers for their presentations. Does anyone on the Panel have a brief clarifying question for the FDA?

Yeah, Dr. Dodd.

DR. DODD: I have a few questions, one for the statistician.

I just wanted to clarify. My understanding is that the SAP, the statistical analysis plan, was amended without looking at the results in the study. I just want to be clear on that. And the decision of using the nonparametric ANCOVA was made without looking at the data, as well as the change to the RV was not made based on these data but from a European study. Is that correct understanding?

DR. QU: According to the Agency's knowledge, the finalized SAP was done 2 days prior to database lock. Since this is an unblinded study, the Sponsor were required to do the annual report. So each year they were able to look at the study data. But 5 months after database lock, the Agency received a notice of SAP change.

DR. DODD: Okay. So then it is unclear?

DR. QU: Yes.

DR. DODD: Okay. Thank you. Another question relates to the assessor blinding, and what checks does the FDA or what do you know about how assessor blinding was maintained in the course of the conduct of the study?

DR. NATHAN: Just as a reminder, for the transcripts, please identify yourselves before and after and answering the questions as well. Thank you.

DR. QU: So this study, based on the Agency's knowledge, the Sponsor did not conduct any blinding assessment because this is unblinded study.

DR. DODD: Lori Dodd again.

So I'm trying to clarify, the study had a blinded assessor for the 6-minute walk test. So my question is how can one be sure, operationally, that because the patient knew what treatment they had received, that there was no exchange of that information and that the assessor remained blinded during the evaluation?

DR. QU: Yeah, this is a good question. From the Sponsor's report, there is a one U.S. site that the assessor was accidentally not blinded. So this kind of a protocol deviation.

DR. BAHADORI: So just to add to that is that we have -- we take what we're told as far as the blinding or unblinding. And so for the testing, there's a protocol for blinding that they had, and that's what we were informed about. But other than occasional inspections, we really don't have a way of assessing this separately.

DR. NATHAN: Okay. Dr. Cassiere?

DR. CASSIERE: Hugh Cassiere from North Shore.

Just a quick question, why the disagreement to have a sham control in this group? Is it your feeling that the bronchoscopy is going to cause the side effects?

DR. BAHADORI: So this goes back a long ways in the investigational device evaluation plan that had come in many years ago, and I believe that the dates that we saw was 2010. And at the time there had been a brief discussion about sham bronchoscopy, but I believe the decision was made between the company and the Agency that they were not going to do a sham control. That's about all I can give as far as that background.

DR. NATHAN: Dr. Ballman.

DR. BALLMAN: Hi. Karla Ballman.

Just a quick clarification question: So during the pivotal trial, patients were encouraged to do rehabilitation. And during the crossover, they were not?

DR. BAHADORI: So pulmonary rehabilitation was required for entering into the

pivotal trial. It was not required -- it was required initially for before they entered into the study, but a repeat program was not required. All the subjects in the study, whether it was crossover or the pivotal, were encouraged to continue with a maintenance program. The only -- and at every -- at most of these office visits, they were also asked about a maintenance program, but that data was not available to us for review.

DR. NATHAN: Dr. Schoenfeld.

DR. SCHOENFELD: So I'm a little confused about slide number 43 and 44 because they seem to be inconsistent. And I'm just trying to understand. Maybe I don't quite understand the slides. So that shows -- I assume that red line, if we look at this median, you know, difference, that that would imply that the difference was change in -- so how do we interpret that? It says cumulative -- so if interpreted as a cumulative different -- cumulative value, that would be the difference at -- that 20 would be the difference at that value. But then when we go down here to less than 25, there was a negative difference at that value.

I'm not sure just how this top slide is consistent with the bottom slide. And I'm afraid that I don't really understand the top slide.

DR. COURSEY: I think this slide on the slide 43, showing the cumulative difference, so it means that every point is getting to the -- whenever -- when you go from the baseline residual volume and when you cross it, it shows all the subjects who has greater than --

DR. SCHOENFELD: Oh, it's greater than?

DR. COURSEY: So yes. So when you look, it will be showing all the data. It's the cumulative --

DR. SCHOENFELD: Oh, I see. So at the bottom, it's -- so if I understand it, at the bottom, it's everyone who is -- the last point, the point down at 180, it's everyone whose baseline residual volume was --

DR. COURSEY: Greater than --

DR. SCHOENFELD: -- represent -- as the whole trial.

DR. COURSEY: For greater than 180, yes.

DR. SCHOENFELD: And then at 225, it's everyone who is greater than that. So it's not in contradiction with the graph that the Sponsor showed, which showed an increased benefit as you get higher and higher.

DR. COURSEY: What this --

DR. SCHOENFELD: It's not -- it doesn't contradict that fact.

DR. COURSEY: What the Sponsor had showed was, if I'm not mistaken, it was the group difference.

DR. SCHOENFELD: In groups, yeah.

DR. COURSEY: The Sponsor -- it's --

DR. SCHOENFELD: They grouped the subsets by residual volume. And they showed that the biggest different -- that the differences go up, not quite linearly, but sort of more or less up as you get higher and higher residual volume. Okay. So now I understand the slide, and I just wanted to make it -- clarify what the slide means because it just wasn't --

DR. COURSEY: We have a slide --

DR. SCHOENFELD: -- really simple to understand.

DR. COURSEY: So we have a slide 38, extra slide 38, that shows actually, those --

DR. SCHOENFELD: Because, ideally, the way you would do this -- the way I would do this, I mean, there's a million ways to do this, is I would smooth the data using some kind of smooth at all the points to get a continuous graph of how it worked over differences.

DR. COURSEY: What the Sponsor had showed is this.

DR. SCHOENFELD: Is this.

DR. COURSEY: Basically grouping, because we are looking at the subjects who have greater than certain residual. It is not -- you're not looking at each subpopulation.

DR. SCHOENFELD: Yeah. So the argument -- so the purpose of this slide 43 is to say there's nothing really magical about 225. You know, it's still true that probably people with lower RVs are likely to have worst risk-benefit than people with higher, but there's no magic at 225, which is what you'd expect. There is never any magic in any -- you know, dichotomania is usually dichotomania. It's usually there's no magic in a number. So that, at least now I understand that graph. Thank you.

So I have another question, and this has to do with just the whole issue of what is it, the R -- the SG, St. George's questionnaire versus the actual clinical results. What would be nice to look at, I don't know if you've done it or maybe the Sponsor has done it, is just a graph or correlation between the change in St. George and the change in residual volume, because that goes to the true surrogate marker here, which is change in residual volume. And that would only be interesting in the treatment group.

So was there any -- because if there's no association between those two things, then really one would wonder whether the St. George is a placebo effect, while if there's a correlation, it would mean -- be less likely that it's a placebo effect. I'm wondering if anybody has that graph?

DR. NATHAN: I think that the Sponsor did show that in response to my question.

DR. SCHOENFELD: Did they show that?

DR. NATHAN: I believe so. And we can always show it again --

DR. SCHOENFELD: Yeah, so I'd like to --

DR. NATHAN: -- in the afternoon.

DR. SCHOENFELD: Probably should show it again in the afternoon. And then the other question is the same as -- really the same as Lori's question, and I still don't think we -- it's really understandable. And maybe in the afternoon the Sponsor can address this, but it's just clearly if you said, well, I'm going to do two statistical tests and I'm going to take the

best one, you would -- your Type I error would be wrong.

So tests where you do a pretest, you know, I'm going to test this and then do this, they're a little -- they're all -- the Type I error is a little bit hard to deal with. So I was curious as to what the exact procedure was. Now, what you said is, of course, is that whatever the exact procedure was, the Sponsor kind of knew early results because it was an unblinded study, is what you're saying.

Was there any attempt to keep the results from the investigators and from the Sponsor? Sometimes there's a separation of the data center and the clinical control so that it was -- so I mean, we can only be subjective about whether the Type I error was correct, unfortunately. But it would be good to get some more information on that for at least the statisticians that worry about these things.

DR. NATHAN: Sorry. Before you respond, please identify yourselves on both ends, from the Panel and the FDA.

DR. COURSEY: Yes, hi. And Derya Coursey. I'm the lead reviewer.

We did not have the details of whether or not how unblinded the investigators were. I think that might be an appropriate question. Maybe the Sponsor might have the up-to-date information. But we do receive annual reports for IDE submissions that we have that will summarize the results of the data. And so we do not have the extensive details. But I would like to also point out that residual volume change at 12 months was an exploratory endpoint.

DR. SCHOENFELD: Yes. I understand.

DR. COURSEY: It was not pre-specified with multiplicity testing, so there was no other adjustment.

DR. SCHOENFELD: No, I'm not interested in that. I just wanted to get -- I think we need to get some notion as to how seriously we should take the significance of the primary

endpoint given that there was a change in analysis plan, that may have been based on seeing the data before you change the plan. It's hard to say. I mean, even if you don't see the data, I don't know what the procedure ought to be for having a lot -- if there's skewness, I'm going to do this; if there's not skewness, I'm going to do that. Was there a test, formal test of skewness? And so on. I'm just curious what was actually done.

DR. QU: Hi. This is Yanping Qu, FDA statistician. In the review practice, we usually require the Sponsor to send the draft SAP when the IDE was approved. And any change based on the SAP should be reviewed further by Agency. For this study the Sponsor has the original SAP in 2013, and later on they made multiple changes on their SAP. The finalized SAP was done 2 days before database lock; however, 5 months later, FDA received the Sponsor request about the change on SAP.

DR. NATHAN: All right. Let's move on. Ms. Barnes, you had a question?

MS. BARNES: Yes. It's a question related to the patient preference study.

And my question -- a couple of things. One, the study, if I understand it, was done after the data was collected and analyzed, if that's correct. And then the second part is, since this kind of -- first of all, I think it was voluntary as well. So it's voluntary. It's a new type of data collection from a patient-reported type of situation, in this case, a survey. And it's also, there are new sort of guidelines in place for applicants to use for that, but it's all sort of new.

So the question is would you expect the applicant to have been closer adhering to the new guidelines? And are the new guidelines sufficiently clear, especially given that it's a new type of task?

DR. BENZ: Thank you. And this is Heather Benz, patient preference study reviewer.

Yes. We collaborated with a variety of external stakeholders to ensure that information is available that is helpful to applicants submitting a patient preference survey.

A public-private partnership with the Medical Device Innovation Consortium has provided a framework and additional resources to sponsors planning a patient preference survey. And this includes study design considerations and a variety of opportunities for sponsors to come to the FDA with a pre-submission to further discuss the patient preference survey.

In this case there was one pre-submission, and the FDA encouraged additional discussion about the patient preference survey design, but no further pre-submissions came in after that.

DR. NATHAN: Sorry. Go right ahead.

DR. YARMUS: All right. Thank you. Lonny Yarmus.

I had question about adverse events. So you had mentioned the definition was per patient. And I'm curious, was the FDA given information from the Sponsor regarding data of per event adverse event? And do we have that?

DR. BAHADORI: Lila Bahadori from the FDA.

Yes. We did also have information on per events

And slide 43, por favor.

DR. COURSEY: Slide 43. It is in the extra slides.

DR. BAHADORI: Slide 43.

DR. COURSEY: Extra slides.

DR. BAHADORI: So some of these events were increased. Some have been correlated with the percent of subjects.

DR. COURSEY: Lower respiratory?

DR. YARMUS: I guess --

DR. BAHADORI: And is there one that you wanted in particular?

DR. YARMUS: Yeah. Well, I mean, so I guess the, in terms of -- I mean, you know, hospitalizations, ER visits, and then -- those would probably be -- and exacerbations,

between the control and the treatment arms.

DR. BAHADORI: So we don't have the details about the causes of the hospitalizations. You know, at this point we assume that some of these were COPD-related, but we don't have the actual details on that.

DR. NATHAN: Thank you.

Steve Nathan. I have a question myself.

We saw some data going out to 24 months and I believe 36 months. What I don't think we saw were the number of patients who were available at those time points. And if there was any missing data for any of the outcome measures, how was this handled?

DR. BAHADORI: Lila Bahadori from FDA.

So there was a slide that just gave the long-term effectiveness results with the cutoffs. And at 24 months, we had 114 in the coil group and 26 in the crossover, and at 36 months, 49, so much smaller at 36 months, 49 and then 5 in the crossover.

DR. NATHAN: So for something like say the 6-minute walk test, did you just take the patients who were available at that time frame? Or did you take last observation carried forward?

DR. BAHADORI: This was the patients that were available at those time points.

DR. NATHAN: Because then that might be misleading because we don't know what their contribution was at the timed visit before, so any drop-off, I'm not sure how we can evaluate that appropriately, if it's just a subset of the patients who had been in the prior time period.

DR. BAHADORI: Correct. This was the data that we had available to us.

DR. NATHAN: Okay. Thank you.

Dr. Carvalho, you had a question.

DR. CARVALHO: Thank you. This is Paula Carvalho.

I'm wondering if the FDA and the Sponsor agreed on the severity of adverse events. The one I'm concerned about is pneumothorax. So a severe pneumothorax would be one that would require a chest tube for 7 days or so. Yet, in this patient population, a much smaller pneumothorax can go a long way for morbidity. And so I wonder what discussion was held about the classification.

DR. BAHADORI: Unfortunately, I don't have all the details of the initial discussions because this would have been in the setting of the investigational device exemption approvals that went on back in 2010. All these events are always discussed in detail. And usually when these IDEs are reviewed and approved, it is based on safety only. And so any safety events is discussed in detail. But I can't give you the exact background as far as 7 days versus 5 days versus 2 days.

DR. NATHAN: Dr. Dodd.

DR. DODD: Thank you. Lori Dodd again.

I have a question about surrogacy. So if the FDA could just give me a little bit of input about how to think about what the 6-minute walk test is indeed a surrogate for, and what the -- if there are any guidance documents about this. Is it for exercise capacities? Just because it gets a little more complicated thinking about this as a surrogate endpoint when we begin to balance the risk-benefit tradeoff.

DR. BAHADORI: So a lot of the surrogates are based on publication and what's looked at for COPD studies. They're not always the best surrogates, but the 6-minute walk test is looked at as a surrogate for the exercise capacity, and that's how it was evaluated in this study. The FEV_1 percent, again, which is not necessarily the best surrogate, is what was used as the surrogate for lung function. And then the St. George's Respiratory Questionnaire is a surrogate for quality of life. And these are what are usually looked at in most COPD studies.

DR. DODD: Okay, so just to --

DR. BAHADORI: Lila Bahadori, sorry. I didn't identify myself.

DR. DODD: Just to finish then, so there's no concern that the treatment effect, as captured by the surrogates here, wouldn't reflect a treatment effect as captured by the true clinical benefit endpoint? I mean, you think those things should carry over?

DR. BAHADORI: As part of the study. I mean, I won't -- Lila Bahadori. Sorry.

As part of the study, I can't say that there's never a question of a treatment effect that might not be captured, but this is how these studies are designed. And whether it's drugs or devices, these are the endpoints that are typically looked at for treatment effect.

DR. NATHAN: Okay. I'm looking around amongst the Panel. We have another question. Please go ahead.

MS. BROWN: Debbie Brown.

So given that residual volume is a good measure of the reduction of hyperinflation, I'm wondering if you looked at baseline residual volume as compared to changes in residual volume in the study?

DR. BAHADORI: This is Lila Bahadori.

So the residual volume is an indicator of hyperinflation, and there is no real -- there is a reduction of residual volume in the pivotal study and in the crossover. But when you look at this reduction in the residual volume and you look at the various objective parameters, they don't necessarily correlate. For example, in the crossover, you see a reduction, but then the objective parameters are still about the same.

There is little information on the minimal clinical important difference, as far as what residual volume reduction is sufficient and might be important. There's one publication actually from one of the investigators from the Netherlands and his group, and they looked at residual volume reduction over a 1-month period in trying to anchor this to some of

these objective endpoints. But there's not enough information beyond that.

DR. NATHAN: Any other questions from the Panel?

Yeah. Go ahead, Dr. Chen.

DR. CHEN: Alex Chen.

Just a clarification on the device-related mortalities. These are self-reported by the investigators at each site in terms of linking a mortality to possibly or probably device related. Are these reviewed separately by the data safety monitoring board as well to sort of confirm? I'm just trying to understand, you know, complications occurring 150 days or 250 days after the procedure being tied as likely related to procedure, or probably. Any clarification there?

DR. BAHADORI: This is Lila Bahadori from FDA.

All these death reports were reported by the investigator, and there was a review by the CEC, DSMB as well, as far as we know.

DR. NATHAN: Ms. Barnes.

MS. BARNES: Theresa Barnes, patient advocate.

Quick question on the -- some -- one of the -- or a couple of the deaths. I think, in the autopsy results, it showed some fibrotic response. I'm assuming that's around the coil sites, but was that -- was fibrosis an exclusion for the criteria that you saw? And I noticed that most of the U.S. patients had four -- could be allowed four comorbids in the study. So I don't know if there were any patients who had preexisting fibrotic issues or whether this was like if it was visible in the CT scans that were done initially and if that was evaluated or not or whether these -- none of these patients had any sort of fibrotic response prior to the coils but then had fibrotic tissue surrounding the coil sites at autopsy.

DR. BAHADORI: This is Lila Bahadori from FDA.

So several parts to your question. As far as the exclusion criteria, pulmonary fibrosis

was not part of the exclusion criteria. But all of these patients had CAT scans done prior to being enrolled in the study. And so if there was a situation of a patient having pulmonary fibrosis, that would also be picked up on the CAT scans. And so these -- the applicant did show one CAT scan example of what may be fibrosis, and they may be difficult to distinguish, but these are at the site of the coil. And the autopsy results were -- we had very limited autopsy results, obviously. And so this is based on just the autopsy that we had, and this was at the site of the coils.

DR. NATHAN: Dr. Hawkins.

DR. HAWKINS: Randy Hawkins.

So I believe you reminded us that the St. George's Respiratory Questionnaire improvement was maintained by 12 months, that the improvement in FEV_1 and the 6-minute walk was not, by 12 months. I think that's what you said. If that's true, do we have any other independent information beyond that? Does the FDA have information about these three parameters beyond the 12-month?

DR. BAHADORI: I'm sorry. I misunderstood the question.

DR. HAWKINS: So I believe that you told us that the improvement in the St. George's questionnaire in the treatment group was maintained at 12 months, but that the improvement in FEV_1 and the 6-minute walk that we saw early on was not. Is that true?

DR. BAHADORI: Yes. That is true. Lila Bahadori.

DR. HAWKINS: So my question was, do we have any information, does FDA have information beyond 12 months?

DR. BAHADORI: Yes. I also presented three slides, both for the FEV_1, the 6-minute walk test, and the St. George's Respiratory Questionnaire, beyond 12 months. And the FEV_1 and the 6-minute walk test on -- these are slides 48, 49, and this one, 50. And the -- beyond 12 months, there was a persistent improvement in the St. George's Respiratory

Questionnaire on the subjects that were available, the other two having progressive decline.

DR. NATHAN: I'm sorry. We have Dr. Pichurko first, and then we'll come back to you.

DR. PICHURKO: Bo Pichurko, Cleveland.

I have a question about the informed consent process at the entry to the study. Does anyone present here know whether or not the issue of whether entry into the current study and treatment would affect potentially subsequent decisions for other forms of treatment for advanced emphysema, like surgical lung volume reduction or transplantation? Was it discussed, was it not, or do we not know?

DR. BAHADORI: So for -- this is Lila Bahadori from FDA.

So for entry into the study, if somebody had had a -- been either part of a prior study, for example, valve or a lung volume reduction surgery, they were excluded from the study. There was nothing that they could not go on to have any other procedure done, including transplant, after the study.

DR. NATHAN: Okay. We'll take one more question from Ms. Brown.

MS. BROWN: Debbie Brown.

Could you put the 24-month slide up again? Oh, I'm sorry. I don't know the number. So I'm curious, given the NETT trial results, wouldn't we expect the 6-minute walk test to be going down over time so that this -- my understanding of this therapy is that it's going to improve things, but it's not going to stop disease progression. So wouldn't we expect, out at 24 months, the curve to go down? So -- and it's hard to put in context without a control group at 24 months.

DR. BAHADORI: This is Lila Bahadori from FDA.

So part of COPD, there is a progressive decline. And there is no control group for

comparison. Is this decline different than the natural progression of the disease at this point? We don't know without a control group to evaluate. In comparison to studies from lung volume reduction surgery that we have looked at, there seems to be some persistence of the improvement in the 6-minute walk test after 5 years in the literature from lung volume reduction surgery.

DR. NATHAN: I'll just make one point because this is a question I asked earlier. Steve Nathan, once again.

I found a slide like this somewhat difficult to interpret, because if you look at 12 months versus 24 months, we don't know the *n*'s. And it's only -- there could have been 100 patients at 12 months and 50 patients at 24 months. So there's missing patients, might have been great responders, which might have brought the curve up. More likely they were not very good responders, which could have taken it further down. So it's kind of difficult to interpret data without knowing that.

All right. We're at the point now where we will break for lunch. Panel members, please do not discuss the meeting topic during lunch, amongst yourselves or with any other members of the audience. We will reconvene in this room at 1 p.m. Please take any personal belongings with you at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

For the Panel members, there is lunch for us in the Gaithersburg Room on the lower level. Is that correct? Thank you very much.

(Whereupon, at 12:01 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

DR. NATHAN: Okay. It's now just after 1 o'clock, and I'd like to resume this Panel meeting. We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Washington will read the Opening Public Hearing disclosure process statement.

MS. WASHINGTON: 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 of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with the attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, 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 statement, it will not preclude you from speaking.

FDA has received five requests to speak prior to the final date published in the *Federal Register.* Each speaker will be given 5 minutes to speak.

DR. NATHAN: Okay. The first speaker is Ms. Eileen Wilson.

Please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

MS. WILSON: Oh. Am I okay? Should I just start now?

Good afternoon. My name is Eileen Wilson, and of course, I'm here -- I have COPD with severe emphysema. And I'm here to be considered as a candidate for the coil procedure.

I have met a few people that have already had this done, and they are raving about it and saying how wonderful their life has been for them. They've got quality of -- a little quality of life back to them.

My days -- every day -- every morning, when I get up, I can't -- I get up and I go out, and I'll make my coffee, and then I will do all my medications. And then I look forward to going to bed that evening because that seems to be the only place I can go to be relaxed without breathing so heavy. I can't do much anymore. And if it wasn't for my husband -- he does everything, almost, for me. And so I really, really want so badly to have something like this done for me, this treatment, because there's nothing else out there for me. And I would really like to be considered.

And I have a wonderful doctor, Dr. Sciurba, who has been so wonderful and kind, and he is very caring. And I just don't know what else to say, except that I would just hope to be considered. That's about it for me. Everything is -- I just -- I need help.

DR. NATHAN: Thank you.

MS. WILSON: I think that's it.

DR. NATHAN: That's it.

MS. WILSON: I know it's not 5 minutes, but I don't know what else to tell you except I just can't breathe. I feel like I'm being suffocated.

DR. NATHAN: Shorter is better as well. Is any -- are there any comments or questions from our panelists?

MS. WILSON: Pardon me?

DR. NATHAN: I'm asking our panelists if they want to ask you any questions.

MS. WILSON: Oh sure.

DR. NATHAN: Okay. Theresa, sorry. Go ahead.

MS. BARNES: Thank you very much for coming and speaking. It's a very brave thing, much -- and also it can be difficult to do that, so thank you for being here.

What would you -- if you were to be considered for something like this down the road, and based on your conversations with other patients, and I don't know how many patients you mean, but what would you expect if that --

MS. WILSON: What would I expect from this? Well, today, for example, I just met two ladies that have already had this treatment done a couple of years ago, and they're doing wonderful. And that's what I would expect to hope to get to. Is that what you mean?

MS. BARNES: Thank you.

MS. WILSON: Okay. Thanks.

DR. NATHAN: Okay. Thank you, Ms. Wilson.

MS. WILSON: Okay.

DR. NATHAN: Yeah. Next I will call Ms. Jamie Sullivan.

MS. SULLIVAN: Great. Good afternoon. My name is Jamie Sullivan, and I'm here today on behalf of the COPD Foundation, which represents more than 15 million Americans with chronic obstructive pulmonary disease. PneumRx is a corporate partner program member at the supporter level but has had no involvement in the preparation of this statement.

The COPD Foundation's mission is to prevent and cure COPD and to improve the lives of all those affected by the disease. My purpose today is to describe the toll of this disease, as well as to emphasize the important unmet needs of patients with severe emphysema.

Patients with COPD may have chronic bronchitis, emphysema, or both. COPD is a

progressive disease that is often diagnosed in later stages once symptoms have become debilitating. COPD is not all the same, and the impacts felt by patients vary widely based on the type and extent of damage to the respiratory system. Despite these differences, existing treatment and management for COPD tends to be more of a one-size-fits-all approach that's primarily focused on symptom reduction.

Approved inhaled maintenance medications are important to help airflow obstruction and reduce the exacerbations in people with COPD; however, existing options do not prolong survival, and few studies have been done to measure their impact on other critical patient-centered outcomes, such as quality of life, physical activity, and more.

In an age of increased focus on personalized medicine, and on the patient's role in therapeutic development, relatively few COPD or emphysema treatments are currently approved that target unique subsets of patients for whom the benefit is greatest. For example, supplemental oxygen therapy is indicated for prolonging survival in a subset of patients with severe hypoxemia, and oral PDE4 inhibitor can reduce exacerbations in patients with chronic bronchitis and frequent exacerbations, and lung volume reduction surgery can improve survival and temporarily produce gains in lung function, exercise tolerance, and quality of life for a narrowly defined group of patients with upper low predominant severe emphysema. Lastly, lung transplantation is a treatment of last resort but one that's increasingly inaccessible for COPD patients because of organ allocation changes.

Just as COPD does not look the same in everyone, there is no typical person who suffers from its debilitating consequences. Women are affected at greater rates than men, and it tends to start affecting people after age 40 or 45, in the prime of their productivity and careers. While 75% of COPD occurs in former tobacco users, recent evidence is shining a light on the inherent biological basis for its development. People with COPD and

emphysema report exposures to occupational dust, chemicals, and fumes. They may be impacted by indoor and outdoor air pollution, and in 1 to 3% of patients, a genetic variation, alpha-1 antitrypsin deficiency has been identified.

A patient's experience with the diagnosis and treatment of COPD depends on a unique combination of factors, including the risk factors, severity of diagnosis, severity of disease at diagnosis, types of disease, such as emphysema, chronic bronchitis, or both, and factors associated with the knowledge of the healthcare providers treating them, the socioeconomic resources available to them, and the personal goals that they set for treatment.

Even when the best-case scenario has been achieved, meaning an individual's symptoms were identified early, optimal medical management was initiated promptly, and sufficient resources and support exist around the patient, it is not enough. The disease progresses. The impact of inhaled medication wanes. Exacerbation frequency increases, and the toll of the disease becomes much worse. Unfortunately, this best-case scenario is incredibly rare, and the COPD patient's experience often involves long delays until diagnosis, sub-optimal use of existing options, multiple comorbid complicating conditions, and struggles with access to important health and non-health-related resources that are important to controlling their disease.

Patients with severe emphysema desperately need more treatment options. Every day in our online community, patients seek out more options, clinging to the hope that something new is coming that may benefit their particular type of disease. This desperation results in patients trying risky and unproven treatments, like unregulated stem cell clinics, pouring their life savings into false hope. They understand that not every new treatment will be right for them, but they hope that it will. They understand that every new treatment will carry risks, but they hope they will be less than those options before them now.

They describe how they push through the extended morning routines before they can go about their day, diligently undertake the routines of inhaler or nebulizer use, and persist in the struggle to find appropriate oxygen equipment that allows them to leave their homes and actually live their lives. And pulmonary rehab can help but is rarely available.

We appreciate that a patient preference study was developed as a secondary endpoint for this submission. The patients and families we serve need help. The current options provide important benefits for people with COPD, but those with severe emphysema whom you were discussing today likely receive less benefits from these treatments, and there comes a point where their options are exhausted. Patients with severe emphysema need new treatments that may slow or halt the progression of the disease, lower the burden of symptoms, reduce exacerbations, improve their quality of life, and allow them to achieve the goals they have set in life.

Far too long, we have lumped all COPD together and treated all COPD the same. The device you are discussing today could allow a more personalized approach to care and potentially provide hope for carefully selected patients with limited options. It's time for a change.

Thanks to the Panel members for accepting these comments.

DR. NATHAN: Thank you, Ms. Sullivan.

Next I'll call Ms. Kathleen Eschenburg.

MS. ESCHENBURG: Hello. I'm Kathleen Eschenburg. I'm a patient. My travel expenses were paid by the PneumRx company, but I have no financial benefit of the company.

By way of background, there's a story that my family tells about the time I went to a county budget meeting. I didn't go out much in those days, but this was important, I felt. And to make a long story short, near the end of the meeting, I'd become convinced that my

2 cents' worth was worth about a million dollars at the going rate that day. So I got up to speak at the microphone, and thereby I made the local news. My kids wouldn't blink an eye at that. The part of this story that they find hilarious is that the description that was used for their mother. A frail, elderly lady got up to speak. I was 60 years old.

I could tell you that I weighed 89 pounds and other lurid details, but really those two words, "frail," "elderly," worked perfectly as a description of me in those days. I wasn't that old, but I acted the part far more than my 85-year-old mother did. Somewhere around that time, I was told that I could pursue the option of a lung transplant. I did my research, high-risk, multiplicity of complications, costly, added to the drugs with attendant side effects forever, 5-year average survival rate, and I declined.

So that is where I was, soldiering on as best I could in my ever-shrinking world, until a new pulmonologist came to my area and suggested we look into clinical trials. And thus I ended up at Temple University in 2013. After my initial consultation with Dr. Gerard Criner, where we discussed three ongoing possibilities available at that time, my choice was for the RENEW coils.

I couldn't help myself. I began to hope again. I went through the testing. I made it into the study. And you can see this coming, can't you? I was assigned to the control group. I went into instant depression. I seriously considered stopping there, but then after contemplating it, I decided to stay in as a control group because this is a deadly disease, and it robs one of so many of life's pleasures, and if I could do my small part for science so that maybe one day some other frail, elderly someone might have better choices available, even if by that time I expected that I would be dead.

And lucky for me, near the end of my first year, the crossover stage study was approved. So I ended my first year as a control, retested to satisfy the parameters again, and received my first insertion surgery in August of 2014. That date is easy for me to

remember because it was 4 days after my daughter's wedding. I could hardly stand to look at pictures from that wedding because I could see how deathly ill I was with my skeletal arms poking out of my beautiful dress and the facial pallor that was still evident beneath the professionally applied makeup.

I was not so much the mother of the bride that day as a scarecrow on the fence, still the frail elderly lady sitting on the sidelines, watching because COPD literally takes your breath away. And without the ability to breathe, one does not participate. No matter how much one might desire to participate, without breath, one cannot.

And now my life has changed since then. After the first surgery, I was one of the patients who experienced pneumonia. In your statistical evidence, I'm in those numbers who ended up hospitalized post-insertion, and I was also one of the ones that was adjudicated to have opacity.

Due to that hospitalization, I didn't get my second surgery until December of 2014. It was after that one that I began to really notice the difference in my ability. To finally cut to the chase here, my results were among the best when I tested out at the end of my first year post-insertion. Coming now to the end of my 5 years total in the trial, I believe that I've maintained that leader of the post position, or very near to it.

So let me allow -- that's very dry. So let me rephrase to say that the RENEW coils have been an absolutely marvelous, life-altering benefit to me. I live alone. I do my own grocery shopping, basic housekeeping, laundry, etc. I take my portable oxygen with me when I go shopping, but my waking time at home is spent without supplemental oxygen. I have gone from 2 L to 1 L for prescribed oxygen, by the way.

I have been given back the ability to garden. I can once again travel by airplane. I am never going to dance the night away, but I can manage a few minutes of dancing with my granddaughter. A few months back, I was visiting grandchildren in Florida, and we were

in the pool, and I dared my 8-year-old grandson to race me across the width of the pool. I took off, and I have the joy of his astonished face when I beat him. And he looked at his mother, who's my oldest daughter, with this shocked expression on her face, and she said, oh, you got watch your Grammy, she's a tiger. And I thought to myself, take that, you frail, elderly old lady.

(Laughter.)

MS. ESCHENBURG: There are no magic bullets in treating this awful disease, but there is reason to hope. And in my experience, RENEW coils have brought that hope to reality. There is such joy in that. My physical, mental, and emotional states have all improved because I was afforded this opportunity. I would wish that option available for others as well.

I thank you for your time, and I would be pleased to respond to any questions you might have.

DR. NATHAN: Thank you, Ms. Eschenburg.

Next I'll call Dr. Stephanie Fox-Rawlings.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from the drug or medical device agency companies, so I have no conflicts of interest.

As you've heard, we need more treatments for these patients with COPD and particularly emphysema. However, we need those to provide more than hope. And they cannot -- we do not want more treatments that will actually cause more harm.

For a device to be worthy of FDA approval, the Sponsor needs to demonstrate that its benefits outweigh the risks for most patients. And the RENEW trial does not provide

evidence the device is effective or safe. The pivotal trial does not provide sufficient evidence that the coil has improved quality of life, lung function, or exercise capacity.

I realize that using the modified statistical plan, patients treated with the coil did statistically better than controls for the primary endpoint, the 6-minute walk test. However, the difference was small, only 14.6 m, which isn't much considering the patients were walking over 300 m. The 6-minute walk test results are influenced by factors such as motivation and the number of times that a patient has performed the test.

In studies testing the reliability of the walk test on patients with COPD, patients typically improved their distance on their second walk by more than the difference between the control and treatment group. In other words, this improvement could just be noise, given the other variable that can affect the 6-minute walk test by more than 15 m. In addition, since the patients are not blinded, the experimental group were probably more motivated to walk faster. The fact that patients in the crossover study did not have the same improvements as patients in the pivotal study raises more questions about whether the coil improves patients' ability to perform on the 6-minute walk test.

There are similar concerns about whether the change in FEV_1 is clinically meaningful and how the fact that patients knew what treatment they were getting affected the quality of life measurement. It's important to note that these tests are surrogate endpoints, which does not completely reflect the clinical meaningfulness of the treatment. Even if we give these trial results the benefit of these very reasonable doubts regarding effectiveness, these improvements were primarily due to patients outside the U.S., and the difference between the control treatment and -- control and treatment arms in the U.S. were much smaller than those outside the U.S. This could be due to differences in health and BMI in different countries, or it could be due to variations in medical practice or culture. In any event, the FDA should not approve a device that does not work for the people in the U.S.

The Sponsors continued to follow patients with the coil for several years after the study, which could provide valuable data. However, the control group was only followed for the first year, and without a comparison group, it is not possible to interpret these longer-term data.

The pivotal trial showed that there were major safety concerns with the coil as well. There were twice as many adverse events reported for patients treated with the coil compared to controls. All of the treated patients experienced adverse events compared to 88% of controls. Even more concerning, 62% of patients experienced serious adverse events compared to 34% of controls. And the treated patients were hospitalized more often than controls.

It's also important to note that 46% of treated patients experienced serious adverse events that were possibly or probably related to the treatment. While there was a similar number of deaths in both treatment and controls, the investigators report that the deaths in the treatment group were possibly or probably related to the treatment.

Another issue was that 10% of the device implantation procedures included device malfunction due to unusually tortuous airway anatomy. This rate would likely increase if patients are less carefully selected for the procedure if it was approved and used in the real world.

Finally, lack of diversity is also a problem. Over 95% of the study participants were white. Black patients tend to develop COPD at a younger age and with less smoking experience than white patients. The lack of racial diversity in the trial means we can't assume that non-white patients would benefit from the device.

In summary, the pivotal trial does not provide sufficient evidence for effectiveness or safety. Questions about whether the device is effective are exacerbated by the lack of consistency with the crossover data, the differences between U.S. patients and those

outside the U.S., and the lack of blinding. The long-term follow-up data are difficult to interpret without controls. Most important, there are serious concerns of the safety of the device. A single clinical trial with questionable evidence of effectiveness, but clear evidence of harm, does not demonstrate the benefits outweigh the risk.

Thank you.

DR. NATHAN: Thank you, Dr. Rawlings.

Finally, I'll call Ms. Cindy Gasparo.

MS. GASPARO: Hello. My name is Cindy Gasparo.

Before I start, let me say, the study coordinator at Temple University told me about the hearing and asked if I would like to say something here. I said I did. She told me the PneumRx people, who said they would reimburse me for all expenses, neither asked me what I was going to say, but the study coordinator did know that I was happy to have gotten the procedure.

My story begins in July 2013. At the time, I was on oxygen 24/7 and was taking prednisone daily. My pulmonologist told me to check with Temple University Lung Center to see what they could offer. I checked their website and looked at the clinical trials they were doing. I made an appointment for screening, and on July 13th I had my first appointment with Dr. Criner.

I did not qualify for that trial. There was a study I could join, a possibility that I might qualify for a different clinical trial. He recommended that I lose weight and finish my pulmonary rehab. I was struggling to walk 15,000 steps a day.

Fast forward to June 2014. I qualified for the clinical trial. I was selected for the control group. I continued to lose weight and exercise and stopped taking oral steroids. By the end of the year, I could turn off the O_2 if I was sitting quietly at home; my 6-minute walk also improving.

In 2000 -- oh, excuse me, in June of 2015, I requalified to receive the procedure. The first one was done in July 2015. By the next day I was feeling improvement. I was able to go without O_2 even during the night. The second one was done in August. Immediately after the procedure, I suffered a pneumothorax due probably to much -- the lung volume was reduced during the procedure. It was very painful and scary but well worth the benefit I had received from the procedure.

Now I am coming up on my third anniversary of these procedures. I have maintained the improvement on my PFT tests since receiving the coils. Now on a good day I only use O_2 when sleeping, and most days are good days. I use O_2 during strenuous exercise, when walking for long distances or up hills, and at night. As of today I can walk up to 10,000 or more steps a day.

On bad days I do use the oxygen 2 to 3 hours and sometimes at night. My quality of life has greatly improved. I don't have my old life back, but I have a new life to look forward to. I am healthier. I was able to join a fitness center to continue my exercise program. I am able to spend quality time with my husband and family. We have two new granddaughters, and I am able to take an active part in their lives. I actually take care of them, 8, 9 hours a day, sometimes 12.

I volunteer in my community and will hopefully be able to make a difference in the lives of others as well. All this is possible because of the coils and the hard work I did to qualify for them. This procedure made it possible for me to have hope for the future and, if approved, can give others hope for future also. I would ask the members of the Panel to pass on my recommendation that this procedure be approved.

Thank you.

DR. NATHAN: Thank you, Ms. Gasparo.

Thank you to all our presenters for your presentations. Does anyone on the Panel

have any questions for the -- or any of the Open Public Hearing speakers?

Go ahead. Thank you. Remember, introduce yourself before you start, please.

DR. CARVALHO: I'm Paula Carvalho, and thank you very much to all of you for speaking today.

I had a question for both the second and the fourth speakers, and I wondered if -- you seem like very motivated people, and you've done well. And I wonder if you had continued your pulmonary rehab during the time that -- after the coils were put in.

(Off microphone response.)

DR. CARVALHO: I'm sorry. Yeah. The third speaker and the last speaker. Thank you.

MS. ESCHENBURG: Personally, yes. I don't think you could tease these apart, yeah, in my personal experience. I knew nothing about pulmonary rehab until I had to do it to qualify. So that was at 12 weeks, stage 2. And going through the pain of that for the benefit, as again, I realized what a key that was to the disease. But I had reached my limit. You know, during the next year when I was in the control, I continued with the maintenance program. And if I could change the world, I would get Medicare to cover the -- the stage 3 Medicare, maintenance too.

But I had reached limits that I could not get beyond. I could not get beyond 2 mile per hour on the treadmill, for instance, and I could never do it more than 20 minutes. I couldn't move the stationary weight machines at 20 pounds at all. After my coil procedure in the -- I continued in the maintenance program. I can walk 2.5 miles per hour on the treadmill for 30 minutes. I can -- I spend 30 minutes on the cross trainer. And then I go to the other room, and I do the stationary weight machines.

And I can move even -- I'm up to 7 on those machines now. I started at 5. I started at 20 weight resistance, and I'm up to 40 to 60 on those machines. And I do think the difference is the coils; the hyperinflation, they reduce the hyperinflation to the point where

I can actually perform better.

DR. NATHAN: Okay. Thank you.

Ms. Barnes.

MS. BARNES: Yes. I have a question for Ms. Sullivan with the COPD Foundation.

My question is -- actually, it's kind of a couple of prongs. One, from your perspective, the foundation's perspective, what is the level of tolerance -- I just lost my -- there it goes, level of tolerance that the patients -- for risk, that the patients may have for this type of procedure? And then what about the actual -- the study itself? Do you have any concerns about any of the risk that you saw or the patients that didn't do well or even died in the study? Are there any concerns you have for that?

And then if this were to be approved, do you -- how do you see the COPD Foundation maybe helping? Is there a role for helping educate physicians so that, I mean, that this type of situation could be the most positive experience for patients and physicians?

MS. SULLIVAN: Sure. Well, I can address the first one regarding risk tolerance. I think, as I'd like to stress, you know, that that's -- there's not a one-size-fits-all. And I appreciate in the patient preference study that, you know, what was identified is there is a group of people that would be willing to accept this risk. I think that just as with lung transplantation, I think, is a great example that there is a population. You could have two people that look exactly the same in the progression of their disease, but they do not accept the same level of risk, and they are -- they think differently, right. And that could depend a lot on your goals for treatment, your goals in life.

And so I do think that there's a great percentage of the population that we serve that would find the risks of the type that were found in the study acceptable simply because they've run out of options. There's some people that prefer, you know, just as we talk

about an end of life planning and so on, that they want less intervention and that they would choose not to take on that level of risk. And I think that's okay. I think as we've gone towards a more individualized approach to treatment, that that is exactly the scenario we want, that we are fully informed of the risks and benefits and that patients can make that choice. And I think the patients we serve want that choice. That's what they want.

Regarding the study, you know, we have not taken a position or dug into the specifics, like of the deaths, but I would say that, you know, our patients talk about pneumonia constantly. They talk about sort of the types of things that were found in the study, regardless of whether they were in the study or not. And so outside of the -- we're not in a position to necessarily to address the specifics, but I think that it was not unfamiliar type of conversation.

And then regarding education, of course, we're a willing partner. Our mission is to serve the COPD patient population and to improve their lives. And so we'd be welcoming and open to any way that we can do that, should the product be approved, and make sure that our patients have safety and effectiveness treatments.

Thank you.

DR. NATHAN: Thank you. Any further questions from our Panel?

(No response.)

DR. NATHAN: No? Okay, good. Well, now we can begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Both the Sponsor and FDA will be responding to the Panel's questions posed this morning. Does any member of the Panel have a question or comment for the Sponsor or

FDA at this time? I know we had a lot answered this morning, but I want to see if anything else came up, or maybe one -- some questions were not fully addressed.

DR. SCHOENFELD: So I have three questions which I think probably are questions to the Sponsor. Dave Schoenfeld.

DR. NATHAN: Yeah. Can the Sponsor please come up? And Dr. Schoenfeld has a couple of questions for you. Thank you.

DR. SCHOENFELD: Okay. So I'm not sure that you have all these things, but so the first question was the question that arose as to whether the St. George's benefit shown in either in the whole population or the subpopulation was possibly a placebo effect. And so I thought that what would really be helpful would be looking at the change -- looking in the treatment group alone -- ideally, it would have to be in the treatment group alone, of changes in the residual volume versus changes in the St. George's test, with the idea that if there's a correlation, it means that it isn't solely a placebo effect because, after all, everybody in that group did have the surgery, so -- and the effect of the procedure is to change the residual volume. So I thought that would be an interesting slide to see if you have it.

And then I have two other questions. You want me to give them all three, or do you want me to give them one at a time?

MS. ANASTAS: We can start with that.

DR. SCHOENFELD: Okay.

MS. ANASTAS: Ms. Daugherty would -- Julia Anastas for the Sponsor, and I'm calling Ms. Daugherty to present the data of the St. George versus FEV.

MS. DAUGHERTY: Claire Daugherty, BTG International.

This slide depicts the correlation of the effectiveness endpoints with change in RV. So the top slide, you can see 6-minute walk with change in RV. The bottom figure, you can

see percent change with change in RV and SGRQ with change in RV. So as you see, the strongest correlation is between percent change in FEV_1.

DR. SCHOENFELD: Now, is that all -- is that in both pop groups or is that in --

MS. DAUGHERTY: This is just in the treatment group.

DR. SCHOENFELD: This is just in the treatment group. And the -- I don't know -- you don't have -- what are the correlation coefficients? Or what -- were they all significant?

MS. DAUGHERTY: We have other slides that have the correlations on them.

DR. SCHOENFELD: Or they were all -- I assume they all were statistically significant.

MS. DAUGHERTY: We have a table that shows the statistical significance of each of the correlations.

If we could show that table, please.

DR. NATHAN: Just a comment around that, in the meantime. It -- Steve Nathan here -- kind of makes sense that the strongest correlation is with another PFT measure. If you reduce the RV, it follows that you'll increase your FEV_1 most of the time. But the correlation between the other more patient-centric endpoints, like the walk distance and the SGRQ, it'll be interesting to see the R, but it doesn't look like it's a real good correlation there.

DR. SCHOENFELD: Well, yeah. I just want to know how -- I mean --

MS. DAUGHERTY: I think this is --

DR. BALLMAN: See the axes? Does the y-axis start at zero for each of those measures?

MS. DAUGHERTY: Can we have the previous slide?

DR. SCHOENFELD: It's hard to see.

MS. DAUGHERTY: So there's --

DR. BALLMAN: They don't all start at zero? Okay.

DR. SCHOENFELD: Okay. And then the table that you just showed, which I think --

MS. DAUGHERTY: Okay. So this table shows the correlation of SGRQ with the objective measures for the treatment arm in the full ITT population. This is not multiply imputed, so this is just the complete cases. And you can see a significant correlation between SGRQ --

DR. SCHOENFELD: So the correlation coefficient is 0.224 Spearman, and then it's significant at 0.05; is that what the star means?

MS. DAUGHERTY: That's right. That's correct.

DR. SCHOENFELD: Okay. Okay, so --

DR. BALLMAN: So there is no significant correlation between the residual volume and the St. George, right?

DR. SCHOENFELD: No.

MS. DAUGHERTY: Correct. That's not statistically significant.

DR. SCHOENFELD: Between the residual volume and St. George? Oh, I see. So it's 0.16. So it's -- oh, I see. I'm sure. So 6-minute walk was significant as a negative correlation. And FEV, there was significance and not St. George. And then RV/TLC, I'm not sure what that means. That's something else.

MS. DAUGHERTY: So it's RV divided by total lung capacity.

DR. SCHOENFELD: I see. Okay, so that was -- so it was not quite -- not significant. Okay. So the next question, which is my -- probably you should stay up there because -- so is just to give us a little more detail about how the change in the analysis method determined what was in -- what was the way that you assessed the skewness, and how did that -- how was that actually done?

MS. DAUGHERTY: We assessed the skewness using a test for significance of non-normality using the Shapiro-Wilk test. And we have a table for that that I can show

you. And then we also examined graphically the depiction of the residuals using a histogram, a box plot, and a normal quantile plot.

DR. SCHOENFELD: So that was residuals after you -- with treatment group specified, it was residuals that -- from each treatment mean basically?

MS. DAUGHERTY: Correct. So the analysis plan specified that first the residuals from the parametric test would be examined for significant deviation from normality.

DR. SCHOENFELD: From normality.

MS. DAUGHERTY: And these are the results of those tests.

DR. SCHOENFELD: Yeah, okay.

MS. DAUGHERTY: For change in 6-minute walk test, highly significant, for percent change in FEV_1, highly significant, and for change in SGRQ, no evidence of non-normality from this test. If you're interested, the next -- this is the figure that we examined. This is for 6-minute walk.

DR. SCHOENFELD: I see, the peculiar plot. So the -- and, finally, there was a criticism made by the FDA that the risks in the patient preference survey were not adequate, were not well stated, were not stated in a -- were not stated correctly given the results of the clinical trial. And it's very hard for me to judge that because the details of exactly what the risks were, it's just not exactly easy to see. So do you think you could answer that critique, criticism directly, as to whether the patient -- why one would say that they were adequately or --

MS. DAUGHERTY: I'm not a patient preference expert, so I would defer.

DR. SCHOENFELD: Well, so it would be the patient preference expert.

MS. DAUGHERTY: But if you would like me to comment on one --

DR. SCHOENFELD: Well, no. The patient preference expert could comment. I mean, it basically is just comparing the actual risk found in the clinical trial with the risks that were

presented to the patients, I guess, and seeing whether they are reasonably close or very far away or whatever.

MS. ANASTAS: So I would -- Julia Anastas.

I would call Dr. Brett Hauber to come to speak to the way those risks were determined for the purpose of the patient preference study.

DR. HAUBER: Brett Hauber, RTI.

So there were -- is your question about which risks were included, or which numbers in the risks that were included?

DR. SCHOENFELD: Well, there was a criticism made, which you've just heard, that the risks weren't accurately assessed. And I'm sort of giving you a -- and I think it's relevant to the question, to the --

DR. HAUBER: Sure.

DR. SCHOENFELD: -- to the decision of the Panel. So I'm asking you -- I'm giving you an opportunity to rebut that, if you can, if you would.

DR. HAUBER: Yes. Thank you.

Can we pull up the choice question?

So one of the challenges we face in building a patient preference study is we can't address all of the risks.

DR. SCHOENFELD: Yeah.

DR. HAUBER: That's one of the biggest challenges. So in this particular case, we chose to include -- oh, it's already up. We chose to include three risks and death, and they're not going to be -- because we're limited in what we can do, we can't absolutely make them perfectly correspond to outcomes in the trial. So here's how we got there.

We picked the first three risks. We observed that there were three, the three most frequent SAEs, which also happened to correspond, we found out later, to the three most

frequent events observed in commercial use. But that wasn't part of our decision.

So we found the three most frequent SAEs and tried to capture them, in addition to death, because death is important. When we have death, death is sort of always in there. So in this case, what we had was the increase in COPD exacerbations, the increase in the rate of pneumonia, and the increase in pneumothorax. And so what we have -- I think one of the criticisms that FDA has raised, and rightly noted, was that we have pneumonia requiring hospitalization, which is certainly a key factor here that is of interest in this benefit-risk decision. And we don't have -- we have respiratory infections requiring hospitalization because the definition of pneumonia is broader than just the MedDRA preferred term for pneumonia.

We also have -- but what we don't have are some of the less -- the respiratory infections that don't require hospitalization. So we tried to capture the most important ones. COPD exacerbations, we know, are of critical importance. So when we included COPD exacerbations, we had a choice to make between including severe COPD exacerbations that required hospitalization and the larger number of COPD exacerbations that didn't require hospitalization, and then pneumothorax was actually pretty straightforward.

So we had to make some choices, as we do in all of these patient preferences, to try and capture some of the major issues that characterize this decision for patients. And the way that we do that is we -- in this case we had the ability to look at kind of the first cut of the clinical data. Some of that data were available to us at that time, so the Sponsor helped us understand what some of those data looked like.

We then talked with clinical consultants to figure out from them, from their perspective in talking with patients, what are the issues, A, that they're perceiving in the trial as well as what are issues that are going to be relevant for their patients. And then

once we have the survey together, we actually sit down with patients and say, from your understanding of the issues around here, what does this mean to you? Does this capture everything?

Now, from the risk sides, they're not going to be aware of all of the risks. But what we found was that we captured major risks that are the types of considerations that patients would care about. So we don't map perfectly to the trial, but we believe we captured the major issues that were observed in the trial.

DR. NATHAN: Okay. Thank you.

Dr. Carvalho, you had a question?

DR. CARVALHO: Thank you. This is Paula Carvalho.

What I'm wondering, if the Sponsor can shed some light, I was interested in what happens to the bronchial circulation after coil implantation. And I'm wondering if it hypertrophies, if aneurysms develop, if there is a correlation with hemoptysis, and if there's any -- either autopsy findings or your prior animal studies, histology.

MS. ANASTAS: Excuse me. Dr. Criner, can you speak to the findings, the clinical findings in your patients?

DR. CRINER: Criner from Temple.

So there's two explants that have been done for people who underwent transplant that had coils in a lung. And those two patients, around the coil position itself, there was some fibrotic change in the area of emphysema. So it's thought that some of the effect of the coil may be that it induces a local mechanical stress besides compressing the lung tissue that could incite some inflammation and cause some fibrosis that's there.

In terms of the bronchial circulation, there's no effect in the pulmonary vascular circulation. There was one episode of hemoptysis that Dr. Hahn mentioned in his safety profile, but most of the episodes of hemoptysis were transient, and they were related to

the study procedure, time of the procedure, and they were minimal, like less than 5 mL.

DR. NATHAN: Dr. Criner I have a question for you as well, and it pertains to lung transplantation. As you well know, we talk about a window of opportunity for lung transplant, not too early, not too late. If we see patients in the window, we do what we can to get them out of the window and make them early enough for transplant. How do you see this technology fitting in that role? And in the context of the study, were there patients who were transplant candidates who were made well enough to not be transplant candidates?

DR. CRINER: Yes and yes. So from the standpoint of how you approach a patient, the patients that present with end stage emphysema, I just want to clarify that we're not talking about patients with COPD. We're talking about patients with advanced emphysema overall, where the combination of therapies that you could offer them are a procedure like this, or it could be transplantation, or it could be lung volume reduction surgery.

That's the other thing I want to just really clarify is lung volume reduction surgery is approved therapy based on the NETT trial and based on CMS approval for patients with homogenous disease. That's a non-upper lobe predominant disease, which is 60% homogenous. And it's approved in that group, pretty much to improve quality of life and some effect for exercise tolerance.

So some patients, they don't want to undergo surgical option but would have a less invasive option. And it could spare some time to get rehabilitated, like one of my patients mentioned, to get stronger, where a transplant later on in their life might be a possibility. Two of my patients in the trial had 5 years, had progression of the disease, and successfully underwent lung transplant, one about 1 year ago and one about 3 months ago, with no significant impact on the transplant procedure itself.

DR. NATHAN: Thank you. Along similar lines, you know, typically when we evaluate

patients for transplant, we look at the BODE score as an index of severity and outcomes. And when patients score around a 7 to 10, then the outcomes without a transplant are worse than the outcomes with a transplant. It seems like the BODE is a nice composite that perhaps could have been looked at in the context of this clinical trial because it encompasses body mass index, obstruction, FEV_1 dyspnea score, as well as exercise tolerance. Was the BODE looked at in the study?

DR. CRINER: The BODE, I think, was looked at.

Adam, do you have that? Yeah.

We see if we have the slide. At baseline it was looked at, but it wasn't looked at as a responsive parameter overall, but we could give you that, the BODE scores.

Do you have that?

We'll get it for you later.

DR. NATHAN: Including the change?

DR. CRINER: We don't have the change. We didn't calculate it in follow-up, Steve.

DR. NATHAN: Dr. Cassiere, you're next.

DR. CASSIERE: Hugh Cassiere from North Shore.

Just to start the conversation amongst the Panel members, so we all agree that there's some biological plausibility of decreasing residual volume. And I'm looking at the statistics. And this is a question for the statisticians on the Panel.

Tell me if I'm right or wrong, looking at this, saying that there is a correlation with decreasing residual volume and a positive outcome with the 6-minute walk test and the questionnaire? Is that a valid statement or not? And I want the statisticians on the Panel to answer that specifically.

DR. SCHOENFELD: I'm not sure that, I'm not sure I understand. One of the things about the residual volume as a surrogate marker is that there's two questions about

residual volume that you ask. One is whether -- you can ask whether residual volume is a bad factor, you know, is sort of correlated with disability, but in a certain sense, the -- what this study was testing was whether changing -- if you know the residual -- having a high residual volume is bad, is a bad factor for a patient, it doesn't necessarily mean that changing the residual volume would be good for the patient.

So in a certain sense, one of the -- what this study is trying to test, in a sense, is that, is that if we change residual volume with this device, do we then succeed at changing something that is important to the patient? So in a certain sense, the question you're asking, the different changes in the walk, in walk and the SG, the St. George's, and things that are important to patients is more important than -- if it just changed residual volume but didn't change those things, it wouldn't be a good therapy.

I think they did show a correlation between that and the treatment group, but that -- I'm not sure that is the -- the importance is really -- of the study is whether they've changed things that are important to patients, if the patients --

DR. NATHAN: Dr. Ballman, do you want to weigh in on that as well?

DR. BALLMAN: Well, I guess what I'm struck with, and I'm struggling with is, first of all, the correlations were quite modest. I mean, even if they were statistically significant, they weren't like, you know, above 0.5. And so -- but, you know, in the FDA presentation, they have the longitudinal results on slide 48 showing the 6-minute walk change. And, you know, the crossover did not do as well, you know, we know, as did the pivotal study.

But on the other hand, if you look at the St. George's longitudinal changes on 50, you see that the crossover really had a significant change. And so I think, you know, for the St. George thing, I'm thinking there's a lot of placebo going on, to get at your sort of question a different way, if you look at those two slides

DR. NATHAN: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere again, North Shore.

So the reason why I'm asking is because this device, again, biological plausibility, is designed or supposed to work to decrease your hyperinflation and hence decrease your residual volume. So that's how, quote/unquote, it's supposed to work. So that's the relevance of the -- that's why I'm using residual volume as -- excuse me for taking your term -- a biological marker, to see if there's a positive outcome. So I'm relying on that. If I'm being told that the questionnaire and the 6-minute walk test does really not correlate with that, then that takes some of that biological plausibility wind away from me. And that's why I'm asking that question.

MS. ANASTAS: Dr. Nathan, may we have Dr. Criner speak to this question?

DR. NATHAN: Yes, sure.

MS. ANASTAS: Dr. Criner.

DR. CRINER: Criner.

So let me do this in a multi-tiered way, to show that residual volume matters and that patients who have a higher residual volume as time goes by goes worse, and people who have a lower do better. Also, look at the change of residual volume over time with all the other parameters. And a third thing talked about the importance of the potential placebo effects, of it not being a sham procedure, on how that might have affected SGRQ or 6-minute walk test may have changed that.

So this first slide I'll show you looks at residual volume -- we'd shown this before -- in a mechanistic dependence on looking at the magnitude of residual volume at rest, and in the intention-to-treat population shown on the left, and on the EU registry shown on the right, that patients who basically are more hyperinflated overall have a -- let me see the -- different one -- change in -- greater change in residual volume when the RV's greater than 220, both in the RENEW intention-to-treat and in the EU registry.

This second plot looks at the changingness in 6-minute walk test at 12 months, by baseline RV. It should be coming up in a minute.

DR. NATHAN: Sorry. Can I ask the Sponsor a favor? We're all having a tough time seeing the axis. Is it possible to put one of these on at a time? I don't know how long it'll take.

(Off microphone discussion.)

DR. CRINER: They're blowing them up.

(Applause.)

DR. CRINER: So this is the RENEW intention-to-treat, with the change in 6-minute walk test shown on the left and looking at the baseline residual volume. And you can see that the 6-minute walk test basically has an inverse correlation with residual volume, as you can see, the Spearman correlation and the correlation coefficient.

DR. BALLMAN: But that's baseline, right? That wasn't change.

DR. CRINER: Yeah. This is baseline. This is the change in 6-minute walk, also with the correlation in the European registry, with the degree of baseline RV.

DR. CASSIERE: But I don't think that was the question, just to --

DR. BALLMAN: Yeah. Do you have change in residual volume?

DR. CASSIERE: Yeah, I think that's --

DR. BALLMAN: By change in those other --

DR. CASSIERE: The question really is -- the question is do you know the -- underneath all this is the notion that we have a device that changes residual volume and that the change in residual volume mediates, that is, is the pathway by which the device affects quality of life and exercise tolerance. And so we're worried about -- I guess the worry is about what the psychologists would call the direct effect, which is that the fact that being in the -- being treated with the device might have a direct effect that has nothing to

do with residual volume, and that direct would be a placebo effect. And that's basically the story that works against feeling that we have efficacy.

And I think it would have been very hard to do a sham with this procedure as it is, but -- so it may have been impossible to do a sham. But I think that that's the question that I think you want addressed. And I'm not sure how you address it, but --

DR. BALLMAN: And, again, Karla Ballman.

Can you blow those up like you did the other ones?

DR. NATHAN: Sorry. I just have a question going back to the prior one before we move on to this one. Can you show the one with the red dots again? Because if I'm interpreting it correctly, is the correlation going the wrong way?

DR. CRINER: Which one did you want to see?

DR. NATHAN: The one prior, with the red dots.

DR. CRINER: The red dots? That was the control population. That was the European registry.

DR. NATHAN: That was the control population?

DR. CRINER: Yeah, showing that the higher the RV was, the worse they had 6-minute walk test.

UNIDENTIFIED SPEAKER: Yeah, but this is the right slide, I guess.

DR. CRINER: This is the one you asked for that we just put up, about looking at the change in residual volume in RENEW and the intention-to-treat population, with the correlations with change in RV shown in the x-axis on all of them, with change in 6-minute walk, FEV_1 and the SGRQ.

MS. ANASTAS: Can I ask Dr. Berry to speak --

DR. NATHAN: Can you blow up the one in the top left corner, please?

MS. ANASTAS: Can I ask Dr. Berry to speak to this for a moment?

DR. CRINER: Yeah, so that's --

DR. BERRY: Scott Berry, a biostatistician consultant to the Sponsor with no financial interest in the outcome.

So, Dr. Schoenfeld, if we can show the FEV_1 to RV, the bottom left.

So every one of these patients are in the active arm. Every single one of them know they got coils. The RV on the x-axis is an objective measure of what happened in the lung, and the correlation to FEV_1 is 0.63. The negative is because the reduction is good. So if this is nothing but a placebo effect, you'd see a random cloud of points. But this 0.63 is incredibly strong that this is not placebo effect. Now, the other markers of six --

DR. NATHAN: Can I -- sorry. Can I stop you there? Because --

DR. BERRY: Please.

DR. NATHAN: -- these are two PFT parameters, and it makes sense that the one PFT parameter is going to follow the other one. I think what the Panel's focused on are the patient-centric outcomes in the terms of the walk distance and the SGRQ.

DR. BERRY: Yeah. So the -- but this is essentially the surrogate marker of change in RV to FEV_1. Now, as we go to the other markers, as you move to 6-minute walk, which was significant, in the upper left, that the 6-minute walk test is an incredibly noisy endpoint that comes into many things other than just the RV. And so the fact that the correlation is smaller is also reflective of the variability of the y-axis here.

And then St. George is also an accumulation of many things that go into the St. George, not just your breathlessness. And so the variability of that can hide the correlation. But the FEV_1, I think, takes away the notion that this is a placebo effect.

DR. NATHAN: Okay. Any other points or questions around this?

DR. CASSIERE: Yeah. Hugh Cassiere again, North Shore.

So I guess what I'm getting at is not a PFT parameter. We're looking for some type of

clinical finding, whether it be the 6-minute walk test, which sometimes it is, and sometimes it's not, I'm hearing, a good measure of patient outcome and the questionnaire. So for me, at least for the Panel members, some of the hard points you need to take a look at is the questionnaire, and take a look at the 6-minute walk test, with the notion that if we're going to say there's some biological plausibility behind this device, it needs to be linked in some way to the decrease in residual volume, which at least in my mind makes sense.

DR. BALLMAN: Can I ask a quick follow-up question?

DR. NATHAN: Yes, please go ahead, Dr. Ballman.

DR. BALLMAN: Being not in this area -- this is Karla Ballman.

Not knowing the biology, and you were talking about sort of the mechanism, why would it be harmful in volume under, you know, at that -- under the threshold and beneficial over that threshold?

DR. CASSIERE: Hugh Cassiere again.

I guess just basically to say that you are more hyperinflated and less likely to blow the air out when you have a higher residual volume.

DR. BALLMAN: But why would the putting coils in -- this is Karla Ballman again -- when you're not as hyperinflated be detrimental?

DR. CASSIERE: Well, you may -- you're not going to probably get a benefit, and you're going to get all the adverse effects.

DR. NATHAN: Okay. So just a reminder to the Panel, just wait for me to call on you. Otherwise it will be a little bit of a free-for-all. I know I left out a couple of people who had questions along the way.

Dr. Wang.

MS. ANASTAS: Can I have Dr. Criner speak to the question about the below and above 225 and why would they do best -- better or worse or -- no?

DR. NATHAN: Oh, sorry. Yeah. Can you hold on one second? Sorry. I was addressing the Panel members.

MS. ANASTAS: Yes.

DR. NATHAN: Dr. Wang, you had a question?

DR. WANG MEMOLI: Jessica Wang.

I just had a question about how we can sort of bring together the fact that the initial treatment group and then the crossover group results are so disparate, which the FDA kind of pointed out, considering it was 100-and-some patients, which is about two-thirds of the initial group, and why like the 6-minute results are so different. And, you know, you can say there's benefit, but then in another group that is pretty large size, there was not benefit and some worsening than even the baseline numbers. And so I don't know if --

DR. NATHAN: I think that's a very good point that the FDA highlighted. I'd like to give the Sponsors an opportunity to answer that because, as I recall, the baseline characteristics of the crossover group, at the time that they crossed over, was very similar to the other two groups starting out in the study.

MS. ANASTAS: I'd like to ask Dr. Scott Berry to speak to that as well.

DR. BERRY: Scott Berry, biostatistician.

So this is a really subtle issue, and so I want to spend a little bit of time to explain the crossover and why this is not necessarily comparable. Today is -- and I'm going to get there very quickly. Today is the opening day of the U.S. Open golf tournament. I can tell you right now, I can identify 35 players that play on the first day today, and they'll do three shots worse tomorrow by me thinking bad thoughts about them. And all I have to do is identify the top 35.

And so I went to the U.S. Open last year. And if I take the top 25% of golfers on day 1, they will decline by three shots on day 2. If I take the bottom quarter, they will improve

by three shots tomorrow. It's when you have a group of population and the outcome is variable and you pick off the top part, they regress to the mean. And it's exactly what's happening here.

So what happened here is you have this group of patients that, up through 12 months -- let's put this slide up -- they progressed and got worse. And then you measure 6-minute walk test at 12 months, and you only took those that qualified for that, you took the top performers, and this slide shows that those that crossed over were the top performers. They're going to regress to the mean because you self-selected the positive performers.

And I can demonstrate this with the coil patients. So this, the coil patients, what we did is we don't have the other controls through 24. So we took all coil patients at 12 months, where we did nothing to them but followed all of them to 24. Had we self-selected the top half of the coil patients at 12 months and done an intervention to them, they'd decline by an average of 44 meters because they were positive performers at 12, the exact same of self-selecting the top quarter of the golf tournament.

So a 55 m decline by the top quarter, where the bottom quarter went up 19 because of regression to the mean, so that when you take that population, you can't compare it to the original base. They had to decline because of mathematical phenomenon of self-selecting the positives.

DR. NATHAN: Okay. Dr. Ballman.

DR. BALLMAN: A couple of questions.

DR. NATHAN: You want to answer that?

DR. BALLMAN: First of all, I agree with the argument, but it's not the top quarter that went on to crossover. It's the majority. And so it's not the top -- I mean, it might be the top majority, but it's the majority.

Second of all, we've heard from the FDA that these patients did not have to re-undergo a pulmonary rehabilitation. And there are reports that just going through that is bigger than the difference we saw in the treatment group in the pivotal trial. So how do you respond to that?

DR. BERRY: So it was a 102 out of 158 -- 157 of them that moved on. And the slide showed there was a 35 m different. They were self-selected positives. And I was trying to show the magnitude of regression to the mean is enormous. And it can be 30 to 50 m difference because of the self-selection.

DR. BALLMAN: Right, but you didn't show equivalent groups. I mean, you took the top --

DR. BERRY: Yeah.

DR. BALLMAN: -- quarter. You didn't take the -- I mean, you know --

DR. BERRY: Right.

DR. BALLMAN: It's true that you have bigger regression to the mean when you take the very best of a, you know, small group at --

DR. BERRY: Right.

DR. BALLMAN: -- the very best. And that's not what happened in the crossover. That was my point.

DR. BERRY: And they -- there was no control group. Had we randomized the crossover, we would see the control, and hence the difficulty of looking at a single-arm trial, when we have a randomized 300-patient trial right there to look at the internal consistency of the effect between groups.

DR. NATHAN: So I have a question, just to call you on that regression to the mean, which I understand. Fine, if you don't have an intervention. But surely if you have an intervention that works, it should prevent regression to the mean. Are you trying to say

that, oh, forget the walk distance went down 30 m, it would have been 70 m without the intervention? I would have hoped at least that they wouldn't have had a change, and then you could have argued they didn't have a change for the positive, and that's why it's regression to the mean. But they went down despite the intervention.

MS. ANASTAS: Can I ask Dr. Criner to speak to the clinical outcome of these subjects?

DR. NATHAN: Sure.

DR. CRINER: Criner.

So one of the issues is how much would you expect from pulmonary rehabilitation in this patient group to improve 6-minute walk distance? So what was presented was a meta-analysis by McCarthy in 2016, which is in an applicable patient population in this group. That meta-analysis of 31 studies had a mean age of 50. None of the patients had oxygen. None of them had emphysema in that trial. That was patients with COPD, from studies that were accumulated up to 40 years ago, where medical therapy isn't comparable to this. So to expect a 50, 60 m improvement in rehabilitation of this patient population doesn't -- isn't applicable.

If you look at the NETT trial, which is applicable to this patient group, if you look at rehabilitation, it was published in *Chest* by Andy Rees in 2006, that showed that you'll have, at 2 months after rehab, you have about a 20 m improvement in 6-minute walk that dissipates by 40 m in 1 year and 65 m in 2 years. So this is a actively progressive patient population where rehabilitation isn't going to make a big magnitude of difference in outcome.

If you look at the placebo effect of doing an intervention on a patient and affecting the SGRQ -- can we have the slide on from the EASE trial -- the best patient population that looks at that is the EASE trial, which was Exhale stents that were placed in a comparable

patient population, 300 patients, 2 to 1 performance. It was published in 2010 in *The Lancet* at the time that this study was done and had a sham bronchoscopy group in that. And they'll show the slide in a minute -- yes, it's coming now -- which looked at the patients in red, who had sham bronchoscopy, compared to patients in blue.

And as you can see, the SGRQ improves by about 2 points at 1 month. And then at 12 months, the SGRQ is back to the baseline, which limits the ability of using a sham control or expecting that the sham bronchoscopy or the not having a sham bronchoscopy would have affected the improvement in quality of life that patients who underwent a procedure that required bronchoscopy will show.

The other thing, reason why a sham wasn't used wasn't because of the unblinding effect. It was the complications of the sham therapy in this group, that the patients that underwent sham bronchoscopy had a 3.7% mortality at 30 days, either related to the procedure or after the procedure, due to pneumonia, which was almost double what the intervention group had, and also had a higher rate of exacerbation.

So what we're trying to show is that the magnitude of the effect of the 6-minute walk, based on rehabilitation, is minimal in this patient group. We would expect the 6-minute walk to decline over time and that the lack of a sham bronchoscopy did not affect the SGRQ magnitude that we saw.

DR. NATHAN: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere, North Shore.

So help me reconcile the fact that the change in residual volume does not correlate with the questionnaire and does not correlate with the 6-minute walk? How do I reconcile that from a biological plausibility point of view?

DR. CRINER: Well, I guess what was mentioned was that there's other factors that go into the 6-minute walk. As you can imagine, in this patient population, doing a 6-minute

walk in people that are average 68 years of age that may have other comorbid arthritis and osteoporosis, or be in some cases overweight, may limit the 6-minute walk performance even though the residual volume may have gone down by a significant degree, 0.4 or 0.5 liters, or the RV/TLC ratio goes down by 3.5%.

The idea that it correlates the best with the objective measurement of lung function suggests that you do, do a biologic effect of improving lung function overall, which may not always translate into other improvements that are related to how a patient feels with their cough and sputum one day, or how they might feel while they're doing a 6-minute walk test on intermittent sampling overall.

But if you -- we have a slide that looks at the correlation between RENEW and NETT in terms of change in SGRQ. And if you look at these correlations overall, from the NETT trial, you can see the change in SGRQ at 6 months post-randomization was a change in -- the correlation with that is 0.46, and in the RENEW trial it was 0.39 using the Spearman. So you have similar kind of degrees of relationship between a reduction in or a change of SGRQ and change in 6-minute walk test. That's not the change in residual volume, however.

DR. NATHAN: Okay, thank you.

Dr. Van Berkel, you had a question?

DR. VAN BERKEL: Yeah. I'm Victor Van Berkel.

So, one, just a quick statement to what you were talking about, and then I actually have a series of questions for the, for applicant.

Within the surgical literature, there's actually a fair bit of data looking at your FEV_1 and your subjective sense of dyspnea and your response to the questionnaires. And, unfortunately, the correlations are very poor. I mean, a good portion of my job is forcibly removing somebody's FEV_1, cutting out parts of people's lungs. And while we've found that, past a certain point, you can predict surgical complications, for example, and other

morbidities, the subjective sense of dyspnea does not really correlate with FEV_1 very well. And so I'm not particularly surprised that there is not a strong correlation between the questionnaire and the residual volume changes. There is one, but not a particularly strong one.

So forgive me. I actually have a series of questions. So starting off with the study, you guys started off enrolling patients who were only 225% of their residual volume. And then after a certain period, you started enrolling people, in addition, who were between 175% and 225%; is that -- that's correct?

MS. ANASTAS: That's correct.

DR. VAN BERKEL: So what was the rationale behind that change?

MS. ANASTAS: We had some data from -- it was a meta-analysis of several small studies that suggested that subjects between 175 and 225 could also receive benefit, so the trial was expanded.

DR. VAN BERKEL: So was the purpose there to improve your enrollment numbers, or the purpose was to expand the criteria by which you'd be able to use the device?

MS. ANASTAS: The purpose was to expand the therapy to a broader range of --

DR. VAN BERKEL: And how many patients was that decision made on?

MS. ANASTAS: You mean the new set of data? A hundred and -- the meta-analysis --

DR. VAN BERKEL: The meta-analysis.

MS. ANASTAS: -- was 140 subjects from five studies, I believe.

DR. VAN BERKEL: Okay. So in those 140 patients, there was a benefit seen between 175% of residual volume and 225% of residual volume?

MS. ANASTAS: Yes.

DR. VAN BERKEL: And then, however, in your study here, you're asking us to throw that data away, right? Because you're saying that the patients who were in between -- who

were less than 225% did not perform as well, and all of the data that you presented was in the patients who were greater than 225%. You said that was where the maximal impact was, and that was the group that you were asking for approval for now.

MS. ANASTAS: We met the primary and secondary endpoints for the full population, but we saw greater benefit in the population that was originally specified, the 225%. So we are proposing that the indication for use be restricted to 225 and above.

DR. VAN BERKEL: So why do you think that in those 140 patients that you saw a benefit, but then in the 70 patients here, you did not see a benefit?

MS. ANASTAS: I would ask Claire Daugherty to come and speak to the statistical analyses that have been done on those data.

MS. DAUGHERTY: Claire Daugherty, BTG.

The original data was similar to what we've seen in that patients who were -- available data on patients who had low RV looked lower. We did not have a control group in that study, in the original feasibility study, so there was a trend in improvement in 6-minute walk with baseline RV, as we showed in this study. And there was a suggestion that those patients, while they wouldn't do as well, that they might also benefit. So that was the basis of the decision. In that data set, there was no control arm.

DR. VAN BERKEL: Okay.

DR. NATHAN: Dr. Schoenfeld, I'll get to you in one second.

I just have one question of clarification about the 6-minute walk myself. Steve Nathan.

You mentioned that there is a lot of variability around the 6-minute walk and the other factors involved, and that's what your primary endpoint is, and you hit statistical significance on that, which is fine. My question is, to reduce the variability in many of the studies that are being done now, they're doing two baseline 6-minute walk tests and then

two for the primary analysis afterwards and either taking the highest or the average of the two. When you did the 6-minute walk test, was it just one test?

MS. DAUGHERTY: That's correct.

DR. NATHAN: Did you -- also, something else that's being done in some of the clinical trials is to do two tests at the start, and if there's more than say 15% variability between the two 6-minute walk tests, then those patients are excluded. Was anything like that done in the study?

MS. DAUGHERTY: No.

DR. NATHAN: Okay. Thank you.

DR. SCHOENFELD: So I have a --

DR. NATHAN: Dr. Schoenfeld, just a quick question, please.

DR. SCHOENFELD: Okay. So in a way, the -- just a statement on the sort of restricting the indication. I think that the -- restricting the indication seems reasonable to me in the sense that you've got risks, and so you would -- in a situation where there are both risks and benefits, you might want to restrict the indication to where the benefits outweigh the risks, and that seems to be what's been done. And the FDA has done this for several different things. Obviously, restricting indication is a common thing to do.

I wanted to comment on two other things. One is on the correlation between the 6-minute walk and the residual volume, which was something in the order of 0.3 or so, which doesn't look too impressive. But I must say that in the 45 -- in my 45 years as being a statistician, I very rarely see correlations more than 0.3 when there's no commonality in the way the measure is made. So you might see a correlation of high -- 0.5 if things, if two thing -- if you measure two things with two different instruments, you always get high correlations. But between two things that are biologically sort of unrelated and are noisy, 0.3 is usually significant and usually meaningful. I mean, so that -- and I think that's what

the correlation was, roughly. If I'm wrong, correct me. And so it isn't no -- 0.3 correlation, 0.33 is not any -- is not no correlation.

The other question I have is having to do with regression to the mean. So you do have serial data on the 6-minute walk. You did it more than just at 12 months. You did it at 6 months and so on. So there are statistical methods for getting rid of regression to the mean in those situations. And I'm wondering whether you did an analysis which used imputation, which Scott is, of course, knows very well, to remove regression to the mean.

MS. ANASTAS: So, Dr. Berry, do you care to speak to that?

DR. SCHOENFELD: And what would be the results of that analysis, if you did it?

DR. BERRY: Scott Berry.

It's a great idea to do a random effects model that models longitudinally over to estimate the random effect bias of the selection, and we have not done that.

DR. NATHAN: Okay. Mr. Ryan, you had a comment or question.

MR. RYAN: Yeah. Thank you, Dr. Nathan. Mike Ryan, FDA.

I just wanted to clarify on the proposed indications for use that, as written, they are, the coils are intended for severe hyperinflation without any residual volume cutoff, as currently written. So at the moment, there is no 225% cutoff.

DR. NATHAN: Okay. Dr. Dodd, I think you had a question as well.

DR. DODD: Yeah, and I -- first I want to follow up, yeah, to --

MS. ANASTAS: May I just respond to that?

DR. NATHAN: No. If you can wait.

MS. ANASTAS: Okay.

DR. NATHAN: You'll get a chance.

MS. ANASTAS: Okay. Sorry.

DR. NATHAN: Continue, Dr. Dodd.

DR. DODD: You're talking about the -- now the numbers are jumbled in my head. I thought I saw a correlation between the percent change for RV and percent change for the 6-minute walk test of about 0.1 something.

DR. SCHOENFELD: No, I think that was the SG --

DR. DODD: Okay.

DR. SCHOENFELD: The St. George was about 0.15.

DR. DODD: Yeah. I didn't think it was nearly 0.3.

DR. SCHOENFELD: And the other one was about 0.3, but maybe --

DR. DODD: If we could just --

DR. SCHOENFELD: -- you could show those slides again.

DR. DODD: Yeah. I need to write those down because I didn't think it was 0.3. And while you're doing that, I just wanted to follow up with a question that I asked the FDA, just to give you an opportunity to respond because I think you would know.

I had asked a question about what kind of procedural things you put in place to ensure that the assessors remained blinded to the assignment of the patient when they were doing the 6-minute walk test.

MS. ANASTAS: To answer that question, I'd ask Ashley Burns, clinical affairs, to come and speak.

MS. BURNS: Ashley Burns, Clinical Development, BTG.

During the course of the trial, the assessors for 6-minute walk test and PFTs were blinded. And throughout the course of the trial, we monitored the study and asked the assessors if they had remained blinded. Any instances where they had a unblinding, we inserted a protocol deviation. At the completion of the trial, we had an attestation for all of the blinded assessors, if they had become unblinded to any patient. And through that process, we did not find any additional deviations.

DR. DODD: And how many protocol deviations did you have, of unblinding the assessors?

(Off microphone discussion.)

MS. BURNS: We had 13 deviations for PFT assessors being unblinded at 12 months, and one of those had unblinding for 6-minute walk as well.

DR. DODD: Thank you.

DR. NATHAN: I think the Sponsor was going to put up some slides in response to what Dr. Dodd had asked. After that, what I want to do is switch gears a little bit amongst the Panel and think of any questions that we have specifically for the FDA so that FDA gets a chance to address any questions that they have. And then we'll come back to the Sponsor after that. But show those slides first that address what Dr. Dodd was asking.

MS. DAUGHERTY: This slide is the correlation, one of the correlation slides, the one that's difficult to see because it's so small. So the change in 6-minute walk with change in RV is what's plotted. And we have the correlation coefficient, so you see that the strongest is percent change in FEV_1 and that the change in 6-minute walk with change in RV is 0.16 as well as SGRQ.

However, we have another slide that shows the correlation between 6-minute walk and SGRQ, and that is stronger. It's closer to 0.4 or 0.39. And that was also consistent with the correlation between 6-minute walk and SGRQ in the NETT study.

DR. NATHAN: Okay, thank you.

Panel members, do we have any specific questions for the FDA and their presentation?

MS. DAUGHERTY: Would it be possible for me to address the timing of the analysis plan change that was mentioned prior to the break?

DR. NATHAN: We'll come back to you. I just want to make sure that the FDA gets a

chance to have their questions answered. I think we'll have plenty of time to get back to you, hopefully. Okay.

MS. DAUGHERTY: Thank you.

DR. NATHAN: I'd like to ask the FDA if there's any points of clarification that you might have that you want to share with the Panel members, or you guys feel good about everything that was presented?

UNIDENTIFIED SPEAKER: Just one point. Thank you.

DR. COURSEY: Hi. This is Derya Coursey, reviewer.

Can we bring up, please, slide 27 in extra slides?

DR. NATHAN: Sorry. Can you make sure you talk into the mic, please?

DR. COURSEY: Oh, sorry.

Can we please bring the slide 27 in our extra slides?

DR. BAHADORI: This is Lila Bahadori from FDA.

There's been a lot of discussions about the residual volume reduction. And one of the problems is that, yes, we know that hyperinflation is bad, and a reduction in residual volume is probably good. We don't know what degree. There's very little data on what degree of residual volume reduction translates into actual clinical benefit for patients. And that's where we are right now.

We have looked at publications to look at things for minimal clinical important difference. What we found was based on 1-month data. It wasn't enough. When we look at any of these procedures that are done for any kind of bronchoscopic lung volume reduction at 1 month, the data looks fabulous. It's just that what happens past 1 month? This is a high-risk device. So is 1 month sufficient to look at what kind of effect that we're looking?

Now, part of the residual, we saw a reduction in the pivotal study for the residual

volume and some of the effects that were discussed. We're also looked at the -- in the slide that we're showing, and I'm not sure if it shows very well. This shows a reduction in the crossover with the residual volume as well. But then when we looked at the results of the effectiveness endpoints in the crossover, we did not see the same effects. And this is the same amount of residual volume reduction with this crossover study.

So we just don't know what the effect is and at what point are we going to see an effect. These are all hyperinflated patients. We still don't know why the subjects between 175 and 225, who were highly hyperinflated, did worse. We just don't have an answer to some of these right now.

DR. NATHAN: Okay. Thank you. Any other points you want to make?

DR. COURSEY: And we'd also like to bring out the slide 44 in our presentation, main presentation. That shows the RV.

DR. BAHADORI: And so this is the slide that we had that I had shown previously, which has to do with the RV cutoff between the 175 to 225, and then the greater than 225 that included both the pivotal study and the crossover study. And, again, in the pivotal study, we are seeing different results than we saw in the single arm observational study. It just goes to all the uncertainty that we're seeing in some of these results.

DR. NATHAN: Okay. Thank you.

Any last questions for the FDA?

Yeah, Ms. Brown.

MS. BROWN: So my understanding is that the evaluation of emphysema is multi-factorial. It isn't just based on the 6-minute walk. It's not just based on RV. So you'd want to take everything in consideration all together. So you might not expect all of the endpoints to move in the same direction. Maybe two out of three, three out of four go in the same direction; that could be success. So that's one comment.

Second comment is the pivotal trial was designed as a randomized controlled study, treatment and control, scientifically rigorous, really well designed. And then the crossover is a, it's a subset. It wouldn't have a primary endpoint all by itself; is that correct?

DR. BAHADORI: So you're absolutely correct. There is -- you do not expect, just like any drug or device, that everybody's going to have the same effect, and you're going to be looking at a spectrum of a treatment effect. But you also have to have -- for a well-defined study, you have to define the endpoints.

MS. BROWN: Right.

DR. BAHADORI: You need to know what the minimal clinical important differences are. You need to know what some of these endpoints, where they anchor to sound clinical outcomes. And that's where we have been struggling with some of this. The observational study, in a way, represents maybe a group of patients that are going to be treated in the real world. And it's not part of the randomized controlled trial. It is completely different. But it again brings up what are some of the things that we might be expecting to see if this device is being used out there.

MS. BROWN: So it's a smaller group of people. It sounds like it might be a better group, I mean, a group of people that started off better.

The other group I was curious about was the roll-in patients. So the roll-in patients, if I understood correctly, 40 patients who are just like the treatment patients. And they look like they did pretty well. So I was wondering -- so, first of all, I think, looking at the crossover patients by themselves isn't -- for me isn't as scientifically valid as starting with the randomized control piece. But once we start talking about single-arm groups, was the roll-in group -- did you consider them successful?

DR. BAHADORI: So we looked at the roll-in group as well. This was -- two subjects were enrolled at each of the sites for a learning, for learning purposes. There -- it was a

small number. It was about 40 patients. And we did look at these numbers as well, including adverse events and for effectiveness. And the results were not as -- it was not enough for us to be able to make any conclusions based on that.

MS. BROWN: So I understand it's not quite enough. I would say the same thing about the crossover patients, that they're not quite enough. But once we start talking about this is 40 patients, it sounds like a pretty, you know, decent group. And they have 42% responders on 6-minute walk test, 72% responders on SGRQ. So that group that was handled in the same way looks pretty good.

DR. BAHADORI: So when we looked at the randomized controlled trial, some of these endpoints and their minimal clinical important differences were -- even though they met statistical significance, they still did not meet the clinical significance, or there was clinical uncertainties related in terms of how much of a positive effect they may have for patients.

The crossover that we looked at, one of the reasons that we looked at the crossover group as well -- I mean, we actually looked at the data in totality and -- including the roll-in. When we looked at the crossover, the subjects that went into the crossover were the initial control subjects, as long as they met the inclusion/exclusion criteria again after 12 months. And about 65% of these subjects chose -- basically got enrolled into the crossover.

When we looked at their baseline characteristics now, 12 months later, their baseline characteristics were very similar to the group that was initially enrolled and was very similar to the treatment group. So we were taken a little bit by surprise to see -- and there were a lot of confounding effects. There were everything from age, BMI, pulmonary rehab. There were a lot of questions, and all we were saying is that we just don't know what -- which one of these are affecting.

Is it the difference that somebody is a -- was anything happening in the first place?

Is it because these patients are a couple years older? Is it because they're in the United States versus OUS? We just don't know. There was just a lot of things we didn't know about what the differences were.

MS. BROWN: So I can see that what caught you is just that thought that the crossovers weren't doing as well. So the -- it seems to me that the comparison between the treatment and the control group in the primary time, when we know everybody's doing, on the same conditions, is a really valid comparison. Also, those run-in patients -- what are they called -- roll-in patients look like a pretty valid -- better comparator for me because they're being treated under the same conditions as the primary population as well. So, anyway, thank you.

DR. BAHADORI: And if we look at slide 22, it's the baseline characteristics for all the subjects, basically both in the pivotal trial and in the crossover, and these were all similar.

DR. NATHAN: Okay. Thank you.

Dr. Ballman, you had a comment?

DR. BALLMAN: Well, just an observation or a clarification. So the roll-in patients did go through pulmonary rehabilitation before they started, right, whereas the crossover did not have to re-go. Granted, it may not be a 50 m, you know, improvement but, you know, we're looking at an improvement in the randomized that's only 14 m and so.

DR. BAHADORI: And all the subjects underwent pulmonary rehabilitation at the beginning of the study.

DR. BALLMAN: At the beginning, but --

DR. BAHADORI: Correct.

DR. BALLMAN: -- the rollover, the roll-ins --

DR. BAHADORI: Correct. At the beginning, all of the subjects underwent.

DR. NATHAN: Dr. Van Berkel.

DR. VAN BERKEL: Hi. This is Victor Van Berkel again.

So I had just a -- I'm trying not to ask a loaded question, I suppose, but you said that you have seen the data in totality. In your opinion, was the change in the statistical action plan from a parametric to a nonparametric analysis justified, based on the data that was there?

DR. BAHADORI: I'm not in a position to comment on whether it's justified or not justified. All we can do is inform you that this is what we had when we did, when we looked at the final analysis.

DR. VAN BERKEL: Okay. Well perhaps one of our statistical colleagues can give me a little bit of clarification as to what the -- why one would make a change along those lines.

DR. NATHAN: Let me just add to that question, because this is where you have our statistical Panel members -- one of the, I guess, newer concepts is the adaptive clinical trial design, where you adapt the trial along the way based on what you're getting. And perhaps that was what was done with the RV. And that's -- I'm seeing shaking of the head, but maybe not. But can you adjust your statistical plan as well? Is that statistically kosher, so to speak, along the way, based on what you're seeing, if there is a tremendous skewing of some patients?

DR. SCHOENFELD: So according to the IHC guidelines, which is what everybody is supposed to be following --

DR. NATHAN: Sorry. Can I -- could the Sponsor please take a seat? You'll get your turn.

DR. SCHOENFELD: According to the IHC guidelines, you're supposed to have an analysis plan. But if there is a good reason for, that you think that the analysis from the analysis plan would be problematic, you're allowed to change it. And that's my understanding of the guidelines. There is a picture of the whole distribution in one of these

documents, and I'm trying to remember where it is. It's kind of like a bar graph.

DR. COURSEY: Yes. Slide 27.

DR. SCHOENFELD: Do you know what number it is? No. It's the big bar graph with every single -- every --

DR. COURSEY: Yes, slide 27, in FDA slides.

DR. SCHOENFELD: Slide which one? It's in the --

DR. COURSEY: Yes. Slide 27. Can we press the enter?

DR. SCHOENFELD: Twenty-seven.

DR. COURSEY: Enter so that it will come back. It's the next slide. Yes. This is the one. It needs to -- it has a --

DR. SCHOENFELD: It's right --

DR. COURSEY: It has a next. Yes. This one.

DR. NATHAN: That one.

DR. SCHOENFELD: Yeah, that one. So that sort of tells the whole story there. So if you draw bell curves around those two, the two centers of those red and blue distributions, you'll notice that there's a bunch of things on the, way on the outside of those bell curves. So -- and there's a few patients in the coil group that did quite poorly, -200 on the walk. And there's a few that did, a couple, well, 100. And you have the same kind of outliers in the other, in the blue distribution.

And so what that tends to do to normal statistics, to the mean, is that things that are far out tend to -- that are far out of the range tend to create bias in the mean estimate. And, in fact, that's the only kind of thing that does. You can be away from normality quite a bit in lots of ways, but what you don't want is what we often call outliers, but they're not really outliers in this case. They're real values; they're just not -- way outside the normal distribution.

So that would be the, I assume, the rationale for -- that you would get -- the mean result would be swung around a lot by those few people way out there, and that's not really what's of interest here. What's of interest, I think, is the vast majority -- is the comparison of the people right to the -- the red people, right to the right of that 25 m line, and the fact that there are less blue people there, in the bottom. That's -- is that reasonable?

DR. BAHADORI: Yes.

DR. SCHOENFELD: Okay.

DR. NATHAN: Okay. Dr. Ballman.

DR. BALLMAN: Well, I guess I'm a little bit -- I don't know when the plan was changed. I'm a little nervous when data are looked at, in general. I mean, if they had data beforehand on the 6-minute walk test in general, and if -- I mean, I think there's lots of data out there on that. And if the analysis typically are nonparametric, then that's the way it should be, rather than taking a look at the data and saying -- I mean, anything can fail that normality test and still the t-test does quite well. So I'm not impressed that it was highly, significantly skewed. And it's not that much that it's skewed; it's because there's those outliers.

So I'm always a little nervous when the nonparametric and the parametric do not agree when you do not see highly skewed data, which we don't see here. So it calls into question, for me, how robust are the results. But, again, I'm surprised that beforehand, knowing the 6-minute walk test has been analyzed a lot in different trials and so forth, that the decision wasn't made, we're going to do a nonparametric test up front, if that was the issue.

DR. NATHAN: Thank you.

Dr. Pichurko.

DR. PICHURKO: Thank you. Bo Pichurko, Cleveland.

I just wanted to pick up on the crossover population since you indicated that you had looked at their data closely, and specifically with perhaps my own hypothesis, asking your comment on this rather surprising decline in 6-minute walk distance. As was already stated several times, there are numerous factors that weigh in. And it is worth mentioning, I think, that for stage 1 and 2 patients, the 6-minute walk is a submaximal exercise test. For the patients we're discussing, it's a maximal stress test, in people with very limited reserve, one of the reasons the ATS doesn't encourage multiple walks or practice walks.

My question is, in this crossover trial, is it conceivable, particularly in these extreme cases where you saw tremendous drops that influenced mean and median statistics, that these were people who were hospitalized, who were sick, who were deconditioned with reduction in muscle weakness and balance, and things that would influence walks independent of respiratory dysfunction?

DR. BAHADORI: So I can only comment -- and that might be a better question for the applicant. I can only comment on the inclusion/exclusion criteria. So at the end of the 12 months, the subjects that been part of the control had to meet the inclusion/exclusion criteria that was essentially the same as the beginning of the study. And part of this did include things that might affect exercise capacity. That was one of the exclusion criteria.

So not being able to answer that question specifically, but I can say that part of the exclusion criteria, these were expected -- and inclusion criteria, these were expected to be similar patients.

DR. PICHURKO: But then during the course of their 12 months --

DR. BAHADORI: Correct.

DR. NATHAN: I think your point's well taken. When you see a 200 m drop, that's usually not disease progression. That's hospitalization, debilitation, frailty, right. Exactly.

I just -- before we move back to the Sponsor, I want to make sure that there are no

further questions from the FDA and no further comments from the FDA.

(No response.)

DR. NATHAN: Okay. The Sponsor now has the floor --

MS. ANASTAS: Thank you.

DR. NATHAN: -- back, to correct any misstatements of facts, provide clarifying information and call on any experts needed to address the Panel.

MS. ANASTAS: I wanted to the statistical analysis plan and the change in it. I think that's -- at one point there was a comment about an adaptive design. This was not an adaptive design. The FDA had mentioned that we had been providing annual reports on the study to them on an annual basis, which we had, but we had no visibility to the data. Safety data were provided in aggregate form and -- but we did not see additional individual data, and we did not see effectiveness data.

And I'd like to ask Ms. Daugherty to come and please explain the changes to the SAP and why they were made.

MS. DAUGHERTY: Claire Daugherty, BTG.

This slide is a timeline of the study execution. The study started in 2012 and finished enrollment in 2014. In January of 2015 BTG acquired PneumRx as an affiliate, and at this time the BTG team became involved in the project. At that point we reviewed the statistical analysis plan, and it was incomplete. And we updated the statistical analysis plan to include enough details, including assumptions testing in order to execute the analysis plan. And that was finalized in September.

That's the point where we added the additional assumptions testing for the nonparametric, knowing that 6-minute walk is skewed in cardiac trials, and also based on recommendation for testing for skewness and specifying alternative nonparametric analyses from FDA and other programs around that time. That was the basis for the change

to the analysis plan.

MS. ANASTAS: And then one last clarification to Ms. Dodd, regarding the CAO. I just wanted to make sure it was clear that we consider both CAO and pneumonia to be serious events and that we have incorporated learning about it into the mention of it in the IFU and also into the training. We consider them both to be serious.

DR. NATHAN: Are there any further items that came up during the course of the discussion that you'd like to clarify?

MS. ANASTAS: Dr. Sciurba has one more thing to say about residual volume.

DR. SCIURBA: And can I have the table with the -- that includes the RV/TLC correlation as well as the RV with the SGRQ that you had up earlier? You had it up earlier. It showed RV/TLC. It had RV correlation.

So, as you know, I mean, there were some good points made. We certainly would like to see mechanistic ties. And you certainly would like to see some relationship with an objective mechanistic measure. And the point that was made, and I think is a good point, that even in the best trials, when you have these biological mechanistic ties to clinically important outcomes, the correlations are often very low in these independent measurements.

RV can be a driver, but it's mitigated by many complicated things. One is the comorbidity's effect on the 6-minute walk and may separate some of the outcomes down the line. In this case, we see in fact RV/TLC is better correlated with SGRQ than RV. And that would be the case because maybe RV's the driver, but what does TLC do in the context? And when TLC is preserved and RV drops, you get a bigger bang. And so these complicated downstream effects -- and that's one that's observed right there -- are going to mitigate that downstream effect.

Ultimately, what's important is what the patient feels and what they can do. The

problem is that there's a lot more variance in those measurements, but those are most important measurements, and we'd like to see a mechanistic chain of events, and we've got some of that. But I still think we have to rely, despite the necessary flaws in the trial, on those important patient-related outcomes.

MS. ANASTAS: And one last point to Mr. Ryan.

DR. NATHAN: Before we make -- I just want to address something Dr. Sciurba said, because you're quite right. It's what the patient feels and what they can do is what we're interested in. I guess my question is, can they do more because they feel better? And what is the relationship between the SGRQ and the 6-minute walk? Because you show correlations between the RV and everything else, but not those two patient-centered outcomes, and are they -- let's see the correlation between those to know if they're the same.

MS. ANASTAS: Okay. Then I would ask Ms. Daugherty to come to speak to the correlation, the statistical correlation.

DR. NATHAN: I thought everything was against PFTs. Okay. Well, if you've shown it already and all was 0.3, then I'm okay with that.

(Off microphone discussion.)

DR. SCHOENFELD: The previous slide had that on it, didn't it? The one that you just showed us.

MS. DAUGHERTY: This is --

DR. SCHOENFELD: No. You showed us a table.

MS. DAUGHERTY: Right. This is the correlation of change in 6-minute walk with change in SGRQ, which is what I understood to just --

DR. NATHAN: Yeah. That's quite right.

MS. DAUGHERTY: -- be referred to.

DR. SCHOENFELD: And it's point -- I can't see the numbers there. Point --

MS. DAUGHERTY: It's 0.39.

DR. SCHOENFELD: 0.39, so it's fairly high.

DR. NATHAN: Okay. I guess another analysis that could have been done, and you might have done it, is to use the one to validate the other. You used the MID of 25 -- MCID of 25, but arguably it could have been 30 or it could have been 50. In fact, when you looked at 50, the difference wasn't as great. And it would have been nice to see that difference staying at least the same throughout, between the two groups. But --

MS. DAUGHERTY: We did do an analysis that way, if you would like to see it.

DR. NATHAN: Oh, of course.

MS. DAUGHERTY: We did an analysis of thresholds, a responder threshold analysis on the continuous --

DR. NATHAN: I think we did see that, and the difference at 25 wasn't as great at 50, if I recall correctly.

MS. DAUGHERTY: We can show that, if I could have the threshold slide.

DR. NATHAN: I'm actually going to ask a different question. To me, a change of 25 in the walk distance is more valid if there's a -4 change in the St. George's to accompany it, so you use the St. George's to valid the MID of the 6-minute walk.

MS. DAUGHERTY: Right. And there is a paper, the Puhan paper, which showed that in a similar correlation, where SGRQ and 6-minute walk were correlated at a 0.4 level, that that was one of the anchor-based tests to establish the 25 m 6-minute walk. And so we're showing a similar correlation in this study as well.

DR. NATHAN: I'm talking about patient-level stuff for each patient. I'm not sure if you've done that.

MS. DAUGHERTY: I don't think we have that to show you. I thought you were

referring to an analysis that I'm showing here, which shows the separation of the proportion of patients that exceeded any given threshold over the entire range. And what this shows is that regardless of what threshold we would have chosen, whether it's 25 m, 50 m, or 10 m, that the treatment arm was in excess and superior to the control arm, regardless of the threshold we would have chosen.

DR. NATHAN: Got it. Thank you.

MS. ANASTAS: One last point of clarification, Mr. Ryan. The proposed indication for use does not include the 225 number. We're interpreting the severe hyperinflation to be 225. The proposed instructions for use does explain that analysis. But we've left the number off because we do believe that physicians should have some amount of discretion, clinical discretion, to incorporate the holistic view of the patient's health. And, of course, we're open to further discussion on that point.

Thank you.

MR. RYAN: Yes. Mike Ryan, FDA.

Yeah. I certainly understand. Just wanted to clarify that the indications before the Panel today are severe hyperinflation without the 225, as you mentioned.

Thank you.

DR. NATHAN: Any further -- yes. Go ahead. Please introduce yourself.

MS. KLINE: Andrea Kline. Could you please comment on the lack of diversity among the study subjects, with about 95% of the individuals or higher than that being white in the sample?

MS. ANASTAS: The diversity, it has common -- a lack of diversity is a common problem amongst clinical trials. It was a problem in NETT as well. The Sponsor attempted to increase diversity by putting sites in areas, in geographical areas where there was more diversity. We also made adaptations to some of the PFT measurements to make sure that

different -- other races weren't being disqualified. But we ended up with 95% Caucasian.

So I would also ask Dr. Criner to speak to the effect of lack of diversity on the study.

DR. CRINER: The lack of diversity -- Criner.

The lack of diversity wasn't from no effort of trying or having sites or recruiting patients of different minority. The issue is that emphysema is much more prevalent in Caucasians than it is in African Americans or other races overall. That's been shown in several studies, one -- our own internal study at Temple University. We show that the prevalence of emphysema as opposed to airways disease is much stronger in Caucasians than it is in African Americans. And also that was shown in the NETT study, and it's been recently shown also in the COPD gene, that emphysema is much more prevalent in Caucasians than it is in African Americans or other racial groups.

DR. NATHAN: All right. Any further comments from the Sponsor, or any further questions, points of clarification from our Panelists?

Yes. Okay.

DR. CHEN: I just had a quick question for the clinicians. What is the best way to look at the clinical efficacy of this? Is it to state that there's a median improvement in 14 m, which is below the MCID? Or is it to say that a higher percentage undergoing the coil procedure have a positive -- have an actual responder rate, so that when you have that discussion with patients prior to procedures, what is the best way to provide informed consent?

MS. ANASTAS: I'd ask Dr. Sciurba to come to the microphone to speak on how he would describe that to his patients.

DR. SCIURBA: Thank you for asking that question. It's the question that I think is important. I mean, you're not going to tell, in a population of 100 people when you make the explanation to your patients, that the average or the median is 14. You're going to say

what's your chance of feeling that, okay. And so -- and that's how the patient preference study was designed. So if I can say that 42% chance you're going to walk 75 feet further, 67% chance you're going to feel a minimal importance in, I won't say SGRQ, but a symptom questionnaire, 49% chance your lung function will improve in what everybody feels is a meaningful way in what you will feel, then you counter that with but you're going to have 20% chance of pneumonia, 10% chance of any kind of a pneumothorax, some chest discomfort along the way -- and you saw the results of the patient preference study. I thought it was well designed. I thought it was going to be really the points I bring up to the patients. And almost half the patients say, yeah, I have got no other choices. And so that's how I would explain it. So I think that's the right question.

DR. NATHAN: All right. Dr. Van Berkel.

DR. VAN BERKEL: Yes. Victor Van Berkel again.

So this is kind of maybe a little bit of a technical question about the CT scan reading. So the -- I'm just trying to figure out how, once this goes out into the community -- so for lung volume reduction surgery, for example, there has been a lot of data demonstrating that there's terrific inter-operator variability in reading a CT scan and being able to say where there's heterogeneous versus homogenous disease.

And I know that you guys laid out this, you know, 0 through 5 scoring system for the lungs. Especially since at the upper bound of that, you're saying if someone is a 5, they don't get the coil, who makes that decision? Is that going to be your office? Like do the CT scans go to you guys, and then you read them and say, okay, upper lobe on the left is 4, upper lobe on the right is 3? Is that the radiologist at the institution that's going to be doing it? Is it the pulmonologist who's doing it? Like who is ultimately responsible for that?

MS. ANASTAS: It is not our plan to do that as a company. Our plan is to provide training on the instructions for use, indicate a number of visual elements of CT that are in

that instructions for use that exclude patients, and to go over the CT requirements as part of training, but not to do it as a central core. The central lab was used as part of research to ensure that we had absolute consistency across all of the clinical sites. In Europe the individual sites do their own CTs, and that has worked well for us.

DR. VAN BERKEL: Okay. Thanks.

DR. NATHAN: Ms. Brown, you had one more question?

MS. BROWN: Sorry. Thank you. So the question I had had to do with patient preference testing. How much discussion went on with FDA about patient preference testing before the study was initiated?

MS. ANASTAS: We had a pre-submission and then an in-person meeting. And then after that, we did provide the final protocol to them, but there was no further conversation after that point. And then, subsequently, they did request some specific analyses, which we provided.

MS. BROWN: Thank you.

DR. NATHAN: Okay. If there are no further comments from the Sponsor, our Panelists, or the FDA, then we'll break a little bit early. We'll take a 15-minute break. Panel members, do not discuss the meeting topic during the break amongst yourselves or with any other members of the audience. We will now resume at 3:15 p.m.

Thank you very much.

(Off the record at 2:59 p.m.)

(On the record at 3:17 p.m.)

DR. NATHAN: I see our Panel members coming in, so let's get going. But before we get going on the FDA questions, the FDA would like to respond to something that the Sponsor had stated earlier. So I'd like to call on the FDA to provide a clarification.

DR. BENZ: Heather Benz, FDA.

We wanted to provide clarification on a couple of comments the Sponsor made at the end of the previous session.

First, prior to the preference study, the Sponsor did provide a pre-submission and come for a meeting with the FDA. The FDA provided a variety of feedback and opportunities for additional engagement on the patient preference study. At that point the Sponsor later submitted a protocol, without opportunity for feedback, and then later submitted the preference study.

The other point of clarity is there was a statement that almost half of patients were shown in the patient preference to prefer the device. This number likely comes from the RENEW clinical trial site participants, and we wanted to make it clear that these patients had not had experiences with the device and had been presented with the hypothetical profiles that we discussed in the patient preference study portion of the earlier talks.

DR. NATHAN: Okay. Thank you.

Now let's move on. At this time, we're going to focus on discussion of the FDA questions. Panel members, copies of the questions are in your folders. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. Please show the first question.

DR. COURSEY: Derya Coursey, lead reviewer.

The first non-voting question.

1. The clinical study for the ELEVAIR coils demonstrated a statistically significant absolute difference in 6-minute walk test between the treatment and control arm at 12 months (median difference of 14.6 meters, adjusted mean difference of 10.2 meters). In addition, this study demonstrated statistically significant improvement in the secondary endpoints of FEV_1, 6-minute walk test responder rate, and SGRQ. Potential confounders affecting the interpretation of these results include:

- Post-randomization differences in patient management. For instance, data regarding pulmonary rehabilitation maintenance was not collected;

- Open-label design affecting patient reported outcomes such as SGRQ;

- Lack of correlation between US and out-of-U.S. results;

- Single arm observational crossover study conflicting with pivotal study results.

Please discuss the following questions:

a. The primary effectiveness endpoint evaluated the absolute difference in 6-minute walk test between the treatment and control arm at 12 months. The results showed a median difference of 14.6 meters (adjusted mean difference of 10.2 meters). Please comment on the clinical significances of the observed treatment effect in 6-minute walk test.

DR. NATHAN: All right. So we're going to do part (a), part (b), so you want us to discuss part (a) first. Oh, I see there are actually four parts to this question. All right.

(Laughter.)

DR. NATHAN: We've got a ways to go. I'm glad we started a little bit early. Okay. So Panel members.

MR. RYAN: Mike Ryan, FDA.

If I could, just as chair, however you guys feel it's best to discuss these, you can do (a) through (d) at once or go one by one.

DR. NATHAN: I think one at a time. My memory's not that great that I'll remember (a) by the time we get to (b), so --

(Laughter.)

DR. NATHAN: All right. Who wants to have a first crack at this? Okay. Go ahead.

DR. CASSIERE: Hugh Cassiere, North Shore.

So just to answer the question specifically, we're talking about a very debilitated

patient population, and I think, you know, any improvement, 14.6 or 10.2 m, is I calculate that's about 15 yards. So for a patient that -- for us, it may sound like a small distance, but for a patient, that could be, you know, a football field.

So I think using an arbitrary number, 25 as being a threshold for minimally, you know, significant improvement is probably not applicable in this population, especially a population that doesn't respond to drugs and only really has very limited options. I think this is a significant effect.

DR. NATHAN: Go ahead.

DR. DODD: Lori Dodd.

I just want to follow up on that and ask you, given the concerns about potential placebo effect or, you know, concerns about the differences in patient management, I get -- I begin to get concerned when I see small treatment effects, that they may be influenced by other things, particularly in a study that's not blinded. So given that, does that impact your interpretation of the potential clinical significance of the 14.6 m, that it could be related to other factors?

DR. CASSIERE: Hugh Cassiere again.

So that's a loaded question because I have a lot of concerns that I think will play out as we discuss. But to answer the specific question, they met their primary goal in the study, and I think that that distance, I think we're being asked if this is a clinically significant distance or not. My concerns about the interpretation of the data will come later on. Does that help?

DR. DODD: Yeah. I guess I was just taking into context the text above the question that refers to all the potential confounders, so ---

DR. NATHAN: Dr. Chen.

DR. CHEN: So I agree with your statement, Hugh. It's a small difference but

potentially meaningful. But I guess my question is does it fall outside the range of variability of doing the test, I mean reproducibility of the test.

DR. NATHAN: I think, you know, we look at this as statistically significant, but I don't know if we should take that absolute number and say is 14 applicable to every patient and what does it mean for every patient. I think they've shown a difference statistically, and that allows us to look at in other ways, like the categorical analysis of 25 m. How many patients were over 25 m versus -- and that, I think most people would agree, is minimally important difference. It might be relevant to an individual patient.

So having that statistical difference of 14 m, and it could have been 12 m or could have been 10 m, allows us to look with some confidence at other ways that -- in terms of analyzing the 6-minute walk change.

Yeah.

DR. VAN BERKEL: This is Victor Van Berkel.

So I would respectfully disagree, and I don't think that it's clinically relevant at all, to be perfectly honest. I think, you know, in the transplant population, for example, we have limits on the 6-minute walk, that someone has to achieve a minimum number for us to consider them for transplant at our program. So like, yeah, you have to meet 600 feet or whatever. And people will fail that, and we'll say all right, we'll try again tomorrow. And they'll come back tomorrow and they'll do it, and they'll make it by 100 feet. I think that this is a small number that I think is within the noise of what the testing is.

DR. NATHAN: I would say for an individual patient it's within the noise, but when you have many patients and, you know, then I think that kind of noise gets diluted out as well.

I think Dr. Pichurko made a very good point earlier when he said that it's a maximal test for these patients. And I think when you have a maximal test, then there's more

inherent variability for patients who are, you know, can walk as far as they can and can pace themselves, then there's much more variability, rather than it being when it's a maximal test. And I believe that this patient population is sick enough that, yes, they only walked 300 meter, but for them it was a maximal test.

Go ahead.

DR. PICHURKO: Pichurko, Cleveland.

I feel that we probably shouldn't stray too far from the orthodoxy of interpreting 6-minute walks as supported by the ATS statements, several to date. And by that, I mean that the purpose of determining clinically important minimal differences is to separate noise from signal. And, in fact, it's a disease-specific level, as many of you know. So pulmonary hypertension has its distance. Diffuse parenchymal lung disease has its difference.

And this is not to incriminate or diminish the respiratory impact of the intervention. It's simply a reminder that this very important test of functionality, this self-directed test where people are free to stop and start as many times as they want, is simply influenced by factors other than respiratory health.

DR. NATHAN: Sure. Anyone else want to comment on the question from the FDA in terms of clinical significance?

(No response.)

DR. NATHAN: All right. Let me try and sum it up as best I can. That while there was statistical significance, the clinical significance of a 14.6 m change in an individual patient is very uncertain, given the variability in the test and other factors that might affect it. However, I'll caveat that by saying that, you know, this does provide statistical significance for the patient population as a whole, but for an individual patient, you know, there's a lot of uncertainty around the distance of 14.6 m. I'm not sure if that --

Mr. Ryan, does that address your question to your satisfaction?

MR. RYAN: Mike Ryan, FDA.

Yes, I think it does.

DR. NATHAN: Okay. Thank you.

All right. So let's move on to (b). Oh, that's your part.

(Laughter.)

DR. COURSEY:

b. The median percent change in FEV_1 at 12 months was 3.8% in the coil treatment group and -2.5% in the control group, resulting in the median difference between the treatment and control group of 7%. Please comment on the clinical significance of the observed treatment effect in the percent change in FEV_1.

DR. NATHAN: Okay. Who wants to take the first crack at this one?

Ms. Brown.

MS. BROWN: With respect to what should be considered clinically significant, I think that the way that the MCID can be applied is on a per-patient basis, so that what we'd want to look at is the proportion of patients that achieve an MCID. And for the proposed patient population, the treatment group, 49% patients were responders on FEV_1 for MCID, and 19% of patients in the control group, and was statistically significant. So I think that that's clinically significant.

DR. NATHAN: I guess, would the same -- let me pose this to the Panel members. Would the same argument hold here as held for the 14 m change, or does the Panel feel that 7% in the FEV_1 is more meaningful than a 14 m change in the 6-minute walk distance?

Dr. Pichurko.

DR. PICHURKO: Pichurko, Cleveland.

I think, in this case, the FEV_1, although represented as a marker of lung function, is

probably a limited value and a -- I don't want to use an overly strong word -- a poor surrogate for the salutary effects of lung volume reduction surgery on hyperinflation. By that I mean that a single forced exhalation doesn't factor in the changes in configuration of the diaphragm. The movement and deflation of the curve onto a more compliant portion of the respiratory system, pressure volume curve, all of which really augments both inspiration and expiration, so that let's say a test like maximal voluntary ventilation, repeated inspiration and expiration, might give us a more complete picture of the benefit of such surgery.

The FEV_1 is what we have to work with, and my hunch is that it probably understates the benefit of the surgery.

DR. NATHAN: Okay. Anyone else with any comments on this particular question?

So, Mr. Ryan, let me see if I can sum this one up. It appears that the group feels that 7% might be clinically meaningful in patients; however, there is concern that this is not the best surrogate for hyperinflation and might not fully reflect the benefits of the procedure. And I guess the corollary of that is, it might not fully reflect any downside to the procedure as well. But it is, in most -- in the Panel's viewpoint, it is a number that's clinically meaningful.

Does everyone agree with that?

(No response.)

DR. NATHAN: Okay. Let's move on. Let's move on to (c) then.

DR. COURSEY:

c. The SGRQ improved by -8.9 points at 12 months in the coil treatment group as compared to the control group. Please comment on the clinical significance of the SGRQ improvement in the context of an open-label trial and the increase in the COPD-related adverse events, including hospitalization and emergency room

visits for the treatment arm.

DR. NATHAN: Okay. Who's going to pick this one? Who's going to take this one and run with it?

DR. CASSIERE: Hugh Cassiere, North Shore.

So, again, this is like -- I guess what you're getting at, there looks like there's a discordance of data. We have a questionnaire that says life's improved, but we have increased hospitalizations and burden of illness. So that's a little difficult, but the -8.9 is kind of hard to ignore, that there's some -- I mean, I would think that would be clinically significant, in terms of change in the score, but again, you have to wrestle with the fact that, how does that translate into increased hospitalizations, pneumonia, hemoptysis. It makes you question the validity of the data.

DR. NATHAN: I think, especially in the context of -- I just want to remind the Panel of something the FDA mentioned, that it wasn't necessarily measures of shortness of breath within the SGRQ but other psychological domains that appear to drive the difference, and so, to your point as well, in terms of, you know, the effect of being an open-label study.

Ms. Barnes.

MS. BARNES: Theresa Barnes, patient advocate.

You know, I think that sometimes, especially with data, it doesn't speak to individual patients, as you know. And I think that the quality of life measures are so important that even though the hospitalizations and emergency room visits and healthcare utilization was up -- I have concerns about that -- but it doesn't always translate into that everybody is doing horribly. In fact, if a patient can walk to the bathroom whereas before they couldn't walk to the bathroom, that's kind of a big deal.

And I think that if, in the context of this questionnaire, patients perceive that they, you know, are doing better by, you know, almost 9 -- well, more -- 9 points, that's -- I think

that matters, especially in a severe disease that's basically end stage.

DR. NATHAN: So you're saying that even despite the increased hospitalizations, respiratory tract infections, the fact that they can attest to improved quality of life makes it more significant?

MS. BARNES: It does because it doesn't discount those things, but it is, from my perspective, you know, it may be still significant. Yes.

DR. NATHAN: Yes?

DR. CHEN: Alex Chen.

So I think this is a valuable number. My only question is whether or not this is a direct result of the procedure or confounding factors.

DR. NATHAN: I guess you could argue the same in terms of knowing they had the procedure, and by gosh, I'm going to feel better no matter what.

DR. WANG MEMOLI: I was -- Jessica Wang.

I was just going to comment that possibly the reason why people presented to the hospital more, had more exacerbation is because they knew they had a procedure, and maybe they were more hyper-acute and aware that they would have potential side effects as well. So there's always confounders on both ends.

DR. NATHAN: True.

DR. BALLMAN: Yeah. I'm just wondering how many people have had experience with this instrument and how influence is it to a placebo effect. I don't know. But if there's a -- if it's only on the psychological variables where it's better, that brings into question that as well.

DR. NATHAN: Yeah.

DR. SCHOENFELD: So not being a clinician, what I would always --

DR. NATHAN: Sorry. Always remember to introduce yourselves for the

transcription.

DR. SCHOENFELD: David Schoenfeld, yes, which is not a clinician.

(Laughter.)

DR. SCHOENFELD: I always -- when people come to me with what's clinically significant for sample size, I always have a lot of trouble because some things we know what's clinically significant because we have lots of experience with them. And other things we don't have a lot of experience with, and those things it's very hard to know. So what I do in that case -- so I'm not sure that this is the case for everybody, but it's surely the case for me, I don't know, is I look at the standard deviation of the population. And I say, so how far did my change move me relative to all my peers who are equally sick?

And so what I get with the 6-minute walk is not much, because the standard deviation in the population as you started out was about 80 m. And this moved it about what, 10 or 15 m, maybe 20 m for the suite, the group that's greater than 225, so it was only a little bit. So it sort of moved it, moved the median to 60th percentile, and it's not that much.

It's more for the FEV_1. It was 7. It was -- the standard deviation there was 0.22, so it moves it 0.07, so it's about a third of a standard deviation.

The SGRQ is much more positive because the standard deviation there was 12. So a difference of 8.9 points is almost a whole standard deviation, which according to Cohen, who invented this idea, is a large effect. So from that point of view, that it's moving it relative to its peers, this is a fairly large clinical effect. And this is the way statisticians -- well, the way I deal with situations when I don't understand clinical significance very well.

DR. BALLMAN: This is Karla Ballman.

Just in the absence of confounding.

DR. SCHOENFELD: What?

DR. BALLMAN: In the absence of confounding.

DR. SCHOENFELD: Yes.

DR. BALLMAN: If there's no placebo effect.

DR. SCHOENFELD: This is assuming that these are all real.

DR. BALLMAN: Yeah.

DR. NATHAN: I think, as clinicians, we never look at the standard deviation. It's not my first go-to thing when I've got to look at a test.

(Laughter.)

DR. NATHAN: But the statisticians are kind enough to dumb it down into the MID for us. And, you know, the MID for the 6-minute walk is 25; for the SGRQ it's 4. So this is almost double the MID, which takes into account standard deviation and other anchor-based methodologies.

Any other comments on this particular question before I try and sum it up?

Yes.

DR. HAWKINS: So -- Randy Hawkins.

So quality of life is really the important. And I don't think the former and the latter, the latter being the hospitalization and emergency room visits, those two things don't have to be mutually exclusive, particularly since at the end of the year, folks still felt very, very good, which came from the SGRQ. So we have folks who feel a lot better, being able to do things like getting dressed and shopping, play with their grandkids. But they have an exacerbation in the middle of that, and they get sick and go to the ER. But at the end of the year they still felt good. So they don't have to be mutually exclusive.

DR. NATHAN: All right. Let me try and sum it up at this point. So the Panel feels, Mr. Ryan, in response to Question 1c, that the change in the SGRQ is clinically significant and a relative patient-centric measure that stands the test of having -- some of these

patients have respiratory infections and being in the hospital, and still despite that, feeling better, even -- perhaps even if it's just psychologically, they feel better. But the SGRQ is validated as, I would say, kind of the gold standard PRO for patients with COPD.

So, in answer to the question, yes, the Panel does feel like this is clinically significant, and my sense is perhaps even a little bit more so than (a) and (b). I think (a), people were a little bit skeptical, (b) perhaps a little bit more lukewarm, but feel like this is maybe more relevant than (a) or (b) in terms of clinical relevance.

Mr. Ryan, does that answer your question?

MR. RYAN: Mike Ryan, FDA.

Yes, it does. Thank you.

DR. NATHAN: Thank you.

Let's move on to (d), please.

DR. COURSEY:

d. The observed treatment effect for the U.S. subgroup was consistently smaller than that for the out-of-U.S. subgroup for all the primary and secondary effectiveness endpoints. Also, the treatment by region interaction effects were statistically significant for 6-minute walk test, FEV_1, and SGRQ, suggesting that pooled results may not be generalizable --

Okay. At this point I've mispronounced that.

(Laughter.)

DR. COURSEY:

-- to the U.S. population. Please comment on pooling of the U.S. and out-of-U.S. data for an overall assessment of effectiveness of coil treatment for the U.S. population.

DR. NATHAN: Okay. Who wants to comment on that first?

(No response.)

DR. NATHAN: Well, I'll throw something out first, and I think the Sponsor's explanation for this, which I think is a plausible explanation, is that many of the patients in the U.S. -- I think it was 75% or something like that -- had fell in the group with an RV less than 225% of predicted. And driving the difference, rather than regional differences in COPD or COPD management, was their lung function and degree of hyperinflation, where the ex-U.S. group was much more hyperinflated. So I think we got to address this question in the context of that.

DR. SCHOENFELD: I just want to say that I don't really usually believe in interaction testing at a 0.15 level and then saying things aren't poolable. I think the interactions you worry about are qualitative interactions where it doesn't work in one group and works in another. And interactions that are just merely quantitative are not really very useful. And I tend to -- also, since you have more information about the whole group than you have about any subgroup, I always sort of shrink the interactions towards my prior belief, towards the grand mean. So I'm not sure that I'd consider poolability a problem here. Or I don't consider poolability a problem here.

DR. NATHAN: Does anyone from the Panel feel that the poolability is a problem?

(No response.)

DR. NATHAN: Okay. So in answer to this Question 1d, Mr. Ryan, the Panel feels that the poolability of the results is not an issue, and the applicability of the results is not an issue as it pertains to the U.S. population. I think the explanation I gave initially about the differences in the RV is a biologically plausible explanation why we might have seen these differences.

Does that answer the question satisfactorily?

MR. RYAN: Yes, it does. Thank you.

DR. NATHAN: Thank you.

Let's move on to Question 2, please.

DR. COURSEY: Okay. So this has a very long introduction, so please bear with me.

2. Multiple subgroup analyses were performed:

- In the treatment arm, the pivotal study enrolled mainly subjects with homogeneous emphysema, 77%. The median treatment effect for the 6-minute walk test at 12 months for the homogeneous emphysema subjects was 9 meters. In the crossover study the homogeneous emphysema subjects had a median decline of 20 m in the 6-minute walk test at 12 months.

- In the treatment arm, the pivotal study enrolled 23% subjects with heterogeneous emphysema. The median difference between the treatment and the control in 6-minute walk test was 27.4 m based on the small number of subjects with heterogeneous emphysema.

- After study results were available and analyzed, the Sponsor focused on the subpopulation with residual volume greater than 225% predicted for all effectiveness endpoints and included "severe hyperinflation" in the indications for use. Data of 80 subjects (73 in U.S.) with 175% predicted RV and greater than 175% predicted and less than 225% was not included. For the primary effectiveness endpoint of 6-minute walk test, the coil treated subjects with residual volume less than 225% predicted declined more than the control subjects with residual volume less than 225% predicted. Additionally, in the crossover study, residual volume greater than 225 % subpopulation did worse than the RV with less than 225% subpopulation.

Okay. Now, part (a). Okay.

(Laughter.)

DR. COURSEY: Pronounce RV at this point.

a. Based on the proposed mechanism of action of compression of diseased tissue to allow more normal tissue to expand, the prior NETT study results, and pivotal study results, please comment on the observed treatment effect in the homogeneous and heterogeneous emphysema subpopulations.

DR. NATHAN: Okay. Can I answer yes? I'm kidding. Okay. Let's open it up to the group.

Yes.

DR. VAN BERKEL: So this is Victor Van Berkel.

And forgive me. If you can bear with me for a second because I actually think that this is incredibly important, and I have to -- speaking mostly to maybe some of the non-clinicians in the room, I feel I have to give a history lesson about lung volume reduction surgery because I think it's relevant here.

So lung volume reduction surgery was the first non-transplant surgical attempt to help with emphysema. It was initiated in 1957 by this guy named Brantigan, who went and did operations to cut out bad emphysematous portions of lungs. He killed a lot of people, and everybody stopped doing it. They said this is a bad idea.

And then in the late '80s and early '90s, a guy named Joel Cooper at Washington University in St. Louis kind of after starting doing some transplants there, kind of resurrected the idea, and published a paper in 1983 of 20 patients that he had done lung volume reduction surgery to who did incredibly well. They had an improvement in their FEV_1 of something like 86%. They had a dramatic improvement in their exercise capacity, and they did great.

And everyone got very excited about this because this was the first time that we could do anything, short of transplant, that was beneficial to emphysema patients. And so

lots of people in the United States started doing lung volume reduction surgery. And, once again, we killed a lot of people, so much so, then in 1998, if I'm remembering correct, the HCFA, or the Health Care Financing Administration -- it was a precursor to CMS -- basically said you guys can't do this operation anymore until you figure out what the hell is going on, because you had a 25% in 1-year mortality from lung volume reduction surgery.

And that is what led to the NETT trial. You keep hearing about the NETT trial today, and the NETT was this large study, trying to figure out who actually deserved to get lung volume reduction surgery. And what we found out when we did the NETT trial is it got Dr. Cooper, who published that first paper, just got extraordinarily lucky, and he picked 20 people who happened to be in this very small window of individuals that benefit from lung volume reduction surgery.

These were people who had heterogeneous disease, predominantly upper lobe variant, and had a DLCO that was above a certain level. And if you picked people who had a DLCO below a certain level or had homogenous disease, those people did really, really badly.

And I think that that's an important thing to remember when you then look at this data where we're looking at small numbers, and we're lumping everybody together and we're saying that there are some people who are doing well. I'm very nervous that, just like in lung volume reduction surgery, there is going to be a subset of people who will benefit from this procedure, no question, that will get better, but there will be a lot of people who will not.

And I think that you get a hint of that in this data here. If you're looking at A, you can actually see, in the heterogeneous population -- the other thing that bugs me about this data, as multiple people have talked about, is that the crossover population just didn't work very well. The crossover population and the heterogeneous population worked great. And

that's concerning to me, that we're missing a larger picture.

And so I would say, to directly answer the question, I think that there probably is something to the difference between homogenous and heterogeneous emphysema subpopulations. We don't have enough data here to really be able to make an answer to that. But I think that, to use the age-old cop-out that everybody uses, more studies are probably needed on this.

DR. NATHAN: All right. Anyone else want to comment?

(No response.)

DR. NATHAN: I think, you know, you gave a very nice history of lung volume reduction, which was, you know, since -- I don't want to say approved but now reimbursable by Medicare, provided you have the right characteristics, namely low exerciser, upper lobe heterogeneous, upper lobe predominant disease. And so from the NETT study we were able to figure out a subgroup who benefited, not only quality of life but also improved survival.

And so we do, do lung volume reduction surgery today, but it's a very, very small number. Most people, you know, have kind of turned away from it, but there's still definitely that subpopulation who does benefit from it. And, arguably perhaps, lung volume reduction is underutilized.

And I am concerned about the results that you point out here, I mean, and the fact especially that the crossover group didn't, you know, show the same benefit. But as I look at the numbers here, if I'm interpreting correctly, the number's very small; crossover heterogeneous, they did improve 25 m; is that correct? So at least there's some improvement there for sure. They didn't get worse.

And as we start with any emerging technology, and as we enter the era of personalized medicine, and we have different types of morphologic COPD, it's perhaps

naive to think that one size fits all, and maybe it's a high bar to raise that, well, gosh, if everyone doesn't get better, then it doesn't work. Would you be in agreement that there is a subset of patients, maybe heterogeneous, upper lobe predominant disease patients, where perhaps it does work?

So I just want to put that in the perspective of, you know, precision medicine and not blanketing it all as negative, especially lung volume reduction, because there is still a role for lung volume reduction.

DR. BALLMAN: May I comment?

DR. NATHAN: Yeah.

DR. BALLMAN: Hi. This is Karla Ballman.

I mean in, you know, cancer we do precision medicine, but you know, if a trial overall did not pick an enriched group and was negative, it's still a negative trial. And another trial would be done to show that in the small group that looked like it was positive, it really does work. So I agree that there might be a signal here, but I don't agree that it's definitive at this point.

DR. NATHAN: Yeah.

MS. BROWN: In talking about LVRS and the NETT trial, one of the backdrops was that in the beginning, when the homogenous patients were being done with less than 20% FEV_1, there was a really high death rate, and those patients got eliminated. And even when we were dealing with the non-high-risk NETT population, there was still a higher death rate than what we see in this study.

It was comforting to me, in the RENEW study, that the treatment and control mortality rate was equivalent and, you know, reasonably low.

DR. NATHAN: Please remember to identify before you talk.

DR. VAN BERKEL: It's Victor Van Berkel again.

And I absolutely agree with that. And this is obviously a much less morbid procedure than lung volume reduction surgery. I would also say, though, that the effect that we were seeing is substantially less than what we would see for lung volume reduction surgery. The change in 6-minute walk, the change in FEV_1, the change in the quality of life is much less. And the durability is much poorer as well.

DR. NATHAN: Any other comments from the group before I attempt to summarize what has just been said?

(No response.)

DR. NATHAN: Okay. So, Mr. Ryan, in answer to Question 2a, please comment on the observed treatment effect in the homogenous and heterogeneous emphysema subpopulations, there does appear to be a difference in response, with the heterogeneous population seemingly doing better, although the numbers are somewhat small. And there is concern from the group about some of the apparent disparity in the results that we're seeing between the main treatment phase and the crossover phase in particular. But there does appear to be a signal coming out of the study in terms of a benefit for a subgroup of patients.

Would that be fair to summarize it like that? Does that meet with your satisfaction, Mr. Ryan?

MR. RYAN: Yes, it does. Thank you.

DR. NATHAN: Thank you.

All right. Question 3.

DR. COURSEY: 2b. Not there yet.

(Laughter.)

DR. NATHAN: That's it. All right. Oh my gosh. Sorry. I missed a page. Wishful thinking.

DR. COURSEY: I have too. It's 4 o'clock.

DR. NATHAN: Go right ahead.

DR. COURSEY: Okay.

b. Please comment on the study results in the pivotal and crossover studies based on RV cut-offs (specifically, RV>225% versus RV<225%).

DR. NATHAN: I guess we can all look at these numbers for a second. Anyone want to comment on this question?

Go ahead.

DR. CASSIERE: Hugh Cassiere, North Shore.

So this just goes back to my question way back when about using the residual volume as a biological marker for efficacy. On one hand, we're saying that an RV>225% has clinical benefits in the coiled group and not in the crossover group. And in the same breath, we're saying that there's no correlation in the residual volume with the questionnaire and the 6-minute walk test. So that kind of deflates the data for me.

And on the other end, we're talking about in the crossover group, where you actually have, it looks like, at least in the change in the 6-minute walk test, a decrement in that patient population who you originally found the benefit in, in the pivotal study. So this, for me, is very confusing. And the reason why it's confusing is how do you pick which patient population to use this device on? If we're saying hyperinflation, we have the pivotal trial that shows that it has some benefit but no correlation with the 6-minute walk test and the questionnaire. And on the crossover test, it shows actually harm.

So I'm having some difficulty with this, and I'd like to hear what the other Panel members have to say.

DR. NATHAN: Actually, as I look at the numbers, and I look at the RV>225, we have two groups. One's -8, and the other one's +15. And I -- oh, sorry. I listened to -- never

mind. Okay.

Anyone else want to comment on this?

Ms. Brown.

MS. BROWN: Debbie Brown.

So when I look at the overall population and the subset population, they have the same risk profile. I think the risk profile was the SAE rate was the same, whether you were looking at ITT or a subpopulation. So there's no compromise on safety here by going to the smaller population. So I think it seems like going to a smaller population just might be good because when we go to market, we're going to be treating fewer patients than we would with the broader population.

DR. BALLMAN: I guess I'm also troubled a little bit about that threshold because the crossover above that threshold did worse than the crossover below that threshold. So if there's really something biological going on here, it's -- I don't know. And why that number? Why not 200? Why not --

DR. NATHAN: I think we all share that same confusion about it. And maybe I can try and summarize this. So this is in response to Question 2b, that there does appear to be a difference between the group who are above the threshold of 225% on the RV and the group who are less than that, favorable towards the group above 225%. But it appears inexplicable and somewhat troubling why the crossover group who had that RV cutoff at the time of crossover actually did a little bit worse.

So there's some concern from the Panel about this apparent disparity in the results. We would have liked to have seen that crossover group, in my mind, at least do the same rather than get worse, to support the biological plausibility of the coils having an effect in the subpopulation.

Everyone satisfied with that answer?

MR. RYAN: Yes. Thank you.

DR. NATHAN: I'm sorry we can't give you anything more definitive than that, but -- okay.

Let's move on now to Question 3. Thank you.

DR. COURSEY: Yeah.

3. A central core lab was contracted to review all computed tomography scans for the pivotal and crossover studies to make recommendations for each site for lobe location of coil placement. Please comment on the method of centralized scoring and patient selection and how this can be generalized to the real-world use.

DR. NATHAN: Go ahead.

DR. KIRSCH: Jeff Kirsch.

In the stroke world, we see patients all the time who come in with an evolving stroke, who have a CT scan done at the hospital that's going to do the intervention. And the scan gets sent electronically, I think, to Stanford. And a machine there at Stanford does the analysis and then makes the recommendation to clinician at the site.

So I would support -- I think this is very doable. I'm not sure exactly the mechanism that this group would use, but in the stroke world, it's doable, it's done. And it should be doable here, in order to make sure that the right patients are being treated with this therapy, if it's approved.

DR. NATHAN: Dr. Van Berkel.

DR. VAN BERKEL: So this is Victor Van Berkel.

So the -- I believe the applicant did state that they were not planning on doing central core CT reading, that the plan was for there to be an educational process where the site that would be doing the study would -- or the site that would be implanting the coils would be trained up on how to read a CT scan and how to make a decision about which

areas were the most damaged and not too damaged to be able to put the coil in.

I actually think that that's perfectly reasonable, again, from a -- correlating this to lung volume reduction surgery, we have to do the same thing. There is a lot of inter-operator variability in the interpretation of CT scans, especially when it comes to emphysema destruction, but I think that that's something that with training can be overcome. And I think that the plan that the company had in place seems perfectly reasonable to me.

DR. CASSIERE: Hugh Cassiere, North Shore again.

I guess that the problem I have with that is, if I remember correctly, this is a non-validated scoring system. This hasn't been validated in the literature.

(Off microphone comments.)

DR. CASSIERE: So this is a non-validated tool to assess whether a patient's going to get a procedure, and we're supposed to depend upon that and set it free into the community.

DR. COURSEY: Yes. We have some slides on, if you will like to see some slides of the scoring system. We can bring some backup slides.

DR. CASSIERE: But am I correct to say that --

DR. COURSEY: Yes.

DR. CASSIERE: -- this has not been validated in the literature?

DR. COURSEY: Correct.

DR. CASSIERE: Okay.

DR. COURSEY: It was Sponsor generated.

DR. CASSIERE: Okay.

DR. NATHAN: So, you know, I mean, what we didn't hear from the Sponsor either was these areas were identified, and were the coils actually placed in the right areas as

well? So I think it's quite a bit of an unknown, but I agree. I think if this technology gets rolled out, you can't rely on a central lab somewhere to be reading it. I mean, people have to learn to make these judgment calls themselves. And it sounds like the Sponsor is planning extensive training, but invariably there'll be some kind of learning curve on a center-by-center basis.

And it's quite possible that if it's approved in a small number of centers, you know, actually one thing we can encourage is that there be a central repository, so that people can learn from everyone else in terms about these are the areas we identified, and we put them in, good result, bad result. So hopefully there can be a collective experience and learnings from multiple centers.

Yeah, Theresa.

MS. BARNES: Theresa Barnes.

Did I not remember that these are centers of excellence that are going to be doing the treatments? So they're not -- so there has to be some system in place, I would assume, that if they are centers of excellence, it's not just any local hospital. It's -- you know, there is some level of --

DR. NATHAN: Correct.

MS. BROWN: -- of experience.

DR. NATHAN: Yeah. The Sponsor laid out what seems like a very comprehensive, stringent plan to make sure that these are centers of excellence that have been appropriately trained. But even then, there'll be some kind of a learning curve, I suspect.

So, in summary to this question, there are some concerns that the scoring system has not been validated, but the Panel does not feel that this will be a major impediment to real world use, which, in parentheses, isn't for everyone out there but will only be centers of excellence who will be fully and appropriately trained. And we would encourage the

Sponsor to have an ongoing training methodology that collective experience can be shared among centers so that the learning curve isn't that great for individual centers once they get approved.

Mr. Ryan, does that answer your question adequately?

Oh sorry. Was there further comment?

Go ahead.

DR. CARVALHO: It's Paula Carvalho. Thank you.

Just very quickly, one thing I -- because I share these concerns about the validation. One thing I would be interested in seeing is post-procedural imaging with -- as time goes on, to see if these areas where the coils are, are actually doing their job.

DR. NATHAN: Good point.

Okay. Let's move on to Question 4 then, please.

DR. COURSEY: Question 4. There were more adverse events in the treatment arm at 12 months in comparison to the control arm. The device/procedure-related serious adverse events occurred in 45.8% of subjects in the treatment arm. Seven out of ten deaths were possibly or probably device-related.

Adverse events included COPD exacerbation (69.7% of the treatment subjects and 58.0% of control subjects respectively), hemoptysis/hemorrhage (60% versus 0%), lower respiratory tract infections (32.9% versus 8.9%), pneumothorax (11.6 versus 0.6%), cough (18% versus 2%), dyspnea (21.3% versus 7.6%). In the long-term safety follow-up, the most common adverse events were COPD exacerbation and lower respiratory tract infections. Additionally, there was no reduction in COPD-related complications in coil treated patients. Please comment on the following:

a. Please discuss the safety of the coil treatment with regards to device-related mortality, increased risk of COPD exacerbations, pneumonia, and pneumothorax

in relation to underlying disease.

DR. NATHAN: Okay. Who wants to comment on this question first?

(No response.)

DR. NATHAN: I guess I will, then.

(Laughter.)

DR. NATHAN: Well, it is concerning to see all these adverse events, which appear across the board for all the things that are stated. The ones that's actually interesting to me is dyspnea, 21% versus 7.6%. And was it just one episode of shortness of breath right after the procedure, and the quality of life was improved after that? I think it's a little uncertain, but certainly hemoptysis is an issue. Respiratory tract infection, pneumothorax, healthcare resource utilization, I think, has to factor into this to an extent as well, and that, you know, in terms of hospitalization and antibiotic therapy, etc., etc.

So this is a concern, which has to be balanced against any potential efficacy of the procedure.

Ms. Brown.

MS. BROWN: Debbie Brown.

So I'm looking at table 10, which is the listing of serious adverse events through 12 months. And the ones that I see that are different between treatment and control are pneumothorax and pneumonia. So the pneumothorax rate is about 10%. And compared to LVRS treatment, I think it has like a pneumothorax rate of 90%. It's pretty high. So it just --

DR. NATHAN: Everyone has a chest -- so they have a pneumothorax by definition. That's probably the biggest reason they stay in the hospital is for those air leaks, you know.

MS. BROWN: And then the pneumonia adverse event, LVRS in a 30-day period has an 18% incidence of pneumonia, and this has -- oh, what is this? Oh, in the RENEW trial, I think in the executive summary it said 11%, so 18% LVRS versus 11% RENEW, in 30 days. So

relative to LVRS, I think the safety profile looks pretty good.

And the other thing that I found still comforting is that the mortality rate for treatment versus control in RENEW is comparable.

DR. NATHAN: Just another point to be made about those coil-related opacities, I think is a lot of gray zone between that and pneumonia in terms of the criteria. I think they had to have purulent sputum and a temperature more than 100.5. But there's certainly patients with COPD exacerbations who don't have temperatures above 100.5 and don't have a cough productive of sputum. So I don't know if some of the pneumonia events went away. And in actual fact, if you want to be more of a purist, maybe the pneumonia rates might have been even higher than this.

Yeah.

DR. CASSIERE: Hugh Cassiere.

So, you know, you have to look at safety in the context of clinical benefit. So I don't think any of us around the table would accept this kind of safety profile if we were looking at preventing asthma exacerbations, right. So some of these are not safe. But you got to take a look at the clinical context and the patients that we're dealing with. These are very fragile patients, and we're doing invasive procedures on them, and they're going to have adverse effects. But are those adverse effects worthwhile?

So I'd have to say that, yes, these adverse effects are alarming, but if we can determine that there's a clinical benefit, well, we take that into context.

DR. NATHAN: I think that you're right. I think for any procedure we do, and we're dealing with a group of patients with advanced lung disease. You know, the next step down the road is LVRS. Well, that carries with it some mortality risk. And the next step down the road is lung transplantation, which certainly carries with it mortality risk. And you have to weigh that against any potential upside obviously. The upside of transplant, hopefully, is

better than what we've seen with this procedure. So it's kind of you get what you pay for. The less invasive, maybe not as much benefit, and maybe not as much in the way of adverse events. But for any individual patient, this needs to be weighed up very carefully.

Yes.

DR. VAN BERKEL: So -- this is Victor Van Berkel again.

So I would absolutely agree with those things. And it is true that the morbidity profile associated with this is substantially less than lung volume reduction surgery and transplant, to be sure. Again, as you said, though, the benefit would be a little bit less. The one thing that bothers me about all that is not so much the hemoptysis and pneumothorax and respiratory tract infections, although those are certainly concerning.

The thing that worries me is the increase in hospitalizations over the coming year, because even for lung volume reduction surgery, which has a severe upfront morbidity -- if you make it out of those first 30 days, you're usually okay, but those first 30 days can be really rough. But one of the big benefits, and this was demonstrated both in the NETT trial and then other studies afterwards, was a reduction in hospitalizations for those patients afterwards. And the fact that that was not seen in this particular study, I find more troublesome.

DR. NATHAN: Okay. So in answer to Question 4a, we've certainly discussed the safety of the coil treatment with regards to potential complications. And I think the consensus of the Panel members is if the procedure is approved in any individual patient, this needs to be weighed up and serious consideration and being fully informed. The patient needs to be fully informed, if they are to undergo the procedure, not only what the potential upside is but what the potential downside is.

And so we share -- we all, I think, unanimously share the concerns of the safety but in the context of other things that might be available for the patient, be it LVRS or lung

transplant, the safety is even worse or the potential adverse events are even worse in a fragile group of patients.

So, Mr. Ryan, we discussed it. I'm not sure we answered any questions there, but hopefully you're satisfied with the discussion.

MR. RYAN: Mike Ryan, FDA.

Yes. Thank you for the discussion.

DR. NATHAN: Thank you.

Okay, 4b.

DR. COURSEY:

b. After the completion of the study, pneumonias were retrospectively adjudicated by the CEC to re-define some of these cases as noninfectious localized tissue reactions to the coils (termed coil associated opacity, or CAO). The safety of CAOs has not been established as there were related deaths with autopsy reports with fibrosis at the site of the coil implantation. Please discuss the increased risk of pneumonia, definition, and implication of the CAO with progressive fibrosis in coil treated subjects.

DR. NATHAN: Okay. I probably jumped the gun a little bit in terms of mentioning a gray zone between these coil-associated pneumonias and opacity. I guess it's not surprising that there's a little bit of a fibrotic response around these foreign bodies that are inserted, and it might be a normal reaction, maybe a little bit more exuberant in some patients versus the others. And in actual fact, the fibrosis that it induces might be partly responsible for the volume reduction that takes place, in terms of shrinking the lung tissue around it.

I wouldn't be concerned that this is going to set off a diffuse fibrotic response like we see with any of the idiopathic interstitial pneumonias like IPF. I sense, never having done this and not knowing, is that this is just a localized scarring process in relation to the

foreign body being in there.

DR. CASSIERE: Hugh Cassiere, North Shore.

I don't think it's surprising. These patients' airways are not sterile, and you're collapsing part of the airways, and you're going to turn into -- whether you call it pneumonia or a localized inflammatory reaction. You know, you're going to both treat them the same, and it still has the same burden of illness, hospitalization, antibiotics. So I think we're talking about semantics here and really just coining a new term for a coil-related local pneumonitis.

DR. CASSIERE: Okay. Dr. Van Berkel.

DR. VAN BERKEL: It's Victor Van Berkel again.

So I guess the question is rather -- and it seemed like -- I remember seeing this on, I believe it was one of the applicant's slides, that if we are calling it a coil-associated opacity rather than a pneumonia, whether or not the treatment is different, as you just mentioned, with a pneumonia, if we're going to be focusing on antibiotics. And if we're calling it a coil-associated opacity without infection, just a fibrotic reaction, which again I would say is not surprising, that if the patient is symptomatic, that they would be treated, for example, with steroids or other anti-inflammatory medications.

And so I think that it's irrelevant as far as that goes. But in terms of defining this other entity, I think that it's reasonable to do so. I do worry about the possibility of getting a post-obstructive pneumonia that may be very difficult to treat in these patients, but that's sort of a secondary issue than the coil-associated opacities.

DR. NATHAN: Yes, Theresa.

MS. BARNES: Just a couple of quick things. One is it would -- you know, the fibrosis is it says progressive. I don't know if that's defined. But if it's isolated, I get that. I understand that. If it is not an exclusion criteria, though, for the comorbids in the patient

population, I'd be a little concerned that if people already have some fibrosis going on, that this could exacerbate that. So maybe, you know, checking to see if these patients have that prior and then making a decision based on that. And then secondarily, having some sort of surveillance, post-treatment, to see if that, you know, that what looks like it's just an isolated fibrotic response is, in fact, that and it doesn't continue.

DR. NATHAN: I think all good points. I believe that patients with pulmonary fibrosis were excluded, and this certainly doesn't sound like a procedure for patients with combined pulmonary fibrosis emphysema, so those patients shouldn't be treated with this. I don't believe they were included.

Yeah.

DR. SCHOENFELD: I think, to the degree possible, even retrospectively, if some distinguishing factors could be determined between the tissue reaction to implantation as opposed to what turned out ultimately to be pneumonia, this may be useful for future clinicians to avoid unnecessary hospitalization and to guide treatment decisions. If some set of discriminating factors does exist, perhaps that can be gleaned from the patients that have already been treated and studied.

DR. NATHAN: I think that's a very good point. And if it can't be answered with the current dataset, should the procedure be approved? Maybe that's something that would be answered in the context of a big registry. But it does make me wonder, and I'm not sure when the infections occurred, whether or not patients should be prophylaxed and given a 5- or 7- or 10-day course of antibiotics afterwards. So I'm not sure if that happened or not.

Any other comments?

Ms. Brown.

MS. BROWN: Debbie Brown.

I think we ought to ask the -- it's up to the Chair to ask the Sponsor if they want to

respond to that, to this question.

DR. NATHAN: Okay. If you'd like to hear that, maybe the Sponsor could come up and comment if antibiotics were given routinely in the context of this clinical trial.

MS. BROWN: I think it'd also be interesting to hear if they have a training plan post-approval for handling the opacities.

DR. NATHAN: If you could answer both questions, please.

MS. ANASTAS: In the RENEW study and in crossover study, prophylactic antibiotics and steroids were recommended. The crossover study had more specific requirements, but prophylactic antibiotics and steroids were recommended under both protocols. It is our intention to incorporate discussion of this, the CAO and looking at the two as part of -- pneumonia and CAO and distinguishing and how one might think about prophylaxis as part of training.

DR. NATHAN: You say recommended, but was that implemented? It's different --

MS. ANASTAS: The algorithm?

DR. NATHAN: It's different recommending antibiotics versus mandating that they be given. So what percentage of the patients were given antibiotics, do you know?

MS. ANASTAS: I don't -- do I know?

(Laughter.)

MS. ANASTAS: Ashley Burns.

MS. BURNS: Ashley Burns, Clinical Development, BTG.

We're just going to get a slide with the number of patients who received prophylactic steroids and antibiotics in both the RENEW and crossover studies.

DR. NATHAN: The next question that will come up when you show that is did it make a difference?

Yeah.

MS. BROWN: One question that arises when you talk about fibrosis is whether or not it continues since the coil stays in place. And if you have isolated -- I mean, a short course of steroids might decrease some inflammation, but does that fibrosis response continue? So is there any data on lung function in these patients who had these coil-associated opacities?

DR. NATHAN: Okay. We can come to that, and maybe you can address that as well, in terms of the difference in outcomes, be it RV or otherwise FEV_1 in those patients who had the coil-related opacities, or even pneumonia for that matter, because pneumonia probably induced -- was on the other end of spectrum or within that spectrum of fibrosis and pneumonitis.

MS. BURNS: To specifically answer the number of patients in the RENEW study who received prophylaxis for both procedures, it was 114 of the patients.

DR. NATHAN: So the majority and -- but then we still had this rather high infection rate, it seems.

MS. BURNS: Yes.

DR. NATHAN: Okay. And just the subgroup analysis of those patients who did develop the opacities or pneumonia, in terms of did they have a more -- a better response, in other words, the fact that you have a fibrotic process shrinking the lung tissue giving you what you want, did that translate to clinical benefit?

MS. ANASTAS: I would ask Claire Daugherty to come to the podium to speak to that.

MS. DAUGHERTY: Claire Daugherty, BTG.

We did do an analysis of all patients who had either a pneumonia or CAO versus patients who didn't have either, and we looked at the effectiveness results by those two groups within treatment and control. And what you can see here on the slide is that between the patients who had either a pneumonia or a CAO event, those effectiveness

outcomes were similar to those who did not have a pneumonia or CAO event in the treatment arm.

So on this slide, you can see that a median change in 6.8 m for 6-minute walk occurred in the 52 subjects who had either pneumonia or CAO, as compared with a 10 m median change in the patients who did not have either one, and similarly, 44% improved in 6-minute walk, 7.8% FEV_1, and 7 --

DR. NATHAN: Okay. Thank you.

Everyone's questions answered adequately by that? So let's go back to Question 4b. Please discuss the increased risk of pneumonia, definition and implication of the CAO with progressive fibrosis in coil treated subjects. We are concerned by it, but it might be, perhaps in some patients, a necessary evil if they're going to have a pneumonitis in response to the coils. We are concerned that this may result in increased hospitalization, which has other downstream detrimental effects.

If the device and technology is approved, we would recommend that this be monitored very closely in the context of some kind of a registry so that we can learn from it. Not -- I don't think any of us are concerned that these coil-related opacities are going to go on to something more exuberant, that if you have some fibrosis it's going to be a progressive process. Don't show any evidence of that, out 1 year, 2 years, or 3 years. But that's one of the -- and to me, it seems like it's a spectrum, no response versus the CAOs versus a full-blown pneumonitis or infectious pneumonitis. And it's just something that would need to be monitored, and certainly patients need to be informed about if the procedure is approved and they are candidates to have it.

All right. Is that -- does that answer or address this particular issue adequately?

MR. RYAN: Mike Ryan, FDA.

Just one more clarification, if I could. The registry that would come after any

approval, we would have to actually formulate the labeling and approve the labeling before that point, without the benefit of the registry data. Does the Panel have any recommendations on how we would discuss the coil-associated opacities or tissue reactions in the labeling, if approved, without the benefit of that registry data?

DR. NATHAN: I guess, in terms of -- and feel free to chime in. I'm probably going to need some help here. In terms of the prescribing information or however it's labeled or the label, I think there needs to be an emphasis on the adverse events and balancing any potential benefit with the likelihood of adverse events. And this is just one of many adverse events that can happen. I think that all the adverse events of note need to mentioned, including pneumonia, pneumothorax, and what are we calling it, coil-associated opacities.

And I do wonder if just having a generic under the, under pneumonitis, because that's what it is -- it's either -- it's pneumonia or infectious pneumonitis or an exuberant inflammatory response, which would lead to these coil-associated opacities. So one way of simplifying it is just to call it all pneumonitis.

Go ahead.

DR. CASSIERE: Yeah. Hugh Cassiere, North Shore again.

Yeah, so I'm in agreement. So I would use a blanket statement, procedure-related pneumonitises, possibly infectious and noninfectious in origin, and treat based upon, you know, your clinical acumen, if that makes sense. You know, again, with the -- the chart says someone has purulent sputum, you know, they're growing an organism, they're short of breath, you can call it whatever you want, it's an infectious pneumonitis, whether it's from the coil or not. I don't know if that's helpful.

MR. RYAN: Thank you. That's helpful.

DR. NATHAN: Does that address that satisfactorily?

MR. RYAN: It does. Thank you.

DR. NATHAN: Thank you.

Let's move on to 4c, please.

DR. COURSEY:

c. There is limited data on the applicant's recommendation for bronchoscopic coil removal within 2 months of deployment. There were no coil removals during the clinical trial, and furthermore, the limited autopsy results have shown fibrosis around the coils. Please comment on the coil removal recommendation provided in the labeling for patients with severe emphysema.

DR. NATHAN: Go ahead.

DR. CASSIERE: Sorry. Hugh Cassiere again.

So basically, in summary, it's the -- recommending a procedure when it was not done in the clinical trial. Is that correct?

DR. COURSEY: Correct. There were none in the clinical trial.

DR. CASSIERE: So at least my opinion would be that I would not put that in the label, recommend removing a device. They haven't shown efficacy. They haven't shown any experience with it. And that would be my opinion.

DR. NATHAN: I think what you -- if you say something, it should be there's no data attesting to the feasibility or safety of removing these devices because we don't have anything, I don't believe, in humans.

Ms. Brown.

MS. BROWN: Debbie Brown.

I believe there was experience in the commercial setting with device removal. Anyway, they talked about --

DR. NATHAN: In which study?

MS. BROWN: Pardon? And not so -- there was one in the clinical study, one device

removal, correct?

DR. COURSEY: Which --

MS. BROWN: Sorry. There was one in the -- there was only one in the clinical study.

DR. COURSEY: Which person died.

MS. BROWN: Right.

DR. COURSEY: Subsequent to removal. Yeah.

MS. BROWN: But then there was -- anyway, I think there's been some experience.

DR. NATHAN: Let's get the Sponsor up to comment on coil removals.

MS. ANASTAS: There was the only one removal in the IDE studies, but as Ms. Brown noted, in the summary of our commercial experience, we noted that there were a number of removals that have been reported. That's our greatest experience. So we've received reports of 22 removal procedures where 44 coils were removed. A portion of those were done bronchoscopically, and then the remainder were done surgically.

DR. NATHAN: I still think that in -- if this device and technology is approved, we're going on the clinical trial information, so what I said initially, I would stand by, that there's no data supporting the feasibility and safety of removing the coils, and leave it at the physician's discretion.

MS. ANASTAS: And may I add one more thing? It isn't more data, but I feel like it's important information.

DR. NATHAN: Sure.

MS. ANASTAS: We did put this together in a recommendations document that was given to the clinical sites and also submitted within our IDE to the FDA. So we have collated this information.

DR. NATHAN: Okay. Thank you.

MS. ANASTAS: Dr. Criner, do you have? No. Okay.

DR. NATHAN: Thank you.

MS. ANASTAS: Thank you.

DR. NATHAN: Mr. Ryan, did we address that adequately?

MR. RYAN: Yes, it does. Thank you.

DR. NATHAN: Thank you.

All right. Let's move on to the -- is this actually a question? The future postmarket study, is that an additional question?

DR. COURSEY: Yes.

DR. NATHAN: Okay. Go ahead, then.

DR. COURSEY: So this question is about the future post-market study.

So please note that the presence of a postmarket study plan does not alter the requirements for pre-market approval and a recommendation from the Panel on whether the benefits outweigh the risks. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable, and any future post-market study could be considered.

The applicant is proposing a post-market study with the primary effectiveness endpoints of change in SGRQ from baseline to 12 months post first implant. The proposed primary safety endpoint is the composite rate of device- and/or procedure-related serious respiratory adverse events (RAEs) through 12 months. RAEs will be defined as adverse events of the following types: lower respiratory tract infection/pneumonia, COPD exacerbation, severe hemoptysis, pneumothorax, respiratory failure.

So we go to Question 1. Should the device be found approvable, please comment on whether a post-approval study would be recommended, and if so:

Part (a), please comment on which safety and effectiveness endpoints should be collected.

And part (b), please comment whether a registry would be an appropriate mechanism to collect the desired information.

DR. NATHAN: Okay. From the Panel, we've heard some of these safety events that are proposed to be monitored in terms of pneumonias, exacerbation, hemoptysis, pneumothorax, respiratory failure. I would certainly add hospitalization to that. Any other elements that should be added? I don't know if physician visits and ED visits might also be thrown in there. Any other safety measures?

DR. YARMUS: So Lonny Yarmus from Hopkins.

I do. It's a little bit outside of what we've been discussing, but there is a concern. Separate from lung volume reduction, where the parenchyma is removed, here there's residual tissue. And we're talking about a patient population that's at a very, you know, considerable risk of lung cancer. And so screening -- putting lung cancer and screening aside, but an imaging portion of this within the registry, I think, would be important to follow not only the coil, you know, the coil-associated opacity issue but as well as hopefully adjudicating concerns that have been seen in prior bronchoscopic lung volume reduction attempts with hidden underlying cancers.

DR. NATHAN: I agree. I think imaging follow-up should also be a part of any registry. I see that it says severe hemoptysis, but I'm not sure I'd just limit it to severe hemoptysis. And trivial hemoptysis, maybe you don't need to record, but I'd be curious about any hemoptysis that occurs in these patients.

Anything else that should be captured?

Yeah.

DR. CARVALHO: Monitoring for fibrotic responses.

DR. NATHAN: Monitor fibrotic responses? I think that would be captured with imaging. I'm not sure what else, or how else.

DR. CARVALHO: Yes. With imaging and looking at if these fibrotic changes are associated with localization to where the coils are.

DR. NATHAN: Okay.

DR. YARMUS: Lonny Yarmus again. One more. Just when specific imaging -- I'm talking about the CT imaging, not chest x-ray imaging.

DR. NATHAN: Yeah, I agree. Yeah.

DR. VAN BERKEL: And just -- Victor Van Berkel.

Just you had mentioned before, perhaps, instead of just talking about pneumonia, but having a lump of pneumonitis that would catch both pneumonias, infectious pneumonitis as well as the coil-associated pneumonitis. That would be probably valuable for the registry.

DR. NATHAN: Oh, that wasn't in there. Yeah. I would -- I agree, pneumonitis, yeah.

All right. Let's see how we're doing. Should the -- please comment -- plus -- should be -- and if so -- we've commented on the safety. We haven't commented on the effectiveness endpoints. The Sponsor is proposing the St. George's. But I do wonder if there should be more than just the St. George's, certainly PFTs. What about the 6-minute walk? That's a -- you know, the primary outcome measure. Let's show some confidence in that. What else?

Yeah. I think that's a missed opportunity and maybe one that you can capture here in terms of looking at something like the BODE index as one of the outcome measures and serial change in the BODE index.

MS. ANASTAS: I just want to make a point of clarification. We'd identified SGRQ as the primary, but it -- what we -- in the proposal, what we were proposing is collecting all of the same, to still do the 6-minute walk and the FEV. We had just identified SGRQ as the primary.

DR. NATHAN: Okay. Any other thoughts for the Sponsor should this be approved and a registry comes to fruition?

(No response.)

DR. NATHAN: All right. Let's move on to (b), please comment whether a registry would be an appropriate mechanism to collect the desired information. And I think it would. Short of doing another study, I don't know another way that this information could be collected. Anyone else got any other ideas aside from a registry?

(No response.)

DR. NATHAN: Okay. Mr. Ryan, did we answer that question to your satisfaction?

MR. RYAN: Mike Ryan, FDA.

I wonder if there is any comments on SGRQ as primary versus secondary.

DR. NATHAN: Go ahead, Dr. Dodd.

DR. DODD: Lori Dodd.

Yeah. I was going to ask you what it means to have a primary endpoint in a registry trial. And a concern I have is, you know, I'm still not convinced that the differences we're seeing are outside of the realm of a placebo effect. And the SGRQ is much more subjective. And so for that reason alone, I would really push to have something else as the primary.

DR. NATHAN: I think -- yeah. We've heard enough concerns about the SGRQ and the fact that it wasn't the elements of dyspnea that drove the difference. So I would agree with it. Certainly it can be in there, but maybe not as the primary.

DR. BALLMAN: Yeah. Karla Ballman.

I just want to second that. If it could be something more objective that's not sort of prone to some placebo thing, I think that would be a better primary.

DR. NATHAN: Anyone else want to -- if the Sponsor's looking for a recommendation, you could go back to the 6-minute walk, or I like the BODE. It gets you FEV_1, it gets you a

measure of dyspnea, and it gets you a 6-minute walk all rolled into one.

(No response.)

DR. NATHAN: Okay. Mr. Ryan, have we answered that to your satisfaction?

MR. RYAN: Yes. Thank you.

DR. NATHAN: Thank you.

All right. Let's move on. Okay. At this time the Panel will hear summations, comments, or clarifications from the FDA. And the FDA has 10 minutes to address this.

DR. BAHADORI: Thank you. Lila Bahadori from FDA.

And we will put up slide 77, please.

So we thank the members of the Panel because this has been very helpful to us as we have also been looking at this data and to get the input that we have been getting. And, you know, as we have previously discussed, there was a lot of clinical issues as we were evaluating a lot of data that you can see has been very complicated, to tease out what the effectiveness is, what the safety is, what the implications of these are for patients that are very severely diseased and have a poor quality of life and what can be offered to them. And at the same time, when they have limited options, is to make sure that we are giving something that may potentially have a benefit and not cause more risks or adverse events.

And so the clinical issues, again, that we had as we were going through this is what is the clinical significance in the setting of the safety data with the risk-benefit analysis? Is there a reasonable assurance of safety and effectiveness?

One of the biggest factors that we were concerned was the impacts that were seen in terms of the confounding factors in the treatment effect. One of the most important things was that the -- we, as we were looking at the 6-minute walk test as the primary endpoint, there was a modest change. And we were not sure if part of this was because patients were encouraged to be -- to continue with a pulmonary rehabilitation program that

we do know can affect patient outcomes, both from a psychological and from a physical standpoint.

And so whether this was because the confounding results of not knowing what the effect -- whether -- which patients actually continued with a maintenance program and whether this had some effect on some of the results. Other things were just at what point do you do pulmonary rehabilitation, because pulmonary rehabilitation does help with all aspects. It's not just the 6-minute walk test for patients with severe COPD.

And then there was again the lack of study blinding on the St. George's Respiratory Questionnaire. And, you know, do patients feel better because you've done a procedure or do they really feel better? And so what were some of the -- we were also seeing increased adverse events, so does this actually correlate or not?

I think a lot of the questions related to the target lobe selection has been discussed here quite a bit, because we did have questions about whether -- how this was going to translate in the real world, between having a center, a central core lab versus having each center making their own decisions for treatment.

Next slide.

And then as we looked at the study results, again, there were uncertainties in the endpoints, both the primary and secondary endpoints, that we did have some clinical uncertainties, although they met their statistical significance. And then there was a lot of exploratory endpoints that were presented, and we weren't sure what to make with these exploratory endpoints and how this would be further evaluated in the context of the patients that we were looking at.

We still have not, even today, understood what the comparison of the controls are, because there is a big difference. I mean, a lot of the results are being driven by the difference with the controls. And so we are seeing a big difference in the controls between

the OUS population and the U.S. population. And so I think that's still an uncertainty for us here.

Again, there were issues between the main, the pivotal study and the crossover study and some of the inconsistencies between some of the subpopulations that were looked at with the primary endpoint of 6-minute walk test. And so these are still questions that remain for us.

I think Dr. Schoenfeld answered our question very well about whether these results can be pooled and generalizable to the U.S. population, so thank you.

We still do have questions on the effect of the emphysema heterogeneity, as has been discussed by Dr. Van Berkel. The NETT trial was a large study, and it took a long time to determine which kinds of patients would actually benefit from lung volume reduction surgery. And I'm sure that as time goes on, we're going to have to tease out that which types of patients will benefit from a less invasive bronchoscopic lung volume reduction surgery. And so we still don't have those answers. And I'm not sure that another small trial is going to give you that answer either. And that's going to be something that will come out over time.

There was a lot of data presented based on a lot of sub-analyses. Some of the data cutoff -- again, most of the data that was excluded was from the United States. A lot of this data was based on residual volume. These are again subjects that are all hyper -- very hyperinflated. I don't think anybody would disagree that a patient that has a residual volume of 175 is not hyperinflated compared to a residual volume of 225. And we just don't know where that magical cutoff is that the patients that should be treated with this type of treatment. It's -- we couldn't identify a specific point where we saw the improvements that were associated with the residual volume.

And, then again, there was the observational arm of the study that showed some

results that was inconsistent. And so we had a very useful discussion here. And I think we as the Agency will take everyone's comments and really appreciate it.

Thank you.

DR. NATHAN: Thank you.

Now the Panel will hear summations, comments, or clarifications from the Sponsor.

You also have 10 minutes.

DR. SCIURBA: Thank you. I will attempt to summarize today what you heard. Once again, I'm Frank Sciurba from the University of Pittsburgh.

I'd also like to thank the FDA reviewers and the Panel for really your careful considerations. These are important jobs.

Now I'd like to summarize and try to put the data into perspective. First, please consider the unmet need in patients with GOLD 3 and 4 emphysema and severe hyperinflation, particularly homogenous patients. They have very limited treatment options. Pharmacotherapy and pulmonary rehabilitation have a limited impact on breathlessness, so significant burden remains for these patients, even after maximal treatment.

Lung volume reduction surgery is one of the only interventions that's currently available. It's only an option for the most heterogeneous patients, but it's an invasive surgical procedure and often not chosen by even those patients who would qualify for it. As a result, LVRS is infrequently performed. The mortality rate in homogenous hyperinflated patients in the NETT trial was about 17%.

Other devices such as valves are also promising but limited to a smaller subset of the patients we've addressed today, with more heterogeneous disease and absent interlobar collateral ventilation. Lung transplantation is a limited option, given its age restriction, and it depends on available donor organs. So the vast majority of patients on guideline-based

therapy have no other options, particularly those with homogenous disease.

To help address this unmet need, PneumRx developed the ELEVAIR Endobronchial Coil System to provide minimally invasive bronchoscopic lung volume reduction. The goal of this therapy is to help patients with both heterogeneous and homogenous disease achieve meaningful improvement in quality of life, lung function, and exercise capacity. The mechanism of action in mechanical reduction of hyperinflation, through compression of diseased tissue and restoration of lung elastic recoil, to maintain airway patency, is complex to measure but drives these clinical events that we feel are important.

Endobronchial coil treatment is already included in recommendations and reviews by recognized pulmonary experts, including the Global Initiative for Chronic Obstructive Lung Disease, a committee Dr. Criner sits on, the German Respiratory Society, and it's supported by a Cochrane review.

Based on the RENEW trial data, PneumRx is proposing that the indicated population for the ELEVAIR coil treatment should be patients with severe emphysema, homogenous or heterogeneous, and severe hyperinflation. RENEW was a well-designed and conducted pivotal trial with high retention and nearly complete follow-up. All patients were on optimal medical therapy according to GOLD guidelines, and treatment groups were well balanced for comorbidities.

As agreed in discussion with the FDA, there was no sham bronchoscopy due to the likely futility of maintaining the blind in patients who would undergo future x-rays, particularly at health facilities not associated with the study centers. And it's important here to remember that the RENEW trial met the primary and all secondary endpoints in the ITT population. We met the primary and all secondaries statistically significant in the ITT population.

Reduction in RV led to consistent improvements across all primary and secondary

endpoints, including FEV_1, 6-minute walk distance, and SGRQ. These improvements were represented by clinically meaningful differences in responder rates and validated the randomized controlled trials that had preceded it in Europe.

Thus, RENEW provides compelling evidence of effectiveness in terms of quality of life, lung function, and exercise capacity. However, despite the success in meeting all the endpoints on the whole ITT population, the Sponsor is choosing a more prudent and responsible approach. They're recommending restricting the indication to the population with severe hyperinflation, as defined in the study as greater than 225% predicted, since this group receives the greatest benefit in both heterogeneous and homogenous disease in the randomized controlled portion of this study.

In this severely hyperinflated group, we saw a 24 m median improvement, representing 42% response rate, an 11-point mean improvement in SGRQ, representing fully a two-thirds response rate, nearly three times the minimal important difference, equivalent to what we see nearly with lung volume reduction surgery, not the transient effect you see with pulmonary rehabilitation. We believe this is very meaningful. And a 9% median improvement in FEV_1, represented by a 49% response rate; 49% of individual patients who I talked to felt the FEV_1 response.

These patients with severe hyperinflation were the original protocol-defined population. They represent 75% of all patients enrolled, and they were a predefined subgroup in the final protocol. This was a predefined subgroup.

It's all important to remember that in this intended severe hyperinflation group, there was benefit across U.S. and OUS populations. The apparent regional differences discussed today between these groups were largely driven by the higher percentage of low-RV patients enrolled in the U.S. population.

You've heard discussion of crossover today, but it's inappropriate to directly

compare the results of this single-arm observational study cohort without a concurrent control arm to those of the randomized controlled trial. Remember, the crossover was designed to aid retention in RENEW by providing treatment to all eligible patients who stayed in the control arm for a full 12 months. It was not designed as a validation of effectiveness. The level of evidence of this single-arm study is not equivalent to a randomized controlled trial. In fact, one-third of the control patients were not included in the crossover study, and disease progression and regression to the mean of those that remained may have confounded the results.

The FDA, in fact, cautions this directly in their guidance for industry for the choice of control group and related issues in clinical trials. Without a control group, you cannot account for the unmeasured confounding factors. It's called science.

Next.

In terms of safety, the primary endpoint was major complications. This was a pre-specified composite of events of greatest interest. As expected in patients undergoing two bronchoscopic interventions, there were more major complications through 12 months, largely due to a higher rate of pneumonia. Other MCs were balanced between treatment groups, and mortality rates were similar in the treatment and control groups.

As expected, SAEs of pneumothorax, COPD exacerbation, and hemoptysis were more common in the treatment group, but the majority of these events were resolved and decreased in frequency over the 12 months and beyond, toward the control rate. Clinically significant sequelae occurred in a limited number of cases. During the trial, coil-associated opacity was recognized to be a treatment-specific event, presenting similarly to pneumonia. It is now described and incorporated into the physician training.

So considering all the evidence, ELEVAIR coils, we believe, have an acceptable safety profile that's consistent and predictable across studies and commercial experience through

24 months post-implantation. Importantly, PneumRx is committed to studying the safety and effectiveness of the ELEVAIR system and is conducting a post-approval study recommended from the FDA and the Panel. Further, PneumRx is also committed to rigorously training physicians and support teams to ensure safe and appropriate use.

The patient preference study suggests that the substantial portion of severe emphysema patients would choose a therapy like ELEVAIR if it were available to them, and some of our patients you heard from today.

So, finally, when we weigh the benefits and risks, the ELEVAIR system is safe and effective minimally invasive bronchoscopic lung volume reduction procedure. Data support a favorable overall benefit-risk profile in conjunction with standard of care medical therapy in patients with severe hyperinflation, which is proposed in this indication. The risks associated with treatment are manageable and are outweighed by the benefits of treatment.

So, in conclusion, the ELEVAIR system will provide a much-needed minimally invasive treatment for patients with severe emphysema, severe hyperinflation, despite optimal medical therapy. Many of my patients would benefit from this option. So I urge the Panel to consider the totality of the evidence, which I believe supports a favorable benefit-risk profile and warrants the availability of this technology to have an evidence-based discussion in offering this therapy to my patients.

Thank you.

DR. NATHAN: Thank you.

Before we proceed to the Panel vote, I would like to ask our non-voting members -- Dr. Hawkins, our Consumer Representative; Ms. Debbie Brown, our Industry Representative; and Ms. Theresa Barnes, our Patient Representative -- if they have any additional comments.

Dr. Hawkins.

DR. HAWKINS: No.

DR. NATHAN: Okay. Thank you, Dr. Hawkins.

Ms. Brown, do you have any comments?

MS. BROWN: Debbie Brown. So, first, I want to compliment the company and the FDA on participating in the patient preference testing. I know it's something that the FDA is really working on right now, incorporating the patient's perspective. I know that the company that did the work is a very sophisticated company. It's hard work to do. It's big work to do. And so I appreciate that it was done and provided some insight on the kind of risk that these patients are willing to take.

For diseases like this, where the procedure can have a lot of risk to it but provide benefit, it's important to get the patient's perspective on that. And in this case, half the patients in the selected population said that they would be willing to take on that risk, and I thought that was very positive.

I also thought it was very positive that the ELEVAIR system has been incorporated into international treatment guidelines, like the GOLD guidelines, which those considerations are done in groups much like this, expert groups.

And, finally, I'm sure you're all aware that the FDA issued a guidance document in 2016 that addresses the factors to consider when making benefit-to-risk determinations for premarket approvals like this application we're considering today. And in that guidance, the FDA says we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.

The ELEVAIR system addresses such a population, a population with limited alternatives. And I believe that this guidance gives this Panel and FDA the ability to tolerate

some uncertainty in this very desperate patient population. In addition, our patients, these patients are going to be monitored post-approval, so that's going to be a comfort, going forward, in terms of both efficacy and safety, continuing for these patients.

DR. NATHAN: Okay.

MS. BROWN: Thank you.

DR. NATHAN: Thanks, Ms. Brown.

Ms. Barnes, any comments?

MS. BARNES: Yes. Theresa Barnes.

I just wanted to also thank the FDA and the company for including the patient voice in your effort. I think that obviously it's an area where we're still learning. But it obviously -- you know, in every other business in the world, people consider the customer first. So I think it's applicable that we do that.

Also, I think that it -- you know, we should thank the patients who were involved in the studies. It's a big deal to be involved in a study when you can barely walk across a room. So I think that, you know, that the extent to which they were involved in the study, and it looks like they were, and they stuck with it, is to be commended, and also to thank the patients who are here today because that's also not a small feat. So I just want to thank them.

DR. NATHAN: Thank you, Ms. Barnes.

Next I would like to invite Dr. Tina Kiang, the Division Director, to come up and say a few words.

DR. KIANG: Thank you. Good afternoon. My name is Tina Kiang, Dr. Tina Kiang. I'm the Acting Director for the Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices.

I'd like to take the opportunity today to thank both the applicant for their hard work

on this application and bringing this to Panel in such a timely manner. I would also like to thank the FDA team for all their hard work on this presentation today. And I think we can thank everyone for their thoughtful, considered, and robust discussion today during this Panel meeting.

I would like to remind you, as we did earlier today, that in considering the totality of the data that is presented today, that as you prepare to vote on the three voting questions that will be following my comments, that you are voting on the indications for use as proposed. So there has been a lot of discussion about subpopulations and subgroup analyses, but please consider the indications for use as written and as proposed when you vote.

Thank you.

DR. NATHAN: Thank you.

We are now ready to vote on the Panel's recommendation to the FDA for the ELEVAIR Endobronchial Coil System. The Panel is expected to respond to three voting questions relating to safety, effectiveness, and risk versus benefit. Ms. Washington will now read two definitions to assist in the voting process. Ms. Washington will also read the proposed indications for use statement for this device.

MS. WASHINGTON: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by the applicable publicly available information.

The definitions of safety and effectiveness are as follows: Safety, as defined in 21

C.F.R. 860.7(d)(1) reads, "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of this device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."

Effectiveness, as defined in 21 C.F.R. 860.7(e)(1) reads, "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

The Sponsor has proposed the following indications for use. The ELEVAIR Endobronchial Coil System is indicated for bronchoscopic placement of ELEVAIR coils in patients with severe emphysema, homogenous and/or heterogeneous, and severe hyperinflation, to improve quality of life, lung function, and exercise capacity.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three voting questions.

Voting Question Number 1: Is there reasonable assurance that the ELEVAIR Endobronchial Coil System is safe for patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WASHINGTON: All right. The second question reads: Is there reasonable assurance that the ELEVAIR Endobronchial Coil System is effective for use in patients who meet the criteria specified in the proposed indication for use?

Please vote now, yes, no, or abstain.

(Panel vote.)

MS. WASHINGTON: Okay. Voting Question Number 3: Do the benefits of the

ELEVAIR Endobronchial Coil System outweigh the risk for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WASHINGTON: Okay. Please give us a minute to tally all the votes and verify the official votes. Thank you.

(Pause.)

MS. WASHINGTON: Okay. The votes have been captured, and I will now read the votes into record.

On Question 1, the Panel voted 7 yes, 5 no, and no abstain that the data shows reasonable assurance that the ELEVAIR Endobronchial Coil System is safe for use in patients who meet the criteria specified in the proposed indications.

On Question Number 2, the Panel voted 5 yes, 7 no, and no abstain, that there is reasonable assurance that the ELEVAIR Endobronchial Coil System is effective for use in patients who meet the criteria specified in the proposed indications.

Third and final question, the Panel voted 3 yes and 8 no and 1 abstain that the benefits of the ELEVAIR Endobronchial Coil System outweigh the risk for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete. Thank you.

DR. NATHAN: I will now ask the Panel members to discuss their votes. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer. Please state your name and how you voted for each question for the record.

I guess we bypass our three non-voting members. And I think Dr. -- who was the first one? Oh, Dr. -- Ms. Kline, Dr. Kline. Ms. Kline, sorry.

MS. KLINE: Thank you. Okay. Andrea Kline.

So am I stating how I voted for each question? Okay. For Question 1, I answered yes; for Question 2, I answered yes; and Question 3, I answered yes.

DR. NATHAN: Okay. Dr. Van Berkel.

DR. VAN BERKEL: So this is Victor Van Berkel.

So I answered -- for Question 1, I said yes. I think that that's probably worth defining. I think that this is a relatively safe procedure in the grand scheme of things. I guess, perhaps speaking as a surgeon, so that doesn't mean a whole lot, I guess, to the rest of the world.

(Laughter.)

DR. VAN BERKEL: For Question 2, about reasonable assurance of effectiveness in these patients, I said no, mostly because I am concerned about the broad nature of the proposed indications. And I think that it needs some more clarification regarding which patients the coil should go into.

And then similarly for Question 3, I would say that given my caveat for Question 2, I don't think that the marginal benefits that were demonstrated and the lack of the durability of the benefits that were demonstrated within the study population outweigh the -- although they are, I think, acceptable risks, I don't think that those benefits outweigh them.

DR. SCHOENFELD: So on Question 1, I voted yes. And on Question 2, I voted yes. But on Question 3, I voted no, which seems quite inconsistent, but basically my thinking was first as a -- I thought this was a very tough question. I think this is a tough -- was a controversial meeting. And I think the long-term risks of such -- of procedures like this are sort of uncertain, whatever you do. The short -- there were surely short-term risks.

The benefits have a certain -- I think -- although I think that on -- that there probably were benefits, the size of those benefits are also somewhat uncertain. And so it seemed to me quite premature, with the data we have, to put this in hundreds of thousands of

patients, which is, I suppose, what would -- which is what I would guess would happen. And so I think it needs to be studied further, or new -- or maybe more effective devices developed. But I'm sure the direction is good, but I'm not sure that we're ready.

DR. YARMUS: So Lonny Yarmus.

So I thought the discussion today was great. I think the final decision on my end was based on the specific indications for use. So I think the technology has promise, but I think, as was just stated, there are additional studies that are needed. So I actually voted no on all three.

DR. KIRSCH: Jeff Kirsch.

I voted yes on the first question and no on the subsequent two questions, and for much of the same reasons, although anesthesiologists don't often agree with surgeons, for many of the same reasons my surgical colleagues stated. And although personally I'm always very moved by the patients who make their way to the public hearing, very moved, I feel badly for the patients who may have been hurt by the device and couldn't be here to tell us of their experiences as well.

And I think to present a situation where it's perceived that this device isn't hurting anybody I think is super naive, not a reasonable approach. And I feel badly that those people were not here to maybe say something that wasn't as positive as the patients who were benefited by this device.

So, again, I -- yes, no, and no.

DR. NATHAN: Steve Nathan.

As the Chair, I didn't vote. My role is to break any ties, which there weren't. But I will render my opinion; if I were to vote, how I would have voted, and my vote would have been yes to all three.

I share some of the concerns that were expressed, but I try to put this whole dataset

in the context of this very sick patient population that we alluded to who don't have much that we can offer them, short of what's been mentioned, pulmonary rehab. The next step along the way is the surgery itself, which is potentially more morbid, and then lung transplantation, which few patients qualify for and carries with it significant risk and safety issues, and yet we do it.

I don't think it would be hundreds of thousands of patients. I don't think it would be thousands of patients. I think it would develop into kind of a niche for a subset of patients. And my reason to vote yes, wanting it to be approved, is that it could be an option for us, as physicians who deal with these patients day to day, to be able to offer them as a potential option, provided they are fully informed with all the caveats, much like we do a discussion around LVRS or lung transplantation. And, yes, sometimes the outcomes aren't what we want. But it's also what patients want and want to try.

So I think having this in select centers as an option for patients would be good for us who deal with these patients on a day-to-day basis. So that's how I would have gone, if I were to have voted.

DR. CASSIERE: Hugh Cassiere, North Shore.

I voted no across the board for various reasons. My opinion is, looking at the totality of the data and the discussion, is that really can't signify who we're going to benefit and who's going to hurt. And there's a large burden on healthcare and patients who do not benefit. And I don't see a biological signal that tells me we can pick those patients out yet.

DR. BALLMAN: Karla Ballman.

And I voted no across the board too, much for the same reasons that were just stated. For the safety, I was more torn on that. But it's not clear to me that, in the group that's -- for the broad indication that -- I mean, had it been a more narrow indication, I probably would have voted yes for the safety. But I'm not sure what it's doing in the

patients that are below the threshold, if it's actually hurting them or not.

And also, it's a very frail population. And I do think that patients may potentially be harmed. And I don't think that the benefit that a few patients might experience is that large to outweigh the risks.

DR. PICHURKO: Bohdan Pichurko, Cleveland.

I voted no for the first. I was alarmed that the incidence of serious adverse events was twofold greater in the treated population compared to the medically treated group. While there is testimony to the fact that patients survived their morbidities, we should not forget the burdens to patients and their families in a generally elderly population of repeated and frequent hospitalizations and related morbidity and their impact on the family's economy and conditioning and so on, and their overall health.

On Number 2, I voted yes. I believe that the measures used in this study although answer kind of important facets of patients' existence, their functionality, their lung function, and their respiratory symptoms, and quality of life, I think they, in some respects, understate the impact of reducing pulmonary hyperinflation by bronchoscopic volume reduction surgery. I would have liked to have had some assessment of patient's maximal ventilatory capability. That is a measurable entity, but it wasn't measurable by the FEV_1 that was used.

Thirdly, on the third question I voted yes. I think patient selection here is going to be important. I was a bit surprised by a remark made during our discussion about allowing clinicians some latitude in patient selection, whether it's RV or RV/TLC. We should keep in mind that this is a very desperate and highly discouraged population and will line up, sometimes against their better judgment, for anything that holds promise for some improvement.

For example, in 1984 -- I go back that far -- Atrovent became a number one seller

overnight because it was that new product that was going to treat their patients' dyspnea. And, of course, as we heard today, it's a highly debilitated population, desperate to get better. And I think patient selection and attendance to safety, if this should be implemented and go forward, would be particularly important as the number of centers are expanded to include centers of a lesser but hopefully growing proficiency.

DR. WANG MEMOLI: Jessica Wang, MedStar Washington Hospital Center.

I voted yes for the first two. I think there's -- in this patient population, because they're so sick, despite the fact that there are some increase in sort of short-term adverse events, most patients said they felt better, which was a pretty good indication that maybe it's worthwhile in these patients.

I voted yes for the second. Although small, you know, maybe it's enough for the patients to be okay, and they're willing to accept that, which some of that patient criteria sort of surveys kind of indicated that they're willing to take on any risk.

I was the wuss who abstained from the last one because I think, based on the way that it's written, this indication is not clear enough for me to say that it's worth it. I think there has to be a little bit more clarity. And instead of just saying no, that it wasn't -- that I would -- it didn't outweigh. I think it just needs a little bit more clarity, and maybe that would sway one way or the other for me.

DR. DODD: Lori Dodd.

I voted no on all three questions. This is a single trial with a small effect. I was unsure of the clinical significance. I was also concerned that the effect was within the zone of being a placebo effect. I think there's a lot of room here for some psychological effects leading to improved, say motivation to follow their regimen for adherence to pulmonary rehabilitation and other effects that might have led to this observed improvement that might not be related to the treatment.

There are also lots of inconsistencies in the results, including the difference between the nonparametric and parametric approach, which is just concerning. And so, taking that all together, I just -- I felt like it wasn't -- I couldn't vote yes for any of them.

I also would agree with Dr. Wang that the language in the indication is a bit vague. It says quality of life, lung function, exercise capacity. So I think if there was more focus on what those mean, that would have helped a little bit.

DR. CHEN: Alex Chen.

I voted yes on safety and then no to the subsequent two questions. I do feel that this technology probably does help a certain patient population, but I couldn't glean from the results, which were very variable in my opinion, and sort of after a very exhausting and thorough discussion of the data, to understand which population that was. So I feel that the indication right now may be too broad, again, putting it in context of having that discussion with the patients, taking them through a procedure. I would like more clarity before going through that process, to have that discussion with a patient.

DR. CARVALHO: Paula Carvalho.

I voted yes for the first one. It was -- the numbers that were presented were reassuring to me. I struggled with the other two questions and for the reasons that my colleagues have already discussed.

The efficacy seems to be small and slight, if there at all. But I do think that the Sponsor is being very responsible with limiting the indications that they're going to be -- if they're going to go forward with this. And so for that reason, I did vote yes on Question 2.

And I struggled even more with Question 3 because of the way it was written. And I also voted yes for that one, and the reason was that although we don't know the long-term risks of this device, we do know the prognosis for these patients long-term. And so because of that reason, I gave a yes.

DR. NATHAN: Okay. Thank you.

I'd like to thank the Panel, FDA, and the Sponsor for their contributions to today's Panel meeting.

Mr. Ryan, do you have any final remarks?

MR. RYAN: Mike Ryan, FDA.

Yes, thank you. I'd like to thank the Panel. I'd also like to keep you here for just another couple of minutes, if I could. One clarifying question. A lot of you, as when you went around, touched on the indications for use and the broadness of the indications for use, both in terms of the patient population and a couple of you also mentioned the claims at the bottom. And I'm not sure if we can show it one more time, but the quality of -- treatment of quality of life, treatment of lung function, and exercise capacity.

So for those of you who didn't comment on it, I'd like to hear if any of the Panelists have any further thoughts, if the indication were limited, whether that would make you more comfortable, and what those limitations should be, and finally whether you think any further evidence would be needed to change your vote to say that the benefits do outweigh the risks.

DR. NATHAN: I'll defer to the folks who were uncomfortable with the broad indication.

Go ahead.

DR. CASSIERE: Yeah. I'll weigh in on that. I'll give you an example, the bronchoscopic valves, right. We determined that you have to have an intact fissure, and those patients benefit. I don't see any biological marker here that tells me which patients will benefit or not. So I think that needs to be the focus. And that tells you what the patient population is you're going to use it on.

And then the other measures, I agree, we should be using something more specific,

like the BODE index, which is -- I'm not really sure why it wasn't used in the primary study, which would probably weigh heavily on the data.

MR. RYAN: Could I actually ask that everyone weigh in on this? Just one last question for you. Thank you.

DR. NATHAN: Well, I think, you know, what we're interested in, in this patient population is palliating their symptoms. And if it ever gets to the point where there's a labeling, maybe just the broad term, as a palliative measure, because I think that also helps contextualize it in terms of what it's going to do. It might help your symptoms to some extent.

DR. BALLMAN: So I said it was a bit broad. I mean, I was concerned that they focused on one subgroup, but then they said, well, we're just not going to indicate for that subgroup. And then also, there's just a whole lot of uncertainties right now as to which group will benefit, if any, just due to what's been stated. You know, the primary -- you know, the St. George's, I think, you know, might be really biased. And I think there might be some bias in the 6-minute walk, as mentioned, that people are more motivated to keep up their rehabilitation. We had no data on that.

So it was just hard to really understand. I think there is a signal here, but I don't know who it's for at this point.

DR. NATHAN: I guess the difficulty that the Panel is having is if the company were to undertake another study, you know, what would we advise them? There's dissatisfaction with the St. George's, there's dissatisfaction with the blinding process. And so another study that doesn't replicate this one would be quite difficult, I think. I'm not sure how I'd recommend, moving forward, should the decision be made to do another study.

MR. RYAN: Just one last opportunity. Any last comments from anybody else on that question?

(No response.)

DR. NATHAN: All right. Thank you all very much. This meeting of the Anesthesiology and Respiratory Therapy Devices Panel is now adjourned.

(Whereupon, at 5:24 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

June 14, 2018

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

SHAYLAH BURRILL

Official Reporter