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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC)

Tuesday, May 12, 2015

8:00 a.m. to 3:53 p.m.

Hilton Washington DC North/Gaithersburg

The Ballrooms

620 Perry Parkway

Gaithersburg, Maryland

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1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Dennis Ownby, MD	12
5	Conflict of Interest Statement	
6	Cindy Hong, PharmD	16
7	FDA Opening Remarks and Regulatory History	
8	Anthony Durmowicz, MD	20
9	Sponsor Presentations - Vertex Pharmaceuticals	
10	Introduction	
11	Jeffrey Chodakewitz, MD	36
12	Disease Background and Medical Need	
13	Michael Konstan, MD	41
14	Mechanism of Action	
15	Fredrick Van Goor, PhD	56
16	Clinical Development Program and Clinical	
17	Efficacy and Safety	
18	Charlotte McKee, MD	64
19	Clinical Perspective	
20	Bonnie Ramsey, MD	104
21	Clarifying Questions to the Presenters	112
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	FDA Presentations	
4	Introduction to FDA Efficacy Review	
5	Robert Lim, MD	149
6	Review of Efficacy for Phase 3 Trials	
7	Lan Zeng, MS	156
8	Contribution of Lumacaftor and Review of	
9	Sweat Chloride Data	
10	David Petullo, MS	163
11	Clinical Considerations for Efficacy and	
12	Summary of Safety	
13	Robert Lim, MD	176
14	Clarifying Questions to the Presenters	
15	Open Public Hearing	
16	Charge to the Committee	
17	Anthony Durmowicz, MD	267
18	Questions to the Committee and Discussion	
19	Adjournment	
20		
21		
22		

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. OWNBY: Good morning, everyone. If everyone could please take their seats, we will get started. I'd like to remind everyone present to please silence your cell phones, Blackberrys, and other devices if you haven't already done so. I also want to remind the attendees of today's meeting that there will be multiple persons with cystic fibrosis in the room. If needed, we have the items recommended by the Cystic Fibrosis Foundation outside of the meeting room.

People with CF and their families should be aware that individuals with CF might choose to attend this advisory committee meeting without notifying the staff, therefore we cannot guarantee that you will not encounter others with cystic fibrosis at this meeting.

At this time, I would like to identify the FDA press contact for this meeting, Mr. Eric Pahon. If you are here, will you please stand up? Way in the back of the room. Thank you.

1 My name is Dennis Ownby. I'm the chairperson
2 for the Pulmonary-Allergy Drugs Advisory Committee.
3 I'm now calling this meeting of the Pulmonary-Allergy
4 Drugs Advisory Committee to order. We will start by
5 going around the table and introducing ourselves.
6 Let's start at the far right.

7 Dr. Druce, are you on the phone?

8 (No response.)

9 DR. OWNBY: Apparently, we don't have
10 Dr. Druce on the phone.

11 DR. AU: I'm David Au. I'm from the
12 University of Washington and the VA Puget Sound Health
13 Care System. I'm a pulmonologist and health services
14 researcher. Thank you.

15 DR. BRITTAIN: I'm Erica Brittain. I'm a
16 statistician at National Institute of Allergy and
17 Infectious Diseases.

18 DR. RAGHU: Hi. I'm Ganesh Raghu from the
19 University of Washington Medical Center, UW. I'm a
20 pulmonologist.

21 DR. PARAD: I'm Richard Parad. I'm a
22 pediatric pulmonologist and neonatologist from

1 Children's Hospital Boston, Brigham and Women's
2 Hospital, Boston.

3 DR. YU: I'm Yanling Yu, Washington Advocates
4 for Patient Safety, consumer representative, and I'm
5 also a researcher at the University of Washington.

6 DR. CONNETT: I am John Connett. I'm a
7 biostatistician at the University of Minnesota.

8 DR. MORRATO: Good morning. I'm Elaine
9 Morrato. I'm an epidemiologist in the Department of
10 Health Systems Management Policy at the Colorado School
11 of Public Health.

12 DR. HARKINS: I'm Michelle Harkins, pulmonary
13 and critical care from the University of New Mexico in
14 Albuquerque.

15 DR. OWNBY: I'm Dennis Ownby. I'm a pediatric
16 allergist from Georgia Regents University in Augusta,
17 Georgia.

18 DR. HONG: Hi. This is Cindy Hong. I'm the
19 designated federal officer for the Pulmonary-Allergy
20 Drugs Advisory Committee.

21 DR. TRACY: I'm Jim Tracy. I'm a pediatric
22 allergist, Creighton University, Omaha, Nebraska.

1 DR. GRAYSON: Hi. I'm Mitch Grayson. I am an
2 allergist at the Medical College of Wisconsin.

3 DR. OWNBY: I'm sorry. Stacy Motenko, are you
4 on the phone?

5 (No response.)

6 DR. OWNBY: Okay.

7 DR. CASTILE: I'm Bob Castile. I'm a
8 pediatric pulmonologist from Nationwide Children's
9 Hospital at the Ohio State University.

10 DR. PETULLO: David Petullo, statistician,
11 FDA.

12 DR. LIM: Robert Lim, medical officer, FDA.

13 DR. DURMOWICZ: I'm Tony Durmowicz, medical
14 team leader in the Division of Pulmonary, Allergy, and
15 Rheumatology, FDA.

16 DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the
17 division director, Division of Pulmonary, Allergy, and
18 Rheumatology Products.

19 DR. OWNBY: For topics such as those being
20 discussed at today's meeting, there are often a variety
21 of opinions, some of which are quite strongly held.
22 Our goal is that today's meeting will be a fair and

1 open forum for discussion of these issues and that
2 individuals can express their views without
3 interruption. Thus, as a gentle reminder, individuals
4 will be allowed to speak into the record only if
5 recognized by the chair. We look forward to a
6 productive meeting.

7 In the spirit of the Federal Advisory
8 Committee Act and the Government in the Sunshine Act,
9 we ask that the advisory committee members take care
10 that their conversations about the topic at hand take
11 place in the open forum of the meeting. We are aware
12 that members of the media are anxious to speak with the
13 FDA about these proceedings. However, FDA will refrain
14 from discussing the details of this meeting with the
15 media until its conclusion. Also, the committee is
16 reminded to please refrain from discussing the meeting
17 topics during breaks or lunch. Thank you.

18 I'll now pass it to Cindy Hong, who will read
19 the Conflict of Interest Statement.

20 **Conflict of Interest Statement - Cindy Hong**

21 DR. HONG: The Food and Drug Administration is
22 convening today's meeting of the Pulmonary-Allergy

1 Drugs Advisory Committee under the authority of the
2 Federal Advisory Committee Act of 1972. With the
3 exception of the industry representative, all members
4 and temporary voting members of the committee are
5 special government employees or regular federal
6 employees from other agencies and are subject to
7 federal conflict of interest laws and regulations.

8 The following information on the status of
9 this committee's compliance with federal ethics and
10 conflict of interest laws covered by, but not limited
11 to, those found at 18 USC Section 208, is being
12 provided to participants in today's meeting and to the
13 public. FDA has determined that members and temporary
14 voting members of this committee are in compliance with
15 federal ethics and conflict of interest laws.

16 Under 18 USC Section 208, Congress has
17 authorized FDA to grant waivers to special government
18 employees and regular federal employees who have
19 potential financial conflicts when it is determined
20 that the agency's need for a particular individual's
21 services outweighs his or her potential financial
22 conflict of interest.

1 Related to the discussions of today's meeting,
2 members and temporary voting members of this committee
3 have been screened for potential financial conflict of
4 interest of their own, as well as those imputed to
5 them, including those of their spouses or minor
6 children and, for purposes of 18 USC Section 208, their
7 employers. These interests may include investments,
8 consulting, expert witness testimony, contracts,
9 grants, CRADAs, teaching, speaking, writing, patents
10 and royalties, and primary employment.

11 Today's agenda involves new drug application
12 NDA 206038, lumacaftor and ivacaftor combination
13 tablets for oral use submitted by Vertex
14 Pharmaceuticals proposed for the treatment of cystic
15 fibrosis in patients age 12 years and older who are
16 homozygous for the F508del mutation in the cystic
17 fibrosis transmembrane conductance regulator gene.

18 This is a particular matters meeting during
19 which specific matters related to Vertex's NDA will be
20 discussed. Based on the agenda for today's meeting and
21 all financial interests reported by the committee
22 members and temporary voting members, no conflict of

1 interest waivers have been issued in connection with
2 this meeting. To ensure transparency, we encourage all
3 standing committee members and temporary voting members
4 to disclose any public statements that they have made
5 concerning the product at issue.

6 With respect to FDA's invited industry
7 representative, we would like to disclose that
8 Dr. Howard Druce is participating in this meeting as a
9 nonvoting industry representative, acting on behalf of
10 regulated industry. Dr. Druce's role at this meeting
11 is to represent industry in general and not any
12 particular company. Dr. Druce is an independent
13 pharmaceutical consultant.

14 We would like to remind members and temporary
15 voting members that if the discussions involve any
16 other products or firms not already on the agenda for
17 which an FDA participant has a personal or imputed
18 financial interest, the participants need to exclude
19 themselves from such involvement, and their exclusion
20 will be noted for the record. FDA encourages all other
21 participants to advise the committee of any financial
22 relationships that they may have with the firm at

1 issue. Thank you.

2 DR. OWNBY: We will now proceed with the FDA
3 opening remarks and presentation from Dr. Anthony
4 Durmowicz. I would like to remind public observers at
5 this meeting that while the meeting is open for public
6 observation, public attendees may not participate
7 except at the specific request of the panel.

8 Dr. Durmowicz?

9 **FDA Opening Remarks and Regulatory History**

10 **Anthony Durmowicz**

11 DR. DURMOWICZ: Good morning, and welcome to
12 the Pulmonary-Allergy Advisory Committee meeting for
13 NDA 206038. My name, as I mentioned earlier, is Tony
14 Durmowicz. I'm a pediatric pulmonologist and critical
15 care physician and also a clinical team leader in the
16 Division of Pulmonary Allergy and Rheumatology at the
17 FDA.

18 Today we are here to discuss new drug
19 application 206038 for lumacaftor/ivacaftor tablets for
20 the treatment of cystic fibrosis in patients 12 years
21 and older who are homozygous for the F508 deletion
22 mutation of the CFTR gene. While we will be discussing

1 safety at today's meeting, the primary focus will be on
2 efficacy. Lumacaftor/ivacaftor is a combination drug
3 product of a new molecular entity, lumacaftor, with an
4 FDA approved product, ivacaftor.

5 We will be discussing the overall efficacy at
6 today's meeting. However, because combination products
7 need to define the contribution of each individual
8 component, to the benefit of the combination, we will
9 be also discussing the contribution of lumacaftor to
10 the lumacaftor/ivacaftor combination today.

11 Very briefly, as most of you know here, cystic
12 fibrosis is the most common genetic disease in the
13 U.S., affecting approximately 30,000 people. It is
14 caused by a defect in the cystic fibrosis transmembrane
15 conductance regulator, from now on called CFTR, which
16 is a chloride conducting ion channel. It's an
17 autosomal recessive disease, and therefore you need two
18 copies of the mutant gene to result in cystic fibrosis.

19 The mutation we're going to talk about today,
20 patients with the F508 deletion gene, is the most
21 common mutation by far that causes cystic fibrosis.
22 Approximately 90 percent of CF patients have the F508

1 gene on one allele, and approximately 50 percent of
2 patients are homozygous for the F508 deletion gene.
3 And this is the patient population for which
4 lumacaftor/ivacaftor combination is proposed for today.

5 Mutations that cause cystic fibrosis can be
6 generally classified based on the defect that results
7 in the CFTR ion channel. With regard to the F508
8 deletion gene, there is a block in adequate processing
9 and transport of the CFTR defective protein insofar
10 that it doesn't reach or very little reaches the
11 epithelial cell membrane where it's active. This is in
12 direct contrast to mutations for which ivacaftor
13 monotherapy is approved in which the CFTR protein is
14 able to make it to the epithelial cell membrane,
15 however, it has deficient regulation or conductance.

16 Ivacaftor is a small molecule ion channel
17 potentiator. It increases chloride transport through
18 the CFTR chloride channel by increasing the opening
19 time. In January 2012, it was initially approved for
20 CF subpopulations 6 years of age and older with a G551D
21 mutation in the CFTR. In February 2014, it was
22 subsequently approved for 8 of 9 subpopulations defined

1 by the presence of gating mutation that was similar to
2 the G551D mutation in at least one allele. It should
3 be noted that the one mutation that it was not approved
4 in had in vitro data that supported efficacy, however,
5 there was no clinical or pharmacodynamic effect.

6 In December 2014, ivacaftor was approved for
7 the CF population 6 years of age and older, with the
8 R117H mutation in the CFTR, a so-called conductance
9 defect gene. And just a few months ago, the CF
10 indication was extended down to 2 years of age for
11 these subpopulations' mutations based on the
12 availability of a pediatric friendly granule
13 formulation, matching PK, and a lack of additional
14 safety concerns.

15 With regard to lumacaftor, lumacaftor is
16 thought to affect CFTR processing and trafficking.
17 While the exact mechanism of action is not known,
18 lumacaftor may promote more proper folding of the
19 defective F508 CFTR protein, allowing it to get to the
20 cell surface. In vitro data suggests that lumacaftor
21 may partially restore F508 CFTR channel function by
22 approximately 14 percent or so. However, as I'll show

1 you in a few minutes, this potentially positive
2 in vitro data is a disconnect with the clinical effect
3 of lumacaftor monotherapy, as lumacaftor monotherapy
4 results in a dose-dependent decrease in pulmonary
5 function in patients with cystic fibrosis.

6 Lumacaftor is sometimes called a CFTR
7 corrector, however, it should be noted that the actual
8 F508 CFTR defect, the deletion of a phenylalanine, is
9 not corrected, and the CFTR that does reach the
10 epithelial cell membrane remains deficient.

11 As I mentioned, lumacaftor/ivacaftor is a
12 combination product. As I mentioned also earlier,
13 combination product development programs are typically
14 required to show the contribution of the individual
15 components to the effective combination.

16 For example, the benefit of ivacaftor could be
17 shown by assessing the effects of the combination
18 product to a single component lumacaftor monotherapy.
19 Similarly, the benefit of lumacaftor could be shown by
20 comparing the effects of a combination product to the
21 single component ivacaftor monotherapy.

22 As I'll go through, this was not the case for

1 the lumacaftor/ivacaftor development program. On the
2 following slides, I'm going to summarize the
3 lumacaftor/ivacaftor clinical program briefly and point
4 out the FDA's rationale as to why the comparator
5 products were not included in phase 3 studies.

6 With regard to lumacaftor monotherapy, most of
7 the clinical data comes from studies 809-101 and 809-
8 102. Study 809-101 discovered that there was little
9 clinical effect of lumacaftor at doses of
10 200 milligrams and below. Study 809-102 was a primary
11 dose-ranging study for lumacaftor and was a randomized,
12 double-blind, placebo-controlled multi-cohort study in
13 which multiple doses of lumacaftor from 200 milligrams
14 once daily to 400 milligrams twice daily were
15 administered to CF patients for 28 days. After 28
16 days, there was an addition of ivacaftor 250 milligrams
17 twice daily for another 28 days.

18 With regard to the ivacaftor monotherapy, most
19 of the clinical information we have about it comes from
20 the ivacaftor monotherapy program for the G551D
21 mutation. In addition, study 770-104 assessed
22 ivacaftor monotherapy in patients homozygous for the

1 F508 mutation. This study was a randomized,
2 double-blind, placebo-controlled parallel group study
3 in which patients were randomized 4 to 1 to receive
4 ivacaftor 150 milligrams twice daily or placebo for 16
5 weeks.

6 It should be noted that this was a relatively
7 small study compared to the kind of studies that were
8 done for the combination therapy with 140 patients in
9 the study, 112 receiving ivacaftor and 28 receiving
10 placebo.

11 With regard to the lumacaftor/ivacaftor
12 combination product, the primary clinical data come
13 from studies 809-103 and 809-104 in which patients were
14 randomized 1 to 1 to 1 to receive 1 of 2 doses of
15 lumacaftor/ivacaftor combination therapy,
16 600 milligrams once daily combined with 250 milligrams
17 of ivacaftor twice daily, or lumacaftor 400 milligrams
18 and ivacaftor 250 milligrams both twice daily, or
19 placebo for 28 weeks.

20 You should note that the lumacaftor/ivacaftor
21 combination program studies were rather atypical for
22 studies that are done to support efficacy and safety

1 for orphan programs insofar as that they were
2 replicate, large, highly-powered studies of standard
3 design.

4 I'm going to go through briefly the results
5 from the different programs at this time. For the
6 ivacaftor monotherapy program, the ivacaftor dose and
7 dosing interval was established that was highly
8 effective for patients with the G551D mutation, the
9 gating mutation that I mentioned earlier. As you can
10 see from the graph, patients with the G551D mutation
11 had a robust 12 to 13 percent increase in FEV1 at the
12 24-week time point. Other endpoints were also
13 positive, CFQ-R exacerbations and weight gain.

14 This effect was in fairly significant contrast
15 to studies 770-104, in which patients with F508
16 deletion received ivacaftor monotherapy. While the
17 secondary endpoints for that study trended positive, it
18 was only a statistically significant small effect on
19 sweat chloride.

20 It was this large discrepancy back in the
21 2011-2012 period, when we were reviewing the initial
22 ivacaftor programs, combined with the treatment effect

1 that we usually see with CF drugs that are approved,
2 that resulted in the FDA stating in the label that the
3 ivacaftor monotherapy was not effective for the F508
4 deletion mutation. This is an issue that has come into
5 question when you take the findings of the combination
6 therapy phase 3 studies into context. For this reason,
7 the non-effective reason, the ivacaftor monotherapy was
8 not initially included in the combination product
9 phase 3 trials.

10 With regard to lumacaftor monotherapy, as I
11 mentioned, study 809-101 showed that there was no
12 clinical effect at doses of 200 milligrams and below.
13 Again, study 809-102, the main dose-ranging study, the
14 clinical results were different than the positive
15 in vitro findings insofar as that there was a
16 dose-dependent decrease in FEV1 looking at doses of
17 lumacaftor from 200 milligrams once daily to
18 400 milligrams twice daily.

19 Based on our previous experience with CF
20 programs with gene-modifying therapies, the day 28
21 results are generally consistent with chronic therapy
22 results. As such, this was viewed as a safety concern.

1 And for that reason, the lumacaftor monotherapy was not
2 included in the phase 3 trials.

3 Moving on to the lumacaftor/ivacaftor
4 combination program in studies 809-103 and 104, as you
5 can see, there was a small but statistically
6 significant increase in FEV1, which was the primary
7 endpoint. The range was about 2 and a half to 3.
8 There was a lack of cystic fibrosis respiratory CFQ-R
9 effect, and there was an inconsistent BMI benefit.
10 There was a nominal decrease in exacerbations, which
11 was not considered statistically significant because of
12 the statistical analysis hierarchy in which it was
13 placed.

14 This figure combines the FEV1 information that
15 I've just gone through with you with regard to the
16 combination of the ivacaftor programs. As you can see,
17 the G551D mutation had a robust effect with ivacaftor
18 monotherapy. The lumacaftor/ivacaftor program, as you
19 can see here, had a lesser effect, like I mentioned,
20 2 and a half to 3 percent FEV1 range.

21 When the FDA saw that data, which was, by the
22 way, different than the phase 2 data, which I'll go

1 into in a second, they realized, in looking at the
2 ivacaftor monotherapy data from study 770-104, that
3 these results were fairly close, which brought up the
4 question of the contribution of lumacaftor to the
5 combination product.

6 What we have here is we have, with regard to
7 lumacaftor monotherapy, a dose-dependent decrease in
8 pulmonary function, which was not predicted by in vitro
9 data. This became a safety concern and was an
10 unacceptable comparator for phase 3. With regard to
11 ivacaftor monotherapy in study 770-104, there was a
12 small increase in pulmonary function that was not
13 statistically significant.

14 It was viewed, as I mentioned, as
15 non-effective in patients with the F508 mutation. And
16 that was viewed in the context of the robust G551D
17 mutation response and the treatment response of FEV1
18 that you generally see with treatments that are
19 approved for cystic fibrosis. But it did bring up the
20 question that it was probably not without clinical
21 activity, and therefore it was probably a better
22 comparator or the more appropriate comparator than

1 placebo in phase 3 trials.

2 As such, FDA did additional analyses looking
3 at the question does the lumacaftor/ivacaftor
4 combination impart a clinical benefit over ivacaftor
5 alone using the information from study 770-104 as a
6 historical control.

7 This figure summarizes the FDA rationale for
8 not having the ivacaftor monotherapy program in
9 phase 3, as well as the issue about the question of
10 whether lumacaftor contributes to the combination.
11 Again, as you can see in the upper right, this is a
12 robust effect from the G551D population. Down at the
13 very bottom, you can see the effect of the ivacaftor
14 monotherapy program, which is right in the lower range
15 there, around 2 or so.

16 In this graph, which you did see earlier, is
17 the phase 2 data from the lumacaftor/ivacaftor program.
18 And that phase 2 data resulted in an FEV1 improvement
19 of about 5 percent. At the time, it was felt that if
20 the phase 3 data from the combination program were
21 similar to the phase 2 data treatment effect of about
22 5 percent, then the contribution of lumacaftor would be

1 evident when you look at the 5 percent compared to the
2 2 percent that you would receive from ivacaftor alone.
3 However, this was not the case, and the FDA analyses
4 have shown that the lumacaftor/ivacaftor combination
5 FEV1 results are very similar to those for the
6 ivacaftor monotherapy results.

7 Now, we know that FEV1 is not the only
8 important endpoint for cystic fibrosis or cystic
9 fibrosis trials, but it was the primary endpoint in
10 these phase 3 studies and all the phase 3 studies that
11 the company has done. However, we did look at other
12 important endpoints, most specifically exacerbation
13 rate ratios.

14 For ivacaftor alone in study 770-104, the
15 exacerbation rate ratio in this fairly short 16-week
16 study was not statistically significant probably
17 because of the study design, but was 0.61. This was
18 very similar to the exacerbation rate ratio seen in the
19 combination lumacaftor/ivacaftor program that we're
20 here today to discuss. When you combined the two rate
21 ratios here, it becomes 0.62, so they're virtually the
22 same. This also brings into question the contribution

1 of lumacaftor to the combination therapy.

2 So just to summarize a little bit, today, as
3 the meeting progresses, you're going to need to think
4 about the overall efficacy of the combination program,
5 specifically the clinical significance of the
6 lumacaftor/ivacaftor treatment effect. You're going to
7 need to think about the contribution of lumacaftor to
8 the combination and is there a clinical benefit over
9 ivacaftor alone. I think you're also going to need to
10 consider the risk-benefit profile.

11 Now, as I finish up, just to keep in the back
12 of your mind the questions that are going to be asked
13 at the end of the day while the meeting progresses, I
14 want to go through them very quickly.

15 Question 1, we ask you to discuss the
16 available efficacy data for the lumacaftor/ivacaftor
17 fixed-dose combination in the CF patients with the F508
18 deletion mutation. Specifically, it's important to
19 consider the following issues: the clinical
20 significance of the treatment effect and the
21 contribution of lumacaftor in the context of that for
22 ivacaftor.

1 Question 2, we ask you to discuss the
2 available efficacy data for ivacaftor monotherapy in CF
3 patients who are homozygous for the F508 mutation.

4 Question 3 is a voting question, and it asks
5 does the available data demonstrate that lumacaftor
6 contributes positively to the clinical efficacy seen
7 for the lumacaftor plus ivacaftor fixed-dose
8 combination. Now, this is an important point, but
9 you're going to notice that there are three possible
10 answers. There's one that says yes -- or A says yes;
11 B, no; and C, cannot determine.

12 So it will be important to please comment on
13 the rationale for your vote and whether a clinical
14 trial should be conducted to ultimately compare
15 lumacaftor/ivacaftor fixed-dose combination to
16 ivacaftor alone.

17 Question 4 asks you to discuss the safety data
18 for the combination product.

19 Question 5 asks you to vote do the data
20 support the safety of the lumacaftor/ivacaftor
21 fixed-dose combination, and if not, what further data
22 should be obtained.

1 Finally, question 6 asks do the available
2 efficacy and safety data support approval of lumacaftor
3 400 milligrams/ ivacaftor 250 milligrams fixed-dose
4 combination when given twice daily to CF patients
5 homozygous for the F508 deletion mutation.

6 Importantly, if not, what additional data should be
7 obtained to further define the benefit-risk profile?

8 With that, I'll finish up. Thank you very
9 much.

10 DR. OWNBY: We will now proceed with the
11 sponsor's presentation. However, before we do that, I
12 need to remind you that both the Food and Drug
13 Administration and the public believe in a transparent
14 process for information-gathering and decision-making.
15 To ensure such transparency at the advisory committee
16 meeting, FDA believes it is important to understand the
17 context of an individual's presentation.

18 For this reason, FDA encourages all
19 participants, including the sponsor's non-employee
20 presenters, to advise the committee of any financial
21 relationships that they have with the firm at issue,
22 such as consulting fees, travel expenses, honoraria,

1 and interest in the sponsor, including equity interest
2 and those based upon the outcome of the meeting.

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

9 We will now proceed with the industry
10 presentations, and I believe Dr. Chodakewitz will
11 introduce.

12 **Sponsor Presentation - Jeffrey Chodakewitz**

13 DR. CHODAKEWITZ: Good morning. Mr. Chairman,
14 members of the advisory committee, FDA participants,
15 ladies and gentlemen, my name is Dr. Jeff Chodakewitz,
16 and as the chief medical officer at Vertex, I'm pleased
17 to start the discussion of Orkambi, the combination of
18 lumacaftor and ivacaftor, by reviewing our planned
19 agenda.

20 Following my brief introduction, I'll turn the
21 podium over to Dr. Michael Konstan, from Case Western
22 Reserve and Rainbow Babies and Children's Hospital, to

1 provide some background on the disease and the medical
2 need in this specific population. We'll then turn to
3 Dr. Fredrick Van Goor from a research part of Vertex to
4 discuss the mechanism of action and what's known about
5 lumacaftor and ivacaftor.

6 Dr. Charlotte McKee, responsible for clinical
7 development for cystic fibrosis will review the
8 clinical data that have been obtained with this
9 combination. And then finally, Dr. Bonnie Ramsey from
10 University of Washington and Seattle Children's
11 Hospital, will provide her clinical perspective on the
12 information from lumacaftor and ivacaftor. In addition
13 to Drs. Konstan and Ramsey, Vertex has also invited
14 additional external experts to be with us today,
15 Dr. Janet Wittes and Dr. Willis Maddrey.

16 As you know, cystic fibrosis is a systemic,
17 life-shortening, orphan disease, which impacts more
18 than 30,000 people in the United States. Both
19 ivacaftor and lumacaftor represent medicines, which
20 have emerged from a very deliberate precision medicine
21 strategy, which utilizes our understanding of
22 differences in CFTR genetic defects to specifically

1 address the great medical needs of patients living with
2 cystic fibrosis.

3 Ivacaftor monotherapy as Kalydeco, as you
4 heard from Dr. Durmowicz, was first approved in January
5 2012 for patients with G551D mutations and subsequently
6 approved for patients with several other gating
7 mutations. These patients have dysfunctional CFTR on
8 the surface of their cells, which ivacaftor can
9 potentiate. As we will discuss, ivacaftor monotherapy
10 is not labeled for providing clinical benefit for
11 patients homozygous for F508del mutations. In these
12 patients, minimal CFTR reaches the cell surface.

13 Briefly highlighting milestones of lumacaftor
14 in combination with ivacaftor, lumacaftor/ivacaftor was
15 awarded breakthrough designation in December of '12,
16 and in that context, we've had the opportunity to have
17 frequent interactions with the FDA. The luma/iva
18 development program, as you heard, had two pivotal
19 phase 3 trials, which included more than 1100 patients
20 with cystic fibrosis. And finally, in November of
21 2014, the luma/iva NDA was submitted.

22 Lumacaftor/ivacaftor combination therapy

1 targets the underlying cause of cystic fibrosis in
2 these patients. As you've read and we'll summarize
3 this morning, consistent and sustained respiratory and
4 systemic benefits were demonstrated in phase 3 through
5 48 weeks. The primary endpoint absolute change in
6 percent predicted FEV1 was met in both studies' all
7 four treatment groups.

8 There were also substantial reductions in
9 pulmonary exacerbations, including the most severe
10 exacerbations, as well as meaningful improvements in
11 BMI. All of these improvements were seen on top of
12 patients' usual CF treatment. Importantly,
13 lumacaftor/ivacaftor was generally well tolerated with
14 a favorable safety profile in over a thousand CF
15 patients.

16 These results clearly demonstrate consistent
17 and important clinical benefit being delivered to
18 F508del homozygous patients by lumacaftor and
19 ivacaftor. This is not the case with ivacaftor
20 monotherapy for these patients. We recognize that this
21 is an important topic for today's ADCOM discussion. As
22 we will summarize, addressing this question requires

1 that we use all the types of information available.
2 This should include our understanding of the disease
3 biology for patients with this mutation, the way in
4 which the combination of lumacaftor and ivacaftor
5 together target that genetic defect, and evidence that
6 this understanding actually translates into the
7 clinical setting.

8 In addition, we must approach cross-study
9 comparisons with caution and look at consistency and
10 patterns across multiple parameters as much or more
11 than individual point estimates. And taken together,
12 this information provides compelling evidence that the
13 combination of lumacaftor and ivacaftor is needed to
14 deliver the greatest clinical benefit to patients.

15 Based on all the information available, this
16 combination has a favorable benefit-risk balance, which
17 supports approval of lumacaftor and ivacaftor for
18 treatment of CF patients homozygous for F508del who are
19 age 12 and older.

20 Lastly, I want to especially thank the CF
21 community, the patients who participated in these
22 trials, along with their families and caregivers, and

1 the investigators and staff of so many CF centers
2 contributed to these studies, all of whom made the
3 program possible.

4 With that, I'd like to turn the presentation
5 over to
6 Dr. Konstan.

7 **Sponsor Presentation - Michael Konstan**

8 DR. KONSTAN: Good morning. I'm Michael
9 Konstan, and I'm the principal investigator and a site
10 investigator for the ongoing, rollover extension study
11 to the phase 3 lumacaftor/ivacaftor studies in patients
12 homozygous for F508del. In addition, I was a site
13 investigator on a number of other studies in the Vertex
14 cystic fibrosis program. I am being compensated by
15 Vertex for my time and travel expenses to participate
16 in this meeting, but I have no direct financial
17 interest in the company.

18 As a pediatric pulmonologist, I've been caring
19 for patients with cystic fibrosis for 30 years at
20 Rainbow Babies and Children's Hospital in Cleveland,
21 Ohio, and I've been very passionate about bringing a
22 curative therapy to my patients. I would like to take

1 this opportunity to highlight for you the key unmet
2 medical need for CF patients homozygous for the F508del
3 mutation.

4 As you've heard, and to review briefly, cystic
5 fibrosis is a life-shortening, orphan genetic disease
6 that afflicts approximately 30,000 people in the United
7 States. Although expected survival has doubled over
8 the past 30 years, of those who died in 2013, half did
9 not reach their 28th birthday. This figure from the CF
10 Foundation patient registry shows that a substantial
11 proportion of those who die from cystic fibrosis die as
12 children.

13 Although the vast majority of CF-causing
14 mutations are rare, the F508del homozygous genotype,
15 where patients have two copies of the F508del mutation,
16 is the most common CF genotype and represents
17 approximately 47 percent of CF patients. Most notably,
18 patients who are homozygous for F508del generally
19 present with more severe clinical disease.

20 These patients typically have an early onset
21 of progressive lung disease, they have high sweat
22 chloride concentration, and they're pancreatic

1 insufficient. Life expectancy for those who are
2 homozygous for F508del is less than the general CF
3 population, further illustrating the urgent need for
4 treatment options for this group of patients.

5 We know what causes cystic fibrosis. It's a
6 genetic mutation in the CFTR gene that causes
7 reductions in the quantity or function of CFTR protein
8 at the cell surface. CFTR's an ion channel that
9 regulates chloride and bicarbonate secretion across
10 epithelial and numerous organs. Reduced CFTR function
11 leads to a loss of chloride transport. This defective
12 ion transport leads to abnormalities such as thickened
13 secretions, mucus plugging, and fluid and pH imbalance,
14 that lead to manifestations of the disease. And what
15 is quite clear is that the severity of disease in CF
16 patients is related to the level of dysfunction in the
17 CFTR protein activity.

18 CF is often thought of as a pulmonary
19 disorder, which makes sense because CF patients have
20 frequent lung infections and an exaggerated
21 inflammatory response. But it's also important to
22 remember that CF is multisystemic in nature, and other

1 manifestations of the disease can be seen even in the
2 absence of overt lung disease.

3 Underlying liver disease with transaminase
4 elevations and gall bladder abnormalities are common in
5 the CF population. There are also a number of
6 additional GI as well as endocrine manifestations,
7 including pancreatic insufficiency, CF related
8 diabetes, and digestive problems, including failure to
9 absorb adequate nutrients.

10 Sinus infections and nasal polyps occur in the
11 upper respiratory tract. In the sweat gland, you have
12 high sweat chloride concentration, and this is a
13 biomarker of reduced CFTR activity and a hallmark of
14 the disease. CF patients have abnormal sweat loss,
15 which may lead to heat prostration and dehydration.
16 The effect of CF on the reproductive organs results in
17 reduced fertility in women and infertility in men.

18 Finally, we're back to the lungs. Ultimately,
19 it's the progressive loss of lung function that's the
20 primary cause of morbidity and mortality in CF
21 patients, resulting in disruptions of normal
22 activities, frequent visits to the clinic to address

1 complications, absences from work or school, and
2 hospitalizations to treat pulmonary exacerbations and
3 other complications of CF. In caring for CF patients,
4 the goal is to address all aspects of the disease.

5 I've talked about the multisystem nature of
6 cystic fibrosis. Now I would like to tell you about
7 our therapeutic approaches for treating this
8 devastating disease. There are three major goals: to
9 maintain lung function, to reduce pulmonary
10 exacerbations, and to improve nutritional status, as
11 these are the most critical determinants of survival.

12 Before I share with you our current
13 therapeutic approach for achieving these goals, I just
14 want to step back and briefly review how lung disease
15 develops in CF. CFTR mutations lead to viscous mucus
16 and impaired mucociliary clearance, which causes
17 obstruction of the airways. This sets up an
18 environment for infection to occur, followed by a
19 robust inflammatory response. This vicious cycle of
20 airway obstruction, infection, and inflammation leads
21 to frequent pulmonary exacerbations of lung destruction
22 and ultimately death.

1 These CT scans from a CF patient show the
2 progression of lung disease. The bottom image, taken
3 shortly before her death at the age of 23, shows
4 extensive bronchiectasis with plugged airways and lung
5 destruction. Physicians who treat CF patients rely on
6 pulmonary function tests to monitor the progression of
7 lung disease, who most commonly rely on the forced
8 expiratory volume in 1 second or the FEV1.

9 This figure, which comes from a
10 cross-sectional data from the nearly 30,000 patients
11 that are followed annually in the CF Foundation's
12 patient registry, illustrates the progressive nature of
13 CF lung disease. It is clear that older patients have
14 significantly lower lung function than younger
15 patients. One can see that by the early 20's, more
16 than half of patients have an FEV1 that has fallen
17 below 70 percent of their predicted value.

18 Although patients at any given age have
19 considerably higher lung function today than they did
20 more than 10 to 20 years ago, the rate at which they're
21 losing lung function has not changed despite advances
22 in CF therapies. Even with our current standard of

1 care, the average rate of lung function decline across
2 the CF population is estimated at 1 to 3 percentage
3 points per year.

4 One reason there is so much focus on
5 maintaining lung function is that FEV1 is the strongest
6 predictor of mortality in CF, as demonstrated by this
7 figure. The mortality rate is on the vertical axis and
8 cohorts according to baseline FEV1 status are on the
9 horizontal axis. The green and blue bars represent 1-
10 and 2-year mortality rates, respectively. It is clear
11 that the lower FEV1 values are strongly associated with
12 increased rates of death.

13 The progressive nature of the lung disease is
14 illustrated in this figure for an individual patient.
15 This is the FEV1 pattern that has occurred during the
16 teenage years of a 23-year-old patient of mine who is
17 homozygous for F508del mutation.

18 This patient has lots of ups and downs in his
19 FEV1 occurring during these years. Since the age of
20 6 years, when his lung function was no different from
21 most healthy 6-year-olds, his average annual loss of
22 FEV1 is 3 percent per year. This progressive decline

1 has occurred even while receiving standard of care
2 treatment. In a struggle to maintain his lung
3 function, my patient spends more than 2 hours each day
4 on maintenance therapy.

5 Beyond pulmonary aspects of the disease,
6 systemic factors such as nutritional status also
7 significantly impact the health and the quality of life
8 of these patients. Pancreatic insufficiency occurs in
9 about 98 percent of F508del homozygous patients and
10 leads to a loss of digestive enzymes and maldigestion
11 and malabsorption of fats and proteins.

12 As with FEV1, measures of nutritional status
13 such as BMI have improved over the past 20 years.
14 However, even with these improvements, the median BMI
15 falls below the CF care goal, beginning in early
16 adolescence, and it continues to decline after that.
17 We focus on nutritional measures because lower BMI is
18 associated with reduced lung function. In addition,
19 nutritional status is important because it also has
20 been shown to be a predictor of reduced survival.

21 I will now discuss the third major goal of CF
22 care, and that's reducing pulmonary exacerbations. The

1 life course of nearly every CF patient is punctuated by
2 these acute episodes of pulmonary exacerbations. These
3 episodes are characterized by worsening of respiratory
4 symptoms such as cough, sputum production, and
5 shortness of breath.

6 They're typically treated with oral and
7 inhaled or IV antibiotics, and they often result in
8 hospitalization and/or absences from school or work for
9 two weeks at a time or more. Despite our advances in
10 CF treatment over the past 20 years, there's been
11 really no reduction in the proportion of individuals
12 with CF who experience an exacerbation.

13 Pulmonary exacerbations have major clinical
14 consequences. They're associated with a progressive,
15 irreversible and a more rapid loss of lung function,
16 increased risk for future exacerbations, reduced health
17 related quality of life, and an increased risk of
18 death.

19 This figure illustrates the effect of the
20 number of exacerbations per year on three year
21 survival. The occurrence of an exacerbation is shown
22 to reduce survival with greater than 2 exacerbations

1 per year having a profound effect. For a patient,
2 pulmonary exacerbations result in a vicious downward
3 spiral of progressive disease, and these acute episodes
4 lead to a loss of lung function and more frequent
5 exacerbations.

6 This is demonstrated by my 23-year-old
7 patient. This figure now has the addition of the
8 pulmonary exacerbations that he had during his teenage
9 years that require treatment with IV antibiotics. In
10 purple are the exacerbations that were treated in the
11 hospital, and in gold are those treated at home. And
12 as you can see, his need for IV antibiotics has
13 increased as his lung disease has progressed.

14 It goes without saying just how disruptive
15 these exacerbations must be for this patient. Despite
16 many days of missing school, my patients obtained a
17 college degree and is now working five days a week as a
18 chef. He loves to cook, but he struggles each and
19 every day to stay healthy enough to go to work, fearful
20 that an acute exacerbation will jeopardize his job.
21 He's trying his best to live a normal life, but his
22 daily routine is anything but normal. He's diligent in

1 completing his maintenance therapies each and every day
2 in hopes of preventing the next pulmonary exacerbation.

3 I've shown you the importance of preserving
4 lung function and nutritional status, as well as
5 preventing exacerbations in our patients. As we look
6 at the pathophysiologic cascade of CF and consider the
7 currently available therapies for F508del homozygous
8 patients, it's important to recognize that current
9 therapies do not treat the underlying cause of the
10 disease. Instead, it only targets its complications.

11 For the lungs, we have airway clearance
12 modalities, mucolytics, bronchodilators, and
13 antimicrobial and anti-inflammatory agents.
14 Malnutrition is addressed with pancreatic enzyme
15 replacement therapy, high caloric diets, and other
16 therapeutic nutrients.

17 CFTR modulators work upstream in the cascade
18 targeting the actual cause of CF. And for the roughly
19 8 percent of CF patients who have specific gating
20 mutations in CFTR, ivacaftor monotherapy is currently
21 available, and it works by improving CFTR function in
22 these patients.

1 Ivacaftor clinical trial experience and its
2 use in practice has shown that restoring CFTR function
3 results in dramatic improvement in clinical outcomes in
4 patients with gating mutations, and listed on this
5 slide are just a few of the benefits observed so far
6 with ivacaftor therapy. As a physician who treats CF,
7 I'm very impressed by these results. The effects of
8 ivacaftor have been truly transformative in the very
9 small number of patients who are appropriate for this
10 treatment.

11 I mentioned earlier that FEV1 is relied upon
12 to monitor health and disease progression, and what is
13 encouraging to me is that we have evidence from studies
14 of ivacaftor in these patients with gating mutations
15 that restoring CFTR function does result in improved
16 FEV1. In CF patients with the G551D mutation,
17 treatment with ivacaftor demonstrated not only its
18 acute improvement in FEV1, but a response that was
19 sustained for up to 3 years.

20 Moreover, if we're really going to make a
21 significant impact on CF, we need therapies that reduce
22 the rate of disease progression over time. On this

1 front, I'm again encouraged by evidence that we have
2 from our experience with ivacaftor in G551D patients.
3 Compared with mass controls, the annual rate of lung
4 function decline was reduced by nearly 50 percent for
5 G551D patients treated with ivacaftor. On the right
6 side of the slide, you can see this effect on FEV1
7 decline over this 3-year period.

8 To me, these data are very exciting as they
9 provide evidence that CFTR modulators -- these are
10 therapies that are directed at the basic defect of
11 CF -- have the potential to modify the actual course of
12 disease.

13 While we now have ivacaftor homozygous to
14 treat the 8 percent of CF patients with a gating
15 mutation, for those who are homozygous for F508del,
16 which represent nearly 50 percent of our patients, we
17 know that ivacaftor monotherapy is not effective. This
18 highlights a significant unmet medical need for these
19 patients, as there are no CFTR modulators currently
20 available to treat the underlying cause of disease.

21 In summary, CF is a multisystem,
22 life-shortening disease that is caused by defects in

1 CFTR approaching activity. People with CF who are
2 homozygous for the F508del mutation have a severe
3 clinical phenotype, rapid disease progression, and
4 reduced survival. FEV1, pulmonary exacerbation, and
5 nutritional status are not only key measures in
6 assessing clinical response and disease stage, but they
7 are also key goals of treatment.

8 We have supportive therapies to target the
9 downstream manifestations of CF, but progressive lung
10 disease still leads to significant morbidity and early
11 death in these patients. For the large segment of the
12 CF population, those homozygous for F508del mutation,
13 we sorely need a therapy that would allow us to restore
14 CFTR activity, a more proximal event in the cascade, to
15 improve clinical outcomes.

16 Thank you, and I will now turn the
17 presentation over to Dr. Van Goor.

18 DR. OWNBY: I'm sorry, Dr. Van Goor. We're
19 going to need to take about a 5-minute break because
20 we're having difficulties with our phone connection.
21 So we're going to take, hopefully, a very short break,
22 and then we'll come right back to your presentation.

1 (Whereupon, at 8:52 a.m., a brief recess was
2 taken.)

3 DR. OWNBY: I believe we're ready to go. I'm
4 sorry about that. There were some technical problems.
5 The people on the phones were not able to hear what was
6 going on. I need to just briefly ask, Dr. Druce, would
7 you please introduce yourself to the group, for the
8 record?

9 (No response.)

10 DR. OWNBY: Dr. Druce, can you hear us now?

11 (No response.)

12 DR. OWNBY: How about Ms. Motenko, the patient
13 representative? Can you introduce yourself?

14 (No response.)

15 DR. OWNBY: Apparently, what we thought was
16 fixed is not.

17 Dr. Zeng, would you like to introduce
18 yourself?

19 MS. ZENG: I'm Lan Zeng. I'm a statistics
20 reviewer in the Division of Biometrics II.

21 (Pause.)

22 DR. OWNBY: We've had a problem with panel

1 members on the phone not being able to hear, but we're
2 going to have to go ahead and restart because we can't
3 run too far late. So Dr. Van Goor?

4 **Sponsor Presentation - Fredrick Van Goor**

5 DR. VAN GOOR: Thank you very much, and good
6 morning. My name is Fredrick Van Goor, and I have been
7 involved in the research program at Vertex for the last
8 14 years. And during that time, I have spent a lot of
9 time trying to understand the molecular defects in the
10 CFTR protein caused by CFTR mutations. And by
11 understanding these molecular defects design new
12 medicines to target the underlying defect to treat the
13 underlying cause of cystic fibrosis. And it's my
14 pleasure today to tell you about two of these new
15 medicines.

16 As you've heard from Dr. Konstan, it is well
17 established that defects in the CFTR protein cause
18 cystic fibrosis. The molecular defect associated with
19 the most common mutation in CF, the F508del, has been
20 well understood since the discovery of the gene over
21 25 years ago. This drove the discovery of two
22 complementary medicines to target the underlying

1 molecular defect in the CFTR protein caused by the
2 F508del mutation.

3 Normally, CFTR is expressed at the cell
4 surface where it transports chloride ions. In people
5 with cystic fibrosis, mutations in CFTR can cause one
6 of two different types of defects. They can decrease
7 the function of the CFTR protein that reaches the cell
8 surface or they can decrease the amount of the CFTR
9 protein at the cell surface. And in some cases, some
10 mutations can cause defects from both the function and
11 the quantity of CFTR at the cell surface.

12 Because mutations can affect either the
13 function or the quantity, we designed two different
14 types of medicines called CFTR potentiators and CFTR
15 correctors. CFTR potentiators are medicines that work
16 on CFTR protein at the cell surface but because they
17 have an inability to open properly, potentiators like
18 ivacaftor help the protein open more often and longer,
19 and this allows more chloride transport to be delivered
20 across the cell surface.

21 However, for the most common mutation in CF
22 F508del, it is a different problem. Very little to no

1 CFTR gets to the cell surface. To solve this problem,
2 we designed molecules called CFTR correctors. CFTR
3 correctors increase the amount of CFTR protein at the
4 cell surface. And because they deliver more CFTR to
5 the cell surface, you can then use a potentiator like
6 ivacaftor to further increase the function of the CFTR
7 protein delivered to the cell surface by the CFTR
8 corrector; in this case, lumacaftor.

9 In the next set of slides, I'm going to go
10 into more detail into the molecular defect caused by
11 the F508del mutation and describe to you the mechanism
12 of action of ivacaftor and lumacaftor.

13 The molecular defect caused by F508del occurs
14 when the protein is folding in the endoplasmic
15 reticulum. It is not able to fold correctly. And
16 because of this, it is not processed and trafficked
17 normally to the cell surface. As a result, very little
18 to no CFTR reaches the cell surface, and the
19 consequence of this is the lost of chloride transport
20 that causes cystic fibrosis in people with an F508del
21 mutation.

22 Lumacaftor, a CFTR corrector, facilitates the

1 processing and trafficking of the F508del CFTR protein
2 to increase the amount of functional CFTR protein
3 delivered to the cell surface. Because we get more
4 F508del that's functional delivered to the cell
5 surface, we can then add ivacaftor, a CFTR potentiator,
6 to further increase the function of the CFTR protein
7 that is delivered to the cell surface.

8 In the next set of slides, I'm going to show
9 you how this works in cells derived from people that
10 are homozygous for the F508del mutation. I will refer
11 to these as F508del HBE because they come from the
12 human bronchial epithelial cells.

13 We used two important experimental methods to
14 characterize both the molecular defect and the
15 pharmacological activity of CFTR correctors and
16 potentiators, and I'll describe those to you briefly
17 here. On the bottom left-hand corner is an example of
18 a Western blot experiment.

19 Normally, CFTR protein is processed and
20 trafficked to the cell surface. In a Western blot
21 experiment, this occurs as that thick, heavy band that
22 you see there labeled as mature CFTR protein. This is

1 the hallmark of normal CFTR processing and trafficking.
2 In cells derived from people homozygous for F508del,
3 there is little to no mature CFTR, and this is
4 consistent with the severe defect in the processing and
5 trafficking of the CFTR protein. It was using this
6 method that it was first described that F508del
7 mutation causes a severe defect in the processing and
8 trafficking over 25 years ago.

9 The consequence of this CFTR processing and
10 trafficking on CFTR function at the cell surface can be
11 directly measured using Ussing chamber recording
12 methods. As you would expect in cells derived from
13 people without CFTR mutation, there's a large increase
14 in chloride transport, shown here on the top left-hand
15 corner by the green dots. In contrast, in cells
16 derived from people homozygous for F508del, there is
17 minimal chloride transport consistent with the severe
18 defect and processing and trafficking and a lack of
19 protein at the cell surface.

20 On the next series of slides, I'm going to
21 show you the effects of ivacaftor and lumacaftor on
22 CFTR processing and trafficking and function using both

1 Western blot and Ussing chamber studies. On the
2 right-hand side are going to be the Ussing chamber
3 experiments in which I've normalized chloride transport
4 to the percentage of that that occurs in human airway
5 cells derived from people without CFTR mutations and
6 expressive as percent normal. As you can see on the
7 left-hand side, there's little to no mature CFTR
8 protein in these cells, and as a consequence, there is
9 minimal chloride transport, as you would expect.

10 When you incubate ivacaftor, a CFTR
11 potentiator, overnight, there is no increase in the
12 processing and trafficking of the protein. This is
13 consistent with a known mechanism of action of
14 ivacaftor, which is a CFTR potentiator that works on
15 CFTR channels at the cell surface. Because there's
16 little CFTR at the cell surface, ivacaftor has a
17 minimal effect on chloride transport on its own.

18 In contrast, when you incubate the cells
19 overnight with lumacaftor, a CFTR corrector, you
20 increase the processing and trafficking of the CFTR
21 protein as indicated by the appearance of the mature
22 CFTR in the Western blot experiment on the left-hand

1 side. On the right-hand side, you see an increase in
2 chloride transport consistent with the delivery of
3 functional CFTR proteins to the cell surface.

4 When you incubate both lumacaftor and
5 ivacaftor overnight, you see a similar improvement in
6 the processing and trafficking of the CFTR protein to
7 the cell surface, but you see a further increase in
8 chloride transport. This is because you've been able
9 to potentiate the CFTR proteins delivered to the cell
10 surface by lumacaftor using the ivacaftor, the CFTR
11 potentiator. It helps the channels delivered to the
12 cell surface work better.

13 Let me tell you why this increase in chloride
14 transport is important. In people with cystic
15 fibrosis, the airway surface is dehydrated and the
16 cilia don't beat normally. This impairs the
17 mucociliary clearance of the airway that traps that
18 thick, sticky mucus that keeps the bacteria and causes
19 the chronic infections and inflammation of the airway.

20 An important component of mucociliary
21 clearance is the ability of the cilia to beat normally.
22 We can measure this in a laboratory using our cultured

1 F508del HBE. And what you're looking at here is the
2 cell surface of the airway epithelial cells from
3 F508del HBE. Now don't be surprised that you're not
4 seeing anything. This is consistent with the lack of
5 ciliary beat frequency that one would expect in the
6 lung of people with cystic fibrosis who have the
7 F508del mutation. As you can see, the movie is on a
8 constant loop here.

9 When we treat the cells overnight with
10 ivacaftor, there is a minimal improvement in the
11 ability of the cilia to beat. This is consistent with
12 the minimal increase in chloride transport due to
13 minimal amounts of CFTR at the cell surface. There's a
14 little bit of movement as you can see by the arrows
15 there.

16 When we incubate the cells overnight with
17 lumacaftor alone, there's a marginal improvement in the
18 ciliary beat frequency consistent with an improvement
19 in chloride transport. However, where we see the
20 greatest benefit is when we incubate both ivacaftor and
21 lumacaftor together. And now you can start to see the
22 cilia beating not only in more places but with higher

1 frequency. It is expected that in the lung of people
2 with cystic fibrosis that the increase in ciliary beat
3 frequency by lumacaftor and ivacaftor would help to
4 clear out the blockages and the thick, sticky mucus in
5 the airway of the lungs.

6 In summary, F508del causes a severe defect in
7 the CFTR processing and trafficking of the CFTR
8 protein. Ivacaftor, a CFTR potentiator, has a minimal
9 effect on chloride transport, which is consistent with
10 the little to no F508del CFTR at the cell surface.
11 Lumacaftor, a CFTR corrector, improves F508del CFTR
12 processing and trafficking to increase the amount of
13 functional CFTR protein delivered to the cell surface.
14 And the CFTR protein delivered to the cell surface by
15 lumacaftor can be further potentiated by ivacaftor such
16 that the combination of lumacaftor and ivacaftor
17 provide the superior improvement in chloride transport.

18 Now I'd like to turn the presentation over to
19 Dr. Charlotte McKee who heads up our clinical
20 development program at Vertex.

21 **Sponsor Presentation - Charlotte McKee**

22 DR. McKEE: Thank you, Dr. Van Goor.

1 My name is Dr. Charlotte McKee, and I'm the
2 vice president of clinical development for cystic
3 fibrosis at Vertex. I'm especially pleased to be here
4 today because I'm a pulmonologist who specializes in
5 lung transplantation, and it's one of my personal
6 missions to help make lung transplant obsolete in
7 cystic fibrosis. I believe that we're one step closer
8 to that goal with the combination of lumacaftor and
9 ivacaftor therapy.

10 I'm going to pick up where Dr. Van Goor left
11 off. The next step was to determine whether the
12 compelling in vitro data he just showed could be
13 translated to patients who are homozygous for the
14 F508del mutation, which is the most common form of
15 cystic fibrosis. The main objectives of the early
16 clinical development program were, first, to confirm
17 the activity of lumacaftor/ivacaftor in patients who
18 are monotherapy for F508del and that the combination
19 provides greater benefit than either drug alone, as was
20 shown in the laboratory.

21 Second, to identify the doses to be taken into
22 phase 3 with particular emphasis on a couple of

1 endpoints that provide signals of CFTR modulation and
2 clinical benefit; that is sweat chloride, which is a
3 pharmacodynamic endpoint that's a direct in vivo
4 measurement of CFTR function, and FEV1, which is of
5 course a well established clinical endpoint both in CF
6 and in other lung diseases and a direct measure of lung
7 function. And then, third, to evaluate the safety
8 profile of combination therapy.

9 Over 400 subjects were enrolled in the phase 1
10 studies in the lumacaftor/ivacaftor combination
11 program, and in phase 2 dose-ranging studies, 189 CF
12 patients homozygous for the F508del mutation received
13 lumacaftor monotherapy for up to 28 days followed by
14 lumacaftor in combination with ivacaftor, again, for up
15 to 28 days.

16 Lumacaftor doses of 200, 400, and
17 600 milligrams once a day and 400 milligrams every
18 12 hours were studied, and ivacaftor doses of 150 and
19 250 milligrams every 12 hours were also investigated.
20 In a prior study, ivacaftor monotherapy was
21 investigated in 140 subjects/patients who were
22 homozygous for F508del for 16 weeks.

1 First, I want to describe the ivacaftor
2 monotherapy results. We're going to come back to this
3 topic later, but here I want to discuss it in the
4 context of planning the phase 3 program. In this
5 earlier study, treatment with ivacaftor alone in 140
6 patients who are homozygous for F508del did not show
7 meaningful clinical benefit. The study did not meet
8 its primary endpoint, which is the absolute change in
9 percent predicted FEV1 from baseline through week 16
10 shown here. And even for those patients who met a
11 prespecified threshold of FEV1 or sweat chloride
12 improvement at week 16, this wasn't sustained.

13 There was a minimal improvement in sweat
14 chloride, which is at 2.9, consistent with the effects
15 seen in F508del HBE cells in vitro and described by Dr.
16 Van Goor. Treatment effects on the other secondary
17 efficacy endpoints -- pulmonary exacerbations, CFQ-R
18 respiratory domain, which is a CF-specific quality of
19 life instrument, and BMI -- were also not significant.
20 The exacerbations numerically favored ivacaftor. CFQ-R
21 results were negative in both dosing groups, but they
22 were less negative in the ivacaftor group, and the

1 effect on BMI actually favored the placebo group.

2 These clinical results, together with the
3 other evidence available -- the biology, the mechanism
4 of action, and the in vitro findings -- led to the
5 conclusion by Vertex, by the CF community, and the
6 agency that ivacaftor alone does not provide a
7 meaningful clinical benefit in patients who are
8 homozygous for the F508del mutation. The Kalydeco
9 label, as Dr. Chodakewitz mentioned, reflects this,
10 stating that ivacaftor alone is not effective in these
11 patients. And as a result and in consultation with the
12 agency, as you've heard, an ivacaftor monotherapy arm
13 was not included in the combination phase 3 studies.

14 Where lumacaftor monotherapy at several doses
15 provided an improvement in sweat chloride, shown here
16 in the top line of this table -- and improvement I
17 should mention is associated with a negative change in
18 sweat chloride -- it unexpectedly caused a decline in
19 FEV1. Therefore, also as mentioned in consultation
20 with the agency, a lumacaftor monotherapy arm was not
21 included in the combination phase 3 studies.

22 On the other hand, patients who received the

1 combination of lumacaftor and ivacaftor had
2 dose-dependent improvements in both FEV1 and sweat
3 chloride. The day 56 phase 2 results are shown here.
4 They reflect the net effect of 28 days of combination
5 therapy coming after 28 days of lumacaftor monotherapy.

6 Highlighted here in the red box on this slide,
7 the two regimens with the highest total daily dose of
8 lumacaftor, 600 milligrams once a day and
9 400 milligrams twice a day, showed the greatest
10 improvements in FEV1 at day 56 and consistent
11 improvements in sweat chloride, that is changes of 9 to
12 11. Because of the initial decline with lumacaftor
13 alone, the largest improvements in FEV1 in this phase 2
14 study were actually from day 28 to day 56. And these
15 aren't shown here, but they were in the range of
16 6 percentage points for these two regimens.

17 Turning now to safety, the combination therapy
18 was generally well tolerated across the phase 1 and the
19 phase 2 studies with no dose-limiting toxicities
20 identified. There were short-term declines in FEV1
21 observed with combination treatment immediately
22 post-dose -- that is within about 2 to 4 hours -- and

1 believed to be due to off-target bronchoconstriction.
2 These were only rarely associated with clinical adverse
3 events or with discontinuation of dosing.

4 FEV1 was back to baseline or near baseline
5 after 7 days of continued dosing in these studies, and
6 the effect was reversed or largely prevented with
7 bronchodilators. So in phase 2, this was a transient
8 effect that was seen early in the dosing course, which
9 could be managed and treated through in almost all
10 cases. We were vigilant for this as we went into phase
11 2. And as you'll hear in the next section of the
12 presentation, this effect was in fact transient and
13 generally very manageable across the phase 3 program.

14 Results of the early phase studies I just
15 described informed selection of the doses of both
16 ivacaftor and lumacaftor used in combination regimens.
17 As I'd mentioned, ivacaftor doses of 150 milligrams
18 twice a day, which is the approved monotherapy dose,
19 and 250 milligrams twice a day were studied in
20 combination regimens. Ivacaftor exposure is reduced
21 compared to the approved monotherapy exposure when it's
22 given in combination with lumacaftor. This is because

1 lumacaftor is a strong CYP3A inducer, and ivacaftor is
2 a sensitive CYP3A substrate.

3 So because of this, the higher ivacaftor dose
4 of 250 milligrams twice a day was chosen for all of the
5 combination regimens. And based on the phase 2 sweat
6 chloride and FEV1 results, regimens that contained
7 lumacaftor 600 milligrams once a day and lumacaftor
8 400 milligrams every 12 hours were selected for further
9 study in phase 3.

10 Therefore, in conclusion, the improvements in
11 F508del CFTR function that were observed with the
12 combination therapy in vitro did in fact translate into
13 patients who are homozygous for F508del in the phase 2
14 program. And lumacaftor/ivacaftor combination was
15 superior to either drug alone across in vitro,
16 pharmacodynamic, and clinical endpoints. Monotherapy
17 arms were not included in phase 3 for all the reasons
18 you've heard about.

19 Two combination regimens 600 milligrams once a
20 day and 400 milligrams every 12 hours of lumacaftor,
21 both in combination with ivacaftor 250 milligrams twice
22 a day, were taken into phase 3 as these were the most

1 promising regimen based on FEV1 and sweat chloride
2 results with favorable safety profiles. So these
3 phase 2 data supported moving into phase 3 with
4 combination therapy with the objective of confirming
5 these findings in two adequate and well-controlled
6 pivotal studies, which I'm going to describe in the
7 next section.

8 In this section, we review the phase 3 study
9 design, describe the efficacy and the safety results,
10 and provide our dosing recommendation. I'll also
11 summarize the benefit-risk profile of
12 lumacaftor/ivacaftor combination. And finally, I'll
13 address the comparison of combination therapy in
14 ivacaftor monotherapy.

15 Our phase 3 program was designed to study the
16 effect of combination therapy on the three primary
17 goals of cystic fibrosis treatment, which you heard
18 Dr. Konstan just describe: maintenance of lung
19 function, reduction in pulmonary exacerbations, and
20 improvement in nutritional status.

21 Lumacaftor/ivacaftor has an effect on every cell in the
22 body with a CFTR protein, and therefore, it was

1 important for us to evaluate the multisystem effect of
2 combination therapy in our phase 3 studies.

3 Here, I want to point out two things about the
4 phase 3 program. The size of the studies allowed us to
5 fully evaluate these critical secondary endpoints as
6 well as to generate a robust safety database. And the
7 combination therapy was evaluated in these phase 3
8 studies on top of all of the usual CF medications that
9 these patients were taking.

10 Studies 103 and 104 were two randomized,
11 double-blind, placebo-controlled, parallel group
12 studies conducted at 187 sites globally. They were
13 identical except for minor substudies. Patients who
14 completed these initial studies were offered enrollment
15 in study 105, which is a blinded, 96-week extension
16 study and is still ongoing. Patients on the active
17 treatment in the initial studies continued on the same
18 treatment in the extension study, while patients on
19 placebo were randomized to one of the two active dosing
20 arms.

21 The primary objective of both studies was to
22 evaluate the efficacy of lumacaftor/ivacaftor

1 combination therapy at week 24 in CF patients
2 homozygous for the F508del mutation. And the primary
3 endpoint in both studies was the change from baseline
4 in absolute percent predicted FEV1 at week 24 using the
5 average of measurements at week 16 and 24.

6 The multisystem effects of combination therapy
7 were evaluated through multiple secondary endpoints,
8 many speaking to those three main goals of CF therapy,
9 including BMI, pulmonary exacerbations, and the
10 proportion of patients with at least a 5 percent
11 relative improvement in FEV1. The studies enrolled
12 patients who were homozygous for the F508del CFTR
13 mutation with a percent predicted FEV1 between 40 and
14 90 at screening, and the other key eligibility criteria
15 are listed here.

16 Before we move on to the actual phase 3 data,
17 I want to review first some of the key elements of the
18 statistical analysis plan. FEV1 endpoints were all
19 analyzed using a mixed model for repeated measures, and
20 multiplicity associated with the five key secondary
21 endpoints was controlled for in the individual studies
22 in a couple of different ways.

1 There was a simple Bonferroni adjustment that
2 was made for each dosing arm's treatment comparisons
3 with a significance level of 0.025, and a hierarchical
4 testing procedure was used within each dosing arm of
5 each individual study. And finally, a prespecified
6 pooled analysis was performed for both efficacy and
7 safety endpoints given that the two pivotal trials were
8 nearly identical.

9 This was helpful of course to better
10 understand the profile of combination therapy and was
11 particularly important for the evaluation of pulmonary
12 exacerbations, which occur relatively and frequently
13 compared to some of the other endpoint evaluations.

14 With that background, I want to now look at
15 the phase 3 data, beginning with the overall patient
16 disposition and baseline characteristics. 1,122
17 patients were randomized in the phase 3 program, and
18 1,108 patients received at least 1 dose of study drug.
19 Only 54 subjects total stopped taking study drug during
20 the trials, meaning that 95 percent of patients who
21 received at least 1 dose of study drug completed
22 24 weeks of treatment, and nearly all of these patients

1 enrolled in the rollover extension study 105.

2 Baseline characteristics and demographics,
3 which are shown here from the pooled data, were similar
4 across the three treatment arms, and these
5 characteristics were also well matched within the
6 individual studies. Baseline FEV1 was about 60 percent
7 predicted across the program, and a quarter of patients
8 were adolescents.

9 I also want to point out here that 8 percent
10 of patients had a baseline percent predicted FEV1 that
11 was below 40 percent predicted. However, all of these
12 patients had a screening percent predicted FEV1 between
13 40 and 90, consistent with the eligibility criteria.

14 The majority of patients in these studies were
15 taking multiple chronic standard of care CF
16 medications, and the most common ones are listed here.
17 About three-fourths of the patients were taking dornase
18 alfa, and 60 to 70 percent of them were taking inhaled
19 antibiotics. And treatment arms were also well matched
20 with respect to these background medications.

21 Now let's look at the efficacy results
22 beginning with the primary endpoint. Both of these

1 studies were positive, as has been mentioned. The
2 primary endpoint of percent predicted FEV1 was met in
3 both of them, and it was also met in each individual
4 treatment arm of each study with absolute improvements
5 versus placebo that ranged from 2.6 to 4 percentage
6 points. These results were highly statistically
7 significant, both within each individual dosing arm and
8 within each study overall, and recall that these were
9 on top of patients' usual CF medications.

10 This figure illustrates the individual study
11 results for the primary endpoint, and it shows the
12 consistency in the patterns and the magnitude of
13 response between the two studies. The lumacaftor
14 600-milligram, once-a-day group is shown here in green,
15 the lumacaftor 400-milligram, twice-a-day group is in
16 blue, and the placebo is in gray. And this color
17 scheme will remain constant throughout the
18 presentation.

19 The results of the pooled primary endpoint
20 analysis are shown here demonstrating the rapid,
21 consistent, and sustained improvements in FEV1 in both
22 dosing groups. There were consistent improvements by

1 the first study visit at day 15, and these were
2 sustained throughout the 24-week treatment period. And
3 as you'll see later in the presentation, this effect on
4 lung function and the magnitude of this effect was in
5 fact sustained through 48 weeks of active treatment
6 through the extension study. In contrast, the FEV1 in
7 the placebo group declined slightly as you would expect
8 over the 24-week placebo-controlled period.

9 Prespecified subgroup analyses of the primary
10 endpoint across multiple baseline characteristics
11 demonstrated consistent effects favoring active
12 treatment. These subgroups include age, sex, inhaled
13 antibiotic use, and Pseudomonas colonization. And this
14 forest plot demonstrates that all of the effects
15 favored the active treatment regardless of the
16 subgroup, confirming both the robustness of the effect
17 on lung function and demonstrating that improvements
18 with combination therapy were consistent across all
19 F508del homozygous patients.

20 This table here presents an overview of the
21 key secondary endpoint results for each individual
22 study listed in order of the statistical hierarchy.

1 Improvement in the relative change in FEV1 was
2 statistically significant in all active treatment
3 groups in both studies, and those results are therefore
4 shaded here. The improvement in BMI was statistically
5 significant in both dosing arms of study 104 but not in
6 study 103. And therefore, the hierarchy was broken
7 here in that study, and the hierarchy was broken at the
8 CFQ-R results for study 104.

9 For the rest of these endpoints, we note the
10 results did all favor active treatment numerically in
11 all four dosing arms of both studies, and the results
12 were nominally significant for many of them. The
13 consistency of these secondary endpoint results in the
14 individual studies give us confidence that the pooled
15 results, which are shown here on the next slide, are
16 both representative of the effects of combination
17 treatment and meaningful.

18 Many of these results are related, as you'll
19 recall, to those three primary goals of CF treatment:
20 maintenance of lung function, reduction in pulmonary
21 exacerbations, and improvement in nutritional status.

22 I'm going to go through each of these

1 secondary results in more detail, but I want to step
2 back here at this point and consider the consistency
3 across all of these endpoints, the primary and
4 secondary endpoints in both studies and in all dosing
5 groups. Every analysis of every endpoint favored
6 active treatment across multiple systems, and this is
7 on top of the best medicines that these patients
8 currently have available.

9 Let's look now at the pooled results of each
10 of these key secondary endpoints in a little more
11 detail beginning with the pulmonary exacerbations. We
12 did hear from Dr. Konstan earlier how important these
13 events are because they are in and of themselves highly
14 destructive and may even be life-threatening, but
15 they're also associated with reductions in lung
16 function and increases in mortality.

17 This figure here demonstrates the reduction in
18 pulmonary exacerbations in both dosing groups presented
19 as the event rate per year on the Y-axis. Overall
20 exacerbations were reduced by 30 percent relative to
21 placebo in the 600-milligram, once-a-day group, and by
22 39 percent relative to placebo in the 400-milligram,

1 twice-a-day group, representing statistically
2 significant and clinically meaningful reductions in
3 both dosing groups.

4 Here we break down the effect on pulmonary
5 exacerbations further through a prespecified analysis
6 looking at the most severe events, those that required
7 IV antibiotics or hospitalization. And this was an
8 important analysis because while we knew that the
9 overall rate of exacerbations was reduced, this could
10 have been achieved in multiple ways; for example,
11 through just a reduction in the mild exacerbation
12 events.

13 However, as we see here in this figure, there
14 were significant and meaningful reductions in the
15 severe categories of exacerbations with both dosing
16 regimens. The 600-milligram daily regimen reduced the
17 events requiring hospitalization by 39 percent, and the
18 400-milligram, twice-a-day regimen reduced these by
19 61 percent, and the 600-milligram, once-a-day regimen
20 reduced events requiring IV antibiotics by 45 percent,
21 while the 400-milligram, twice-a-day regimen reduced
22 these by 56 percent. There were, we should note,

1 consistently greater reductions in pulmonary
2 exacerbations in both the overall and the severe events
3 with the 400-milligram, twice-a-day regimen.

4 Now still focusing on the treatment effect on
5 pulmonary exacerbations, this Kaplan-Meier figure here
6 shows that a substantially larger proportion of
7 patients, each in the active treatment groups, were
8 free of exacerbations compared to the placebo groups at
9 every time point through the 24 weeks of treatment,
10 indicating that the active treatment prolonged the time
11 to the first pulmonary exacerbation. And this effect,
12 too, was greater for the 400-milligram, twice-a-day
13 regimen than the 600-milligram, once-a-day regimen.

14 Looking now at BMI results, improvements were
15 seen with both dosing regimens, showing that the
16 combination therapy has a beneficial effect on
17 nutritional health, again, one of the three main goals
18 of cystic fibrosis treatment. Recall that most of
19 these F508del homozygous patients are pancreatic
20 insufficient. And because of this, together with the
21 chronic inflammation associated with chronic lung
22 disease, these patients often struggle to maintain an

1 adequate weight. And as we heard from Dr. Konstan, a
2 low BMI is also independently associated with reduced
3 lung function and increased mortality.

4 All treatment groups, including the placebo
5 group, showed an improvement in BMI through the first
6 4 weeks of the studies. However, there was no further
7 improvement in BMI in the placebo group after this,
8 while BMI continued to improve in both active dosing
9 groups over the full 24 weeks. And as I'll show you
10 shortly, BMI actually continued to improve through the
11 extension rollover study. The pooled treatment
12 differences relative to placebo are shown in the table,
13 and they were very similar in both of the dosing
14 groups.

15 Improvements in the CFQ-R respiratory domain
16 consistently favored the active treatment for both
17 dosing regimens in both studies. The differences were
18 not statistically significant compared to placebo.
19 However, the pooled within group changes, that is the
20 change from baseline for patients on active drug in
21 both dose groups were at or above the well established,
22 minimal clinically important difference, or MCID of 4,

1 which is depicted by the horizontal dotted line in this
2 figure at week 24.

3 Now I want to turn to the FEV1 response
4 analysis, which was one of the key secondary endpoints,
5 looking at how many patients had at least a 5 percent
6 relative improvement in percent predicted FEV1 from
7 baseline. We also conducted a prespecified analysis of
8 patients with at least a 10 percent relative
9 improvement in FEV1.

10 Both of these analyses explored the impact of
11 combination therapy on lung function at an individual
12 patient level. And this figure demonstrates that
13 almost twice as many patients in the active treatment
14 arms had at least a 5 percent or a 10 percent relative
15 improvement in their FEV1 compared to placebo. And
16 this is an important point because it means that almost
17 half of patients on combination therapy had at least a
18 5 percent relative improvement, and about a quarter had
19 at least a 10 percent relative improvement in FEV1;
20 again, above and beyond the usual CF medications that
21 these patients are all taking.

22 The final two efficacy data slides I'm going

1 to show you are from an interim analysis of the
2 extension study 105. Recall that over 90 percent of
3 patients in the placebo-controlled studies 103 and 104
4 enrolled in this extension study. And the patients and
5 study sites are still blinded to treatment assignment
6 both in the original studies and in this rollover study.
7 The interim analysis was conducted when about a hundred
8 patients had been on active treatment for at least
9 48 weeks.

10 Here on this figure are the primary results I
11 just showed you from the two studies 103 and 104 with
12 the addition of the FEV1 results from both regimens for
13 patients on active treatment through 48 weeks. This
14 figure shows that the improvement in FEV1 was sustained
15 through 48 weeks with both active regimens in contrast
16 to the decline that was observed and expected in the
17 placebo group during the first 24 weeks. And these
18 results clearly demonstrate the durability of
19 improvement in lung function with combination therapy
20 achieved on top of what are currently the best
21 medicines that these CF patients have available.

22 Improvements in BMI were also sustained and in

1 fact continued to improve through the 48 weeks with
2 both active treatment regimens during the rollover
3 extension study, demonstrating again the durability of
4 improvement in systemic nutritional parameters with
5 combination therapy.

6 To conclude the efficacy portion of the data
7 review, the lumacaftor/ivacaftor combination therapy
8 demonstrated rapid, clinically meaningful and
9 significant improvements in lung function in both
10 pivotal studies and in all treatment arms. Both
11 studies were positive, and the primary endpoint was met
12 in all four active dosing arms.

13 These lung function effects were sustained out
14 through 48 weeks, and they were accompanied by
15 additional important benefits of CFTR modulation,
16 including substantial reductions in pulmonary
17 exacerbations, especially those that require
18 hospitalization or IV antibiotics, and meaningful
19 improvements in BMI through 48 weeks, while CFQ-R
20 improvements favored the active treatment in both
21 dosing groups. And recall that all of these
22 improvements were seen on top of patients' usual CF

1 medications.

2 Now, let's move on to the safety results.
3 Over 1600 patients with CF have been exposed to
4 lumacaftor/ivacaftor combination therapy, making this a
5 very substantial safety database for this orphan
6 indication. More than a thousand patients were exposed
7 to combination therapy in phase 3, and at the time of
8 the NDA filing, substantial numbers of patients had
9 been exposed to phase 3 doses for meaningful periods of
10 time, shown here on this slide.

11 The rollover extension study 105, as I
12 mentioned, is still ongoing and continuing to
13 accumulate data. And in fact, those patients who were
14 enrolled at the beginning of the program have now been
15 on active drug for nearly two years. I'm going to
16 focus primarily on the pooled safety data from
17 studies 103 and 104 in this presentation, as well as
18 provide long-term follow-up safety data from the
19 extension study.

20 Not surprisingly, in a program in cystic
21 fibrosis, adverse events were common in all treatment
22 arms, and almost all patients had at least one adverse

1 event. As shown here, patients on the active treatment
2 actually experienced fewer serious adverse events than
3 placebo patients, while the incidence of grade 3 or
4 grade 4 adverse events overall was similar to placebo.

5 There were no deaths in study 103 or 104.
6 There have been 4 deaths in subsequent studies, all due
7 to complications of underlying CF and all considered
8 unrelated to lumacaftor/ivacaftor by the treating
9 investigators.

10 Shown here in this table are adverse events
11 with an incidence of at least 10 percent in any
12 treatment group, and they're ranked by the frequency
13 with which they occurred in the pooled active
14 lumacaftor/ivacaftor group. Events that occurred more
15 frequently in the active treatment group are
16 highlighted here on the table. The two most common
17 adverse events overall were pulmonary exacerbation and
18 cough, both of which were more common in the placebo
19 groups than the active treatment.

20 This table here shows adverse events that
21 occurred in at least 5 percent of active treatment
22 patients and that were more common in the active

1 treatment groups than placebo by at least 3 percent.
2 I'm going to provide more detail on the respiratory
3 events in a couple of slides, but here I want to
4 address the category of menstrual abnormalities.

5 Among female patients, these occurred in
6 10 percent of patients on active drug and only
7 2 percent of patients in the placebo group. It was
8 also that it turns out that these events were more
9 common in female patients who were on the active drug
10 who were also taking hormonal contraceptives, and we
11 believe they may reflect a drug-drug interaction due to
12 CYP3A induction by lumacaftor such that hormonal levels
13 are effectively lowered in these patients.

14 The events themselves were generally very
15 manageable and well tolerated. There were no treatment
16 discontinuations, for example, because of them.
17 However, we note them, as well as the potential
18 implications for female patients taking combination
19 therapy and hormonal contraceptives. And I also want
20 to point out here on this table that the two profiles
21 of the two dosing groups were very similar.

22 In general, laboratory abnormalities are

1 common in patients with CF because of their background
2 and significant systemic disease. However, the phase 3
3 studies revealed no clinically meaningful differences
4 in either mean values or shifts in laboratory values
5 for safety labs, and adverse events related to
6 laboratory abnormalities were also generally similar
7 between the treatment and placebo groups.

8 Serious adverse events were less frequent in
9 the active treatment group, highlighted here, than in
10 the placebo group. And this table here shows SAEs that
11 occurred in at least 3 subjects in any treatment group.
12 Pulmonary exacerbation was the most common SAE and
13 occurred more often in patients in the placebo group
14 than in the active treatment groups.

15 There were few treatment discontinuations due
16 to adverse events in general across the studies and
17 throughout all the dosing arms, although there were
18 numerically more in patients on active drug. The most
19 common adverse events that were leading to treatment
20 discontinuation included respiratory events, increased
21 CPK, and liver related adverse events, each of which
22 occurred in 4 or 5 patients all on active treatment.

1 And I'm going to discuss the respiratory and the liver
2 related events in more detail in the next few slides.

3 First, let's look more closely at the
4 respiratory events, which occurred more often in the
5 active treatment group than in the placebo group. We
6 looked closely at these events because of the phase 2
7 experience, conducting a comprehensive, integrated
8 review of respiratory signs and symptoms across the
9 phase 3 studies.

10 To do this, we combined similar respiratory
11 adverse event terms: dyspnea, respiration abnormal,
12 which was most commonly reported as chest tightness,
13 wheezing, and then the other preferred terms that you
14 see here on the slide, and we analyzed them together.

15 As shown here in the table, these respiratory
16 events occurred in 17 percent of placebo patients and
17 about 26 percent of active treatment patients. So
18 there was an increase of just under 10 percent of these
19 events in the active treatment group. They were
20 generally mild to moderate in severity. There were 4
21 respiratory serious adverse events all in the active
22 treatment group, and 5 out of 738 patients on active

1 treatment discontinued dosing because of a respiratory
2 event. That is about less than 1 percent of the group
3 that received active drug.

4 Now, looking a little more closely at these
5 events here on this table, we see that they tended to
6 occur early in the dosing course, and that's
7 highlighted in the shaded row, and more specifically
8 within the first week after dosing. They lasted a
9 median of 6 days, and they tended to resolve even with
10 continued dosing over the first week of treatment. And
11 after the first week, there was no difference in the
12 incidence of these events between active treatment and
13 placebo groups.

14 The events are consistent with the post-dose
15 decline in FEV1 that was seen in the early phase
16 studies, and both events are most likely due to a
17 transient, off-target, bronchoconstriction. Therefore,
18 there was an imbalance in respiratory adverse events
19 that was seen soon after dosing with the combination
20 therapy. However, these events were transient,
21 generally mild to moderate, and they could be managed
22 without treatment discontinuation in almost all cases

1 in the phase 3 studies.

2 Now, I want to turn to the liver related lab
3 findings and adverse events. As Dr. Konstan noted in
4 his presentation, underlying liver disease is common in
5 cystic fibrosis. Liver test abnormalities are also
6 common, and, in fact, about 5 percent of patients, as
7 you can see in this table, in both the placebo and the
8 active treatment groups, had amino transferase
9 elevations of at least 3 times the upper limit of
10 normal. In particular, these were also balanced in the
11 thresholds of greater than 5 times or greater than
12 8 times the upper limit of normal. Elevations in total
13 bilirubin were also balanced between the active
14 treatment and the placebo groups.

15 Three patients, all in the active treatment
16 group, had elevations in both amino transferases and
17 total bilirubin. Liver related adverse events -- these
18 included events in the hepatobiliary disorder category
19 or adverse events related to elevations in amino
20 transferases -- occurred in 5 to 6 percent of patients
21 in both the placebo and the active treatment groups.

22 Finally, 7 patients had liver related SAEs all

1 on active treatment, including the three with the
2 elevated amino transferases and total bilirubin. And
3 while these patient numbers are small, there was this
4 numerical imbalance, so we reviewed these cases
5 extremely closely, and I'm going to discuss them
6 further on the next slide.

7 The 7 liver related SAEs which occurred in the
8 738 patients on active treatment tended to be complex
9 cases confounded by alternative etiologies -- for
10 example, concurrent CF pulmonary exacerbations -- as
11 well as underlying risk factors. For example, one of
12 these patients had cirrhosis with portal hypertension.
13 And other than the elevation in the amino transferases
14 themselves, there was no unifying pattern among these
15 cases. The events ranged from asymptomatic amino
16 transferase elevations to cholestatic hepatitis.

17 Most of the patients did have a history of
18 liver abnormalities, but this is common, as we know, in
19 cystic fibrosis. And it was also common in the phase 3
20 program. And overall, the patients in the studies with
21 a history of liver abnormalities were not at increased
22 risk for amino transferase elevations while on active

1 drug. There was no relationship with lumacaftor or
2 ivacaftor exposures in these events.

3 All of these cases resolved, and liver tests
4 returned to baseline in all 7 patients. Two patients
5 were rechallenged, and drug was reinitiated without
6 concurrent elevations in liver tests. Therefore, while
7 there was an imbalance in the liver related SAEs in the
8 active treatment group, and the data overall do not
9 provide a causal link between combination therapy and
10 liver events, because a contribution can't be excluded
11 entirely and because these patients do have a
12 relatively high incidence of liver abnormalities at
13 baseline, we have provided recommendations for liver
14 test monitoring in our proposed guidance. These are
15 consistent largely also with the Kalydeco label.

16 All of the safety data we've just reviewed
17 came from the placebo-controlled, 24-week studies, the
18 phase 3 studies. And as I mentioned, there was an
19 interim analysis performed in the rollover extension
20 study when about a hundred patients had been on active
21 treatment for at least 48 weeks, and nearly 90 percent
22 of patients had actually been on study for at least

1 40 weeks at that time.

2 The long-term safety analysis from this
3 analysis was entirely consistent with the 24-week
4 safety profile from the placebo-controlled phase 3
5 studies that I've just shared with you, with similar
6 types and frequencies of adverse events. There was a
7 low incidence of amino transferase elevations and
8 related SAEs in the extension study, and there was a
9 similar incidence of these early transient respiratory
10 events in patients from the placebo group who were new
11 to active treatment. In summary, there were no new
12 safety concerns identified with combination therapy
13 with longer treatment duration.

14 Now, to conclude the lumacaftor/ivacaftor
15 safety data review, the most common adverse events
16 observed in this large phase 3 program were typical for
17 a CF population and occurred with similar frequencies
18 in the active treatment and the placebo groups. Most
19 of the adverse events were mild to moderate in severity
20 and were manageable without stopping treatment,
21 including the transient respiratory events that were
22 seen soon after dosing.

1 Serious adverse events were actually more
2 frequent in the placebo group due to a higher pulmonary
3 exacerbation rate. There was no imbalance in amino
4 transferase elevations or overall liver related adverse
5 events. However, there was an imbalance in liver
6 related SAEs without a causal link to combination
7 treatment. Based on the data from the rollover
8 extension study, the longer-term safety profiled
9 remained favorable through 48 weeks.

10 Thus, these data demonstrate that the overall
11 safety profile of lumacaftor/ivacaftor is favorable,
12 and the profiles are very similar for the two phase 3
13 dosing regimens.

14 Now, I'm going to move on to the final section
15 of the presentation. First, I'm going to address the
16 dosing recommendation. We studied two regimens of
17 lumacaftor and ivacaftor in the phase 3 program with
18 results, as you've seen, that were largely similar for
19 both efficacy and safety.

20 Although we did see numerically greater
21 reductions in pulmonary exacerbations in the lumacaftor
22 400-milligram, twice-a-day dosing group, this is the

1 regimen we are recommending -- it's shown here on this
2 slide on the right -- because of its potential
3 advantages for patient adherence and convenience. With
4 this regimen, patients take only one type of tablet
5 twice in the morning and twice in the evening. And
6 given the complexity of CF patient regimens, we think
7 that this offers an advantage.

8 At this point, I'd like to stop and summarize
9 the overall benefit-risk profile of combination therapy
10 in people with CF who are homozygous for the F508del
11 mutation. Earlier today, Dr. Konstan told us about the
12 three main goals of CF therapy, all of which
13 lumacaftor/ivacaftor treatment achieved in this phase 3
14 program with a favorable safety profile and a robust
15 safety database of over a thousand CF patients.

16 There were sustained, meaningful, systemic
17 clinical benefits with combination therapy across
18 multiple endpoints, lung function, pulmonary
19 exacerbations, including the severe exacerbations which
20 require IV antibiotics or hospitalization, as well as
21 BMI.

22 All of these effects were seen on top of the

1 best medications that these patients currently have
2 available. And the combination therapy is the first
3 treatment to address the underlying cause of CF in
4 these patients who have a severe form of this disease
5 and a very high unmet need with the potential to change
6 the course of this disease. Therefore, the data I've
7 shown you demonstrate that lumacaftor and ivacaftor's
8 highly favorable benefit-risk profile supports its
9 approval in F508del homozygous patients, age 12 and
10 over.

11 Now, before I close, I just want to take a few
12 minutes to address the agency's specific question about
13 the contribution of lumacaftor to the effect of
14 combination treatment in these patients. Fortunately,
15 there is a tremendous amount of data generated over
16 decades of scientific research in CF to help us answer
17 this question.

18 Dr. Van Goor reviewed the biology earlier, and
19 I'm not going to repeat it all here. But recall that
20 there is little to no F508del CFTR on the cell surface
21 in F508del homozygous patients. Lumacaftor is required
22 to deliver functional F508del CFTR to the surface of

1 the cell. The preclinical and the translational
2 biomarker data confirmed these findings. Ivacaftor
3 alone has minimal effects on in vitro and on sweat
4 chloride responses, while the combination of lumacaftor
5 and ivacaftor results in clearly superior improvements
6 in both.

7 Finally, the clinical data, which I'm going to
8 address in more detail, confirm these findings.

9 Ivacaftor alone did not provide consistent significant
10 or clinically meaningful benefit in these patients in
11 sharp contrast to what I just reviewed with the
12 lumacaftor/ivacaftor combination.

13 I want to look a little more closely at the
14 translational biomarker data, which, as we've all
15 mentioned, is important because sweat chloride is a
16 direct in vivo measurement of CFTR function in
17 patients. The improvements in sweat chloride that are
18 observed with CFTR modulators, first of all, give us
19 confidence that the preclinical outcomes do in fact
20 translate into patients. And in addition, this
21 biomarker allows us to directly assess the contribution
22 of lumacaftor to the combination treatment effect.

1 In this figure here, we see the improvement in
2 sweat chloride, shown on the Y-axis, in ivacaftor
3 exposures and increasing quartiles of lumacaftor
4 exposures across the X-axis from combination regimens
5 across the phase 2 program.

6 Ivacaftor alone, which is in red, and
7 lumacaftor, which is shown in the blue bars, at the
8 lowest quartiles provide a minimal improvement in sweat
9 chloride. However, moving from left to right, sweat
10 chloride responses increased with increasing lumacaftor
11 exposure, directly demonstrating an important
12 contribution of lumacaftor to the improvement in CFTR
13 function in patients. I also want to point out here
14 that the phase 3 dose exposures fell within the two
15 far-right exposures of lumacaftor.

16 Next, let's look at the clinical studies, but
17 first I want to point out that these studies were
18 conducted as part of two separate different development
19 programs, and the studies themselves are actually quite
20 different. Here in this table are some of the major
21 differences. For example, they were conducted four
22 years apart. The mean baseline FEV1s were different,

1 and baseline therapies were also different.

2 This illustrates the difficulties associated
3 with drawing highly quantitative, post hoc, cross-study
4 conclusions, particularly because these studies were
5 not designed to address those questions. That said, we
6 can compare the outcomes of the studies themselves, the
7 patterns, and the consistency of the results.

8 Here shown on this table are results of the
9 ivacaftor monotherapy study and the combination phase 3
10 studies, together with the in vitro data and the sweat
11 chloride results. And the pooled data from the
12 400-milligram, twice-a-day combination regimen are
13 shown here.

14 First, looking at results of the combination
15 regimen, the primary endpoint, which was the absolute
16 change in percent predicted FEV1, was met in both
17 studies and all treatment arms, and all secondary
18 endpoints favored active drug with significant
19 differences for BMI and exacerbations.

20 With ivacaftor alone in contrast, the same
21 primary efficacy endpoint was not met, and none of the
22 secondary endpoint results were significant. But

1 independent of the statistics, the combination showed
2 superior improvements in ever endpoint compared to
3 ivacaftor alone.

4 When we step back and we look at all of the
5 evidence, which is substantial, the biology, the
6 mechanism of action, the preclinical and the
7 translational data, as well as the clinical results, it
8 all shows us that combination therapy is better than
9 ivacaftor alone. And therefore, there are three clear
10 conclusions from the data we've just reviewed.

11 First, that lumacaftor is contributing in a
12 substantial way to the efficacy in the combination
13 treatment; second, that the combination is better than
14 ivacaftor monotherapy on every measure; and finally,
15 and most importantly, with respect to the question that
16 we're here today to address, we can be confident that
17 the combination therapy provides substantial meaningful
18 clinical benefit for those patients who are homozygous
19 for the F508del mutation, who have severe disease and a
20 high unmet need.

21 Now, I'm going to turn the podium over to
22 Dr. Bonnie Ramsey to provide her clinical perspective

1 on the data we've just reviewed. Thank you.

2 **Sponsor Presentation - Bonnie Ramsey**

3 DR. RAMSEY: Thank you, Dr. McKee.

4 Good morning. My name is Bonnie Ramsey, and I
5 am a pediatric pulmonologist. I have been caring for
6 patients with cystic fibrosis for over 30 years at
7 Seattle Children's Hospital. I served as one of the
8 principal investigators for the Vertex 103 and 104
9 studies that you've just heard about. In addition, I
10 was one of the PIs of the phase 3 ivacaftor study in
11 patients greater than 12 years of age who had the G551D
12 mutation. I have been compensated by Vertex, both for
13 my time and travel, to come to this meeting today, but
14 I have no direct financial interest in Vertex.

15 I would like to take this opportunity to
16 provide my personal clinical perspective on the role
17 lumacaftor and ivacaftor will play in the management of
18 patients with two copies of the F508del mutation. To
19 put it in perspective, about 50 percent of my patients
20 are homozygous for this mutation, so any new therapy
21 for this population is going to have a major impact on
22 my patients and on patients worldwide.

1 Over the course of my career, I've observed
2 significant progress in the health of patients with CF
3 through the introductions of several therapies that are
4 more effective in treating the secondary consequences
5 of CFTR dysfunction. These include malabsorption and
6 obstructive airway disease.

7 Although all of these were rewarding
8 experiences, they've been incremental, and they've not
9 targeted the underlying cause of the disease, which is
10 the abnormal protein and its physiologic consequences
11 on abnormal ion transport. In spite of all of our
12 efforts, CF remains a life-shortening disease for
13 thousands of individuals worldwide.

14 Now today, by contrast, lumacaftor/ivacaftor
15 combination will treat the underlying defect, and that
16 has the potential to substantially change the lives of
17 patients with CF. As a clinician, I want to echo what
18 Mike Konstan mentioned as the three primary goals of CF
19 care. It's known to all of us in this room: to
20 maintain lung function, to reduce pulmonary
21 exacerbations, and to improve nutritional status. I
22 have therefore chosen three of the slides that

1 Dr. McKee has previously shown you to summarize how I
2 feel the combination therapy has impacted these three
3 goals.

4 First, we're going to look at the primary
5 endpoint, the improvement in FEV1 for the first
6 24 weeks, and then in the blinded rollover study 105.
7 Now, the improvement was very rapid. It was seen by
8 the first study visit at 15 days. And while some may
9 say it is modest, I see it as very clinically
10 significant, and I will tell you the reasons why.

11 Number one, it was consistent across all the
12 subpopulations regardless of the age of the patient,
13 the gender, whether they were colonized or not with
14 Pseudomonas, and whether they had severe disease.

15 Number two, very important to me is that it's
16 persistent for 48 weeks. You see on the right-hand
17 side that it remains consistent. The only other place
18 that I have seen this kind of consistency was the
19 ivacaftor monotherapy in the G551D mutation. And
20 remember that this was on top of standard of care.
21 These were highly treated patients, so all the
22 treatment effect is because of the drugs.

1 Maintenance of lung function is not the only
2 goal that we have. We also want to see an improvement
3 in nutritional status. And this next slide shows you
4 the BMI, again, for the 24-week randomized, placebo-
5 controlled part of the study, and then the open-label
6 extension.

7 Here you see, as Dr. McKee noted, there was
8 some improvement in the BMI of the placebo group in the
9 first month. But thereafter, there's no change, but
10 you see a consistent improvement in both dose regimens
11 through the 24 weeks and then extension to 48 weeks.

12 Historically, we have seen some improvements
13 in BMI for treatment of pulmonary exacerbations or with
14 antibiotics, but it's always transient. Here, the
15 sustained effect to me represents an impact beyond the
16 lung, further emphasizing the importance of treating
17 the underlying defective protein in this illness.

18 Third, the most compelling data to me is the
19 reduction in pulmonary exacerbation, which is shown
20 here. This is the pooled analysis that was shown by
21 Dr. McKee. As previously mentioned by Mike Konstan,
22 pulmonary exacerbations have a very negative impact on

1 our patient population.

2 Twenty-five percent of patients will have a
3 permanent loss in lung function after a pulmonary
4 exacerbation. The increasing rate of pulmonary
5 exacerbation leads to more rapid decline in lung
6 function and increased mortality. And third, a
7 reduction in quality of life is associated with
8 pulmonary exacerbations. And I think it would be best
9 expressed in the words of my patient, Barry.

10 Barry was in his early 20's. He had severe
11 disease, so he spent frequent number of days in the
12 hospital. And he always complained to me that he
13 didn't like the hospital. He didn't like the loss of
14 privacy, and he wanted to go home. So one day I went
15 in to discharge him, and he looked at me, and he said,
16 "This is the saddest day of my life." And I said,
17 "Why? You're going home." He said, "Today, is the
18 best I know I will feel. Tomorrow, my cough will be
19 worse. I'll have more chest congestion. I'll be more
20 short of breath. And that will continue every day
21 until I can't tolerate it anymore, and I'm back here in
22 the hospital with my next exacerbation."

1 I just want you to think about what it's like
2 to live daily with these unrelenting symptoms. And
3 that's why looking at these data are so clinically
4 significant to me. If you look at particularly the
5 blue bars, because that's the 400 twice daily, which is
6 the dose that has been recommended, you'll see a
7 40 percent decrease in the overall rate of pulmonary
8 exacerbation. And then if you look at the more severe
9 exacerbations, you're going to see a 60 percent
10 decrease in hospitalization. This was consistent,
11 again, across all the subpopulations, even those with
12 the most severe disease like Barry. To me, this
13 clearly demonstrates significant benefit.

14 Now, I'd also like to review the risk of the
15 combination therapy from my perspective. Overall, I
16 was very reassured by the safety profile of the
17 combination. Since Dr. McKee has already reviewed the
18 safety data, I'm just going to focus on two of the
19 adverse events of special interest, first, the
20 discussion on the respiratory adverse events that were
21 more common at treatment initiation with combination
22 therapy.

1 As noted, a few of the patients discontinued
2 in the treatment arm, but the vast majority of the
3 patients stayed on the drug, and the symptoms resolved
4 usually within the first week. They were easily
5 manageable, and in the end did not affect the lung
6 function. To me, that is a manageable adverse effect.

7 The second issue is that the majority of CF
8 patients experience liver transaminase elevations at
9 some time during the course of their illness. And
10 therefore, it makes it very difficult to tell whether
11 changes are due to drug toxicity or to the underlying
12 disease. I've looked through the liver function data,
13 and the overall rates are comparable between the
14 treatment groups. It is true that there is an
15 imbalance in that there were more serious adverse
16 events reported in the treatment arms.

17 I am very pleased that Vertex has chosen to
18 take a conservative approach and to continue to monitor
19 liver function should the combination be approved.
20 This is very similar to what they're doing for the
21 ivacaftor monotherapy. With the close observation that
22 is planned, I am very comfortable prescribing this

1 combination therapy to my patients with two copies of
2 delta F508.

3 In summary, the accumulated efficacy and
4 safety from over 1500 patients who have received the
5 combination demonstrates to me a very strong benefit-
6 risk balance in favor of clinical benefit. Today, we
7 have no therapy to treat the underlying cause of cystic
8 fibrosis in patients with two copies of delta F508.
9 Combination therapy offers us the best chance to change
10 the course of this illness. I'm a pediatrician, and
11 what I look forward to is in the future, this will be
12 available to infants and children with CF, and that
13 will alter the course of this disease.

14 I'd like to return to Barry, who unfortunately
15 lost his battle with cystic fibrosis. One of the last
16 statements he made to me is he wished that he could
17 have survived to see the impact of new therapies in
18 this illness. I truly believe it will help the lives
19 of thousands of Barrys. As a clinician, I strongly
20 encourage you to support approval. Please do not
21 delay. Thank you very much. And now Vertex is ready
22 for questions.

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Clarifying Questions to the Presenters

DR. OWNBY: Okay. We are now open for questions to Vertex. Do any of the panel members -- Dr. Brittain?

DR. BRITTAIN: Several times during the presentation, you mentioned that the monotherapy did not reach its primary endpoint. I wanted to know was it powered to do so. And I have a second related question after that.

DR. CHODAKEWITZ: We can summarize the specific powering for you. It was a moderate size study, as you heard, about 140 patients. There was an intent to put more of the patients on active than on placebo for a couple reasons, both to gain more safety experience with the drug at that time, so that it depended of course on what treatment effect was being looked for. And we can show you the numbers.

I would say that it was an effort to really just discern whether there was a signal in patients with -- homozygous patients, remembering that, in fact, there was not an expectation that it was going to offer much benefit.

1 DR. BRITTAIN: The related question I have is
2 on CE-46.

3 DR. CHODAKEWITZ: We can show that for you.

4 DR. BRITTAIN: I'm sorry. That's not the
5 right slide. CE-48. Again, this doesn't really
6 reflect the differences in the sample sizes in power,
7 so the p-values could be a little misleading. Do you
8 have any confidence intervals that present this same
9 sort of information?

10 DR. CHODAKEWITZ: We do have a slide that
11 includes confidence intervals. Let us pull that up for
12 you. Slide up, please. Let me let you take a look at
13 that for a moment.

14 DR. BRITTAIN: You don't have side by side,
15 then, like you did in the other table?

16 DR. CHODAKEWITZ: It actually got extremely
17 cluttered. To your question, I think the point that we
18 particularly wanted to highlight on the first study
19 that you asked us to re-show is to look at all the
20 different lines of evidence, in addition to the
21 specific values, but to really talk about -- actually,
22 if you could put the one that was requested back up,

1 48.

2 I think what we thought that this was helpful
3 for, to your question, is really trying to look at all
4 the different kinds of evidence that was available in
5 terms of preclinically -- in terms of sweat chloride,
6 which is a translational biomarker, then all the
7 different clinical parameters. It wasn't just the
8 individual numbers because we are very cautious about
9 cross-study comparisons, particularly when it's
10 focusing on a specific number. It was really the
11 pattern and the consistency across the evidence for the
12 combination therapy.

13 DR. BRITTAIN: Just to confirm, it would be
14 true that the confidence intervals for the monotherapy
15 are going to be much wider than the others.

16 DR. CHODAKEWITZ: Yes, that's correct. And
17 that was reflected on the other slide.

18 DR. OWNBY: Dr. Morrato, you had a question?

19 DR. MORRATO: Sort of a follow-on, a
20 complement. I'd like to focus on understanding the
21 point estimates, not just the p-values. I read in the
22 FDA's briefing materials that they had really

1 encouraged you to discuss the clinical relevance of the
2 treatment effects, both the primary and the secondary
3 endpoints. And I had a few questions on your slides.

4 I'll try to follow how you've outlined the
5 three that you think are important, the maintain lung
6 function, BMI, and exacerbation rate. As I understand,
7 you were clearly arguing that ivacaftor alone is not
8 effective for F508del mutation. That point estimate
9 was around 1.7 to 2 percent. I'm interpreting that to
10 me a 2 percent change is really not clinically
11 meaningful.

12 In phase 2, it looked like you had
13 demonstrated 4 to 6 percent. I'm interpreting that to
14 maybe be a bottom line of moving forward because the
15 decision was to move forward into phase 3. And if I'm
16 understanding the phase 3 results, it's somewhere in
17 between 2 to 4 percent.

18 I put this into contrast with the extremely
19 strong robust findings that you had with G551D, which
20 was around 10 percent. So I'm trying to understand how
21 best to interpret a 2 to 4 percent change in terms of
22 clinical significance.

1 DR. CHODAKEWITZ: Great. Thanks very much for
2 the question. I think you are raising a couple of
3 different things. One was specifically about the value
4 on monotherapy, and then I think there was also a
5 couple questions linked to both our phase 2 data, and
6 then contrasting that to our phase 3 information. So
7 let me try to take each piece of that for you.

8 I think in terms of monotherapy, I don't think
9 we were trying to draw a concrete conclusion about any
10 specific point estimate. I think that the point for us
11 on monotherapy was that all the biology, all the
12 translation, everything told us that there was not
13 going to be substantial clinical benefit with
14 monotherapy. We then did that clinical study that had
15 a 1.7, but it was non-statistically significant.

16 As Dr. McKee summarized, it wasn't just the
17 one number --

18 DR. MORRATO: I know.

19 DR. CHODAKEWITZ: -- it was the pattern across
20 all those different parameters that actually led to the
21 conclusion by us, importantly by the clinical community
22 in CF, and by the FDA, that that was not providing

1 important clinical benefit. So that's how -- I don't
2 think there was any implicit kind of number cutoff. It
3 was the totality of the data.

4 Now, let me get to your other question about
5 the phase 2 point estimate and our phase 3 results.
6 The phase 2 data, as you said, showed around a 4 to 5
7 percentage point improvement. Just to remind you of
8 the numbers, actually, if we can just put CD-6 back up.
9 This is just the slide that I think you're referring to
10 that came from our primary presentation.

11 I would, to your question, actually just call
12 your attention also to the point estimates there. They
13 were limited size cohorts of patients, and so there was
14 uncertainty about what the exact number is going to be,
15 which I think brings me to the third part of your
16 question, which was our phase 3 information and the
17 strength of that data.

18 To us, we look at a variety of parameters. We
19 saw that acute increase, as you saw, at week 2. But we
20 also saw a sustained effect. And this is in the
21 setting of a patient population where, unfortunately,
22 you know that what is going to happen to those patients

1 is a steady decline. And seeing both an improvement
2 and a sustained improvement, we think is quite
3 clinically impactful, and I think that Dr. Ramsey
4 commented on that.

5 In addition, we have other robust information,
6 both in terms of pulmonary exacerbations.

7 DR. MORRATO: Which if I could get to.

8 DR. CHODAKEWITZ: Sure.

9 DR. MORRATO: Thank you. The exacerbation
10 ratio, which is one of the other ones, I think in one
11 of your slides, you made the case that it was extremely
12 strong. And yet, the FDA's data is showing that that
13 combination ratio, the exacerbation, 0.62, is no
14 different than the ivacaftor alone.

15 So again, I'm trying to understand how there
16 is increased benefit with the combination when the
17 point estimates are almost identical to the ivacaftor
18 alone of which you argued is not effective.

19 DR. CHODAKEWITZ: Can we go back to this
20 primary slide that was requested. I think it's 46, the
21 table -- 48. Thank you. I actually think that, again,
22 I want to go back to that, and that table is shown

1 here. Again, it has to do with our confidence in those
2 numbers.

3 As you've seen in our primary data, we have
4 very consistent, significant evidence of benefit in
5 pulmonary exacerbations with the combinations. These
6 are the summaries, but actually as you saw, looking
7 across the individual arms of the individual studies,
8 you saw substantial reductions then, not just in
9 overall exacerbations, but even among the most severe.

10 The point estimate is there for the
11 monotherapy, but it's not significant. And more so, to
12 your question, it's actually driven by very small
13 numbers, particularly that the placebo arm was 28
14 patients, so very small shifts in events would have had
15 big effects on that.

16 DR. MORRATO: Right. But the confidence
17 interval is what gets at the robustness of the sample
18 size. Right? The point estimate is getting at what
19 you're estimating is the effect. So I guess I don't
20 agree with the argument that the robustness of the
21 finding is just based on a sample size.

22 DR. CHODAKEWITZ: No. We agree with that.

1 DR. MORRATO: All right. And then the third
2 question, I'm trying to understand -- again, with the
3 FDA's encouragement in mind, I'm trying to interpret
4 the clinical significance of a .1 to 1 .4 change in
5 BMI. Can you help me better understand that? Did you
6 break it out in children versus adults. I know there's
7 a cutoff as a percentile cutoff as opposed to just an
8 absolute change in BMI.

9 DR. CHODAKEWITZ: Actually, let me do two
10 things. One is to ask Dr. Waltz to show you just the
11 data broken out by baseline, which perhaps can be
12 careful, and then I think ask Dr. Konstan, as someone
13 who takes care of these patients, to comment on the
14 clinical meaningfulness.

15 DR. WALTZ: Dave Waltz, Vertex
16 Pharmaceuticals, clinical development. We did look at
17 BMI by different cutoff points. Slide up, please. We
18 actually looked at all of the primary and key secondary
19 endpoints, looking at adolescents and adults.

20 As you may remember, approximately a quarter
21 of the subjects were adolescents and three-quarters
22 were adults. The BMI is shown in the middle of the

1 slide. And there were similar if not somewhat greater
2 improvements in BMI in the adolescent population
3 compared to the adult population.

4 DR. CHODAKEWITZ: Dr. Konstan?

5 DR. KONSTAN: Let me just give you my clinical
6 perspective as a treating physician. As both myself
7 and Dr. Ramsey presented to you about the difficulty in
8 maintaining weight in our patients, it's a huge
9 problem. Patients are taking enzymes with all of their
10 meals. Many of them get two fed at night. Whenever we
11 see any increase in BMI with an intervention, that
12 quite honestly is very pleasing to us because we work
13 pretty hard, and they work even harder at it to
14 maintain their weight.

15 So when you take that combined with all of the
16 other things that we're seeing here -- and again, as a
17 clinician, we think about the totality of the data. I
18 know your question was specifically about BMI, but when
19 we think about this change in the FEV1, which you're
20 talking about whether that's significant or not, it's
21 clinically meaningful to us. Anytime we can move,
22 particularly, a population of patients a percent or two

1 above where they were without that intervention is
2 clinically meaningful to us. And then of course, the
3 exacerbations, 60 percent reduction, that's
4 unbelievably tremendous for a patient.

5 DR. MORRATO: I'm just trying to -- and I'll
6 just say it -- I'm just trying to put into context the
7 totality of the data with the combination against the
8 totality of the data with ivacaftor alone. And I'm not
9 seeing much of a difference. And you, the company, has
10 argued that ivacaftor alone in its totality is not
11 effective. So I'm just trying to put those pieces
12 together. That's all. Thank you.

13 DR. OWNBY: Okay. I've got Dr. Castile and
14 Dr. Tracy.

15 DR. CASTILE: I have a few questions, and the
16 first two go to risk, actually. What has been shown is
17 that the percentage of patients that had increases in
18 FEV1 above 5 and 10 percent were substantial. And in
19 terms of risk, though, I wonder about the total
20 distribution. How many patients actually had FEV1s
21 that declined or declined greater than 5 percent or
22 greater than 10 percent? Is there a subset that is

1 potentially harmed?

2 DR. CHODAKEWITZ: Thanks, Dr. Castile. Let me
3 show you a couple pieces of data on that, one that
4 you've seen, and then one additional piece. To your
5 question about specific subsets -- slide up,
6 please -- one way of looking at that is this slide that
7 you've already seen from Dr. McKee, which is showing
8 that with all the different subgroups, that
9 regardless -- and that includes patients with lower
10 FEV1s and other kind of -- Pseudomonas, other kinds of
11 status kind of conditions. You don't see any
12 difference.

13 Another way of looking at that, that I think
14 links directly to your question, is looking at an
15 overall distribution --

16 DR. CASTILE: Correct.

17 DR. CHODAKEWITZ: -- is this being shifted
18 by --

19 DR. CASTILE: I want to see all the points.

20 DR. CHODAKEWITZ: Yes.

21 DR. CASTILE: Show me the data.

22 DR. CHODAKEWITZ: Then slide up. Let me do

1 that for you.

2 This is I hope exactly what you're looking
3 for, which is really the cumulative distribution curves
4 for all three treatment groups. That's the solid bar
5 on the left is the placebo, and then you can see both
6 active doses with lumacaftor and ivacaftor, where we
7 see, really, is an overall shift to the right.

8 DR. CASTILE: Could you use that slide to
9 directly answer my question? I'm not sure -- I see
10 what you're showing, but I -- what percentage declined?
11 What fraction of patients actually declined? If you
12 could point that out, it would be helpful to me.

13 DR. CHODAKEWITZ: Actually --

14 DR. CASTILE: I can't find zero.

15 DR. CHODAKEWITZ: -- unfortunately there's no
16 pointer. What we can do is actually get the exact
17 number for you. Zero is in the middle.

18 DR. CASTILE: I think it's behind somebody's
19 head actually.

20 DR. CHODAKEWITZ: What we can do is get a --

21 DR. CASTILE: Well, I can't see that.

22 DR. CHODAKEWITZ: We can get the exact number

1 for you.

2 DR. CASTILE: Just to go to the question, what
3 fraction actually went down by 5 percent or 10 percent?

4 DR. CHODAKEWITZ: Right. You want the
5 inverse --

6 DR. CASTILE: And this could be monitored, and
7 I would assume it's common or it's per routine to
8 monitor lung function. But if there was a steady
9 decline like you saw in the lumacaftor alone trial, I
10 would assume somebody would stop the drug. So I don't
11 think it's a great risk, but because of the lumacaftor
12 alone trial showing decline without explanation, I'm
13 concerned that there may be a subset.

14 I mean, clearly there's a subset of 40 percent
15 or more who do very well. Is there a subset that
16 doesn't do too well?

17 DR. CHODAKEWITZ: One way, Dr. Castile -- and
18 we'll work on the exact number. But if I'm hearing you
19 correctly, I think one of your concerns is the patients
20 who say had low FEV1s at the beginning are patients who
21 had adverse events in terms of some of those early
22 symptoms. And what we can tell you is in those

1 particular patients, just looking at them specifically,
2 even at those very early time points, they actually had
3 a -- that subset of patients actually had a net
4 improvement at the first time point, which was week 2.

5 DR. CASTILE: But this is showing me that
6 there's a significant group that had declines of
7 certainly minus 5, and some as much as minus 15
8 percent. Am I interpreting that correctly?

9 DR. CHODAKEWITZ: Yes, but it's very small
10 numbers, and so --

11 DR. CASTILE: Very small numbers, but that
12 wouldn't be a good thing if it was my son or daughter.

13 DR. CHODAKEWITZ: We will get the exact number
14 for you.

15 DR. CASTILE: The second question that I've
16 alluded to, really to risk, is do you have any
17 explanation of why lumacaftor alone produced a
18 dose-dependent decline in FEV1?

19 DR. CHODAKEWITZ: We do. We've thought about
20 it, and --

21 DR. CASTILE: Well, could you share it?

22 (Laughter.)

1 DR. CHODAKEWITZ: I'm going to ask Dr. McKee
2 to summarize that information for you.

3 DR. McKEE: Thank you, Dr. Chodakewitz.

4 The exact -- we don't have an exact mechanism
5 for the decline, but our hypothesis is that it is an
6 off-target, bronchoconstriction. We have a couple of
7 different lines of evidence for that.

8 So first of all, it does appear to be a
9 bronchoconstrictive effect, and this information comes
10 primarily from the fact that in phase 1 studies where
11 healthy subjects were given combination, there was an
12 immediate post-dose drop in their FEV1, which was
13 reversed or largely prevented with bronchodilators. So
14 that is fairly good evidence that this was a
15 bronchoconstrictive effect.

16 Then the hypothesis that this is an off-target
17 effect comes from a couple of different lines of
18 evidence. First is that if this was an on-target
19 effect, we would expect to see evidence of the same
20 effect with other correctors that work on the same
21 mechanism. And we have taken a couple of molecules
22 that are actually from the same scaffold and bind to

1 the same target through early clinical development, and
2 we have not seen this same effect.

3 Also, the time course of the effect, which is
4 within the first couple of hours after dosing, is
5 really not consistent with the time course of
6 correction of F508del CFTR. So through all these lines
7 of evidence, this appears to be an off-target
8 bronchoconstrictive effect.

9 DR. CASTILE: I have two more questions that
10 go to more the efficacy. The primary endpoint was
11 FEV1, but you clearly have data on other measures, like
12 FEF25-75, FEF75, FVC or the ratio. Are they
13 supportive, or do they provide any additional insight
14 into how this drug impacts lung function?

15 DR. McKEE: Yes. Thank you, Dr. Castile.
16 They are all supportive. All the trends are within the
17 same direction. And actually I can show you -- slide
18 up here. This slide shows the other components of
19 spirometry here, shown in the pooled 600-milligram,
20 once a day and in the 400-milligram, twice a day group.
21 I don't think they provide any additional specific
22 mechanistic information, but they are all generally

1 supportive.

2 DR. CASTILE: I think they're revealing, but I
3 won't explain to you why.

4 The last question I have is what is your
5 thinking or what is the recommendation going to be for
6 this combination drug for patients who are heterozygote
7 for the delta 508 deletion?

8 DR. CHODAKEWITZ: We would not be recommending
9 this drug for -- actually, let me just pause. When you
10 say heterozygote, I just want to be sure that we're
11 talking about the same --

12 DR. CASTILE: Delta 508 and something else
13 that's not already remediated by ivacaftor.

14 DR. CHODAKEWITZ: Right. So specifically with
15 patients who have a null mutation on the other allele.

16 DR. CASTILE: Right.

17 DR. CHODAKEWITZ: Our recommendation is that
18 we don't think there's evidence of efficacy for that
19 population, and we would not be recommending use in
20 that patient population.

21 DR. CASTILE: The other part of the question
22 is I agree there's no evidence that you've presented,

1 but what is your thinking about that? Should it work?

2 DR. CHODAKEWITZ: We actually have done a
3 limited study in that population. We did not see
4 evidence of benefit when you look across all the
5 information. We can put the slide up and show you the
6 data. Slide up, please. But overall, we don't think
7 that there is sufficient evidence to draw a conclusion
8 of efficacy. We did wonder, and I think the FDA also
9 wanted to have some sense of that.

10 DR. CASTILE: Thank you. And it wasn't a
11 plant at all. It's nice that you have a slide for
12 every question I asked. That was good.

13 DR. OWNBY: Dr. Durmowicz, did you want to
14 make a comment before Dr. Tracy's question?

15 DR. DURMOWICZ: Right. I just wanted to go
16 back really briefly to the respiratory adverse events
17 with regard to lumacaftor alone and the
18 lumacaftor/ivacaftor combination. And I just wanted to
19 point out that at no time has the FDA made a conclusion
20 or thought about, in looking at all the data available
21 to us, that this is an acute bronchoconstriction
22 effect.

1 Secondly, it seems incongruous with a
2 bronchoconstriction effect if you look at the
3 lumacaftor only study in which these decreases in FEV1,
4 which were 5 percent of absolute percent predicted
5 FEV1, and even more so when you look at it relative,
6 occurred at day 28, and the drug was at steady state by
7 that time for quite a few weeks.

8 So once again, we don't really
9 understand -- and I don't think you can say that you
10 really do understand -- what the adverse event profile
11 is. You can say that it probably is not as bad with
12 the combination as you could with lumacaftor alone.
13 But to pin it on bronchoconstriction is incorrect at
14 this time.

15 DR. CHODAKEWITZ: Dr. Ownby, can I make just
16 one other comment? Two points. One is just to remind
17 everyone, as you heard from Dr. McKee, that in fact
18 all but 5 patients out of over 700 actually managed the
19 adverse event and continued on therapy. Another way of
20 thinking about that, Dr. Castile, to your comment about
21 our distribution curves, is regardless of what cutoff
22 you choose -- because anyone is arbitrary -- at every

1 point, the proportion on the placebo group was actually
2 above the lumacaftor/ivacaftor group. So I do think
3 that there is some comfort in thinking more broadly
4 about the adverse events profile.

5 DR. OWNBY: Dr. Tracy, you had a question?

6 DR. TRACY: It's possible I just missed this,
7 but I was wondering if you could comment a little bit
8 more on the quality of life data. In the 103 and 104
9 studies, it wasn't particularly impressive. I know
10 that it seemed to get better as you moved through it.
11 Any thoughts why that might be?

12 DR. CHODAKEWITZ: Dr. McKee?

13 DR. MCKEE: Yes, we do have some thoughts. If
14 I could just have slide up, please, I'll just return
15 you to the core slide. This is a slide you saw in the
16 core presentation. The CFQ-R, obviously we were
17 interested in CFQ-R results. And as I did mention
18 earlier, the effects in both dosing groups at various
19 time points over the 24 weeks were numerically
20 positive. They did favor active treatment. And at
21 some time points through the course of the 24 weeks
22 were significant even compared to placebo.

1 So there's no evidence that quality of life
2 declined in these patients over the course of the
3 treatment. However, the effect compared to placebo was
4 not statistically significant, nor did it meet the
5 MCID. But I would just want to point out that the MCID
6 of 4 was actually identified within open-label
7 treatment. And so perhaps it is also instructive to
8 look at the within-group changes for those patients who
9 are on active treatment.

10 So while these changes are not as robust or
11 may be more modest than some of the objective changes,
12 they don't indicate a decline in quality of life.

13 DR. TRACY: It's just that when we're looking
14 at small percentages of FEV1, I'm trying to figure out
15 what that means. Then I've kind of got to go back and
16 look at the patient and how are they seeing this. So
17 that was the genesis of the question.

18 DR. McKEE: Yes. I think as Dr. Ramsey
19 pointed out, CFQ-R is one measure of quality of life,
20 obviously, but also taking the other benefits in terms
21 of -- or looking at the exacerbation reductions also
22 clearly speaks to quality of life as well.

1 DR. OWNBY: We've got Dr. Harkins and
2 Dr. Parad, and then Dr. Raghu.

3 DR. HARKINS: Thanks. You alluded to this a
4 little bit. I was just wondering about the numbers of
5 these severe exacerbations requiring hospitalizations,
6 when did they occur, especially in the treatment arms.
7 But you alluded that they were small in number. But I
8 just kind of wondered what those numbers were and where
9 they were in the treatment spectrum.

10 DR. CHODAKEWITZ: So a couple of different
11 questions. I think just to clarify, I think my
12 comment, particularly on the very small numbers, was
13 really linked to the point estimate from the ivacaftor
14 monotherapy study. What we can do is show you the
15 specific numbers that drove the results for the
16 lumacaftor/ivacaftor combination. Slide up, please.

17 This gives you hopefully a little more detail
18 that would be helpful in addressing your question. And
19 I think you can see that whether you're looking at
20 certainly all pulmonary exacerbations, but even as you
21 get to the most specific subcategories -- which we
22 wanted to be careful, as Dr. McKee I think

1 mentioned -- that we wanted to understand if there was
2 a reduction, was it only happening in those pulmonary
3 exacerbations that were less severe. And those second
4 two rows actually specifically address that. You can
5 see that, in fact, if anything, they were even more
6 favorably impacted, and the numbers are pretty robust
7 in those numbers.

8 I don't know if we have data in terms -- you
9 also asked about the timing of those. I don't
10 know -- maybe Dr. Waltz can provide comment on that.

11 DR. WALTZ: Yes. The events did occur
12 throughout the course of the 24 weeks. They weren't
13 concentrated at the beginning or at the end.

14 DR. OWNBY: Dr. Parad?

15 DR. PARAD: Sorry I'm turned around.

16 DR. CHODAKEWITZ: I understand. Thank you.

17 DR. PARAD: I have three questions. The first
18 one reflects back on sort of the homerun that ivacaftor
19 seemed to have in the G551D patients and that huge
20 effect on FEV1 relative to the small one that we're
21 talking about. My favorite slide of Dr. Konstan's is
22 actually the long-term view of those patients to show

1 that the rate of decline of FEV1 is actually impacted
2 by the drug, which you could translate into that
3 slowing the processes in the disease.

4 For this scenario where we just see a tiny
5 change in FEV1, I'm trying to get a grip on that
6 longer-term picture. And you mentioned that you had
7 two-year follow-up on some of the phase 2 subjects. So
8 I'm wondering whether for combined therapy, you have
9 any FEV1 decline-over-time data to give us some picture
10 of how this might prevent decline over time as opposed
11 to seeing a bit reversal of symptoms starting on the
12 drug.

13 DR. CHODAKEWITZ: I'll ask Dr. McKee to give
14 you what information we have.

15 DR. McKEE: We do have data, actually a very
16 recent cut of the interim analysis data -- slide
17 up -- from when all subjects were actually out to at
18 least 48 weeks of treatment. This is the updates.
19 These are very recent data, so they haven't yet been
20 shared with the agency. But these show that there is
21 not a decline in the FEV1. And this is a little busier
22 slide. This is all the patients out to at least

1 48 weeks, and including here also those patients who
2 rolled over from the placebo group on to the active
3 treatment group.

4 Even though some of those patients are now out
5 actually as long as two years and there is not yet
6 enough data to look in a robust way at the decline in
7 FEV1, it does look like there are trends in terms of
8 improvement in decline in FEV1, but we can't say
9 anything with robust statistics. And I would also
10 mention, also, that the pulmonary exacerbation rate in
11 these patients has been similarly low, maintained at a
12 low rate out into the extension study.

13 DR. PARAD: The second question, it goes back
14 to Dr. Tracy's question about the CFQ-R and why
15 patients are feeling better, which maybe is no surprise
16 again with the small change in FEV1. Do you have data
17 looking at the subgroup of patients who had, say, a
18 15 percent improvement in their FEV1 and whether those
19 patients had better scores, just as a reality check?

20 DR. MCKEE: We don't have those data. I think
21 that's an interesting analysis.

22 DR. PARAD: My last question is trying to

1 understand the hierarchical order analysis of the key
2 secondary outcomes. How is that order chosen? I mean,
3 if you put the exacerbations up higher on the list,
4 then you would have been able to officially call that
5 more significant. How did the order get changed?

6 DR. CHODAKEWITZ: Let me try to summarize that
7 for you. Also, we put this slide up. This is just the
8 data slide that you've seen before, but since the
9 endpoints are in rank order according to hierarchy,
10 it's just visually helpful to look at your question.

11 We did it in a couple of considerations. And
12 there is imperfect information of course when we go
13 about trying to make estimates of how to rank order.
14 The relative is because there's a line with
15 absolute -- actually, that's why that was at the
16 top -- perhaps it was somewhat arbitrary for the next
17 couple. I think perhaps the one that is most specific
18 that I want to comment on, that you raised in your
19 question, was why is pulmonary exacerbations at the
20 bottom, given how important, you heard from
21 Dr. Konstan, and we agreed, those are clinically.

22 It really had to do with the power in the

1 individual studies because only a subset of patients
2 will experience those, and you can't predict what the
3 background rate is going to be. We did intentionally
4 put that on the bottom not because of less importance
5 but because of that. But as we noted, and I think the
6 FDA slides noted as well, that we did want to look
7 specifically, and particularly in the pooled analysis,
8 at pulmonary exacerbations because of that. So that
9 hopefully gives you a sense of how we thought through
10 that approach.

11 DR. RAGHU: Acknowledging that the percent
12 predicted FEV1, the primary endpoint, has been met and
13 statistically significant and sustained and all of
14 that, but the numbers are relatively a small
15 proportion, was there any quality control in terms of
16 these parameters done in this across sites? I
17 acknowledge that all the data gathering were the same
18 in the placebo and all of that, but were there
19 any -- how well were you controlling these parameters
20 across the countries?

21 DR. CHODAKEWITZ: I'm going to ask Dr. McKee
22 to summarize that. I do want to come back to this

1 comment about small FEV1s, as, obviously, people will
2 assess that. But I do think remembering that the fate
3 of these patients is a loss of FEV1, of lung function,
4 I think it's both the magnitude and the durability of
5 the FEV1 that we think about in terms of clinical
6 impact. So I do just want to acknowledge that. We did
7 do careful quality control on the specific data, and
8 I'll ask Dr. McKee to summarize that for you.

9 DR. MCKEE: As you would expect, all of the
10 spirometry was standardized according to ATS and ERS,
11 you have quality control measures. If there are
12 specific criteria, we can ask Dr. Waltz to speak to
13 maybe specific. Are you thinking of a specific --

14 DR. RAGHU: No. I was thinking in terms of
15 flow volumes, effort dependent, and so many variables
16 that go into it, even though it's ATS/ERS standards.
17 So I'm just wondering if there was any central review
18 of how well the flow volumes were done and how
19 predictable, and those kind of things.

20 DR. MCKEE: Well, there was not central
21 adjudication or review, but they were of course -- the
22 flows had to be reproducible, and there was internally,

1 according to the criteria -- of course, spirometry
2 wouldn't be used if it didn't mean reproducibility
3 criteria, for example.

4 DR. RAGHU: And since they were already
5 receiving standard of care, the maximum treatment, that
6 you would want to make sure that they are doing well,
7 the bronchodilator. I would think you would have asked
8 them to not take 12 hours or how well do you control
9 that? Because most of these patients, I would think
10 that they would have sneaked some inhalers.

11 DR. McKEE: No. That's an excellent point
12 actually, and I think it is a good point to point out,
13 that across the study, patients were asked to withhold
14 their bronchodilators prior to all-study spirometry.
15 We do actually have a couple of patients for whatever
16 reason forgot or didn't withhold. It was a minority of
17 patients. And the FEV1 result at the endpoint was no
18 different for those patients. But they were all asked
19 to withhold.

20 DR. RAGHU: I have a couple of questions in
21 terms of the pulmonary exacerbations and
22 hospitalizations. There were 12 components of the

1 exacerbations, that any four of them would have met the
2 exacerbations. Most of them are symptoms, as I see.
3 There are two objective assessments, including FEV1 as
4 well as the radiological, so I don't see, at least the
5 data, if there was any adjudication of the radiological
6 findings or any objective findings.

7 Among the majority of the symptoms, I would
8 think that all patient reported outcomes that you're
9 capturing during follow-up -- did you come across any
10 major components that were giving you a feel that there
11 is more quantity of sputum, or fever or malaise, or any
12 one of those components?

13 DR. McKEE: I think you're addressing
14 specifically the criteria used for exacerbations.

15 DR. RAGHU: Yes.

16 DR. McKEE: There were no trends within the
17 subcriteria of exacerbation criteria. I would just
18 point out that these are the modified Fuchs' criteria,
19 which have been used for decades in CF research, so
20 they are certainly validated from that perspective.
21 But there were no trends in terms of set components.

22 I should also point out that across the study,

1 there was not an adjudication panel, per se, for
2 exacerbations. However, there was a rigorous
3 monitoring cross-check, so all of the exacerbations had
4 to have met source data documentation criteria. It was
5 not just a general investigator call, if you will.

6 DR. RAGHU: Lastly, hospitalizations. Who
7 decided the patients needed to be hospitalized. Is it
8 a site investigator? Is it subjective? Were there
9 regional differences in the hospitalizations? I would
10 think the quality of care, even though it is
11 standardized for cystic fibrosis all across, but the
12 subjective decision-making of hospitalizations, an
13 important aspect, how did you account for that?

14 DR. McKEE: No. You're correct that it was
15 according to standard of care. Obviously, these
16 patients are cared for. And the investigative sites
17 are experienced CF centers, so there will be of course
18 some variability, perhaps regionally or in terms of
19 standard of care. But the hospitalization, they were
20 not -- I guess if you're asking, there were not
21 prespecified criteria for hospitalization, but it was
22 according to the cystic fibrosis standard of care.

1 DR. RAGHU: But you didn't see any regional
2 differences in terms of hospitalizations?

3 DR. McKEE: I'm not aware of regional
4 differences, no.

5 DR. OWNBY: One more question. Sooner or
6 later, we ought to take a break.

7 DR. AU: Okay. I'll make this quick. These
8 are actually two questions. First, I'm actually
9 curious about the quality of life data and whether or
10 not you have data about the proportion of people who
11 actually achieved an MCID or better, or MID I guess
12 now, on the quality of life data and functioning, what
13 are the odds, or what are the relative benefits for the
14 cohorts.

15 Why don't I just stop at that one, and then
16 I'll ask a second question.

17 DR. CHODAKEWITZ: Yes, we do have that data.
18 We can show you a slide with the specifics. Slide up,
19 please. This is from the pooled analysis looking
20 specifically at the placebo and the recommended 400 q12
21 dose. I think what you could see if that, in general,
22 it varies a little bit at time, but numerically all the

1 values are higher on the lumacaftor/ivacaftor arm. And
2 not surprising, given the graph that we've shown you,
3 actually that last time point at week 24 was the
4 closest because there was that bump in the placebo arm
5 at that time point.

6 DR. AU: And then my second question is a
7 follow-up about the -- it's related to the slide CP-3.
8 I was wondering if you had a similar slide to ivacaftor
9 in terms of long-term follow-up on change in FEV1.

10 DR. CHODAKEWITZ: Yes, we do. I'll ask
11 Dr. McKee to go through that because, actually, the
12 studies are a little different because they were not
13 conducted in the same way, so that will have to be
14 taken into account. But we actually think that this is
15 actually another piece of evidence, suggesting that the
16 effect of ivacaftor is really not meaningful for these
17 patients. I'll ask Dr. McKee to walk through the
18 specifics with you.

19 DR. MCKEE: As Dr. Chodakewitz mentioned, an
20 ancillary question in that ivacaftor monotherapy study
21 was to determine whether there was a subset of patients
22 who might benefit in a sustained way. So unlike in the

1 combination studies, not all patients rolled over or
2 were offered enrollment in an open-label extension.
3 Patients -- actually slide up. We'll start with this
4 slide.

5 What this graph here shows, patients who
6 met -- at week 16 in the ivacaftor monotherapy study
7 who met a prespecified threshold of either greater than
8 or equal to 10 percent increase in relative FEV1 or at
9 least a 15 millimole change in sweat chloride, those
10 patients were offered enrollment in an open-label
11 extension. So this figure here shows just for those,
12 there were 33 subjects in the active treatment arm who
13 elected to roll over, 36 patients total met those
14 criteria.

15 For those 33 patients who enrolled in the
16 extension, this is their FEV1 curve, showing here that
17 that effect was not sustained out through up to 64
18 weeks for this population. The vertical dash lines
19 show the end of the placebo controlled period, and the
20 effect linearly declines after that, indicating that
21 there wasn't a sustained benefit and perhaps calling
22 into the question the initial benefit.

1 This also, I would point out, is in contrast
2 to the sustained effect across the population in the
3 combination treatment. However, we did actually -- to
4 go a little bit further -- because these were a
5 population of patients selected by specific criteria.
6 We asked whether the curve might look different with
7 that same selection criteria in the combination study.

8 Next slide up. This is based, again, on that
9 more recent interim analysis data, so also not yet
10 shared with the agency. But this shows those patients
11 in the combination program who also met that, at least
12 a 10 percent, that same 10 percent relative FEV1
13 threshold, who actually then were followed out to a
14 total of 48 weeks, which is the data that we have. I
15 think the figure shows that the effect here is
16 sustained in contrast to the effect with the ivacaftor
17 monotherapy.

18 DR. OWNBY: Dr. Brittain?

19 DR. BRITTAIN: Just to clarify, did you use
20 exactly the same criteria? It didn't look like it was
21 exactly the same.

22 DR. McKEE: So it is -- it's a complicated

1 comparison because the way that those patients were
2 studied -- there were a couple of criteria for the
3 ivacaftor monotherapy study. They could meet this
4 increase of relative improvement in FEV1 at any time
5 point post bass line. Or they could meet it by sweat
6 chloride.

7 Now, three of the patients in the ivacaftor
8 monotherapy study met those criteria by sweat chloride.
9 All of the others met them by changing FEV1. And then
10 for the combination therapy, we use the same percent
11 FEV1 change because, obviously, sweat chloride was not
12 done in the phase 3 study. So that's the best
13 apples-to-apples comparison we have.

14 DR. OWNBY: Thank you. I think we will now
15 take a short 10-minute break. Panel members, please
16 remember that there should be no discussion of the
17 meeting topic during a break or among yourselves, or
18 with any member of the audience. We'll resume at 11:15
19 according to my watch, and I'm afraid we may lose some
20 of our lunch time since we're still running a little
21 late. Sorry.

22 (Whereupon, at 11:06 a.m., a recess was

1 taken.)

2 DR. OWNBY: We'll call the meeting back to
3 order and proceed with the FDA presentation. Dr. Lim?

4 **FDA Presentation - Robert Lim**

5 DR. LIM: Good morning. My name is Robert
6 Lim, and I'm the medical officer with the FDA in the
7 Division of Pulmonary, Allergy, and Rheumatology
8 Products. I am also a pediatric pulmonologist by
9 training.

10 Here is an outline of the FDA's presentation
11 for this morning. In this first presentation, I will
12 provide an introduction to how the FDA approached the
13 review of efficacy for lumacaftor/ivacaftor. This
14 presentation will be followed by the statistical
15 presentations, and I will then return to the podium to
16 provide clinical considerations for efficacy and a
17 summary of safety.

18 The rationale to develop lumacaftor/ivacaftor
19 to treat CF was supported by in vitro data, which is
20 very briefly summarized here. In F508del human
21 bronchial epithelial cells, lumacaftor exposure
22 increased chloride transport to approximately

1 14 percent of normal. With the addition of ivacaftor,
2 chloride transport increased further to 25 percent of
3 normal.

4 These in vitro data suggested that both
5 lumacaftor and lumacaftor/ivacaftor would have a
6 beneficial effect in the clinical setting. As such,
7 both were explored in the lumacaftor/ivacaftor clinical
8 development program.

9 Consistent with the in vitro findings,
10 treatment with both lumacaftor and lumacaftor/ivacaftor
11 resulted in decreases in sweat chloride. However, for
12 clinically relevant endpoints, the in vitro findings
13 did not translate as well, as you will see in the FDA
14 presentations.

15 This table summarizes the studies from the
16 lumacaftor/ivacaftor development program the division
17 considered key in the assessment of efficacy. Study
18 770-104 was a small study evaluating ivacaftor
19 monotherapy in F508del homozygous patients. Study
20 809-102 was a dose-selection study for lumacaftor alone
21 as well as lumacaftor/ivacaftor. And studies 809-103
22 and 809-104 were the confirmatory efficacy studies for

1 the combination product.

2 Typically for a combination product,
3 monotherapy comparators are included in the
4 confirmatory studies to demonstrate that the
5 combination offers an added benefit above its
6 individual components. However, as has been explained,
7 the confirmatory studies did not include the individual
8 components lumacaftor and ivacaftor.

9 A key question for this application is that
10 given the results of the confirmatory studies and with
11 only a placebo comparator, can one conclude that
12 lumacaftor/ivacaftor provides a benefit above
13 monotherapies. In the next few slides, I'll discuss a
14 rationale as to why only a placebo comparator was
15 included.

16 The decision not to include an ivacaftor
17 monotherapy treatment arm in the confirmatory studies
18 was largely based on study 770-104 in the context in
19 which the data were interpreted. The study evaluated
20 ivacaftor monotherapy in F508del homozygous patients
21 and was performed during the G551D development program.
22 The study was primarily meant to augment the ivacaftor

1 safety database. As such, it was not specifically
2 sized nor powered to demonstrate efficacy.

3 That being said, the study did include
4 efficacy endpoints. Results for percent predicted
5 FEV1, which has been the primary endpoint from all of
6 Vertex's CF studies, are summarized in this figure.
7 Along the Y-axis is absolute change from baseline in
8 percent predicted FEV1 versus placebo, and along the X-
9 axis is time in weeks.

10 As you can see during the 16-week treatment
11 period, the difference from placebo was small, and it
12 was not statistically significant. Results were also
13 similar across other efficacy-related endpoints and
14 generally went in a positive direction, but again were
15 not statistically significant.

16 The interpretation of these results also
17 considered the data from the G551D program where much
18 larger improvements were observed across multiple
19 parameters. This figure illustrates a large difference
20 in effect size for the ivacaftor effect in G551D
21 patients versus F508del homozygous patients. A similar
22 contrast was observed across other parameters such as

1 CFQ-R respiratory domain scores, exacerbation, and
2 sweat chloride.

3 With this in mind, the division interpreted
4 the 770 results to mean that ivacaftor monotherapy was
5 not effective in the F508del homozygous patients.
6 Based on this interpretation, no ivacaftor monotherapy
7 comparator was included in the confirmatory studies.
8 While this interpretation of 770-104 is reflected in
9 the current label, given the results from the
10 lumacaftor/ivacaftor program, this interpretation is
11 being revisited. The decision not to require
12 lumacaftor therapy was based on results from
13 dose-selection study 809-102.

14 In this multi-cohort study, multiple doses of
15 lumacaftor and lumacaftor/ivacaftor were evaluated.
16 Results for percent predicted FEV1 are summarized in
17 this figure. Along the Y-axis is absolute change from
18 baseline in percent predicted with time in days across
19 the X-axis. From baseline to day 28, patients received
20 lumacaftor only, and for the following 28 days,
21 patients received ivacaftor in addition to the
22 lumacaftor dose. The solid lines in this figure depict

1 the doses carried to the confirmatory studies.

2 During the initial 28-day lumacaftor-only
3 treatment period, there was a clear dose-dependent
4 decline in percent predicted FEV1, which is circled in
5 red in this figure. As such, no lumacaftor monotherapy
6 arm was included in the confirmatory studies for safety
7 reasons. These clinical data are in contrast to the
8 in vitro data, which predicted that lumacaftor
9 treatment would result in a beneficial clinical
10 response. Thus, for this product, the in vitro data do
11 not appear to be a reliable predictor of clinical
12 response.

13 Following the addition of ivacaftor to
14 lumacaftor, increases in percent predicted FEV1 were
15 observed. For the doses carried to phase 3, the
16 treatment effect in terms of percent predicted FEV1
17 versus placebo were approximately twice that observed
18 for the ivacaftor monotherapy study 770-104 at around
19 5 percent compared to placebo from baseline to day 56.

20 Based on the data just shown, there was
21 agreement between the division and the applicant that
22 no monotherapy comparators were needed and that

1 demonstration of lumacaftor/ivacaftor superiority to
2 placebo would be sufficient to demonstrate efficacy.
3 This decision was based primarily on several factors,
4 the first being the previous conclusion that ivacaftor
5 monotherapy was not effective in F508del homozygous
6 patients; the second being that lumacaftor monotherapy
7 could not be included due to safety reasons; and the
8 third was the expectation that the lumacaftor/ivacaftor
9 treatment effect in the confirmatory studies would be
10 in line with that of the dose-selection studies at
11 around 5 percent versus placebo.

12 This effect size would have potentially been
13 large enough to suggest that the lumacaftor component
14 contributed to the combination. However, results from
15 the confirmatory study suggested the need for an
16 ivacaftor comparator.

17 Given the data from the lumacaftor/ivacaftor
18 dose-selection study, the confirmatory studies
19 demonstrated a smaller than expected
20 lumacaftor/ivacaftor treatment effect that was
21 numerically similar to the ivacaftor monotherapy effect
22 in study 770-104. Given this numerical similarity, it

1 could not be determined if lumacaftor/ivacaftor offered
2 an added effect above ivacaftor monotherapy and that
3 lumacaftor contributed to the combination.

4 To address this issue, FDA statisticians
5 performed an analysis of the lumacaftor/ivacaftor and
6 ivacaftor treatment effects using data from the
7 confirmatory studies and study 770-104. This analysis
8 along with the efficacy results from the confirmatory
9 studies will be presented in the following statistical
10 presentations.

11 **FDA Presentation - Lan Zeng**

12 MS. ZENG: Good morning. My name is Lan Zeng.
13 I'm a reviewer at the Division of Biometrics II at FDA.
14 I will present the statistical evaluation of efficacy
15 for the two phase 3 studies, study 809-103 and 809-104.
16 My presentation will focus on three aspects of these
17 studies, the large sample size, the multiplicity issue,
18 and the analysis results.

19 As you already know, the two studies each had
20 three arms, 1 placebo arm and 2 doses of
21 lumacaftor/ivacaftor combination therapies. Each study
22 enrolled about 550 patients, or approximately 185 for

1 every treatment group. At a meeting in January 2014,
2 FDA commented that the pivotal trials were powered to
3 detect even small effects on percent predicted FEV1 and
4 that review of effect would consider not only
5 statistical evidence but also the clinical importance
6 of the treatment effect.

7 Again, at the pre-NDA meeting, FDA noted the
8 small improvement in percent predicted FEV1, especially
9 in the context of the results from studies 770-104 in
10 the ivacaftor program. FDA recommended that the
11 applicant's submission should address the clinical
12 relevance of the observed treatment effect and the
13 level of evidence that lumacaftor contributes to the
14 efficacy of the combination product.

15 For both studies, the primary efficacy
16 endpoint was absolute change from baseline in percent
17 predicted FEV1 at week 24, which was assessed as the
18 average of the treatment effect at weeks 16 and 24. A
19 mixed model for repeated measures was used to analyze
20 the data making adjustment for gender, baseline age
21 group, and disease severity. All patients who have
22 taken any study drug were included in the analysis.

1 According to the prespecified statistical
2 analysis plan, each of the phase 3 trials was analyzed
3 separately. Pooling was not a planned analysis.
4 Additional sensitivity or subgroup analyses were
5 performed on percent predicted FEV1. Details are
6 provided in the FDA briefing document.

7 There were five key secondary efficacy
8 endpoints: relative change from baseline in percent
9 predicted FEV1, absolute change from baseline in BMI
10 and CFQ-R respiratory domain score, at least a
11 5 percent increase in relative change for percent
12 predicted FEV1, and number of pulmonary exacerbations
13 through week 24. Please note that similar to the
14 primary endpoint, for the FEV1 secondary endpoints,
15 relative change or response with at least a 5 percent
16 increase were both evaluated as the average of the
17 treatment effect at weeks 16 and 24.

18 In order to account for the comparison of two
19 doses of combination versus placebo, a Bonferroni
20 correction was applied to control the overall type 1
21 error rate at 0.05 significance level. A sequential
22 testing strategy was utilized to address multiple

1 endpoints. For each individual trial, the primary
2 endpoint was tested first at 0.025 for each active
3 treatment arm. If the primary endpoint was significant
4 within dose, then the key secondary endpoints were
5 tested in the prespecified order as listed here.

6 At each step, the comparison was considered
7 statistically significant if the p-value is less than
8 0.025 and all previous tests also met this level of
9 significance. If a test failed, all results from
10 subsequent tests were considered not statistically
11 significant. This is an adequate procedure to control
12 overall type 1 error rate and is commonly used in
13 hypothesis testing.

14 Please note that although the former
15 comparison of each active treatment versus placebo was
16 conducted at 0.025 level, the 95 percent, instead of
17 97.5 percent, confidence intervals are presented here
18 in the following slides.

19 The applicant's presentation showed results
20 from pooled analysis of the two studies. Pooling,
21 however, was not a planned analysis when sequential
22 testing was considered. The statistical analysis plan

1 states that the primary analysis for the number of
2 pulmonary exacerbations through week 24 will be based
3 on the pooled data. Regardless, exacerbation was the
4 fifth key secondary endpoint and the last to be tested
5 within the hierarchy testing structure. Therefore, the
6 pooled results presented by the applicant are
7 considered post hoc and do not fit into the
8 prespecified sequential testing frame.

9 Next, I'm going to present results separately
10 for each study. This table shows the primary efficacy
11 results. It shows change from baseline in percent
12 predicted FEV1 and difference of this change versus
13 placebo. In study 809-103 for the proposed dose of
14 lumacaftor 400 milligram, ivacaftor 250 milligram
15 combination, the mean change from baseline in percent
16 predicted FEV1 was 2.2 percent. The placebo response
17 was negative .4 percent. The average treatment
18 difference between the lumacaftor plus ivacaftor and
19 the placebo group was 2.6 percent. The difference was
20 statistically significant.

21 Likewise, in study 809-104, the average
22 treatment difference between the lumacaftor

1 400/ivacaftor 250 combination and the placebo group was
2 3 percent, which was also statistically significant.
3 In both studies, treatment with the proposed dose of
4 lumacaftor/ivacaftor combination resulted in
5 statistically significant improvement in percent
6 predicted FEV1 over placebo. The effect size was
7 between 2.6 to 3 percent. Results from additional
8 analyses were consistent with this finding.

9 This table presents results for the five key
10 secondary endpoints. For the first key secondary
11 endpoint, relative change from baseline in percent
12 predicted FEV1, there was a significant treatment
13 effect in favor of lumacaftor/ivacaftor combination
14 over placebo regardless of dose in both studies.

15 Based on the hierarchy testing procedure, the
16 second endpoint, absolute change from baseline in BMI,
17 was tested. Significance was only observed in
18 study 809-104. The testing continued for CFQ-R in
19 study 809-104, and the results were not statistically
20 significant.

21 As shown by shaded tests here, the testing
22 hierarchy was broken at BMI in study 809-103 and at

1 CFQ-R endpoint in study 809-104. Based on the
2 prespecified analysis plan, none of the subsequent
3 endpoints were considered statistically significant
4 regardless of their p-values.

5 In summary, the two phase 3 trials generated
6 very similar results. Both demonstrated superiority of
7 lumacaftor/ivacaftor combination over placebo in terms
8 of spirometric function. For the primary endpoint of
9 absolute change from baseline in percent predicted
10 FEV1, the average improvement over placebo was between
11 2.6 to 3 percent.

12 Consistent improvements were also observed for
13 the five key secondary endpoints. However, because of
14 the sequential testing strategy used to control the
15 overall type 1 error rate, only the first one, relative
16 change from baseline in percent predicted FEV1,
17 provided replicate evidence of a treatment effect. The
18 analysis of BMI, CFQ-R, response rate based on FEV1,
19 and pulmonary exacerbations were not considered
20 statistically significant.

21 It should be noted that both studies were
22 highly powered with large number of subjects. With

1 about 185 patients per arm, the study could detect a
2 treatment difference as low as 1.65 percent in absolute
3 change from baseline for percent predicted FEV1. The
4 clinical relevance of this 2.6 to 3 percent improvement
5 in FEV1 over placebo is a question for discussion.

6 I will now turn the podium to David Petullo,
7 who is going to present the second part of the
8 statistical presentation.

9 **FDA Presentation - David Petullo**

10 MR. PETULLO: Hello and good morning. First
11 of all, excuse my voice. My allergies have started
12 kicking in just recently. My name is David Petullo,
13 and I am the statistical team leader supporting the
14 Division of Pulmonary, Allergy, and Rheumatology
15 Products. In my presentation, I compared the efficacy
16 of lumacaftor/ivacaftor to ivacaftor and evaluated the
17 effect of lumacaftor/ivacaftor on sweat chloride.

18 I will first present some history on why the
19 agency agreed that the individual components did not
20 need to be evaluated in confirmatory studies and why
21 the agency now thinks, given the results of these
22 confirmatory studies, that ivacaftor as a monotherapy

1 should have been evaluated.

2 Utilizing the data available, I conducted an
3 analysis where I directly tested the superiority of
4 lumacaftor/ivacaftor to ivacaftor with respect to lung
5 function and pulmonary exacerbations. I did not
6 examine changes in BMI and CFQ-R, as the confirmatory
7 studies did not provide replicated evidence of a
8 treatment benefit, nor did I consider multiplicity. I
9 will finish up by presenting the effects of
10 lumacaftor/ivacaftor on sweat chloride using the
11 results from a dose-selection study, as sweat chloride
12 was not measured in the confirmatory studies.

13 First, I will cover the effect of lumacaftor.
14 In study 809-1 and 2, as previously stated, treatment
15 with lumacaftor monotherapy for 28 days demonstrated a
16 dose-dependent decrease in lung function. Given this
17 potential safety signal and the fact that lumacaftor
18 was not to be developed as a monotherapy, the agency
19 agreed with the applicant. Inclusion of a lumacaftor
20 arm in the confirmatory trials as not required. This
21 information was conveyed to the applicant in 2013.
22 Now, I'll move on to ivacaftor.

1 In the original NDA review of ivacaftor, the
2 results fro study 770-104 did not establish the
3 efficacy of ivacaftor in patients homozygous for the
4 F508 mutation. The change at 16 weeks in percent
5 predicted FEV1 was 2.5 percent. The number you are
6 more familiar with is the change through 16 weeks or
7 1.7 percent. This effect was deemed not clinically
8 relevant given that the mean effect noted for the G551D
9 mutation was 10.6 percent and that preliminary results
10 indicated the effect of lumacaftor/ivacaftor would be
11 larger than ivacaftor alone, approximately 5 percent.

12 Just a quick comment here, the 10.6 that I
13 reported here was through 24 weeks. The number that
14 Dr. Durmowicz reported previously this morning of 12 to
15 13 percent was at week 24.

16 Based on these facts, in 2012, the agency
17 agreed with the applicant, an ivacaftor monotherapy arm
18 was not required in the confirmatory studies. However,
19 the effect of lumacaftor/ivacaftor in the confirmatory
20 studies was not that much different than what was
21 observed with ivacaftor. In fact, as I will present,
22 there's not enough evidence to include with any

1 reasonable level of confidence that lumacaftor plus
2 ivacaftor was any different than ivacaftor monotherapy
3 with respect to changes in lung function and pulmonary
4 exacerbations.

5 The applicant's rationale for not including an
6 ivacaftor monotherapy arm in the confirmatory studies
7 was essentially a noninferiority argument that
8 implicitly relied on cross-study comparisons. They
9 claimed that placebo is similar to ivacaftor in
10 study 770-104 and that lumacaftor/ivacaftor was
11 superior to placebo in the confirmatory studies.
12 Therefore, lumacaftor plus ivacaftor was better than
13 ivacaftor.

14 However, there is a weakness to this argument.
15 The absence of a significant difference between placebo
16 and ivacaftor in itself does not establish that placebo
17 is similar to ivacaftor. Lack of a statistical
18 difference from placebo simply means that there was not
19 enough evidence to reject the process that they were
20 the same. And as I will point out, we do not have
21 enough evidence to conclude that placebo and ivacaftor
22 are similar enough to conclude that lumacaftor plus

1 ivacaftor is better than ivacaftor.

2 To avoid the assumption that placebo is
3 similar to ivacaftor, I utilized an approach that
4 integrates or synthesizes the data from the
5 confirmatory studies in the ivacaftor study to directly
6 test the superiority of lumacaftor/ivacaftor versus
7 ivacaftor. Since this method treats both sources of
8 data as if they came from the same randomized trial, I
9 assumed that the effect of ivacaftor would have been
10 the same had an ivacaftor arm been included in the
11 confirmatory trials. I must also evaluate the
12 constancy assumption: are the studies similar in
13 design, population, standard of care, and so forth.

14 This process combines the variance from the
15 confirmatory studies and the ivacaftor study to yield a
16 single confidence interval for the difference between
17 lumacaftor and ivacaftor. With respect to changes in
18 percent predicted FEV1, if this 95 percent confidence
19 interval excludes zero, one could conclude with
20 95 percent confidence that the lumacaftor/ivacaftor was
21 superior to ivacaftor. For exacerbation rates, this
22 95 percent confidence will need to exclude 1.

1 First, I will cover the results from
2 study 770-104, the ivacaftor-only study. This study
3 evaluated 140 patients homozygous for the F508
4 mutation. Twenty-eight patients were randomized to
5 placebo, 112 to ivacaftor, 150 milligrams. Important
6 features of design that I want to point out are
7 treatment duration, 16 weeks; the inclusion criteria of
8 lung function greater than 40 percent at baseline; and
9 use of hypertonic saline. It was not allowed.

10 The results in this study were not sufficient
11 to conclude that ivacaftor was any different from
12 placebo with respect to lung function and
13 exacerbations. However, although superiority was not
14 established, it could also not rule out an effect as
15 large as 5.9 percent for change in percent predicted
16 FEV1 and a 71 percent reduction in exacerbations.

17 Next, I'll briefly cover the results from the
18 lumacaftor/ivacaftor study. The main design issues I
19 want to point out here are treatment duration,
20 24 weeks; baseline lung function between 40 and
21 90 percent; and the use of hypertonic saline. It is
22 also important to note that these two arms randomized

1 366 patients, 184 placebo and 182 to
2 lumacaftor/ivacaftor, over double the sample size noted
3 in the ivacaftor study.

4 As previously stated, I'm going to focus on
5 the proposed dose, lumacaftor 400 milligrams plus
6 ivacaftor 250 milligrams twice daily. The results from
7 these studies indicated a significant difference with
8 respect to changes in percent predicted FEV1 and
9 exacerbation rate. Note, exacerbation rate was a key
10 secondary endpoint that failed in the sequential
11 testing strategy.

12 As I just stated, the main difference as noted
13 between the lumacaftor and the ivacaftor study were
14 study duration and based on lung function. The
15 lumacaftor/ivacaftor studies were 24 weeks in duration
16 and excluded patients with a baseline lung function
17 greater than 90 percent. Other aspects that were
18 considered but not accounted for in my analysis were a
19 derivation of percent predicted FEV1 and use of
20 hypertonic saline.

21 First, to consider change in percent predicted
22 FEV1. To avoid any difference due to the statistical

1 modeling and study design, I considered the change at
2 16 weeks rather than through 16 weeks and used an
3 ANCOVA model with baseline line function included as a
4 covariate. I will present the results from two
5 analyses, one where I included all randomized and
6 treated patients, and one where I excluded patients
7 with a baseline function greater than 90 percent.

8 As expected, baseline lung function was higher
9 in study 770-104, that included patients greater than
10 90 percent baseline function, than in the confirmatory
11 studies. However, changes from baseline were similar
12 in all studies regardless of baseline function, near
13 zero for placebo patients and 2 to 3 percent for
14 patients on the active arms.

15 This figure presents the difference from
16 placebo for each individual study for all randomized
17 and treated patients. Although the 95 percent
18 confidence interval for the effect of ivacaftor is
19 wide, it was relatively a small study, it clearly
20 overlaps the 95 percent confidence interval for the
21 effect of lumacaftor/ivacaftor, and the point estimates
22 are virtually the same.

1 Next, I directly test the superiority of
2 lumacaftor to ivacaftor for changes in percent
3 predicted FEV1 at week 16. I integrated the
4 lumacaftor/ivacaftor studies and combined or
5 synthesized these results with the results from the
6 ivacaftor study to compute a 95 percent confidence
7 interval for the difference in treatment effect.
8 Regardless of lung function at baseline, we cannot,
9 with any reasonable level of confidence, conclude that
10 lumacaftor plus ivacaftor is superior to ivacaftor as
11 the 95 percent confidence interval for the difference
12 includes zero.

13 Next, I examined pulmonary exacerbations. And
14 exacerbation is defined as a new or changed antibiotic
15 therapy for any four of the listed signs or symptoms.
16 For the sake of time, I am not going to read each one.
17 The point is the definition of an exacerbation was
18 consistent across studies.

19 Again, to avoid any confusion with modeling, I
20 reported crude rates defined as the number of events
21 divided by the number of days on study. And as I did
22 with changes in lung function, I present the results

1 using all randomized and treated patients and one where
2 I exclude patients with baseline function greater than
3 90 percent.

4 This slide presents the rate ratio for each
5 individual study. Clearly, there was a reduction in
6 exacerbations that favored the active drug, and this
7 reduction was similar amongst all studies.

8 This figure presents the 95 percent confidence
9 interval for the rate ratio for each individual study.
10 As with changes in lung function, the 95 percent
11 confidence interval for ivacaftor is wide but clearly
12 overlaps the effect of lumacaftor/ivacaftor, and the
13 point estimates again are virtually the same. Next, I
14 directly test the superiority of lumacaftor/ivacaftor
15 using the synthesis method.

16 To test the superiority with respect to
17 exacerbations, I calculated the rate ratio for the
18 lumacaftor/ivacaftor and ivacaftor and computed a 95
19 percent confidence interval for this rate ratio by
20 combining the variance from the lumacaftor/ivacaftor
21 studies and the ivacaftor study.

22 Results indicate that regardless of baseline

1 lung function, we cannot, with 95 percent confidence,
2 rule out the possibility that the effect of
3 exacerbation is any different between lumacaftor plus
4 ivacaftor and ivacaftor as the 95 percent confidence
5 interval for the rate ratio contains 1.

6 In summary, the results from my analysis could
7 not, with any level of confidence, conclude that
8 lumacaftor plus ivacaftor was significantly different
9 from ivacaftor with respect to changes in percent
10 predicted FEV1 and pulmonary exacerbations. The
11 conclusion that ivacaftor was ineffective in study 770-
12 104 may need to be revisited. Even though the results
13 from this study did not establish superiority, it also
14 did not rule out an effect as large as 5.9 percent for
15 changes in percent predicted FEV1 and a 71 percent
16 reduction in exacerbations.

17 In my opinion, it would be incorrect to say
18 that ivacaftor was similar to placebo and even worse to
19 conclude that lumacaftor/ivacaftor was better than
20 ivacaftor.

21 Now I move on to sweat chloride. As sweat
22 chloride was not measured in the confirmatory studies,

1 I examined the results from the dose-selection study
2 809-102. This study was conducted in four different
3 cohorts evaluating patients either heterozygous or
4 homozygous for the F508 mutation. I will focus on the
5 results from homozygous subjects in cohorts 2 and 3.

6 In this dose-selection study, patients were
7 administered varied doses of lumacaftor for 28 days
8 followed by 28 days of treatment with
9 lumacaftor/ivacaftor. Only subjects in cohort 3
10 utilized the proposed dose of lumacaftor/ivacaftor.
11 Details of this are included in the AC briefing
12 document.

13 Sweat chloride was measured at baseline and on
14 days 28 and 56. On days 28 and 56, sweat chloride was
15 measured twice, at dosing and 4 hours post-dose. I
16 evaluated the change from baseline at week 8, using the
17 values measured at each time, using an ANCOVA model
18 with treatment and baseline function as a covariate.

19 This slide shows the difference from placebo
20 for change in sweat chloride for homozygous patients.
21 Regardless of dose, there was a decrease in sweat
22 chloride at days 28 and 56. I grayed out the

1 95 percent confidence interval so this would be easier
2 to see. It should be noted that this decrease seemed
3 variable depending on when sweat chloride was measured,
4 either at dosing or 4 hours post-dosing.

5 When measured at dosing, there appeared to be
6 some additional benefit following an additional 28 days
7 of dosing with lumacaftor/ivacaftor. However, if sweat
8 chloride was measured 4 hours after dosing, the
9 additional benefit was inconsistent. In fact, in some
10 cases, the sweat chloride increased although it did not
11 return to baseline levels.

12 There was no clinical expectation that sweat
13 chloride would differ based on when measured. It could
14 just be the variability of the sweat chloride assay.
15 But regardless, there was still a decrease in sweat
16 chloride, though it was small numerically, around
17 10 millimoles per liter. The mean decreases noted for
18 the G551D and the R117H mutations were 50 and
19 24 millimoles per liter, respectively. This taken in
20 context with the variability noted in the measurements
21 of sweat chloride further support the questions, is the
22 magnitude of the efficacy for lumacaftor/ivacaftor in

1 the F508 mutation clinically relevant, and is it any
2 different from ivacaftor?

3 Thank you. I now turn the podium back over to
4 Dr. Lim.

5 **FDA Presentation - Robert Lim**

6 DR. LIM: This is Robert Lim again. I'll
7 provide clinical considerations for efficacy as well as
8 a summary of safety. Here's an outline of my
9 presentation, and I will begin with a discussion of
10 efficacy.

11 This table summarizes the results for the
12 primary and key secondary endpoints for studies 809-103
13 and 809-104 at the proposed dose. These endpoints are
14 listed left to right in order of the applicant's
15 prespecified hierarchical analysis strategy. Note that
16 the non-statistically significant results are grayed
17 out. This didn't show up as well as in the handouts,
18 but you can see it here in the slide. It's also worth
19 noting that based on the division's experience, the
20 applicant's ordering of the analysis hierarchy appears
21 to correspond their expectation of a positive response.

22 For the primary and first key secondary

1 endpoints of absolute and relative change from baseline
2 in percent predicted FEV1, in both studies, the
3 proposed dose demonstrated statistically significant
4 improvements compared to placebo. For BMI, the
5 treatment effect was inconsistent between studies, and
6 for CFQ-R, the results were not statistically
7 significant in either study. And it's also worth
8 noting that compared to placebo, in neither study was
9 the MCID of 4 reached with values of 1.5 and 2.9.

10 With regard to responder and exacerbation
11 rate, while the treatment effects favored
12 lumacaftor/ivacaftor, they were not statistically
13 significant due to earlier failure in the analysis
14 hierarchy.

15 While lumacaftor/ivacaftor demonstrated
16 superiority to placebo in terms of percent predicted
17 FEV1, for a combination product, we also typically
18 expect that the combination has a benefit over
19 monotherapy. When the treatment effect of the
20 combination is expected to be relatively large, this
21 does not necessarily require a monotherapy comparator,
22 and placebo comparator may suffice.

1 This was the case for lumacaftor/ivacaftor
2 given the expected percent predicted FEV1 effect size
3 of around 5 percent based on the dose-selection study.
4 However, the actual lumacaftor/ivacaftor effect size
5 was less than expected and grossly similar to that
6 previously observed for ivacaftor monotherapy in
7 study 770-104. Because of this, an ivacaftor
8 comparator would likely have been more informative than
9 a placebo comparator.

10 As no ivacaftor monotherapy comparator was
11 included in the confirmatory studies, FDA statisticians
12 performed additional analyses to compare the treatment
13 effects of lumacaftor/ivacaftor and ivacaftor at week
14 16 of treatment. Their analysis is summarized in this
15 table.

16 Given the point estimates for both percent
17 predicted FEV1 and exacerbation rate ratios, as well as
18 the overlapping 95 percent confidence intervals, it
19 cannot be concluded that lumacaftor/ivacaftor offers an
20 added benefit above ivacaftor alone and that lumacaftor
21 contributes to the combination.

22 These data run contrary to the in vitro data,

1 which predicted an added clinical effect of lumacaftor
2 and ivacaftor. This suggests that for
3 lumacaftor/ivacaftor, the in vitro data does not
4 necessarily predict clinical response, as was the case
5 with lumacaftor alone.

6 Additionally, given the results of these
7 analyses, the question is raised had ivacaftor
8 monotherapy study 770-104 been sized similarly to the
9 lumacaftor/ivacaftor confirmatory studies, would the
10 results have also been statistically significant?

11 With regard to sweat chloride, it was only
12 assessed in dose-selection study 809-102. And as
13 Mr. Petullo discussed, in that study, both lumacaftor
14 and lumacaftor/ivacaftor treatment resulted in
15 relatively small decreases in sweat chloride. Whether
16 or not there was an additive effect was dependent on
17 when sweat chloride was measured. And this disparity
18 would suggest that either there is no additive effect
19 or that it is simply not that robust. Either way, the
20 effect is small.

21 To add context to the effect size, this table
22 places study 809-102 sweat chloride data next to that

1 observed for ivacaftor monotherapy in the approved
2 G551D mutation and R117H mutations. This is expressed
3 in terms of both absolute change from baseline and
4 sweat chloride and relative change. Whether or not
5 these small changes in sweat chloride observed for
6 lumacaftor/ivacaftor are clinically relevant is
7 uncertain.

8 To summarize efficacy, lumacaftor/ivacaftor
9 treatment resulted in small decreases in sweat chloride
10 and modest improvements in percent predicted FEV1.
11 Exacerbation results favored lumacaftor/ivacaftor.
12 However, based on the statistical analysis hierarchy,
13 they could not be considered statistically significant.

14 It can also not be concluded that
15 lumacaftor/ivacaftor offers an added benefit above
16 ivacaftor alone. In the figure below that was
17 previously shown by Dr. Durmowicz this morning, the FDA
18 analysis for percent predicted FEV1 for
19 lumacaftor/ivacaftor and ivacaftor at week 16 are
20 summarized and are circled in red.

21 As can be seen for percent predicted FEV1, the
22 data points are close and overlapping. Similar results

1 were also observed for exacerbation as are summarized
2 in the table to the right of the figure. Additionally,
3 it should be noted that in vitro data can also not be
4 used to conclude an added efficacy benefit for the
5 combination because, as seen for lumacaftor monotherapy
6 and in the lumacaftor/ivacaftor confirmatory studies,
7 the in vitro data did not appear to reliably predict a
8 clinical benefit. These results also raise a
9 possibility that ivacaftor monotherapy may have an
10 effect in F508del homozygous patients that could
11 potentially be on par with lumacaftor/ivacaftor.

12 I will now switch gears and briefly discuss
13 safety. The safety profile of lumacaftor/ivacaftor is
14 derived primarily from placebo-controlled data from
15 confirmatory studies 809-103 and 809-104. These
16 studies exposed 738 patients to either
17 lumacaftor/ivacaftor dose for a median of 168 days. Of
18 these patients at the time of NDA submission, 116 were
19 exposed to lumacaftor/ivacaftor for a total of 1 year
20 when including exposure in the ongoing extension study
21 809-105.

22 This slide summarizes the overall adverse

1 event data from the confirmatory studies. There were
2 no deaths, and AEs leading to discontinuation were more
3 common in lumacaftor/ivacaftor groups compared to
4 placebo. Serious adverse events were less common in
5 lumacaftor/ivacaftor groups. And additionally, as
6 cataract is a known risk for ivacaftor monotherapy, it
7 is worth noting that no cataracts were reported in the
8 placebo-controlled studies.

9 Given the liver safety concerns associated
10 with ivacaftor monotherapy, liver related events were
11 of particular interest. For overall liver related
12 events, there were no large differences between placebo
13 arms and lumacaftor/ivacaftor arms. However, for liver
14 related serious adverse events and adverse events
15 leading to discontinuation, which are boxed in red,
16 events only occurred in the lumacaftor/ivacaftor dose
17 groups and not in placebo.

18 In addition to the analysis of adverse events,
19 liver related lab assessments were also performed.
20 Elevations in transaminases occurred with similar
21 frequencies across all treatment groups. However, when
22 looking at cases of elevated transaminases of greater

1 than 3 times the upper limit of normal that were
2 associated with total bilirubin elevations greater than
3 twice the upper limit of normal, which are boxed in
4 red, there were 3 cases in the lumacaftor/ivacaftor
5 groups and none in the placebo.

6 It is also worth noting that in the ivacaftor
7 development program, such cases were not reported, and
8 overall, these findings may suggest that
9 lumacaftor/ivacaftor exposure may potentially be
10 associated with increased liver toxicity compared to
11 ivacaftor alone.

12 Given the dose-dependent drops in percent
13 predicted FEV1 observed following lumacaftor in
14 monotherapy, respiratory related adverse events were
15 evaluated as events of particular interest. Overall,
16 these events were more common in the
17 lumacaftor/ivacaftor groups compared to placebo. This
18 appeared to be driven by respiratory symptom related
19 events, which are boxed in red. For the symptom
20 related events, the time to onset was generally within
21 days for lumacaftor/ivacaftor groups versus on the
22 order of weeks in the placebo groups.

1 Respiratory related serious adverse events and
2 adverse events leading to discontinuation, which are
3 boxed in red, occurred rarely but only in
4 lumacaftor/ivacaftor groups. These data suggest that
5 lumacaftor/ivacaftor exposure may trigger respiratory
6 symptoms in some individuals. However, the mechanism
7 by which this is occurring is not certain.

8 In summary, with regard to efficacy,
9 lumacaftor/ivacaftor treatment had modest effects on
10 both sweat chloride and percent predicted FEV1 versus
11 placebo. While there was a reduction in exacerbation,
12 it was not statistically significant due to its
13 positioning in the analysis hierarchy. Further, based
14 on FDA analysis in terms of both percent predicted FEV1
15 and exacerbation reduction, it can also not be
16 concluded that lumacaftor/ivacaftor treatment offers a
17 benefit above ivacaftor monotherapy and that lumacaftor
18 contributes to the combination.

19 This runs contrary to the in vitro data, which
20 predicted an additive effect of lumacaftor/ivacaftor.
21 This is a significant issue as, typically, combination
22 products are expected to demonstrate an added benefit

1 above monotherapy. These results also suggest that
2 ivacaftor monotherapy may have an effect in F508del
3 homozygous CF patients. With regard to safety, the
4 primary safety concerns raised in this program are
5 liver related toxicity as well as increased respiratory
6 related adverse events.

7 In closing, as you discuss the questions posed
8 to you, we hope that you will keep in mind these
9 issues. Thank you, and this concludes the FDA
10 presentation.

11 **Clarifying Questions to the Presenters**

12 DR. OWNBY: Does the panel have any questions
13 about the FDA presentation they'd like clarified?

14 DR. BRITTAIN: I have two questions. First,
15 at the time the study was designed, did you anticipate
16 the possibility of this outcome? I mean, was the
17 sponsor warned that if you get a modest effect, then
18 we're going to have to reconsider whether we should
19 have had the other arm -- was this discussed?

20 DR. DURMOWICZ: I'll take that question. At
21 the time the study was designed -- the combination
22 studies I think you mean, right -- we already had the

1 information from the G551D population studies as well
2 as the study information from the F508, and had already
3 made a decision that was placed in the original label
4 that ivacaftor monotherapy was not effective.

5 I think, as you've heard several times here,
6 that was probably a bit of a hasty decision being made
7 on a clinical study that wasn't designed for efficacy,
8 but that was the decision that we made. And that was
9 one of the primary reasons why ivacaftor monotherapy
10 was not included in the phase 3 trials. And in some
11 aspects, I think we've learned over the course of years
12 that in vitro data is a nice entry point, and it gets
13 you a ticket to the dance, but it doesn't really
14 necessarily convey true clinical endpoint.

15 At that time, I think we were also intrigued
16 by the science that it probably shouldn't be able to
17 work for the F508 population, and that helped
18 considerably to make that decision as well. So we did
19 know and did call it ineffective and prospectively
20 agreed that it would not need to go into the phase 3
21 trials for the combination.

22 DR. BRITTAIN: And also, I guess related to

1 that, can you explain the rationale for requiring that
2 the combination is superior to each of the components,
3 and why that is a critical consideration?

4 DR. DURMOWICZ: Well, I think that you've got
5 a combination product, and you usually have two
6 effective products at some level. And when you develop
7 a combination of them both together, you would expect
8 that that combination offers something above and beyond
9 the individual components by themselves. And that's an
10 integral part of regulatory development for combination
11 programs.

12 Just to tail an aside, it doesn't have to be
13 statistically superior to each individual monotherapy
14 product, but it has to show a benefit of some sort
15 above that, and that you show a contribution of each
16 individual component.

17 The applicant, Vertex, a lot of their
18 contribution of the individual component information is
19 based more on in vitro data and in vivo sweat chloride
20 information. And as I mentioned to you earlier, over
21 the course of the past five years or so, we've learned
22 a lot about the in vitro data and the correlation of

1 sweat chloride.

2 We actually published a small vignette stating
3 that for the 551D population that changes in sweat
4 chloride on a patient basis did not correlate with
5 change in FEV1. So that is one of the reasons we don't
6 use sweat chloride as a surrogate endpoint for efficacy
7 and call the study done at that point.

8 With regard to the in vitro data, we've
9 already pointed out that the in vitro data were very
10 positive for several mutations but didn't translate
11 into a clinical effect. Also, in vitro data are
12 somewhat variable depending on how the in vitro model
13 is done. Dr. Van Goor also published a paper from 2013
14 in the Journal of Cystic Fibrosis in fischer rat
15 thyroid cells instead of human bronchial epithelial
16 cells that were treated with ivacaftor. And the
17 interpretation you could make from its effect on the
18 F508 mutation with ivacaftor could be somewhat
19 different.

20 So with that variability in mind, the in vitro
21 data, again, are able to be hypothesis-generating but
22 not predict a contribution or a clinical effect, at

1 least in our opinion.

2 DR. OWNBY: I've got Dr. Grayson, Yu, Morrato,
3 and Connett. Dr. Grayson?

4 DR. GRAYSON: Thanks. I had a quick question
5 on the respiratory AEs. I'm struggling with the
6 lumacaftor 600 versus 800 dosing issue. For the severe
7 AEs for respiratory, it's only in the 600, not in the
8 400 twice-a-day dose. I'm trying to -- am I looking at
9 noise or do we think that there's a dose response, and
10 more lumacaftor would be protected? I don't get that,
11 to be honest with you.

12 DR. LIM: I think we have the same thoughts on
13 that. It's not clear. It's unlikely that -- it
14 doesn't appear to us that it would be a dose response
15 because the exposures actually would be lower. And so
16 given the small numbers, we think that it may just be
17 random, but it is notable that it's only in the
18 lumacaftor/ivacaftor groups.

19 DR. OWNBY: Dr. Yu?

20 DR. YU: Yes. I have a question about the
21 differences between ivacaftor study 770-104 -- and you
22 said that in this study it did not -- the study did not

1 allow you to use hypertonic saline. And that's
2 different. In this study 809-103 and 104, hypertonic
3 saline was used. So I'm just wondering what's the
4 difference and what is the significance of that.

5 MR. PETULLO: This is David Petullo. I did
6 look at that. Phase 3 studies allow use of hypertonic
7 saline. I went in to make apples to apples. I
8 excluded those patients. And what happened was I was
9 excluding about two-thirds of the patients from the
10 phase 3 confirmatory studies. And I have a backup
11 slide. Basically, just my confidence intervals were
12 that much wider for the phase 3 studies, so it just
13 further supported my conclusion.

14 DR. YU: So it's simply for the sample size
15 consideration.

16 MR. PETULLO: Exactly. Correct.

17 DR. YU: Thank you.

18 DR. OWNBY: Dr. Morrato?

19 DR. MORRATO: I was wondering if the FDA had
20 any thoughts on a minimum effect size for FEV1.

21 DR. DURMOWICZ: I don't think we have a
22 minimum effect size for FEV1 for any particular

1 disease, although if you look at bronchodilator
2 therapies like albuterol or something for asthma, you
3 have a general sense that at least a 10 to 12 percent
4 increase would show that people's respiratory symptoms
5 were relieved.

6 I think for a therapy that's not a
7 bronchodilator, like this, or corticosteroids for
8 asthma, then you see a smaller improvement in FEV1, and
9 you wonder what that means. I think it was important
10 that other endpoints are also looked at, at that point
11 in time. And what you have here in the
12 ivacaftor/lumacaftor combination program, and to a
13 certain extent, the ivacaftor monotherapy study as
14 well, is that you saw a decrease -- nominally if you
15 will or statistically significant, however you want to
16 slice that based on the statistical hierarchy -- of
17 exacerbations, which is the will true clinical endpoint
18 and not the surrogate endpoint for FEV1.

19 So could you make the jump that an FEV1
20 improvement of 2 to 3 percent predicts an important
21 clinical benefit in exacerbations, you could make that
22 link potentially in the lumacaftor/ivacaftor

1 combination studies. Although the data are not nearly
2 as robust for the ivacaftor monotherapy study, you
3 could also make that link as well if you look just at
4 the point estimates.

5 DR. MORRATO: Then I was just curious from a
6 statistical interpretation how strict should we be in
7 the fact that they didn't meet the statistical
8 hierarchy prespecification. Is that something
9 that's --

10 DR. DURMOWICZ: I'll do that first, and then
11 I'm going to hand it to Mr. Petullo and Ms. Zeng. I
12 did have a clinical lifetime before I became Mr.
13 Regulator here at the FDA. And the clinical part of me
14 goes, "Who the heck cares?" Because it's there; I
15 can't close my eyes to it kind of thing, and it's a
16 meaningful benefit. I can't pull myself away from
17 that.

18 Now, on the other hand, as the regulator who
19 knows not that much about statistics, but a little
20 bit -- a very little bit depending on who you ask -- we
21 pay very, very much attention to how the statistical
22 analysis plan is set up in the hierarchies, and we do

1 that for a very important reason because we're trying
2 to decide is this drug truly effective or not.

3 Now, if you don't pay particular attention to
4 it and hold to it rather rigidly from a regulatory
5 approval, drug approval type standpoint, what happens
6 is that a clinical study could devolve into a
7 subsequent morass of post hoc analyses that people are
8 trying to find out what worked and what didn't. And
9 that's really not appropriate for what we do. So I
10 think that's the two-sided answer I guess.

11 MR. PETULLO: David Petullo. I'm just going
12 to make one additional comment. And I agree with
13 everything Tony said. FEV1 is typically -- we use as a
14 surrogate for exacerbation, so it's not surprising it
15 was significant. So there is some correlation, so
16 multiplicity is less of an issue. But again, strictly
17 statistically, they failed in their sequential testing
18 strategy.

19 DR. OWNBY: I've got Dr. Connett and Dr.
20 Castile, and we are going to break at 20 after, so
21 we've only got a couple of minutes. Please try to make
22 it brief.

1 DR. CONNETT: Some of my questions have been
2 answered. But it sounds like there's no study here
3 that looks at sweat chloride responders and see if
4 they're more likely to have an effect on the primary
5 outcomes.

6 DR. DURMOWICZ: I don't think for this study
7 in particular. But you have to realize for this study,
8 when you talk about sweat chloride and doing a response
9 analysis based on sweat chloride, you're looking at a
10 maximum change of about 10 out of 100. So you're
11 looking at trying to find a dose response from a zero
12 to 10, really, difference, which is hard to do.

13 We looked at it for the G551D population,
14 where there was a zero to 50 difference in sweat
15 chloride back several years ago. And while we all know
16 that sweat chloride improvements will trend with
17 benefit, to a certain extent, at least from zero to 50,
18 you can't say on a patient basis that this patient had
19 a 10 percent improvement in sweat chloride, so they're
20 going to have a 5 percent improvement in FEV1. We
21 don't know that.

22 DR. OWNBY: Dr. Castile?

1 DR. CASTILE: I have a specific question for
2 Mr. Petullo, and it has to do with his analysis of the
3 ivacaftor and the combination study and the differences
4 between them as it relates to FEV1. These, as I read
5 these studies, were very different populations in that
6 the mean FEV1 in the ivacaftor group was 80 percent of
7 predicted, and it was 60 in the combination group. In
8 terms of progression of disease, those are dramatically
9 different populations.

10 Your correction, I think -- and you can
11 correct me -- was to eliminate the patients who had
12 FEV1s above 90 percent from the ivacaftor group. So
13 the specific question I would have is how did that
14 affect the mean, and were there then more comparable
15 groups in terms of stage of disease, one being very
16 mild and the other being moderate?

17 MR. PETULLO: This is David Petullo. Yes,
18 you're correct. In the ivacaftor study -- in one of my
19 analysis, I excluded patients in the ivacaftor study,
20 770-104, that had a baseline lung function greater than
21 90 percent. I think it was around 46 patients I
22 excluded, and most of those were in the ivacaftor arm,

1 38 and 6, or it might have been 38 and 8.

2 In the end, my conclusions were the same.

3 When I compared the two, I couldn't rule out that they
4 were any different. And I can actually get those mean
5 values. I don't have them here.

6 DR. CASTILE: Well, but were you kind of
7 comparing -- well, I guess, a while ago when I did my
8 master's work in statistics and experimental design,
9 one of the first things I learned, and I still
10 remember, is that it's very inappropriate to extract
11 groups from different studies done at different times
12 on different populations and attempt to draw any
13 conclusions from them. So my view of this entire
14 analysis would be that it is appropriate to use it for
15 speculating about additional future studies, but it's
16 totally inappropriate to draw any conclusions about it.
17 So I don't see it as terribly relevant.

18 The other point that I would make is, as I
19 listened to the discussion from the FDA, the reason we
20 don't have an ivacaftor group, it seems, is based on a
21 recommendation to Vertex from the FDA. So it concerns
22 me that that recommendation may actually serve to

1 penalize not only the company but patients who may
2 benefit from the drug.

3 MR. PETULLO: I'll answer part of that. I
4 agree with you completely. I mean, cross-study
5 comparisons, we don't like them, but that's all we have
6 here. If I could have used this analysis to support
7 the actual in vitro data, it would have been a good
8 thing. And we tried to do that, and we could not do
9 that.

10 DR. CASTILE: If this analysis had shown that
11 ivacaftor -- and there's no way it would. But if it
12 had shown that ivacaftor alone was significantly better
13 than anything else, and you drew the data from
14 populations, one study done in 2009 and one in 2012,
15 you're not telling me that the FDA would approve an
16 additional use for ivacaftor based on that kind of
17 data.

18 MR. PETULLO: My comment was meant that
19 lumacaftor/ivacaftor would have been better than
20 ivacaftor. I agree with you. I would have rather had
21 a randomized controlled trial that had the ivacaftor
22 monotherapy arm in it. We don't have that. I wasn't

1 here when that decision was made and we told the
2 company not to include it. I as a statistician would
3 have said, no, we shouldn't have said that. We should
4 have said there's not enough evidence to establish that
5 ivacaftor didn't work.

6 Tony may have some additional comments.

7 DR. DURMOWICZ: I don't have very much to add.
8 But I think I will point out, as I mentioned before,
9 that back in the 20 -- whatever period of time it is,
10 four or five years ago, we made the best decision we
11 could based on the information that we had with the
12 "science of everything" in addition to the dramatic
13 difference in effect with the G551D population. And as
14 I mentioned earlier, most CF approved therapies in
15 their phase 3 trials have shown approximately around a
16 6 to 10 percent improvement in FEV1.

17 So that being the case and not having any
18 exacerbation data one way or the other, we stated that
19 it was not effective and that it didn't have to be
20 included in the phase 3 trials for the combination.

21 Now, we have to live with that, but we're just
22 bringing up now, with new information, that we know

1 something now that we didn't know several years ago,
2 and it's up for you to discuss what to do with that or
3 how to handle it. That's all I really have to say
4 about it.

5 DR. OWNBY: I think we'll now break for lunch.
6 We'll reconvene again in this room 45 minutes from now
7 at 1:10. Please take your personal belongings you may
8 want with you at this time. Committee members, please
9 remember that there will be no discussion of the
10 meeting during lunch among yourselves, with the press,
11 or with members of the audience. Thank you.

12 (Whereupon, at 12:24 p.m., a lunch recess
13 was taken.)
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A F T E R N O O N S E S S I O N

(1:12 p.m.)

Open Public Hearing

DR. OWNBY: We'll go ahead and reconvene the meeting of the advisory committee. As someone just said, it will take me a while to read through all this script anyway.

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, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your

1 attendance at the meeting.

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

8 The FDA and this committee place great
9 importance upon the open public hearing process. The
10 insights and comments provided can help the agency and
11 this committee with their consideration of the issues
12 before them. That said, in many instances and for many
13 topics, there will be a variety of opinions. One of
14 our goals today is for this open public hearing to be
15 conducted in a fair and open way, where every
16 participant is listened to carefully and treated with
17 dignity, courtesy, and respect. Therefore, please
18 speak only when recognized by the chair. Thank you for
19 your cooperation.

20 Before I call speaker number 1, I would like
21 to inform those attending the meeting that we have
22 offered the speakers to speak from various locations in

1 the room to maintain recommended distances among
2 speakers.

3 Will speaker number 1 step up to the podium
4 and introduce yourself? Please state your name and any
5 organization you are representing for the record.

6 MS. MARSHALL: I'm Kate Marshall. This is my
7 mother Martha Marshall, and at home in York, Maine is
8 my father, Patrick Marshall and little brother Chase.
9 I was diagnosed with CF, specifically double-delta 508,
10 when I was nearly 8 months old, requiring 6 weeks of
11 hospitalization in my first year of life. I was not
12 hospitalized again with any CF complications until I
13 turned 12. Since then, I've been hospitalized seven
14 times for IV antibiotic treatment.

15 My lung function has now declined to
16 87 percent, and I'm expected to lose between 1 to
17 2 percent of my lung function each year due to
18 pulmonary infections. I stand before you nearly a
19 perfect CF patient, complying to everything that has
20 ever been asked, swallowing 40 pills today, doing two
21 to three 25-minute physical therapy sessions per day,
22 and inhaling upwards of six medications through my

1 nebulizer. Additionally, I play on an elite year-round
2 soccer team at my high school varsity lacrosse and
3 soccer teams.

4 I was named Sports Illustrated's December
5 Athlete of the Month, and I'm an honor roll student. I
6 like to think I have the talent and aspiration to play
7 in college. I also consider myself very mentally and
8 physically tough. I have to be. CF battles with me
9 every single day.

10 I am blessed to be living in 2015 and in the
11 United States, having access to the medicines that
12 treat the symptoms and the infections that cause chaos
13 on individuals with CF. These FDA approved medicines
14 and the treatment protocols of the CF care centers have
15 increased life expectancy incrementally since my birth
16 in 1999. However, planning for my future is more
17 difficult than you may even imagine.

18 For instance, by the time I graduate college,
19 I'll be beyond my middle-aged years. This second part
20 of my life will become very compromised, dealing with
21 complications for advanced CF. Aside from the many
22 physical challenges CF will bring, psychologically,

1 socially, and economically, I will suffer. This is not
2 an assumption but a guarantee. There are thousands of
3 individuals like me with CF that will travel down their
4 unique pathways of this disease, but all roads will
5 lead to the same dead end.

6 Now, let's imagine me having access to
7 Kalydeco or lumacaftor this year while my lung function
8 is at 87 percent and why I'm physically strong as I
9 stand before you today. What might my future look
10 like? I can tell you it looks bright. My lung
11 function will stabilize or perhaps gain a few
12 percentage points. Rather than being admitted for
13 treatment for a lung infection, I'm at a soccer or
14 lacrosse practice, or scoring the winning goal for my
15 team.

16 I am an active participant in life without the
17 constant disappointment of CF slowing me down. My
18 family and I are humbled by the science that has
19 brought us here on its behalf, science that will
20 stabilize the rate of decline in decrease yearly
21 hospitalizations. Not losing 1 to 2 percent of my lung
22 function each year is remarkable data. Decreasing the

1 amount of hospitalizations each year will have a huge
2 effect far beyond the obvious.

3 CF is one of the worse genetic diseases
4 mankind has ever seen. Without access to the drug
5 combination for the CF double-delta 508 population, the
6 most common genotype, the decline will continue despite
7 the medicines readily available. This committee holds
8 the key to improving quality of life that our community
9 has been working towards. To not approve it for so
10 many that have suffered will not only be confusing but
11 cruel.

12 On behalf of the thousands of children and
13 adults with double-delta 508 like myself, thank you so
14 much.

15 DR. OWNBY: Thank you very much. Would
16 speaker number 2 please come to the podium and
17 introduce yourself?

18 MS. LANDGRAF: I am Sue Landgraf. I'm
19 representing CFRI, Cystic Fibrosis Research,
20 Incorporated. I am Sue Landgraf, executive director
21 for Cystic Fibrosis Research, Incorporated, CFRI, based
22 on Palo Alto, California with national and global

1 constituents. For 40 years, CFRI has provided
2 education resources and support services for those
3 living with or affected by CF, the most common fatal
4 genetic disease in North America. CFRI has also
5 awarded nearly \$10 million to basic science and
6 clinical CF research.

7 We urge the committee to recommend Vertex's
8 new drug to the FDA for approval. This drug will help
9 those with the double-delta F508 mutation improve,
10 maintain, and stop the slide in lung function.
11 Patients using it had reduced exacerbation, improved
12 weight, and overall better quality of life.

13 Ivacaftor alone, lumacaftor alone, they do not
14 work. The combo drug is the closest thing we have to a
15 cure. It can stem the tide of progression of the
16 disease in approximately 8500 individuals in the U.S.
17 Eighty-five hundred people benefiting from this drug
18 might seem insignificant.

19 To those with this progressive, painful and
20 isolating disease, it is a major breakthrough. It
21 could mean the difference between life and years of
22 progressive damage that literally takes their breath

1 away, painful moment by painful moment, until they are
2 left with such damage that they cannot take another
3 breath. They cannot fight the exacerbations, including
4 hemorrhaging of their lungs.

5 CF is an orphan disease, a silent disease.
6 But to those living with CF, it is loud and
7 excruciating with intense coughing fits as their lungs
8 try to expel the glue-like mucus that clogs the
9 airways. As CF progresses, infections increase. Life
10 is more painful. CFers gasp for breath, hearts racing,
11 wondering if this is the end. Make no mistake about
12 it. CF kills.

13 Today is a significant and ironic day for me.
14 I am also here on behalf of my 30-year-old daughter
15 with the double-delta F508 mutation. Eighteen years
16 ago today, at age 12, she was dying from unexpected CF
17 liver failure. Eighteen years ago tonight, word came
18 that there was a liver. She was successfully
19 transplanted on May 13th and given a second chance of
20 living with this horrendous disease.

21 Life went on with clubbing of her fingers,
22 diabetes, osteoporosis, pulmonary exacerbations, daily

1 respiratory therapies and meds, college, marriage, and
2 no IV drugs from 2005 to 2011. In 2011, with an FEV1
3 at 70 percent, she was given two drugs with severe
4 contraindications that left her with permanent
5 vestibular autotoxicity. She has little balance and
6 lives in a world that bounces up and down around her.
7 This is what she sees. She no longer walks easily.
8 She can't run, bike, hike, swim, or even drive a car,
9 and we know that exercise is key in helping to maintain
10 healthy pulmonary function.

11 Two years ago, her FEV1 was 40 percent. Now
12 it is 25 percent. Last month, she had her fourth
13 hospitalization since October, three weeks of IVs each
14 time. She was on continuous supplemental oxygen for
15 the first time since her liver failure. She takes 15
16 oral meds, another five is needed for pain and
17 coughing, 2 inhalers, 2 to 3 nebulizer drugs, two types
18 of insulin, 2 nasal sprays, various supplements, plus
19 hours of airway clearance daily. She lives with
20 excruciating pain every single moment. And last week,
21 my precious daughter was listed for a double-lung
22 transplant. She is dying. This is CF.

1 I truly believe that those with the double-
2 delta F508 mutation that can take this new drug before
3 significant lung damage occurs will have a healthy
4 future, and those with lower lung functions will have
5 better health. I believe that they will not suffer
6 like my daughter. They would not be facing death.
7 They would be facing a new and longer life.

8 Please recommend approval of this drug for
9 those who will benefit from it now. Give hope. Give
10 life. Do it now. Thank you on behalf of CFRI and the
11 CF community.

12 DR. OWNBY: Thank you very much. Will speaker
13 number 3 please come to the podium and introduce
14 yourself?

15 MISS MASTERS: Hi. My name is Ariana Masters,
16 and I am 6 years old. My daddy has cystic fibrosis,
17 and I love him very much. Please vote for this drug to
18 be approved so my daddy can stay healthy and play with
19 me.

20 MR. MASTERS: My name is Jeff Masters, I'm
21 37 years old, and I have cystic fibrosis. I was
22 diagnosed with this horrible disease when I was born.

1 Day in and day out of my life has been very
2 challenging. I've spent countless weeks in hospitals,
3 years of my time doing nebulizers, and taking millions
4 of pills. Every year of my life, my lungs and my
5 health have declined.

6 Fortunately, that trend of year-over-year
7 decline has stopped when I started taking this study
8 drug, Orkambi. Within five days of starting the trial,
9 I knew I was on the active medication and not on
10 placebo. My quality of life was quickly improving, and
11 I realized it had been several days since I last
12 coughed. I noticed that I was sleeping better, that my
13 resting heart rate was lower. I felt more rested, and
14 I had more energy.

15 At first, I thought this was a fluke, but as
16 time went on, I kept feeling better. My attitude was
17 more positive, and my wife will be happy to point out
18 that I was much less irritable. I also started to
19 notice a dramatic improvement in my exercise tolerance.
20 Before starting the trial, I did not like running. I
21 couldn't do it because it robbed me of oxygen. Four
22 weeks into the trial, I started running. Four months

1 into the trial, I ran my first 5K in 36 minutes. Two
2 weeks ago, I ran a 5K in under 30 minutes, a feat that
3 I never thought would be possible.

4 On top of the improved quality of life Orkambi
5 has given me, I've noticed that I no longer have
6 trouble keeping my weight up. In fact, I actually
7 started to get a little chubby. I have depended on
8 Kellogg shakes my entire life to help me keep my weight
9 up, and I no longer need them.

10 I also have noticed Orkambi has reduced my
11 dependency on nebulizers, and I take less enzymes on a
12 daily basis. This saves thousands of dollars for
13 insurance companies every year. Most important,
14 Orkambi has offered me the improved ability to fight
15 off illness such as colds.

16 Historically, I would have 4 to 6 colds a
17 year, one of which would inevitably trigger an
18 exacerbation and put me into the hospital for several
19 weeks. For the first time in my life, I have been
20 two-plus years without IV antibiotics. For the first
21 time in my life, I feel healthy. I feel confident that
22 I can stay healthy, and I have a lot of hope for the

1 future.

2 All of these wonderful improvements to my
3 daily living have been a result of Orkambi. This drug
4 has given me new life, but on paper, you would never
5 know it. Prior to this study, my baseline FEV1 was
6 62 percent. After the six months study, it was
7 67 percent. That's a mere 5 percent improvement. My
8 best recorded lung function of 70 percent did not come
9 until late summer of 2014, which was well after the
10 trial had concluded.

11 You cannot expect that a drug is going to
12 reduce or reverse 36 years of the scarring in my lungs
13 in a short six months period of time. While on paper
14 Orkambi may not have given me drastic improvement in
15 lung function, I'm here to tell you under no uncertain
16 terms, this drug has saved my life.

17 Orkambi has brought me the best quality of
18 life that I can remember. It has given me the power to
19 take control of the very disease that has always
20 controlled me. A yes vote from you today will help
21 continue this positive trend. A no vote will throw me
22 back into the prison of cystic fibrosis, a life of

1 declining health, a sentencing that I know all too
2 well.

3 When I look at my beautiful daughter, I see a
4 future of amazing events that I can only hope to be
5 around to share with her. I ask you to vote yes today
6 so I can be there to watch her graduate from high
7 school and to watch her graduate from college. I ask
8 you to vote yes today so that I can be there to walk
9 her down the aisle when the time comes that she is wed.

10 Thank you for your time, and I trust that I
11 can count on you for your vote to approve this product.

12 DR. OWNBY: Thank you very much. Will speaker
13 4 please come to the microphone and introduce yourself?

14 DR. BOYLE: Good afternoon. I'm Dr. Mike
15 Boyle. I'm a professor of medicine at Johns Hopkins.
16 I was also the principal investigator for the phase 2
17 and phase 3 clinical trials of the combination therapy
18 that we're discussing today. I've been caring for
19 individuals with CF for 18 years as director of the
20 Johns Hopkins adult CF program before recently joining
21 the CF Foundation to oversee therapeutics development.

22 While I have received support from Vertex in

1 the past for conduct of clinical trials, I'm no longer
2 active in this role, have no financial conflicts, and
3 I'm here strictly to speak on behalf of the CF
4 Foundation, and most importantly on behalf of the CF
5 patients that I see in clinic.

6 What I hope to provide today is some insight
7 into why you will hear such a sense of urgency from CF
8 caregivers, patients, and families who are speaking
9 today. It's first because despite the many advances
10 we've made in CF, the therapies that we have available
11 today are not even close to being enough to really slow
12 down the relentless progression of this disease.

13 The majority of my patients are incredibly
14 dedicated to all the many things we ask them to do.
15 They spend hours a day taking nebulized medicines,
16 pills, supplements, and doing airway clearance. Yet,
17 even when they do absolutely everything right, they
18 still experience recurrent pulmonary exacerbations that
19 require admissions to the hospital, weeks of IV
20 antibiotics, and that result in a progressive decline
21 in lung function that is the key factor in their
22 shortened life expectancy.

1 But now that we have the results of these two
2 trials, the largest ever conducted in CF, they show
3 clear benefit of the combination of lumacaftor and
4 ivacaftor in reducing the frequency of pulmonary
5 exacerbations, hospital admissions, need for IV
6 antibiotics, and a persistently improving lung
7 function.

8 So the first sense of urgency you'll hear
9 today is the CF community, patients and CF clinicians
10 such as myself asking can we please have access to
11 these benefits now. We have sick patients that need
12 them today. But I think the other sense of urgency you
13 will hear is actually not from patients, family, and
14 clinicians, but from researchers that know the CFTR
15 modulator field best.

16 We are particularly concerned about where this
17 discussion of combination therapy versus ivacaftor
18 monotherapy for F508del homozygotes is leading us.
19 That's because every laboratory studying the CFTR
20 modulators in the world agrees that a corrector such as
21 lumacaftor is needed in combination with ivacaftor to
22 see maximal effect in improving CFTR function in

1 F508del homozygotes.

2 This is not just a Vertex finding, but an
3 agreed-upon fact in every one of the dozens of industry
4 and academic CFTR labs around the world. The phase 2
5 study of which I was PI also demonstrated that
6 combination therapy is required to see maximal effect
7 on improving CFTR function as measured by change in
8 sweat chloride. And in the phase 3 clinical trials,
9 the point estimates for the clinical outcomes for
10 combination therapy are superior in every comparison to
11 monotherapy with ivacaftor alone.

12 So I'd just like to step back for a second and
13 hopefully remind us the real question we're deciding on
14 today, is not combination therapy versus monotherapy.
15 Monotherapy is not an approvable option. The truth is
16 there isn't a CFTR investigator in the world who would
17 say that ivacaftor monotherapy makes sense as the
18 approved therapy for F508del homozygous patients. So
19 the real question we're going to ask today is will we
20 allow F508del patients access now to the clearly
21 demonstrated persistent clinical benefits of
22 combination therapy.

1 As a caregiver and a researcher, I recognize
2 that the lumacaftor/ivacaftor combination is not a
3 perfect therapy. That's why we're already working on
4 the next generation with even better correctors and
5 potentiators. I also don't think every F508del
6 homozygous patient needs to immediately start on
7 combination therapy. Patients will need to work
8 together with their physicians on that. But I note
9 there are a significant number of F508del homozygous
10 patients, some of whom are my patients, that need this
11 drug combination now and really cannot afford to wait.

12 My hope is that we use the very clear results
13 from these large phase 3 clinical trials, as well as
14 the knowledge of CFTR modulators we've accumulated over
15 the last decade, to guide us in our decisions today
16 about making the known benefits of combination therapy
17 available to these patients now. Thank you very much
18 for your consideration.

19 DR. OWNBY: Thank you. Would speaker number 5
20 please come to the microphone and introduce yourself?

21 MS. LINAM: My name is Rebecca Linam. I'm 36
22 years old and was diagnosed with cystic fibrosis when I

1 was 17. In the summer of 2013, I started taking this
2 new drug. And I don't know what's called, so I've been
3 calling it the wonder drug.

4 So I started taking the wonder drug in 2013,
5 and within two days, I've noticed that I was coughing
6 less. When I did have to cough, it was more like
7 clearing my throat. I felt better. I had lots of
8 energy. So I pretty much knew I was on the real thing
9 and not a placebo. Instead of coughing every five
10 minutes, I only have to clear my throat. My lungs
11 didn't close up as quickly, so I didn't have to do near
12 as many breathing treatments just to get through the
13 day.

14 Over the next few days, my parents began to
15 ask where I was in the house because they couldn't hear
16 me coughing, and they recognize me by my cough. My dad
17 is legally blind. Sometimes in a restaurant, that's
18 how he knew where I was. He just listened for the
19 cough. Well, it's gotten a little bit more difficult
20 now because of that.

21 When I did have to cough, it did go to a
22 really dry cough, kind of like a normal person cough

1 that doesn't have CF. There were lots of people, for
2 example, in my church that coughed way more than I did,
3 and that was kind of a first. Little old ladies
4 stopped giving me cough drops to try to get me to stop
5 coughing.

6 (Laughter.)

7 MS. LINAM: A few weeks later, I flew to
8 Germany for my annual vacation, and usually flying on
9 planes makes me cough more, and it takes a couple of
10 days to get rid of not being able to do breathing
11 treatments, and it wipes me out for a day or two. This
12 time, I barely coughed on the plane. People didn't
13 look at me like I had the bubonic plague. I got to
14 Germany, and I was fully rested and didn't really have
15 to worry about spending the next two days recuperating.
16 Basically, it's made travel a lot easier for me. I
17 don't have to worry about not having a vest with me.
18 I can travel and still feel good.

19 Other things I have noticed: decreased
20 coughing, decreased sputum, little to no tightness in
21 my lungs, better absorption of food. I don't have to
22 take near as many enzymes now. Now if I take the

1 prescribed amount, I don't go to the bathroom for three
2 days. I've got way more energy. My FEV1 did increase.

3 People tell me that I look way healthier than
4 I used to. I'm now able to teach a class without
5 having to stop for a major coughing fit at least three
6 times per class, which is really good because I teach
7 in both a high school and a university setting.

8 My students tell me that they used to worry
9 about when I would cough. They would pass these
10 secretive looks to each other and kind of look like,
11 "She gonna be okay?" I used to have to use my inhaler a
12 lot of times in my classroom. I've used it twice this
13 year. I used to -- it was at least three times a day,
14 and that's in the school day.

15 I can't imagine life without this drug. I
16 don't want to go back to the way it was. Before I was
17 diagnosed with CF and started taking enzymes, I
18 realized that I must have had a stomach ache all my
19 life. Now, after taking this wonder drug, I must have
20 felt bad for 34 years of my life because now I feel a
21 lot better. This is the one drug, out of all the drugs
22 I take, that I could not live without. If I had to

1 give up any of them, this would not be it. This is the
2 one I want.

3 One reason it's so imperative to get this drug
4 on the market, if I had this when I was diagnosed at
5 age 17, my FEV1 would be a lot higher now. I wouldn't
6 have had all these symptoms and exacerbations. The
7 younger CF patients need this drug so they can live a
8 longer life. And I think that's all I had to say.
9 Thank you.

10 DR. OWNBY: Thank you very much. Would
11 speaker number 6 please come to the microphone and
12 introduce yourself?

13 DR. FLUME: Good afternoon. I'm Patrick
14 Flume. I'm a professor of medicine and pediatrics at
15 the Medical University of South Carolina in Charleston.
16 I'm a CF clinician, an investigator, and have
17 participated as a site investigator in some of the
18 trials that you've heard today. And I was the founding
19 chairman of the CF Foundation's Pulmonary Guidelines
20 Committee.

21 I'm here on the invitation of the CF
22 Foundation to represent my colleagues, CF centers, as

1 well as our patients. I've been engaged in the care of
2 CF patients for 25 years since my training. In that
3 time, we have seen the survival of our patients
4 increase from a median age of survival of 23 to about
5 41 years of age, and that represents a major
6 improvement. But our patients are dying too soon, too
7 young, and they suffer with considerable morbidity with
8 their daily symptoms and frequent exacerbations. We
9 need a new therapy, and we're discussing today a real
10 advance in that direction.

11 I am also the lead investigator and the first
12 author of the 770-104 study that you've been discussing
13 at length today. As you know, that study was designed
14 primarily as a safety trial to be added to the G551D
15 NDA application. Based on our knowledge of the science
16 at that time, we didn't really predict a response.
17 Nonetheless, there was some evidence that there was
18 CFTR presence in the cells, and so we hoped there might
19 be some clinical response that we could detect. So in
20 the study design, we added a placebo group, and we
21 added an open-label extension intended for any
22 responders.

1 I spent a lot of time with those data. I
2 carved them up every direction you could possibly
3 think, looking for any potential evidence of a clinical
4 benefit, and we didn't find one, mainly because there
5 wasn't one there. And I confess, we didn't use any
6 novel methods of analysis by eliminating patients
7 because that wouldn't hold up to peer review.

8 I've also reviewed the data that you've seen
9 today, looking at the combination study. And what we
10 have seen, what I have seen, is clear evidence of
11 benefit in these populations that we didn't see with
12 the monotherapy study, improvements in key clinical
13 parameters that are not only statistically significant
14 but I believe clinically relevant.

15 So we need a new drug, and you have the
16 ability to make that happen for our patients. So I'm
17 asking that you recommend approval of this combination
18 so that we have this to add to our current standard of
19 care for our patients. Thank you.

20 DR. OWNBY: Thank you very much. Would
21 speaker number 7 please come to the microphone and
22 introduce yourself?

1 MR. CALLANAN: Good afternoon. My name is
2 Brian Callanan. I'm the founder of the Cystic Fibrosis
3 Lifestyle Foundation and also live with cystic fibrosis
4 double-delta F508 and have been on the combination
5 therapy [microphone off -- inaudible].

6 Thank you for this opportunity to share the
7 practical side of life with CF and the potential for
8 improvements. CF is an incredibly challenging disease
9 to live with, facing constant changes and progressions.
10 I currently live with lung disease, digestive
11 compromise, and cystic fibrosis related diabetes, along
12 with the other challenges of aging, including
13 hypertension and chronic back pain from having broken
14 my back 19 years ago.

15 I'm the youngest of five boys who was
16 diagnosed with CF at birth, along with my older brother
17 who also has the same mutation. In two days, I'll be
18 turning 39 years old and have been maintaining close to
19 normal lung function with extremely hard work. In my
20 lifetime, I've dissolved [indiscernible] more than
21 215,00 pancreatic enzyme capsules and had my chest
22 pounded on more than 28,000 times by another human

1 being or a machine. For me, that equates to 28,000
2 wishes and hopes for a new medication like this.

3 I grew up in New Jersey and moved to Vermont
4 for 17 years, and now it's Miami, Florida, to pursue
5 active living and doing everything possible for a
6 better quality of life with CF. I not only believe but
7 know this combination is doing everything possible for
8 improving a better quality of life.

9 Eleven years ago, when I founded the Cystic
10 Fibrosis Lifestyle Foundation to help others do
11 everything possible for living with CF and living
12 stronger and longer lives, I've gotten to know more
13 than 700 people with CF through their essays, phone
14 calls, and emails. And I've learned very clearly that
15 we want to live. We want to grow old. We want to have
16 families and take advantage of life, and live life to
17 its fullest.

18 This treatment offers that possibility. It's
19 a game changer. I wake up in the morning and have
20 little to no rattling in my chest anymore. I can take
21 a deep breath and not cough. I can exercise and
22 breathe deeply.

1 Having broken my back over two decades ago,
2 that's not stopped me from cycling the entire east
3 coast, hiking more than 50,000 vertical feet in a
4 single winter, and swimming more than 3 consecutive
5 miles in the ocean. But recently when my back went
6 out, it landed me in the emergency room. I had to stop
7 all exercise. The congestion set in almost
8 immediately, along with risk of infection, anxiety,
9 fear, and fatigue.

10 Two weeks later, I had started on the
11 combination therapy, and two weeks after that, my lung
12 function had jumped from one of its lowest scores at
13 82 percentile FEV1 to my third highest score of
14 88 percentile FEV1, without exercise. With this
15 technology, it's now feasible to have a procedure to
16 fix my back and to get out from under two decades of
17 chronic pain. I feel like between this medicine and
18 allowing a procedure like that, I potentially have a
19 new life ahead of me.

20 Others are just hanging on for this. My
21 brother has had consistent lung function decline over
22 the past few years. I pray for this medication for his

1 life. He needs it now. I pray for the tens of
2 thousands of other people that also are hanging on for
3 this, and for the countless unborn children with CF who
4 could face life without as many hospitalizations, IVs,
5 sicknesses, or losses, children that could one day work
6 for the FDA, solve childhood hunger, or lead to world
7 peace.

8 This drug is a game changer. I know how it
9 works from being on it. I feel like for once in my
10 life I have normal lungs. Thank you for your time.

11 DR. OWNBY: Thank you very much for your
12 comments. If we could have speaker number 8 come to
13 the microphone and introduce yourself.

14 MR. WYNN: My name is Michael Wynn. I have no
15 financial attachment to anything associated with this
16 committee. I'm a firefighter/paramedic from Fort
17 Worth, Texas. As you know, there are 30,000 diagnosed
18 cystic fibrosis patients in the United States, and I'm
19 the father of one of them.

20 At the time of my son's birth, his mother and
21 I lived in our modest apartment in a sleep-deprived but
22 happy delirium that any new parent can relate with.

1 Those were a happy three weeks. When he was 19 days
2 old, we were awoken during a nap by a phone call. I
3 remember the way his mother snapped to a sitting
4 position in a way that was very uncharacteristic. I
5 waited until the phone call was over to ask what it was
6 about. She had already started crying and said that
7 the call was from our local children's hospital, and
8 that the newborn screening for our son had identified
9 abnormalities consistent with cystic fibrosis.

10 We went that afternoon to the clinic, myself,
11 his mother, and my parents. I'm not sure why, but I
12 had assumed that they had a suspicion that he might
13 require further testing or that perhaps it was a false
14 positive. I was told very frankly that that was not
15 the case.

16 In that moment, I knew that my life was about
17 to drastically change. I knew that his mother and I
18 would not have more children as we had hoped. I also
19 knew at that moment that I would eventually outlive my
20 only son. This is not something a parent should have
21 to come to terms with when their child is three weeks
22 old, but this is the hand we were dealt, and we've

1 played it just as well as we can.

2 Without a frame of reference, it's difficult
3 to convey how being a CF parent differs from being a
4 regular parent. I'm sure the members of this committee
5 are familiar with some of the cystic fibrosis
6 treatments and the time-consuming daily schedule. At
7 one point, my son Jack had to be admitted for a
8 month-long feeding program to teach him to eat again
9 after developing an oral aversion from being tube fed
10 most of his life to maintain his weight. That month
11 was easily one of the most difficult hospitalizations
12 we've ever endured.

13 The prospect of more future hospitalizations
14 loom over our heads. We average at least one a year,
15 and I expect the number to increase as he grows, or at
16 least I did until I heard stories about the drug trial
17 results of the therapy in question today and others
18 similar to it.

19 We are constantly fighting to gain ground and
20 keep it, against maintaining weight, preserving lung
21 function, and while performing a balancing act to try
22 and let him grow up as a regular kid if possible. I

1 believe that with this new therapy, he'll have a chance
2 to be just that.

3 According to a quick Google search, the
4 average public speaker speaks about 150 words per
5 minute. I traveled 1400 miles to say 600 words to this
6 committee in hope that I might be repaid in precious
7 minutes, hours, days, and years to my son's life. I
8 believe that in his lifetime, we can make the giant
9 leap from living with a chronic disease to flourishing
10 with a manageable one. Thank you for your time.

11 DR. OWNBY: Thank you very much for your
12 comments. Would speakers number 9 please come to the
13 microphone and introduce yourselves?

14 MS. ROLING: I'd like to direct your attention
15 to the slides while we speak. I am Michelle Roling. I
16 am here today with Alex, my 19-year-old,
17 double-DF508er, and I know his 16-year-old CF brother
18 wishes he were here with us. We are advocating that
19 the panel recommend approval of the Vertex combination
20 drug to the FDA. We are often asked what's it really
21 like for you. Most of the time, we try not to think
22 about the reality of it. It's just too painful. Most

1 of the time, our family works really hard to focus on
2 the joys, the uplifting moments, scientific
3 breakthroughs, and hope.

4 MR. HALL: Today, however, we want you to
5 really understand what our lives are like and see how
6 improving the dual medication will make a difference.

7 MS. ROLING: I had a short 12 weeks of being
8 your typical new mom before the words cystic fibrosis
9 entered my life. I knew in that moment it would never
10 be the same. I had entered a maze, a maze where CF is
11 the monster hunting my boys, our family. The maze is
12 always changing. And just when we are lulled into a
13 sense of security, believing that if we follow the
14 rigid routine, if we're organized enough, focused
15 enough, careful enough, if our house and medical parts
16 are cleaned with obsessive compulsive detail, and we
17 never ever let up, just maybe the monster will stay
18 sleeping a while, and we can enjoy the journey.

19 MR. HALL: During the good time, we forge
20 ahead in the maze, fully taking on life: sports, fine
21 arts, academics. Go, go, go. Yet we find ourselves
22 peeking around corners. Not a day goes by without

1 moments of fear or anxiety bracing for the monster in
2 waiting, scared for the next battle. We are never
3 ready for the monster to grab us. When he grabs hold,
4 my hold life gets put on pause. The world keeps moving
5 forward, yet I am stuck. I'm helpless. I can never
6 get enough air or a full breath. I cough and cough.
7 My sides are aching. My chest contracts, refusing to
8 expand. I solemnly wonder if this is the time I won't
9 get better.

10 MS. ROLING: Over the years, my mom battle
11 with the monster has changed from standing over cribs
12 watching them breathe and beating their torsos for
13 chest PT to so many charts and medication routines.
14 Even if this dual meds simply froze my boys' current
15 health level, it would be a miracle.

16 I have tried all communication styles with
17 this monster, praying, whispering, writing,
18 negotiating, yelling, screaming, shouting. Nothing can
19 stop him. The chaos kicks in, the maze completely
20 changes, and we are thrown through the trap door. I
21 cringe with each deep cough. The gagging fills my
22 heart with fear. Everything except fighting the

1 monster gets put on hold. Family time is hospital
2 bedside time. Dinner, homework, holidays all happen
3 there. The whole family takes the hit. We are
4 helpless. How long will the monster rage and what
5 damage will he inflict?

6 MR. HALL: In the last 12 months, my brother
7 Shane has missed 61 days of school, and I have given
8 myself 130 home IV treatments.

9 MS. ROLING: Team Hall always rallies. We do
10 whatever it takes. We fight the monster. We advocate,
11 fundraise, educate. Dollars means research; research
12 creates miracles. Today we are begging you, help
13 change the maze for my boys and all those 12 and older
14 living with the double-delta F508.

15 MR. HALL: My brother and I are counting on
16 you to approve this miracle. Thank you.

17 DR. OWNBY: Thank you very much for your
18 comments. Would the speakers speaking as the 10th
19 speaker please come to the microphone and introduce
20 yourselves?

21 MS. KRENDRICH: My name is Stephanie Krenrich.
22 I'm a designee for Aaron Stocks.

1 (Video played and transcribed.)

2 MR. STOCKS: [In progress] -- "ivacaftor and
3 lumacaftor, the combination clinical trial. I'd first
4 like to say thank you for allowing me this opportunity.
5 Having CF has been an interesting experience for me. I
6 remember being very sick as a child, sometimes spending
7 weeks and even months in the hospital, and my lung
8 function sometimes reaching 50 percent. But unlike
9 most people with CF, as I got older, I got better. My
10 lung function and my overall health gradually increased
11 over time.

12 "Two years ago when I was strongly encouraged
13 to enroll in this clinical trial, I never could have
14 imagined what was going to become of my health. At the
15 time, my lung function was in the low 80's and I
16 weighed 162 pounds. Before it began, my wife and I
17 were told to hedge our expectations because we didn't
18 know if it was going to produce the same results as
19 Kalydeco.

20 "It was about two weeks after I started the
21 medicine that I knew that I was not receiving the
22 placebo. One of the indicators that I knew the drug

1 was working is that I've always had frequent stomach
2 pain, and I've always had difficulty gaining weight.
3 After a few short weeks, I couldn't recall the last
4 time I had had stomach pain, and all of a sudden, I had
5 gained 5 pounds.

6 "But the strongest indicator was one evening
7 on a Tuesday when Brady and I got home from work. I
8 decided to go for my evening run taking the same route,
9 which is approximately 1 mile. I had gotten back to
10 the end of our driveway, and I couldn't help but
11 freeze. All I could do is smile and cry. I had never
12 felt anything like this in my entire life, no shortness
13 of breath. That night I put in two more miles.

14 "My lung function now has reached the low
15 90's, and I weigh 172 pounds. This medicine didn't
16 meet our expectations, it exceeded them beyond anything
17 that I ever could have imagined. As an adult with CF,
18 I've always felt ok, but now I feel incredible. I feel
19 like I can accomplish anything. This medicine has
20 given me the opportunity to do something that all CF
21 patients desperately want and cherish, to live a normal
22 life.

1 "I'm no longer afraid to start a family. I'm
2 not terrified that someday I'll leave my wife and child
3 abandoned. I'm not afraid that someday I'll have to
4 have a conversation with my child about what horror
5 this disease can bring. This disease is no longer a
6 distraction for me at work. Someday I will be able to
7 leave my mark and in 30 years that I've made a
8 difference in the world.

9 "For me, the most terrifying thing about
10 having cystic fibrosis is its unpredictability, and
11 that even though I've put everything that I have into
12 beating this disease, it might not be enough. I
13 remember the pain this disease can bring, the pain in
14 my chest when I cough not wanting to eat because I know
15 in a few hours it was only going to bring me pain; not
16 wanting to celebrate another birthday because that
17 means one year closer to how long I'm expected to live.
18 That no longer is true. My biggest nightmare is that
19 the way that I feel today could possibly be taken away
20 from me.

21 "My family and I recognize that this drug is
22 not a cure. Someday there will be a cure for cystic

1 fibrosis. Whether that's going to happen within my
2 lifetime, I don't know. But what I do know is that if
3 it isn't created during my lifetime and this drug is
4 approved, I will be able to live a meaningful life and
5 accomplish everything that I've ever wanted to with no
6 regrets. Thank you so much for this opportunity."

7 DR. OWNBY: Thank you very much. Would
8 speaker number 11 please come to the microphone and
9 introduce yourself?

10 MR. PISTONE: Good afternoon. My name is
11 Corey Pistone, and I have cystic fibrosis. I'm the
12 23-year-old patient that Dr. Konstan talked about, the
13 one who is losing 3 percent of his lung function every
14 year and spends a lot of time on IV antibiotics.
15 That's me.

16 I wanted to come here in person and tell you
17 my side of the story, how CF impacts my life, and why
18 I'm anxious to have a new therapy like
19 lumacaftor/ivacaftor for treating my CF. I was
20 diagnosed with cystic fibrosis at birth due to a bowel
21 obstruction. I've had many struggles throughout my
22 life, including several surgeries, many

1 hospitalizations, and several life-threatening lung
2 infections.

3 Both my lung disease and nutritional status
4 have markedly affected my life. I spend several hours
5 every day doing my vest therapy and taking aerosols. I
6 also take many other medications, including enzyme
7 pills every time I eat. I get tube fed, and even
8 that's not enough to keep my weight on. I weighed
9 98 pounds this morning, and that was after I ate at the
10 all-you-can-eat buffet at the hotel. That's pathetic
11 for a 23-year-old man.

12 Last year, I was diagnosed with CF related
13 diabetes, and now I have to take insulin every day. My
14 daily treatment regimen is very time consuming and
15 interferes with my ability to spend as much time with
16 my family and friends as I would like to, doing all the
17 fun things in life that people without CF can do, and
18 that's when I'm presumably healthy.

19 When the infections of my lungs get out of
20 control, Dr. Konstan gives me IV antibiotics. Every
21 year, this seems to get worse and worse. Just last
22 month, I was hospitalized for three weeks, and that was

1 after being treated at home for two weeks. I could
2 barely walk up the steps to my bedroom. I knew it was
3 time to go in the hospital.

4 Over the past year, I've been hospitalized
5 four times for lung infections and had IV antibiotics
6 several more times at home. Every time I go in the
7 hospital, I fear I may lose my job. I love to cook and
8 work as a chef. My boss is understanding, but how much
9 longer I do not know.

10 Even with all this therapy, I'm lucky to keep
11 my lung function in the low 40's, and that's not very
12 good. I desperately need new therapy to keep it from
13 going any lower.

14 I wish I had been eligible to participate in
15 the lumacaftor/ivacaftor trials because I might have
16 gotten a head start on stabilizing my lung disease and
17 staying out of the hospital. I now hope you will give
18 me a chance to do that. I have an awful lot to live
19 for.

20 When I was diagnosed with CF, my parents were
21 told I might not live long enough to become an adult.
22 But with all the advances in CF care, I was not only

1 able to graduate from high school but from college.
2 Almost two years ago, I married my high school
3 sweetheart, and we are now living on our own, anxious
4 to buy a house and start our own family. But if I
5 don't get help, and soon, my goals may not be achieved.

6 The sooner this drug becomes available for use
7 by CF patients, the better. Our lives depend upon it.
8 Thank you for your consideration.

9 DR. OWNBY: Thank you very much for your
10 comments. If we could have speaker number 12 come to
11 the microphone and introduce yourself.

12 DR. ACCURSO: I'm Frank Accurso. I'm a
13 pediatric pulmonologist, professor of pediatrics at the
14 University of Colorado based at Children's Hospital
15 Colorado. I am a site investigator on several Vertex
16 clinical trials, but I have no other financial
17 relationships with them, and I own no individual
18 stocks.

19 I've been involved in the care of individuals
20 with cystic fibrosis for more than 40 years, and it is
21 my job to review with families what happens to the
22 lungs in CF. And in that context, a mother once said

1 to me, "Do you mean we have to fight for every ounce of
2 lung?" And I responded, "Yes, exactly right." And
3 that is what the individuals with CF and the families
4 do, fight for every ounce of lung, hours a day, every
5 day. They also experience exacerbations as you have
6 heard, and there is substantial literature on the
7 deleterious and even devastating effects of
8 exacerbation medically, psychologically, financially.

9 The family stressors are enormous during
10 exacerbation. I'll give you an example. We have a boy
11 in now who's a middle-schooler, and his mother is a
12 single mother. She wants to be there for every
13 procedure, talk to the caregivers, and yet she has
14 another child with CF at home, and a third child
15 without CF. She's trying to maintain a job with all
16 this.

17 The CF Foundation patient registry tells us
18 that exacerbations are as common in adolescents as they
19 are in adults. We frankly have to find a way to
20 decrease exacerbations. You have before you today
21 consideration of Orkambi, which is a drug that improves
22 lung function in a sustained manner over many months.

1 It improves lung function across many subgroups. It
2 also affects exacerbations. And to my clinicians, the
3 exacerbation data frankly looks terrific. I know there
4 are hierarchical questions, statistical questions, but
5 it still looks like something great.

6 The group of people with CF that Orkambi is
7 proposing to treat, those with delta F508 homozygosity,
8 are a very vulnerable group. And just to echo that
9 mother, we have to do everything we can to maintain
10 every ounce of lung function. There is no guarantees
11 that any of the treatments in development, or for that
12 matter, ivacaftor alone, will have the same consistency
13 and safety profile as Orkambi. I'm particularly
14 impressed with the loss of pulmonary function effect in
15 the ivacaftor-alone trial in terms of the follow-on
16 study.

17 I guess I'm in favor. I believe that we need
18 approval of Orkambi now, and we cannot wait. Thank
19 you.

20 DR. OWNBY: Thank you very much. Would
21 speaker number 13 please come to the microphone and
22 introduce yourself?

1 MS. BONNELL: Hi. My name's Laura Bonnell,
2 and I started the Bonnell Foundation: Living with
3 Cystic Fibrosis five years ago. We do everything from
4 CF college scholarships to lung transplants, and we do
5 these inspirational cystic fibrosis calendars that
6 always features my daughters on the cover.

7 Joe and I have two daughters with cystic
8 fibrosis. They both have the delta F508. Molly is 20
9 and at the college in New York, and Emily is 17 and
10 will attend college in the fall in our home state of
11 Michigan. "Everybody has something," I always tell the
12 girls, "and we have CF." As a mom, I hope and pray for
13 a cure every day, and I don't believe we will see one
14 in their lifetime, but I do believe that the
15 medications that Vertex have already put in the
16 pipeline and the real promise of powerful ivacaftor and
17 ivacaftor and lumacaftor almost at the finish line are
18 crucial to my girls' healthy future.

19 We talk about the girls living to be 90 year
20 after year, but also discuss the reality of them dying
21 before both of us. We talk about how they want to be
22 buried and what music we should play loud at their

1 funeral. But then along comes Vertex Pharmaceuticals.
2 They're making great progress with a number of drugs.
3 Ivacaftor and lumacaftor can extend my girls' lives by
4 keeping them healthy.

5 I ask you all to thank of Molly and Emily and
6 all the parents who want their kids to live long lives
7 and approve the drug therapy that can greatly improve
8 their lung function. I have prematurely told them to
9 celebrate this victory because I will believe that you
10 will not let them down. We all have to do our part so
11 that one day, no parent will know the pain of losing a
12 child to this horrible disease.

13 Now, I'm going to read you Emily's note
14 because she couldn't come. She had an AP test today.
15 She says, "My name is Emily. I am 17 years old, and
16 I'm living with cystic fibrosis in Michigan. I've been
17 in and out of the hospital, missing all sorts of school
18 trips and family gatherings over the years due to CF.
19 I've come to terms with all that is CF and with my life
20 expectancy. CF might end my life at a young age even
21 though doctors say I can have a normal life.

22 "Eventually, my lungs, liver, and pancreas

1 malfunctions will catch up with me. The real reason I
2 need this drug passed is for my parents."

3 (Pause.)

4 MS. BONNELL: Thank you. Sorry.

5 "My mother is so positive," she says, "too
6 positive for her own good. The first time I talked to
7 her about dying, she told me that I wasn't going to die
8 young, that everything would be fine. A cure would
9 come or a life-changing medication. As the years went
10 on and there were a few close calls, I talked to my mom
11 about my early death, and she would say that it wasn't
12 going to end this way, but that she would listen to my
13 last wishes anyway. And that was the crappiest feeling
14 in the world, talking about my death with my mom.

15 "No matter how hard I try, no matter how often
16 I run, and how strongly I believe that I can beat this,
17 my body denies me, and my mother could end up losing
18 her daughter. That kills me more than this disease,
19 causing my mom the pain of not being able to help me
20 the way she wants and having to cope with the fact that
21 our time together might not be long enough.

22 "If there is a chance for me to expand my

1 lifetime, I need to take it, not only for myself but
2 for my family. This drug could help me, my sister, and
3 other people with CF. I love my life, and although I
4 wish I didn't have cystic fibrosis, I accept the cards
5 I was dealt. I am great, and I am strong, and I am
6 asking all of you to approve this drug. Thank you.
7 Emily Bonnell."

8 Thank you.

9 DR. OWNBY: Thank you. Would speaker
10 number 14 come to the microphone and introduce
11 yourself?

12 MS. GOVERNOR: I'm Anne Governor, 35 years old
13 with the double-delta F508 mutation. I was diagnosed
14 with cystic fibrosis when I was 18 months old.
15 Wonderful health care, rigorous daily treatment
16 schedules, and a big dose of good luck allowed me to
17 live a relatively normal childhood. I was hospitalized
18 just twice at the ages of 8 and 9 for IV antibiotic
19 treatments and sinus surgeries. I went on to earn my
20 bachelor's degree, hold a full-time job, get married,
21 and start a family.

22 2008 marked the start of an aggressive

1 downward spiral. My intense daily routine of inhaled
2 medications and various forms of physical therapy to
3 loosen and rid my lungs of the thick mucus were no
4 longer an act to keep me healthy. I took handfuls of
5 various supplements to help my body and immune system
6 fight the raging infections in my lungs. Despite
7 high-calorie meals taken with 10 enzyme pills to aid
8 digestion, my weight continued to fall.

9 I had to increase my already aggressive airway
10 treatment schedule to 4 to 6 hours a day. I spent
11 hours on end coughing until I would vomit. My head
12 pounded in pain with each body-rattling cough. I was
13 literally drowning in copious amounts of mucus each
14 cough brought from my lungs. The little sleep I could
15 get in between coughing fits was not nearly enough to
16 sustain my body. I spent hours on the bathroom floor
17 coughing. The bathroom door provided some
18 soundproofing against my incessant cough so my family
19 could sleep at night.

20 My life was slipping away. I could no longer
21 keep up with everyday activities. It took every ounce
22 of my strength to help get our daughters off to school

1 in the morning. My husband had to adjust his work
2 schedule to accommodate my failing health. Family and
3 friends were on call in the event I needed to be
4 hospitalized. Every day brought tremendous physical
5 and emotional trials.

6 I started requiring quarterly IV antibiotic
7 treatments lasting 2 to 3 weeks. The antibiotics would
8 give me two weeks of improved quality of life before
9 the cough would return and slowly overtake every moment
10 of my life. Walking up the stairs became a challenge.
11 Walking across the room was a challenge. I carefully
12 planned outings around my treatment schedule. My cough
13 tormented me in public. My lung function no longer
14 increased in response to antibiotics. Despite these
15 challenges, I continued to fight, doing everything
16 possible to maintain what little bits of normalcy
17 remained in my life.

18 I enrolled in phase 3 clinical research trial
19 of lumacaftor and ivacaftor. On day 3 of the trial,
20 for the first time in seven years, I slept through the
21 night, never once waking to cough. My once incessant,
22 productive morning cough weakened to an occasional

1 non-productive clearing of my throat. I marveled at my
2 lack of coughing. Cystic fibrosis coughs don't just
3 disappear.

4 I am 77 weeks since the open-label phase of
5 this clinical research trial, which has been
6 life-changing. Since entering open label, I've gained
7 nearly 20 pounds. My lung health has improved. I
8 rarely cough. I no longer gasp for every breath. I'm
9 not drowning in my own mucus. I have caught colds and
10 viruses from my school-age daughters, and I've
11 recovered on my own without the need for antibiotics.

12 In the past 77 weeks, I have trained for and
13 completed to half marathons. I have traveled without
14 fear of exhaustion or getting sick away from home. I
15 have taken on numerous volunteer positions,
16 contemplated reentering the workforce or perhaps
17 returning to school for my master's degree.

18 Before lumacaftor and ivacaftor, I never
19 allowed myself to think of the future. Thanks to my
20 involvement in this clinical research study, I now
21 dream of my future, seeing my daughters graduate high
22 school and college, retirement with my husband,

1 traveling, and growing older together.

2 Every cystic fibrosis patient deserves a
3 chance to dream of the future, a future of improved
4 health, a future not marked by unrelenting coughs and
5 uncontrollable lung infections. Lumacaftor and
6 ivacaftor have the potentials to allow others like me
7 hope and promise for a better day to come. Thank you.

8 DR. OWNBY: Thank you very much. Would
9 speaker 15 please come to the microphone and introduce
10 yourself?

11 MS. DWIGHT: [Inaudible - microphone off.]

12 (Video played and transcribed.)

13 MS. BONNER: "While I would not necessarily
14 call it a secret, it's nothing I'm ashamed or
15 uncomfortable discussing, only a handful of people
16 outside of my family are aware that I have cystic
17 fibrosis. Most people are surprised that I even have
18 such a disease, so I must be doing something right. My
19 entire family and I have worked tirelessly to keep me
20 healthy all these years. So far, I think we've
21 succeeded.

22 "I was surprised the first time my clinic

1 doctor playfully told me, 'You don't have CF,' after
2 examining me. Now I love hearing it every time.
3 That's the kind of track record I want to maintain, but
4 it takes a lot of work to do so. I get the feeling I'm
5 not alone when I say having CF has made me one heck of
6 a multitasker and takes me two and a half hours to get
7 ready in the mornings. And that's on the days that I
8 don't work out before I leave the house. I've become
9 proficient at putting on my makeup, coiffing my hair,
10 getting dressed, all with a nebulizer in my mouth and a
11 pulmonary vest beating around my chest.

12 "I'd been following the Vertex study for a
13 long time, and I knew I wanted to be a part of it.
14 Incorporating the study drug into my system made for a
15 lot of changes. I could no longer wolf down copious
16 amounts of food before feeling full, and actually had
17 to pace myself for the first time in 25 years of
18 enforced dietary access. I even began gaining weight
19 almost immediately after being the same 125-pound bean
20 pole for over a decade.

21 "But the best part was that I could breathe.
22 I would cough and mucus would actually shake loose. My

1 lungs felt like they were systematically ridding
2 themselves of caked-on gunk that had been there for
3 years. Different parts of my chest were filling with
4 air, and I realized I'd never felt those portions of my
5 lungs before. I'd never breathed so deeply. And when
6 I worked out, my muscles would tire before my lungs
7 did.

8 "If you look at my numbers from my pulmonary
9 function tests, you can see exactly what I've been
10 experiencing all this time. Over the past year, my
11 FEV1s and FVCs have both risen nearly 9 percent, and my
12 BMI has increased from 18.5 to 20, which translates to
13 a solid 6 or 7 pounds that I could never gain before.
14 I'm sick less often now, too. With more of that mucus
15 out of my system, there's less opportunity for bacteria
16 to linger in my body, and I've taken fewer oral
17 antibiotics, missed less work, skipped fewer social
18 outings, and worked out more since starting the study.

19 "No, being in the study does not reduce the
20 number of drugs I take or the time it takes in the
21 morning to medicate and get my mascara on straight.
22 But now I can tell the difference if I accidentally

1 miss a treatment because the Vertex study drug makes me
2 feel so much better that the maintenance makes a
3 meaningful difference. I'm not just going through the
4 motions, watching my numbers slowly decline over the
5 years as my body tries to compete with the inevitable.
6 Now I watch my numbers go up at the doctor's office. I
7 can feel the difference for the first time in my life,
8 and I actually seem to be getting better for once, not
9 worse.

10 "The average across the board may be an
11 approximate 3 percent increase in pulmonary function
12 numbers, and my nearly 10 percent increase may be less
13 of a widespread trend. But I remember how amazing that
14 3 percent felt when I started this study, and I relish
15 those 7 additional percentage points every single day.

16 "When you go from breathing at 50 percent of
17 the normal healthy adult level to 53 percent, you feel
18 the difference with every breath you take. I don't
19 want a single person eligible for this drug to be
20 denied the chance to feel that 3 percent or greater
21 difference. I don't want future generations of people
22 who will benefit from the drugs that follow this one,

1 because of this one, to miss out on that incredible
2 feeling. And they deserve to begin benefiting from it
3 as soon as possible so they, too, can be sick less
4 often and feel healthier on a daily basis.

5 "If someone told you that someday, just by
6 taking 9 pills a day, you could be 3 percent happier,
7 3 percent healthier, or live 3 percent longer, wouldn't
8 you ask them to hurry up with those pills and to grab
9 you a tall glass of water to help wash them down?"

10 DR. OWNBY: Thank you. Would speaker
11 number 16 please come to the microphone and introduce
12 yourself?

13 MS. McNULTY: Hi, everyone. My name is
14 Jillian, and I'm from Ireland. I attend Saint
15 Vincent's University Hospital in Dublin under the care
16 of Dr. Ed McKone and Professor Charlie Gallagher. When
17 I started Orkambi in July 2013, I was hopeful. I was
18 hopeful that it would stop the sharp progression that I
19 was going through. In the year before I started
20 Orkambi, my lung functions had dropped to a massive
21 20 percent. I was in a sharp decline.

22 Roll forward to now, May 2015, and I have to

1 say that this drug is just incredible. The impact it's
2 had on my life has just been remarkable. I can't
3 actually put into words what it's done for me. Just a
4 few things that I want to point out. Now, on the drug,
5 I no longer need medical intervention with colds or
6 flus. Pre-Orkambi, I would have needed
7 hospitalization, IV antibiotics. I've had four or five
8 colds since I started the drug, and I haven't needed
9 any hospitalizations due to them.

10 Another major factor for me was pre-drug I had
11 chronic sinusitis, which meant I needed daily nasal
12 rinses and two to three different sprays in order to
13 try to keep on top of things, but it was just a vicious
14 cycle. It was constant. Now I know longer need nasal
15 sprays or daily nasal rinses. I don't need anything.
16 My sinuses are perfect.

17 I also suffered quite badly from DIOS, which
18 is bowel obstruction. Pre-drug, I would have needed
19 daily laxatives in order to try and keep on top of
20 things, but again, it was just constant. It was pain.
21 It was agony the whole time. Now, I rarely have a
22 bowel blockage. I no longer need daily laxatives in

1 order to keep on top of things. I'm just normal.

2 Another really significant thing for me is my
3 energy levels. Pre-Orkambi, a simple or 3-hour car
4 journey would have left me exhausted. I wouldn't have
5 been able to do anything. I would have had to sleep in
6 the car on the way to a destination. Now I can get up
7 at 5 or 6 in the morning, travel 2 or 3 hours, spend
8 all day on my feet, travel back home, and I'm normal.
9 I'm not exhausted. I don't need to collapse into bed
10 from pure tiredness.

11 The most miraculous thing for me is my
12 hospitalizations have literally halved. Pre-Orkambi, I
13 would have been in the hospital anything between 24 and
14 30 weeks every single year of my life. My
15 hospitalizations came every 4 to 5 weeks. I was lucky
16 if I got 6 weeks out of hospitals. In the last year
17 alone, I've spent just 11 weeks in the hospital.

18 I'm going to get all emotional now because I
19 can't actually imagine my life pre-Orkambi. It's made
20 such a difference to me. It's given me back a quality
21 of life that I never, ever, ever thought possible. So
22 I appeal to every one of you on the panel to please,

1 please approve this drug. There are so many people
2 worldwide just waiting for this, so many people that
3 are desperate for this. And they're all watching today
4 in the hope that you approve the drug. Thank you.

5 DR. OWNBY: Thank you very much. Would
6 speaker number 17 please come to the microphone and
7 introduce their self?

8 MS. HONAKER: Hi. My name is Meranda Honaker.
9 I'm 32 years old, and I have cystic fibrosis. I've
10 been enrolled in the eight or nine 770 studies since
11 October 2013. Prior to enrolling in the study, I was
12 facing my fourth invasive sinus surgery. I was packing
13 my face in ice packs every day because my head hurt so
14 bad, I couldn't even stand the light coming in the
15 windows. Within one week of starting this combination
16 therapy, my migraines completely disappeared. Nothing
17 else changed in my regimen other than starting this
18 study.

19 Within the two years of being in this study,
20 I've only needed IV antibiotics once. In the two years
21 leading up to this study, I spent 2011 in and out of
22 the hospital. I almost died from massive pulmonary

1 artery hemoptysis. My lungs began hemorrhaging blood
2 because of years of bronchiectatic damage caused by
3 cystic fibrosis. That was the most traumatic thing
4 I've ever been through with CF, and I was on a fast
5 progression and declining very quickly.

6 By 2012, I was in and out of the hospital. I
7 couldn't even unpack my bags when I got home before I
8 had to go right back to the hospital because of getting
9 sick and coughing up more blood. In 2013, once I
10 enrolled in this study, my hemoptysis has not been
11 significant. In fact, I've only had maybe two or three
12 very minor episodes of hemoptysis, none of which would
13 have been bad enough to claim my life.

14 My exacerbations have dramatically decreased.
15 I've not needed sinus surgery since enrolling in this
16 study. I do continue on my normal maintenance
17 therapies with CF. My quality of life has dramatically
18 improved. In fact, I've taken my first and second
19 plane rides since being in this study, which I would
20 not have done previously because I was so sick. My
21 first one was to a CF conference, and my second one was
22 for this today. So I think that speaks volumes to the

1 confidence of improvement in health that I've had with
2 this study drug.

3 My family noticed a huge improvement in me
4 before I was willing to admit that, yes, I felt better.
5 More energy. I wasn't sick as often. My family could
6 find me in stores because I was coughing my head off.
7 Instead it was silent, so I could go missing without
8 anyone really noticing.

9 I'm very grateful to be in this study, and I
10 feel like if I had not enrolled when I did, I could be
11 waiting on a lung transplant. I had actually spoken to
12 a doctor at Duke Hospital about a possible lobectomy to
13 remove my left lung because of repeated episodes of
14 hemoptysis. I no longer need a lobectomy. That's not
15 even a consideration. My lung function's in the 80's,
16 and I've been very grateful to be enrolled in this
17 study.

18 I do ask that the FDA please approve these
19 drugs because they will prolong many lives, including
20 people that I love and care about who also suffer from
21 CF. If these drugs have been able to help me in such a
22 way, I believe the generations coming after us and

1 children who are younger than me may not ever have to
2 endure the things that us older generations with CF
3 have. Thank you.

4 DR. OWNBY: Thank you very much. We have
5 speaker number 18. Would you come to the microphone
6 and introduce yourself, please?

7 MS. MONSON: My name is Samantha Pelican
8 Monson, and I'm here representing myself as a
9 33-year-old cystic fibrosis patient homozygous for the
10 delta F508 mutation. Breakthrough therapy, statistical
11 significance, responders, these are words that I have
12 heard in reference to the lumacaftor/ivacaftor clinical
13 trial over the last two years. From a scientific
14 standpoint, they are meant to be descriptive and
15 informative. But from a patient's standpoint, they are
16 the stuff dreams are made of.

17 For my entire life, I have been dreaming of a
18 medical breakthrough that would change what it means to
19 live with this disease, but this dreaming has been far
20 from idle. I work in incredibly hard every day to stay
21 healthy. I do an hour of respiratory treatments every
22 morning and every night. I take pills to digest my

1 food, inject insulin, get prescribed exercise, and the
2 list goes on and on.

3 I've been doing all of this since I was
4 diagnosed with CF at 18 months old. And yet, despite
5 what my CF doctors refer to as fastidious adherence to
6 this complex regimen, it has never been enough. CF is
7 a progressive disease, and particularly as I grew into
8 adulthood, it started really taking its toll.

9 Living amidst that profound helplessness is in
10 sharp contrast to what I have experienced since
11 starting the lumacaftor/ivacaftor clinical trial. My
12 childhood room had a large poster on the wall that
13 boldly featured the words "Miracles happen." Not
14 knowing at that time if I myself would ever experience
15 a miracle, I can now proudly say that I have
16 experienced two. The first was carrying to term not
17 one but two perfectly healthy twin babies. The second
18 has been my participation in the lumacaftor/ivacaftor
19 clinical trial. The stories of these two dreams that
20 have been realized are inextricably intertwined. Both
21 are miracles.

22 The year following the birth of my son and

1 daughter brought an onslaught of health challenges. My
2 gradually decreasing lung function was non-responsive
3 to IV antibiotics. And before too long, I caught an
4 infection, which turned into a full exacerbation. I
5 had fevers of 105, lost all my energy, and every time I
6 breathed, it felt like I was inhaling a wild fire's
7 worth of smoke.

8 It took five different IV antibiotics and a
9 month of intensive respiratory treatments before I was
10 even able to return to my disappointing baseline. My
11 heart broke as I thought of my two young children who
12 had watched me go through this, and I was terrified
13 that the next exacerbation was right around the corner.
14 But that next exacerbation never came because shortly
15 thereafter, I started the lumacaftor/ivacaftor clinical
16 trial.

17 Over several months, my FEV1 values rose twice
18 that required to be considered a responder. They have
19 remained at this new baseline for nearly a year. I
20 have weathered two virus seasons without a blip, let
21 alone an exacerbation. My insulin requirements have
22 dramatically decreased, and my BMI has risen to goal.

1 All of these incredible facts amount to a
2 lifetime of dreams being realized. They amount to a
3 miracle. As long as I have lumacaftor and ivacaftor, I
4 no longer have to anticipate my regular CF appointments
5 with dread. My downward trending lung function has
6 been reversed. I don't have to fear that the next cold
7 that I get will end in a hospitalization because my
8 body is now strong enough to recover on my own. And I
9 don't panic thinking about my children asking me, "What
10 does it mean to have CF?" because I believe that CF is
11 soon going to be history.

12 I hope my story has demonstrated why approving
13 the lumacaftor/ivacaftor combination medication will
14 help not only me but thousands of CF patients like me
15 realize our dreams of a scientific breakthrough,
16 changing the trajectory of our disease. This approval
17 would safeguard a miracle for us all. Thank you.

18 DR. OWNBY: Thank you very much. The open
19 public hearing portion of the meeting has now been
20 concluded, and we no longer take comments from the
21 audience. The committee will now turn its attention to
22 address the task at hand, the careful consideration of

1 the data before the committee, as well as the public
2 comments.

3 Dr. Chodakewitz has asked for a couple of
4 minutes. We'll grant him 10 minutes to comment to some
5 of the questions that had risen just before we broke
6 for lunch.

7 DR. CHODAKEWITZ: Thank you, Mr. Chairman. We
8 appreciate the opportunity to just briefly comment. I
9 am very aware of the fact that I'm following the
10 eloquence that you heard from patients, including
11 patients in the study, their families, and expert
12 clinicians, so I'll keep the comments brief as you
13 asked and also want to focus it really specifically on
14 the question of mono versus combo. There was a lot of
15 discussion about the mono versus combo topic in the
16 discussion earlier, and I really just want to raise a
17 couple of broad comments, and then as Dr. Ramsey to
18 comment as well.

19 First of all, as we try to lay out, and as I
20 think Dr. Boyle mentioned in his comments, our
21 understanding of the biology does matter. It does help
22 us frame this question. In addition, we respectfully

1 but strongly disagree with the analytic approach that
2 the FDA has focused on, actually for the reasons that
3 Dr. Castile laid out. And I'm going to just show one
4 slide actually -- put the slide up, please -- of the
5 differences in these studies.

6 There are differences that are known, and
7 there are differences that we just can't know. There
8 are differences like FEV1, where we can try to make
9 corrections, but that's really hard to do. But there
10 are many differences that can't be corrected for,
11 differences like the time frame in which the studies
12 were done; differences around concomitant medicine, and
13 not just the differences that we know about, but then
14 also the differences that we don't know about. There's
15 just no way to correct for those things. And
16 ultimately, this kind of analysis really can't allow us
17 to draw sharp conclusions.

18 The other concern that we want to flag is that
19 at some level, the discussion of ivacaftor monotherapy
20 versus combination clouds the most important question.
21 The most important question for the committee today is
22 not about mono versus combo, although we recognize that

1 that is a topic for conversation, but we've presented
2 extensive data showing the clinical benefit of
3 combination therapy over placebo. You've heard
4 patients refer to that. And ultimately, the biggest
5 question for today is does the clinical benefit of that
6 combination therapy that you've seen, that benefit over
7 a very high current standard of care, does that support
8 making the drugs available for the patients who need
9 them?

10 So I think to that, rather than my speaking to
11 that, it seems like it would be better to have Dr.
12 Ramsey comment on it.

13 DR. RAMSEY: Thank you. You've heard very
14 eloquently from 18 speakers about combination therapy,
15 so I'm just going to quickly reiterate what my
16 colleagues, Dr. Boyle, Dr. Flume, and Dr. Accurso said.

17 The data from the monotherapy study was
18 published in 2012. It's been out there for almost
19 three years. There has been no ground swell, no
20 interest in looking at monotherapy in this population.
21 And now with the combination therapy data available, to
22 even consider going out and comparing the two would not

1 be feasible. And I say this not only as a clinician
2 but as an investigator for many studies.

3 I think that, as has been said, we need to
4 look at the benefit-risk of the combination therapy. I
5 stated earlier that I felt that it was strongly in
6 favor of clinical benefit, and I think you've heard
7 from the patients that it's well beyond the lung.
8 They've talked about so many symptoms beyond the lung.
9 So I really think that that's what needs to be our
10 focus, not mono versus combined therapy. Thank you.

11 DR. OWNBY: Thank you very much. I believe
12 now we need to turn to Dr. Durmowicz who is going to
13 give a charge to the committee.

14 **Charge to the Committee - Anthony Durmowicz**

15 DR. DURMOWICZ: Before I go into the questions
16 that we're going to be discussing and voting on today,
17 I just wanted to bring up the slide that I brought up
18 earlier this morning and just point out what we would
19 consider the three main issues for voting and
20 discussion. Those are the overall efficacy of the
21 lumacaftor/ivacaftor combination, especially with the
22 result of the clinical significance of the treatment

1 effects; the contribution of lumacaftor to the
2 lumacaftor/ivacaftor combination; and of course
3 finally, the benefit-risk profile of the drug.

4 So moving on, there are a total of six
5 questions today that you could probably see in the
6 briefing document. Questions 3, 5, and 6 are voting
7 questions. Questions 1, 2, and 4 are statements that
8 we ask you to discuss. I'm going to move through and
9 go through the questions a little bit slower than I did
10 this morning so everybody can get a clear understanding
11 of what they say.

12 Question 1, which is a discussion question, we
13 ask you to discuss the available efficacy data with
14 lumacaftor of 400/ ivacaftor 250 milligrams fixed-dose
15 combination given twice daily in patients with cystic
16 fibrosis 12 years and older who are homozygous for the
17 F508 mutation in the CFTR gene. As I mentioned in the
18 points for discussion, you should consider the
19 following issues: the clinical significance of the
20 treatment effect and the contribution of lumacaftor in
21 the context of that for ivacaftor monotherapy.

22 Question 2 is also a question that we ask you

1 to discuss the available efficacy data for ivacaftor
2 monotherapy -- that would be the study 770-104 -- when
3 given twice daily to patients with CF who are
4 homozygous for the F508 mutation in the CFTR gene.

5 Question 3 I'll go into. It's a little bit of
6 a different question, and it pertains mostly to the
7 fact that this is a combination therapy. Do the data
8 available demonstrate that lumacaftor contributes
9 positively to the clinical efficacy seen for the
10 lumacaftor plus ivacaftor fixed-dose combination
11 product in patients with CF who are homozygous for the
12 F508 deletion mutation in the CFTR?

13 So this is different than the first part,
14 where it asks you to discuss the efficacy. This teases
15 the efficacy down to whether there is a clinical
16 contribution from lumacaftor that you can see. There
17 are three potential answers for this question: A being
18 yes; B being no, or C, we cannot determine.

19 We've asked you -- that it's very important
20 for you to please comment on the rationale for your
21 vote and whether you would consider that it would be
22 worthwhile to do a clinical trial to compare

1 lumacaftor/ivacaftor fixed-dose combination to
2 ivacaftor alone.

3 Question 4, we ask you to discuss the safety
4 data for the lumacaftor/ivacaftor combination when
5 given twice daily to CF patients 12 years and older who
6 are homozygous for the F508 deletion mutation.

7 Question 5 is a voting question, where we ask
8 you do the safety data support lumacaftor 400 and
9 ivacaftor 250 milligrams administered twice daily to
10 patients with cystic fibrosis 12 years of age and older
11 who are homozygous for the F508 deletion mutation? If
12 not, what further safety data would you like to see?
13 If there are safety issues that are a concern for you,
14 you could bring those up at that time.

15 Finally, question 6, the last question, is a
16 voting question that asks do the available efficacy and
17 safety data support approval of lumacaftor
18 400/ivacaftor 250 milligrams, fixed-dose combination
19 product given twice daily to CF patients who are
20 homozygous for the F508 deletion mutation? And if you
21 do not think so, then what additional data do you think
22 should be obtained to better define the benefit-risk

1 profile in that patient population?

2 That being said, I'll turn the podium back to
3 Dr. Ownby. Thank you.

4 **Questions to the Committee and Discussion**

5 DR. OWNBY: Thank you. We will now begin the
6 panel discussion portion of the meeting. While this
7 portion is open to public observers, public attendees
8 may not participate except at the specific request of
9 the panel.

10 So the panel can move back to question
11 number 1, discuss the available efficacy data for the
12 lumacaftor 400/ivacaftor 250 milligram, fixed-dose
13 combination administered twice daily in patients with
14 cystic fibrosis 12 years and older who are homozygous
15 for the F508 deletion mutation in the CFTR gene, with
16 specific consideration and discussion.

17 Does anyone want to make a comment? Dr.
18 Castile?

19 DR. CASTILE: Well, I can summarize my thought
20 on this. After hearing the presentations, it's very
21 clear that you have two trials where the primary
22 endpoint, which is FEV1, shows a highly significant

1 improvement with combined therapy. What's more
2 impressive to me, though, is that not very many years
3 ago, we were doing sample-size calculations based on a
4 hoped reduction in rate of decline of lung function of
5 at least 50 percent.

6 If you look at these data, we have almost a
7 year of data, probably more than a year now, and
8 there's no decline. So it's a zero decline. That's as
9 impressive to me at the 3 percent increase in FEV1,
10 which is highly significant. I know it's small. I
11 also know that the FEV1 is probably not the -- we don't
12 have a really effective surrogate measure of lung
13 function for a distal, non-homogenous airway disease
14 that is the case in cystic fibrosis.

15 So I think the FEV1 data, beyond the primary
16 endpoint, is impressive. I agree with Dr. Konstan that
17 the improvements in BMI are, in my former life as a CF
18 clinician, meaningful. Then as I listen to the patient
19 testimonies, it's very clear that bowel discomfort is
20 relieved and sort of accompanies weight gain. And I
21 hadn't thought about it, but that's a very important
22 effect, which wasn't really measured effectively here.

1 I agree with Dr. Accurso that exacerbations
2 drive the disease along. Although there are some
3 problems with the way the statistics were prespecified,
4 I think there's an impressive reduction in the
5 exacerbations, and they're likely to have long-term
6 effects. So for me, I think there's clear efficacy of
7 the drug.

8 DR. OWNBY: I've got Dr. Brittain and then
9 Dr. Tracy. Dr. Brittain?

10 DR. BRITTAIN: So I agree that the efficacy
11 looks really good for the combination therapy and on
12 many parameters. That just seems very clear-cut. Just
13 to discuss the issue, though, about the monotherapy
14 since it's asked, I don't think we know from the data
15 that we have that the combination is superior to the
16 monotherapy. On the other hand, I don't know if I feel
17 that that's really important, the thing I'm struggling
18 with here.

19 DR. OWNBY: Dr. Tracy?

20 DR. TRACY: Well, when I first started reading
21 this stuff several weeks ago, I had a hard time
22 wrapping myself around the 3 percent improvement in

1 FEV1. As I listened to a lot of the speakers, though,
2 my questions about quality of life are certainly eased.
3 I wish the data presented might have done a nicer job
4 of showing that.

5 But I think that a lot of the other stuff that
6 Dr. Castile brought up about BMI, and diet, and
7 appetite, and all these things, exercise tolerance, I
8 think are critical. Should we have had another arm? I
9 don't know. I don't know the answer to that question.
10 But my concerns about the 3 percent certainly have been
11 addressed.

12 DR. OWNBY: Dr. Raghu?

13 DR. RAGHU: I think that the efficacy endpoint
14 is clearly met, that nobody I think is going to dispute
15 that. The primary endpoint was met, and it's a very
16 clinically efficacious endpoint. The second endpoints,
17 the BMI is very convincing at least in one trial, and
18 the pulmonary exacerbations seems to be also going in
19 the right direction. So all that said, it's very nice
20 and very clear.

21 The fact that we're asked to comment on the
22 ivacaftor monotherapy, I think that is digressing. I

1 don't think that it should be considered here at all.
2 I think it's an aftermath. I think just because there
3 was a relatively small proportion of increase in the
4 FEV1, it was an aftermath thinking, oh, let's go back
5 to the monotherapy and see what it is in terms, and
6 it's not that much different.

7 I think that's a mistake for all the reasons
8 that have been discussed to really compare a
9 monotherapy that cannot be compared to this particular
10 patient population in this context of design studies
11 that has been gone into in a very efficacious way with
12 the input of the FDA. So that being said, I think the
13 efficacy is clearly met in my perspective.

14 DR. OWNBY: Thank you. Other comments? Dr.
15 Connett, and then Dr. Morrato.

16 DR. CONNETT: I want to agree with
17 Dr. Castile, except FEV1 is a surrogate, and I do wish
18 FDA would not habitually approve drugs on the basis of
19 surrogates. In this case, it's not necessary. The
20 real problem here is exacerbations. That's what causes
21 deterioration and ultimately death and hospitalization.

22 It seems somewhat artificial here to not be

1 able to say there's a significance difference with
2 regard to exacerbations because of the hierarchy of the
3 analysis. But FEV1 is a laboratory surrogate for what
4 really counts. And it does look to me like the
5 combination drug is efficacious with regard to
6 FEV1 -- with regard to exacerbations.

7 DR. OWNBY: Did you have a comment?

8 DR. MORRATO: This is discussion, right? I
9 don't dispute that there's efficacy data there for the
10 combination, but in response to the question of whether
11 or not there is evidence that says that the combination
12 is more than a potential individual, I didn't see the
13 evidence as compelling. I think the fact that the
14 estimates of the FEV1, point estimates were similar
15 with highly overlapping confidence intervals with the
16 combination versus the individual. If you look at the
17 exacerbation rates, the estimates there are also very
18 similar.

19 I look at the information as there seems to be
20 evidence of efficacy for the combination. There are
21 clearly patients who have very compelling stories and
22 who are really benefiting from it. They largely

1 represent probably those that are truly the responders,
2 but it's very compelling. But if you go to the
3 question that we're being asked to discuss around is
4 that evidence such that it's more than the individual
5 components, I don't think we saw enough there to make
6 that conclusion.

7 DR. OWNBY: Dr. Grayson?

8 DR. GRAYSON: I would agree with everything
9 that's been said. What I do want to say is that I
10 think, from what I'm seeing with this, the combination
11 may be even better for non-pulmonary outcomes than just
12 the ivacaftor alone. I still agree that I think the
13 problem actually -- and this is not the current
14 studies, the 800 studies. It's the 770 or whatever
15 that number was. It's a monotherapy study, which was
16 small, has huge error bars on it, and then everything
17 overlaps, and you can't tell what's really there.

18 But to me, from what we've seen in terms of
19 the question as it's phrased here, it's efficacious. I
20 just can't tell you what part of it is which drug, but
21 I think my view of this, it's still efficacious. But
22 we'll get to the point of the drug later. So I think

1 together, there's something there.

2 DR. OWNBY: Dr. Yu?

3 DR. YU: Yes, I agree with some of the
4 comments. Definitely, I see the evidence of efficacy
5 in the baseline FEV1. But I'm really struggling with
6 the fact that -- when you have a true drug combination,
7 supposedly you should have compared them against each
8 other to say which one computed what. But the trial
9 didn't do that. It was based on an assumption that the
10 ivacaftor was about the same as placebo. And then
11 lumacaftor is better than placebo, and therefore, the
12 lumacaftor is better than ivacaftor.

13 I'm struggling. I felt that's a flawed
14 assumption to design your experiment because the
15 differences in significance is different from whether
16 those two are significantly different. And especially,
17 a colleague brought up the exacerbation rate, that it
18 didn't show -- the last two trials showed significant
19 improvement or at least didn't show the improved
20 exacerbation rate, which is a very fundamental disease
21 process for CF patients. So I'm struggling on that
22 part.

1 DR. OWNBY: Other comments?

2 (No response.)

3 DR. OWNBY: I'm struck with this dilemma that
4 we've put ourselves into through good intentions of
5 ending up with a combination trial against the placebo.
6 And in my mind, if there was a lot of data that there
7 was an additional toxicity from the combination versus
8 the individual drug, that that would be a terribly
9 critical component of our discussion. But I don't see
10 that there's a lot of additional toxicity.

11 The other part of this seems to be that we're
12 used to thinking of drugs in kind of short-term time
13 frames. You treat an infection, and it gets better
14 over weeks or months, but this is long term. And I
15 think it was Dr. Konstan in his opening remarks that
16 commented that the individuals with cystic fibrosis on
17 average are losing 1 to 3 percent of their FEV1 per
18 year. And we know that that inevitably leads to early
19 mortality.

20 When we think of a 3 percent improvement in
21 FEV1, that's not very much, but over years, that does
22 make a huge difference potentially. And that's why I

1 think I would have to come down in favor of -- the vote
2 to think about approving this drug now versus delaying
3 it with another trial really bothers me. It's a bit of
4 a moral dilemma because I can see both sides of it. I
5 know why the FDA comes out and asks this question so
6 difficult for us, but that's what we're supposed to be
7 discussing.

8 Does anyone else have feelings on weighing
9 this? Dr. Parad?

10 DR. PARAD: I have the same struggles. FEV1
11 is a biomarker. It is not really what we need to think
12 about in this scenario. It is what happens over time
13 to multiorgan problems. And maintaining FEV1 -- or
14 arresting progression of the disease, it's a hard thing
15 to show when you're doing a trial that goes over
16 48 weeks. So we have all these markers, surrogates, on
17 which we're projecting what happens over years.

18 My gut feeling, putting all things together
19 from the biology to all the little growth and organ
20 improvements, is that that these together should allow
21 arrest of progression of the disease or slowing of
22 progression of the disease, which really is the outcome

1 that it would be great to measure. But we don't have
2 five years to do that.

3 DR. OWNBY: I'll forgive the bad pun about
4 guts, but -- Dr. Au?

5 DR. AU: Thank you. Conceptually, I've
6 actually struggled with this as well but have come to
7 some sort of resolution, at least within myself. And I
8 think we just need to deal with the data that we have,
9 and I think we just have to live with the decisions
10 that were made. I think they were made under the best
11 circumstances and the best available evidence at the
12 time.

13 I think we should just treat the data as they
14 are, and we have a randomized controlled trial of two
15 agents against placebo. And we don't actually have,
16 really, a great comparison to the single agent,
17 ivacaftor. So in general, I think we need to take the
18 data as it is and as it stands and just do the best we
19 can with it. And I think the data does show efficacy
20 in totum for the combination therapy. And I think the
21 safety profile overall is generally in favor of the
22 drug as well. I think that's just, on balance, what we

1 have to deal with.

2 DR. OWNBY: Are there other items people would
3 like to comment on about this question or should we
4 move to -- excuse me. We're missing Dr. Druce on the
5 phone. Apparently, you would like to make a comment
6 for us?

7 DR. DRUCE: Hello? Can I be heard?

8 DR. OWNBY: You can be now. Thank you.

9 DR. DRUCE: Thank you so much. This is Dr.
10 Howard Druce. I'll just make the general comments that
11 if [inaudible] were to be made through [inaudible],
12 based on the data that was presented today, it might be
13 very hard [inaudible].

14 DR. OWNBY: Dr. Druce, I'm sorry. You were
15 breaking up some, and I think a lot of people had
16 trouble understanding. Was your comment that it would
17 be very difficult to go back and recruit an additional
18 study based on the ethics, knowing the data on the
19 combination drug?

20 DR. DRUCE: My comment was that it would be
21 very difficult I think for an institutional [inaudible]
22 review board to approve such a practical

1 [indiscernible] design.

2 DR. OWNBY: So you're unsure whether an
3 institutional review board could approve such a design
4 based on the data we have so far.

5 DR. DRUCE: That's correct.

6 DR. OWNBY: Okay. Thank you. Other comments?

7 (No response.)

8 DR. OWNBY: Okay. Why don't we move to
9 question number 2? Question number 2 is also a
10 discussion question. Discuss the available efficacy
11 data for ivacaftor monotherapy 150 milligrams twice
12 daily in patients with CF who are homozygous for the
13 F508del mutation in the CFTR gene.

14 DR. GRAYSON: So we've kind of done that. I
15 think the problem is that the data we have, it was too
16 small of an end. It was a long time ago, relatively.
17 We can't really use it to compare it to what we have
18 now. It suggested that there was no effect, but it had
19 a huge spread because there's only 33 or 36 subjects in
20 it.

21 So from my viewpoint, I've got no real data on
22 monotherapy in the homozygote F508del, from my

1 viewpoint. So I don't really know what to do with that
2 because I think if you want to know whether works as a
3 monotherapy I think you have to do a real study with
4 large numbers and do that. And I agree with Howard,
5 Dr. Druce, that it's probably unlikely in the current
6 environment that any IRB is going to say, okay, fine,
7 we'll allow you to do that. But I think without that,
8 I don't think we really have useful data for that.

9 DR. OWNBY: Dr. Morrato?

10 DR. MORRATO: Can I better understand,
11 then -- I'm just trying to wrap my mind why an IRB
12 would not say because the estimate of effects are about
13 the same. So is it -- I mean, there's a difference
14 between the estimate of effect and the fact that you
15 have a wide confidence interval.

16 So I'm just trying to understand that if we
17 think -- I'm more in the camp of I think the efficacy
18 that we're seeing is probably clinically meaningful.
19 So putting people on two drugs when one can accomplish
20 it, that's what I'm kind of struggling with. So I'm
21 trying -- maybe you can help me understand where an IRB
22 would think on that.

1 DR. OWNBY: Do you want to comment to that?

2 DR. GRAYSON: Yes. I think, at least from my
3 viewpoint, what would be the problem is that -- there
4 are two issues. I think one would be that an IRB would
5 look at this and say, really, the job of the
6 monotherapy is to potentiate the channel. You don't
7 have channels. It's not likely going to work. And
8 then they're going to go back to this poor study but
9 still say there was no real evidence. And I think at a
10 local level, that may be enough for them to say we
11 don't think that that's a good idea to do, given if
12 there are other options.

13 DR. MORRATO: So they would use the biological
14 mechanistic data, the in vitro, in order to give the
15 rationale for why it doesn't make sense. Would they
16 not consider the combination therapy results in the
17 sense that those don't seem to be any different in
18 terms of the clinical outcome, not the mechanistic, and
19 the fact that there's data that we're hearing that
20 would suggest that the mechanism in vitro data is not
21 completely predictive of the in vivo to begin with, or
22 would they be wrapping their mind around this story and

1 the concept more than the evidence?

2 DR. GRAYSON: I think they would make the same
3 potential mistake of jumping into the assumption of
4 what's going to happen and not wanting to do it,
5 especially if the combination therapy is what you want
6 to compare it to. Then the question is why would you
7 do the monotherapy.

8 DR. MORRATO: Right.

9 DR. GRAYSON: That's my experience with IRBs.
10 Other ones could be different.

11 DR. MORRATO: Clearly, this story is more
12 compelling as to the rationale for the design of the
13 combination.

14 DR. OWNBY: I've got Dr. Parad, Dr. Castile,
15 Dr. Raghu, and Dr. Au, in that order.

16 DR. PARAD: The biology doesn't make sense,
17 but let's just say we looked at the data that were
18 presented to us from the ivacaftor monotherapy. Isn't
19 that post hoc analysis just as bad as the other things
20 we're talking about? We seem to be putting a lot of
21 weight on a manipulation of those older data to try to
22 make them equivalent, and that's what we're not

1 supposed to be doing here.

2 I'm having more and more trouble looking at
3 the tweaking of that data to try to make it line up so
4 we can compare things. I don't think it's fair for us
5 to give it the same weight as the truly designed trial
6 that we're supposed to be looking at.

7 DR. OWNBY: Mr. Petullo, you want to comment
8 to that, or should I move on?

9 MR. PETULLO: I agree with you. I think we
10 were struggling here with how do we evaluate this. The
11 company actually put forth an argument that placebo is
12 similar to ivacaftor. Iva/luma was better than
13 placebo, therefore ivacaftor/lumacaftor was better than
14 ivacaftor. That's incorrect. We don't do like that.
15 So we did continue with that approach. That's all I
16 had. There was not a randomized controlled trial. We
17 tried to make it better, and we're unable to show that
18 they were different in the end. It's the data we had.

19 DR. OWNBY: Dr. Castile, and Dr. Raghu, and
20 Dr. Au.

21 DR. CASTILE: I'm beginning to think we're all
22 agreeing.

1 The old ivacaftor monotherapy study was not
2 designed to show efficacy. So we shouldn't be pairing
3 it with other studies in trying to make any decision.
4 Let's see. Where was I going with this?

5 (Laughter.)

6 DR. CASTILE: But in fact, the decision was
7 made, and the decision was to include in the ivacaftor
8 approval that there was no efficacy. And that was
9 based on a study that was not designed to -- it didn't
10 have adequate data to make that decision. We've since
11 heard that that was clearly a mistake to use data that
12 was not adequate; to make a decision about the uses of
13 ivacaftor, in retrospect, would like to withdraw that.

14 It's equally inappropriate to take the same
15 kind of data, partially from the same data set, that is
16 not comparable and make any kind of decision over it.
17 So I don't think we should neglect it, and I think
18 Bonnie Ramsey's statement is a very important one,
19 that after this meeting, it may be very difficult -- it
20 may not be feasible to do this study.

21 Bonnie and I know the CF parents and
22 population. If this study was demanded, the CF

1 population would do this for their brothers and sisters
2 even though they know that they're doing it to get past
3 this. So it is feasible, Bonnie. They'll do it.
4 That's the kind of people that we've heard from. But
5 I'm not sure that it's relevant to the decision that we
6 need to make today.

7 DR. OWNBY: Okay. I've got Dr. Raghu, Dr. Au,
8 and Dr. Brittain.

9 DR. RAGHU: Just to redirect what David Au
10 earlier said, we've got to deal with the facts the way
11 it is right now, the data, what it is, and what the
12 current prospective study has shown. Even if you want
13 to go back to the picture or the slides on page 6 that
14 you have in terms of trying juxtapose the previous
15 data, then you could make it an argument that the
16 monotherapy curve is actually lower than the
17 combination therapy. The caveat side of course, you
18 don't compare post hoc data to prospective data.

19 There is no struggle for me. There is no
20 trouble in accepting what it is. But I'm a little bit
21 surprised that it is even brought to this juncture
22 here.

1 DR. AU: I was just going to go back to the
2 discussion that was going on earlier about the IRB.
3 Actually, the comparative efficacy study I think would
4 actually be fine, actually; if it were the questions of
5 do you need two drugs versus one, are there safety
6 concerns. There are other kind of questions along
7 those lines.

8 You can actually test the -- I think the
9 question of the comparative efficacy is actually
10 unanswerable today. So if there is a question around
11 that, I think that's a perfectly legitimate question
12 that IRBs can wrap their brains around and actually
13 approve. I don't think that would be a huge obstacle.
14 I agree. I think there might be pragmatic issues, but
15 that's a pragmatic issue and not a conceptual issue.

16 DR. BRITTAIN: Just a brief comment. I guess,
17 to me, it doesn't matter so much whether you think the
18 synthesis approach that was presented is appropriate or
19 not. I think we all agree that we don't have the data
20 to make a clear statement about whether the combination
21 is superior to the monotherapy, unless I'm wrong.

22 DR. OWNBY: Other comments or do people want

1 to comment on this discussion? What I'm hearing is a
2 consensus, for a number of reasons we've all batted
3 around, we don't have adequate data to make a very
4 forceful statement on whether one is more effective
5 than the combination, but that doesn't seem to be
6 bothering a lot of people in terms of making an overall
7 decision today.

8 So should we move on to question number 3?
9 Now the tension rises. You will be voting on this
10 question as the panel. Do the available data
11 demonstrate that lumacaftor contributes positively to
12 the clinical efficacy seen in the lumacaftor plus
13 ivacaftor FDC product in patients with CF who are
14 homozygous for the F508 deletion mutation in the CFTR
15 gene? And the voting will be yes, no, or cannot
16 determine.

17 The question has been brought up whether
18 cannot determine is the same as abstain. I don't think
19 that's the way it was intended from the FDA's
20 standpoint. But does someone from the FDA want to
21 comment on that particular question?

22 DR. DURMOWICZ: I agree with you. I don't

1 think the intent was cannot determine to be an abstain.
2 I think if somebody votes "cannot determine," then it
3 would be important to hear their reasons, some of which
4 may have already been brought up by Dr. Brittain, but
5 to do that route.

6 DR. OWNBY: Dr. Brittain?

7 DR. BRITTAIN: Reading the question, I don't
8 understand the difference between "no" and "cannot
9 determine" given the question, because, to me, it seems
10 like it's the same -- if it didn't demonstrate, then
11 that's the same as cannot determine. So I wasn't sure.
12 Do they have a different interpretation for you?

13 DR. DURMOWICZ: I suppose it was an attempt to
14 insert a little bit of indeterminateness or
15 definitiveness about the situation. We thought long
16 and hard about a yes, no, maybe, those kind of things,
17 because from our standpoint and from the statistical
18 analysis in the study that wasn't powered for efficacy,
19 we are asking you, but we couldn't really say that one
20 was definitively better than the other, or that the
21 lumacaftor definitively contributed to the contribution
22 [sic].

1 So I don't know if I can explain it any
2 better, but it was kind of more of an indeterminate --

3 DR. RAGHU: Perhaps you can use the word
4 "uncertain."

5 DR. DURMOWICZ: Uncertain would probably be a
6 similar type synonym, if you will.

7 DR. OWNBY: I'm sorry. I'm shirking my
8 duties. I was supposed to read part of the script
9 before the question.

10 For voting questions, we will be using an
11 electronic voting system for this meeting. Once we
12 began the vote, the buttons will start flashing and
13 will continue to flash even after you have entered your
14 vote. Please press the button firmly that corresponds
15 to your vote. If you are unsure of your vote or you
16 wish to change your vote, you may press the
17 corresponding voting until the vote is closed.

18 After everyone has completed their vote, the
19 vote will be locked in. The vote will then be
20 displayed on the screen. The designated federal
21 official will read the vote from the screen into the
22 record. Next, we will go around the room, and each

1 individual who voted will state their name and their
2 vote into the record. You can also state the reason
3 why you voted as you did. We will continue in this
4 same manner until all questions have been answered and
5 discussed.

6 Are there additional questions or discussion
7 about this question before we vote? Dr. Connett?

8 DR. CONNETT: Well, it seems to me here that
9 the answer is either yes or not yes. I mean, its
10 wording is has it been demonstrated a positive effect.
11 So the answer is yes or not yes. So I don't know why
12 we have a third choice. Why don't we just have yes or
13 no?

14 DR. RAGHU: [Inaudible].

15 DR. OWNBY: Microphone on, please.

16 DR. RAGHU: Sorry. In the button here,
17 there's a number 4; there's an abstain thing, so you
18 may want to look into that. It's yes, no, abstain. So
19 it's clear to me that you can say either yes, or you
20 can say no, or you can even press the abstain. So you
21 need to be clear.

22 DR. OWNBY: Only three lights are flashing, at

1 least on mine.

2 DR. RAGHU: Yes, you're right.

3 DR. OWNBY: So you only get three choices.

4 DR. HONG: So the yes button would be A, the
5 no button would be B, and then the abstain button would
6 be C. C is cannot determine. So yes is A, no is B,
7 and then the abstain button is C, cannot determine.

8 (Crosstalk.)

9 DR. OWNBY: Wait -- let's -- it's going to be
10 very confusing. The poor recorder is going nuts over
11 here with everyone talking at once.

12 (Laughter.)

13 DR. OWNBY: I'm sorry. This does have to be
14 somewhat formal. So Dr. Morrato, and then Dr. Harkins,
15 and Dr. Grayson.

16 DR. MORRATO: So I don't have A, B, and C,
17 so -- attend is a yes, a yes is no, and no is an
18 uncertain?

19 DR. GRAYSON: It's 1, 2, 3, attend, yes, no.
20 But you're saying it's going to be yes, no, cannot
21 determine, which means that the button that says yes is
22 actually going to be no. The button that says "no" is

1 going to be "cannot determine." Is that correct?

2 DR. HONG: So the first button is A. So let's
3 start fro the left, A, B, C.

4 (Thiep Vo explains voting system.)

5 DR. OWNBY: So we're ignoring the words above
6 the buttons. Button 1 for A, 2 for B, and 3 for C.
7 This is almost as bad as the statistics of the data.

8 (Laughter.)

9 DR. OWNBY: Other questions or comments or
10 discussion? I'm sorry. Dr. Harkins?

11 DR. HARKINS: That's okay. I guess I'm just
12 also trying to get a grasp of this question because is
13 the question that lumacaftor was the save-the-day
14 component of this combo? And I don't know that we have
15 that data or issue. Does this really affect the true
16 voting questions that are later? You know like you do
17 consistent voting? Is this more just a discussion,
18 what do we think, feel?

19 DR. OWNBY: Dr. Durmowicz, do you want to
20 comment on that question?

21 DR. DURMOWICZ: I think this question was
22 specific, as I mentioned when I was up at the podium.

1 It's more consistent with the kind of question you
2 would ask for a combination product because we are
3 supposed to show that there's a definitive contribution
4 from each component in a combination product.

5 So in that sense, that's where it fits in. I
6 think there's nothing wrong in our estimation, and
7 there's no need for extreme consistency, that you could
8 vote yes and vote no, don't approve it. You could vote
9 no and say, yes, approve it, at the end of the day,
10 question 6.

11 I view this strictly in the context of a
12 combination product that we were talking about today.
13 Now, I know some people have already mentioned that a
14 cannot determine is really a no, an uncertain, or
15 whatever. However you view that "cannot determine"
16 vote, if you view it strictly as this would be a no and
17 not more indeterminate or uncertain, just vote no.
18 With a clear conscience, vote no. If you're a splitter
19 more than a grouper, then say cannot determine and give
20 your rationale. I think that would be possibly the
21 best way to handle it.

22 DR. RAGHU: Dr. Harkins brings a good point

1 because I hadn't thought about that. Because the
2 question is really very specific. Do the available
3 data demonstrate that lumacaftor contributes positively
4 to the clinical efficacy? Same for the lumacaftor plus
5 ivacaftor product. So we're asked to comment on say
6 yes or no does the lumacaftor contribute to the
7 combination, not to the efficacy of the trial?

8 DR. DURMOWICZ: Yes, lumacaftor contributes to
9 the clinical effect of a combination. That's the way
10 the question is answered -- is asked, rather.

11 DR. OWNBY: Are all the voting members of the
12 panel clear on the question at this point? Any further
13 discussion that anyone wishes to bring up?

14 (No response.)

15 DR. OWNBY: It's your last chance before you
16 have to vote.

17 (No response.)

18 DR. OWNBY: Okay. And everyone's clear that
19 the flashing 1 is A, the flashing 2 is B, and the
20 flashing 3 is C. So it's yes, no, or cannot determine.

21 I always think we need a little Jeopardy music
22 at this point or something.

1 (Vote taken.)

2 DR. HONG: For question 3, we have 3 yeses, 4
3 noes, and 6 cannot determine.

4 DR. OWNBY: Okay. Which side should I pick on
5 first? Let's start over here on the right. Would you
6 like to give us your name and your vote and your
7 reason?

8 DR. AU: Sure. David Au. I voted cannot
9 determine. I'm more of a splitter than a lumper I
10 guess. I just didn't think that we actually had the
11 data to actually do a comparative efficacy question.
12 And that's what this question was asking, was how much
13 does this contribute to another agent. I just didn't
14 think we had the evidence presented.

15 DR. OWNBY: Dr. Brittain?

16 DR. BRITTAIN: Erica Brittain. I voted no. I
17 could easily have voted cannot determine because to me
18 they seem totally synonymous in terms of this question.
19 I cannot determine because we don't have the data. The
20 study was not done to provide that data. And that was
21 probably an unfortunate decision, but here we are.

22 DR. RAGHU: I voted cannot determine for the

1 very specific question that we are asked in terms of
2 the lumacaftor contributing positively. So I cannot
3 determine based on the data.

4 DR. OWNBY: Dr. Parad?

5 DR. PARAD: This is Richard Parad. I voted
6 yes for probably convoluted reasons. But looking at
7 the lumacaftor alone not having effect or having maybe
8 a negative effect, and reflecting on the available
9 data, which is not current but is old, that ivacaftor
10 alone did not seem to have a huge effect, I interpreted
11 it as together they had an effect.

12 DR. OWNBY: Dr. Yu?

13 DR. YU: I voted cannot determine; still the
14 same reason I found, to determine whether contributor
15 is really inconclusive because of the reason I said.
16 And I really think to exclude the treatment from the
17 trial from the beginning is flawed and I think should
18 be able to address this.

19 DR. CONNETT: This is John Connett. I
20 interpreted the question very literally. Maybe I
21 shouldn't. But it says does the data demonstrate that
22 lumacaftor contributes positively to the clinical

1 efficacy. It seems like a clear-cut no.

2 DR. OWNBY: Dr. Morrato?

3 DR. MORRATO: I voted no on this as well. On
4 the one hand, you have a very compelling biological
5 argument and in vitro mechanistic data. On the other
6 hand, the efficacy clinical evidence that was provided
7 did not in my mind demonstrate added benefit. The
8 range of effects were very similar. They may have been
9 differently designed studies, but the range of effects
10 were similar. And therefore, I didn't think there was
11 evidence to suggest the individual benefit of
12 lumacaftor.

13 DR. HARKINS: Michelle Harkins. I voted
14 cannot determine. I think it would have been great if
15 there were all of the arms all together. And then we
16 could really answer that question; what component or
17 what significance does lumacaftor add to the
18 combination? That does not mean I think that that
19 trial should be done because I think we have to act
20 now. I think that the product itself is efficacious,
21 but I think that the question, unfortunately, was
22 difficult. So I voted cannot determine.

1 DR. OWNBY: Dennis Ownby. I voted not yes.

2 (Laughter.)

3 DR. OWNBY: I also took the question fairly
4 literally and did not feel that we had data that
5 clearly showed the efficacy of this component. But
6 that didn't bother me for a lot of the reasons we've
7 already discussed.

8 DR. TRACY: Dr. Tracy. I voted yes. It
9 sounds to me like there's a whole lot of us sitting on
10 one side of the fence or not. So being more of a
11 lumper than a splitter, I went with the yes, but I was
12 working it out with some of the other cannot be
13 determined folks also.

14 DR. OWNBY: Ms. Motenko, are you with us?

15 (No response.)

16 DR. OWNBY: I thought we'd resolved our
17 telephone difficulties. Apparently not.

18 MS. MOTENKO: Can you hear me?

19 DR. OWNBY: We can now.

20 MS. MOTENKO: Okay, great. I voted yes for
21 similar reasons. I felt that the ivacaftor alone did
22 not have the same effect as the combination of the

1 lumacaftor and ivacaftor together.

2 DR. OWNBY: Okay. Thank you. Dr. Grayson?

3 DR. GRAYSON: Mitchell Grayson. I voted that
4 I cannot determine. My issue is that I think we don't
5 have good enough data on the monotherapy. But in the
6 ivacaftor study alone, I'm concerned about the decline
7 in FEV1 that was occurring, which did not occur in the
8 combo drug, which suggests to me there probably is a
9 significant effect there. But I don't know because I
10 don't have enough data. So that to me is cannot
11 determine.

12 DR. CASTILE: Bob Castile. I voted cannot
13 determine because it was closest to my opinion that it
14 should not be determined from these data. I'm not
15 happy with the question. I could have voted for A, B,
16 or C. This should not appear on an exam.

17 (Laughter.)

18 DR. OWNBY: Okay. It's now 3:24 on my watch,
19 and were scheduled to break at 3 o'clock for
20 10 minutes. And I see some of you are already telling
21 me, no, let's trudge ahead to try to finish by 4
22 o'clock. And I know a few of the members have fairly

1 tight plane connections, and I'm sure they would be in
2 favor of continuing on.

3 Is there anyone who disagrees? Or everyone's
4 willing to soldier on for another 30 minutes, he says
5 optimistically.

6 (Committee responds in the affirmative.)

7 DR. OWNBY: Okay. We will continue.

8 Question 4 is a discussion. Discuss the safety data
9 for the lumacaftor 400/ ivacaftor 250 milligram FDC
10 twice daily in patients with CF 12 years and older who
11 are homozygous for the F508 deletion mutation in the
12 CFTR gene.

13 Would someone like to comment on that at this
14 point?

15 (No response.)

16 DR. OWNBY: Fatigue has really set in I guess.
17 Dr. Castile?

18 DR. CASTILE: My summary would be that the
19 risks are small or modest, and that they're all
20 manageable with appropriate monitoring. Even my
21 concern about the possibility of patients that might
22 have a negative effect that can be controlled by

1 monitoring lung function, liver function, I think those
2 things should be in the recommendation for the drug.

3 So I think the risk is very modest.

4 DR. OWNBY: Dr. Parad?

5 DR. PARAD: This was a question I forgot to
6 ask earlier. But because of the cataract issue in the
7 ivacaftor, this is a bigger dose than for monotherapy,
8 right? But the metabolism changes. So really, the
9 levels are probably lower maybe than in monotherapy.
10 Did I understand that correctly? And that's being
11 monitored, I assume, in any follow-on studies.

12 DR. OWNBY: That's an issue that hasn't been
13 discussed. As I remember from the briefing documents,
14 there is a follow-up study for the ivacaftor, and
15 someone can correct me if I'm wrong, looking
16 specifically at the issue of whether cataract formation
17 is a concern.

18 Dr. Durmowicz, do you want to comment on that?

19 DR. DURMOWICZ: Just briefly. You are right
20 in that even though it's a larger dose of ivacaftor,
21 that the systemic exposure is less than the
22 150 milligrams twice daily by a substantial amount.

1 Just to add a little bit more clarity, the cataract
2 signal, which was initially detected in a juvenile
3 animal study, was predominantly for very young
4 pediatric patients.

5 That being said, there have been some
6 cataracts reported through adverse event reporting
7 systems so far, but almost all the handful of them have
8 been very confounded with regard to the use of
9 corticosteroids and other things to be able to pinpoint
10 anything. So that's something that everybody is aware
11 of. It's in the labeling. There's a good chance that
12 would be in the labeling for this drug if approved as
13 well.

14 DR. OWNBY: We have a comment. Do you want to
15 identify yourself, please?

16 DR. CHEN: This is Jianmeng Chen, the clinical
17 pharm reviewer from FDA. Just to answer the question
18 the metabolite, the absolute value of metabolite
19 concentration is lower or the same as monotherapy. So
20 there's no concern about safety for metabolite.

21 DR. OWNBY: Thank you. Other questions?
22 Dr. Raghu, do you have a comment or question?

1 DR. RAGHU: I don't think that the cataracts
2 were formally assessed by a formal ophthalmology
3 evaluation in a consecutive or regular follow-up
4 manner. But it appears that it wasn't an issue,
5 really, based on the data that we have seen. So I
6 agree with Dr. Castile, and that is that the risks are
7 very minimal. Liver function tests are mildly abnormal
8 in a handful of patients but very manageable and
9 monitored.

10 DR. OWNBY: I was impressed when we saw the
11 data curve of this because virtually every drug, even
12 though we don't like to think about it, has some people
13 in large studies that fall on the side where they
14 actually didn't improve and actually got worse. And
15 the fraction in this data appears to be relatively
16 small. So I'm very encouraged. And I think I agree
17 with Dr. Castile that with normal CF management, the
18 concerns about this drug are going to be relatively
19 modest and can be followed and managed relatively
20 easily.

21 Anyone else want to comment on this question?

22 (No response.)

1 DR. OWNBY: Okay. Should we move on, then, to
2 question 5? Voting question. Do the data support the
3 safety of lumacaftor 400 milligrams/ivacaftor 250
4 milligrams -- that's the FDC proposed -- administered
5 twice daily in patients with CF 12 years and older who
6 are homozygous for the F508 deletion mutation in the
7 CFTR gene? If not, what further data should be
8 obtained to more fully define the safety profile of
9 this combination?

10 MR. CASTILE: I have what might be a
11 procedural question. Before we vote on safety, we've
12 not voted on efficacy. Is that going to be a problem?
13 Because the following question is, really, on
14 risk-benefit. I don't want that to come back and bit
15 anybody to say we've never voted on the fact of whether
16 it was efficacious or not. Or did I miss that
17 question? I mean, that's kind of why I came. I was
18 kind of focused on efficacy.

19 DR. OWNBY: We
20 weren't asked to vote on the safety data. Do you think
21 that would be something that you would suggest for us?

22 DR. CASTILE: So procedurally, is that

1 permissible as long -- I mean, I just don't want
2 somebody to say, well, there's no vote.

3 DR. OWNBY: I didn't make up the questions,
4 but we can ask our FDA officials if they consider that
5 a concern.

6 DR. DURMOWICZ: We did make up the questions,
7 and we knew there was no efficacy assessment per se in
8 there. There's a big discussion for efficacy. That
9 was the first discussion question. Then we went into
10 the combination therapy. And then the final question 6
11 asks do you want to approve it, which implicit in that
12 is that's efficacious. So I think that we're
13 comfortable with the way that the questions are right
14 now.

15 DR. OWNBY: Okay. Thank you. Other
16 questions? Interpretations? Dr. Raghu?

17 DR. RAGHU: My only question is which button
18 do we press?

19 (Laughter.)

20 DR. HONG: So for this question --

21 DR. RAGHU: This doesn't have a 3-point thing,
22 so should we press --

1 DR. HONG: Yes. We use the middle three
2 buttons, the ones labeled yes, no, and abstain. So
3 buttons 2, 3, and 4, the middle three buttons.

4 DR. OWNBY: We have buttons 2, 3, and 4; 2
5 will be yes as indicated above the button, 3 will be
6 no, and 4 is abstain. So if there is no further
7 discussion about the question, are you ready to vote?
8 Okay. Go ahead and cast your vote for question 5, do
9 the data support the safety?

10 (Vote taken.)

11 DR. HONG: Question number 5, we have 13
12 yeses, zero no, and zero abstain.

13 DR. OWNBY: All right. We'll start on the
14 other side. Dr. Castile, you want to give us your vote
15 for the record and any reasoning.

16 DR. CASTILE: No, none whatsoever.

17 (Laughter.)

18 DR. CASTILE: Bob Castile for the reasons
19 previously stated.

20 DR. OWNBY: Your vote?

21 DR. CASTILE: Oh. It was yes. Well, they
22 were all yes.

1 DR. GRAYSON: Mitchell Grayson. I also seemed
2 to have voted yes. I think that any of the concerns
3 with the -- I can't even say it. But anyway, by
4 itself, you don't see that signal in the combo, so I
5 thought that there was no problem with that. And the
6 possible respiratory SAEs I think are just random. I
7 could be wrong. But it seems to me that everything in
8 here looks great, and so that's why I voted yes.

9 DR. OWNBY: Ms. Motenko? Can I have the phone
10 mic up?

11 MS. MOTENKO: Hello?

12 DR. OWNBY: Okay. You're with us now. Thank
13 you.

14 MS. MOTENKO: Okay. Great. This is Stacy
15 Motenko, and I voted yes.

16 DR. OWNBY: Thank you. Dr. Tracy?

17 DR. TRACY: Jim Tracy. I also voted yes, and
18 I felt most of the adverse events that they had were
19 fairly predictable. And overall, this is an
20 exceptionally well monitored group of individuals.

21 DR. OWNBY: Dennis Ownby, and I voted yes for
22 reasons already stated.

1 DR. HARKINS: Michelle Harkins. I voted yes
2 for reasons already stated. No big safety signals for
3 me.

4 DR. MORRATO: Elaine Morrato, and I voted yes.
5 And I'd just like to add it was an exceptionally large,
6 I think, database given the orphan drug status.

7 DR. CONNETT: John Connett. I voted yes. I
8 think there are hints of adverse effects, but I think,
9 as Dr. Ramsey mentioned, monitoring for liver
10 abnormalities is warranted and I think they're
11 manageable in general.

12 DR. YU: Yanling Yu. I voted yes, but I do
13 have these concerns because risk-benefit is a relative
14 term. So you think about absolutely when you look at
15 it, it seems like the last trial is generally safe, and
16 compare it with the placebo. But when you start
17 looking at it compared with ivacaftor, you have this
18 uncertainty of that, and ivacaftor shows it seems like
19 safer, less distress for CF patients with respiratory
20 side effects. So if we find that the other one works
21 better, I definitely go with ivacaftor.

22 DR. PARAD: This is Richard Parad. I voted I

1 think yes. I find the respiratory adverse event sort
2 of mysterious. The fact that it appeared reversible
3 after a fairly short period of time, and that I believe
4 probably most CF patients would trade a week of feeling
5 a little crummy for the rest of their life, I think
6 that's an acceptable risk.

7 DR. RAGHU: Ganesh Raghu. I said yes for the
8 stated reasons.

9 DR. BRITTAIN: Erica Brittain, and I voted yes
10 for reasons already stated.

11 DR. AU: Sorry. Wrong button. I hit the yes
12 button again.

13 (Laughter.)

14 DR. AU: I voted yes. This is David Au. I
15 voted yes. This is a relatively new compound. The
16 experience of 48 weeks is a long experience for most
17 drug trials, but it's not long necessarily in
18 comparison to people's lives. I would like to see
19 safety looked at over a longer period of time, maybe
20 through the CF registry or those kind of processes,
21 some systematic way of doing it.

22 DR. OWNBY: Okay. Thank you everyone. We

1 have one additional question. This is a voting
2 question, number 6. In your book, do the available
3 efficacy and safety data support approval of the
4 lumacaftor 400 milligrams/ivacaftor 250 milligrams FDC
5 product administered twice daily in patients with CF
6 who are homozygous for the F508 deletion mutation in
7 the CFTR gene? And then, if not, what additional data
8 should be obtained to further define the benefit-risk
9 profile of the combination twice daily in these
10 patients?

11 DR. YU: I just have two questions. Is there
12 any way FDA can -- there are discussions about maybe it
13 seems impossible to conduct another trial because of
14 time and all these things. Is there any way that FDA
15 can speed up some type of a trial for, really, the need
16 of CF patients? That's the first question.

17 The second question is, is there any process
18 that FDA could say, okay, lots of patients want this.
19 Even if we don't approve, sign the informed consent,
20 and then you can start, go ahead, and use this
21 medication?

22 DR. DURMOWICZ: I don't think you could say

1 you could do a clinical trial at the drop of a hat. I
2 think that if you're talking about a clinical trial,
3 which I presume is ivacaftor versus lumacaftor and
4 ivacaftor combination -- is that what you are trying to
5 ask? That would depend a lot on what type of endpoint.
6 For instance, people were saying that FEV1 is a
7 surrogate and not a very good endpoint, potentially.
8 So then you'd be talking about an exacerbation study,
9 which by definition probably has to be at least six
10 months to a year. So I don't think something could be
11 done quickly. And your second point was?

12 DR. YU: Second point is can FDA facilitate
13 some type of a pre- -- to allow patients to use the
14 drug pre-approval, just allow them to sign an informed
15 consent so they can start and go ahead with the trial
16 if someone would like to go ahead without approval
17 [indiscernible]? I don't know --

18 DR. DURMOWICZ: I'm not a hundred percent sure
19 that that kind of mechanism would be available for
20 everybody unless you approved the drug based on
21 biomarkers or other types of surrogates, and then as
22 for a definitive trial later. But the question that

1 comes up when you do that is everybody's already on the
2 drug, so how can you conduct a trial that's going to
3 give you an answer.

4 I don't know if Dr. Chowdhury has any comment
5 on that or not.

6 DR. OWNBY: Any further questions before we
7 vote on this particular question, or comments?

8 (No response.)

9 DR. OWNBY: Okay. Seeing none, this is a
10 voting question, do the efficacy and safety data
11 support approval of the combination? So we are voting
12 yes, no, and abstain, as we did for the last one. So
13 key number 2 is yes, key 3, no, 4 is abstain. You may
14 cast your votes now.

15 (Vote taken.)

16 DR. HONG: Question 6, we have 12 yeses, 1 no,
17 and zero abstain.

18 DR. OWNBY: Okay. We can start back on this
19 side. Dr. Au?

20 DR. AU: David Au. I voted yes. I thought
21 the data in totum demonstrated the efficacy of the
22 combination against placebo.

1 DR. BRITTAIN: Erica Brittain. I voted yes.
2 It was an uncomfortable yes having voted no on the
3 other question earlier. It's unfortunate that we
4 didn't have the randomized comparison of the
5 monotherapy versus the combination, so we're now in
6 this awkward position. But given that FDA agreed to
7 the study design, I don't think it's fair to the
8 patient to deprive them of the treatment now. And
9 there doesn't appear to be any apparent safety
10 advantage in terms of monotherapy, so I'm not seeing
11 what the advantage is.

12 I hope they can still possibly do the study
13 post-approval. I don't know if that's at all feasible.
14 I think you could put forth the rationale to do it. I
15 also hope that this will be a lessons learned for
16 combination products so that this situation doesn't
17 happen again.

18 DR. RAGHU: Ganesh Raghu. I voted yes. The
19 two replicate studies clearly met the primary
20 endpoints. The safety data has been discussed. I was
21 impressed with the sustained effect of the FEV1
22 improvement, as well as the BMI, so I clearly said yes.

1 DR. PARAD: This is Richard Parad. I said yes
2 for the same reasons just stated by Dr. Raghu. I would
3 maybe use this opportunity, even though I didn't say
4 no, to say what additional data I think might be
5 helpful. I made a little list along the day, and I
6 assume more monitoring will be going on.

7 I think it would be interesting to have more
8 information on what happens with concomitant
9 medications. In other words if they are decreasing
10 over time, that might add another signal. Certainly,
11 bronchoalveolar lavage data, nasal potential or rectal
12 potential difference data might be supportive in some
13 way.

14 I think what we really need is some long-term
15 outcomes, decline an FEV1, and a longer look at BMI to
16 feel even more solid, and perhaps also on what happens
17 to the Pseudomonas over time, whether there's any
18 reversal in colonization or infection. I think
19 ultimately, if this is really a preventive or arrestive
20 therapy, it needs to go down into lower ages. So
21 obviously, any data on younger cohorts would be very
22 important.

1 DR. OWNBY: Dr. Yu?

2 DR. YU: Yanling Yu. I'm the only one black
3 sheep. I voted no. I would have voted yes, but I
4 really -- given my previous vote that I can't determine
5 the efficacy, I just cannot bring myself to say yes. I
6 understand the patients critically need a new drug to
7 help, but sometimes a new drug does not necessarily
8 equal the same efficacy and seem better. So that's why
9 I voted a no.

10 DR. CONNETT: This is John Connett. I voted
11 yes. I'm not totally happy about it, but I think based
12 on what we have at hand, that's where we have to go.

13 DR. MORRATO: Elaine Morrato. I voted yes. I
14 think this was a difficult vote for me. We heard from
15 patients and families living with cystic fibrosis that
16 there's clearly a very strong remaining unmet medical
17 need. The disease is life-shortening with great
18 suffering. And despite advances, there's still
19 desperate need for new therapies. We also heard that
20 some patients truly responded to the therapy, and we
21 heard their stories, and that was very compelling.

22 On the other hand, the average data that we

1 were also shown shows a much more modest effect. In
2 fact, some patients did not have the benefit that
3 others were mentioning. However, I think the risk of
4 patients to continue to take a drug that they're not
5 benefiting from can clearly be managed in clinical
6 practice given the close patient management.

7 I do remain worried, perhaps similarly to
8 Dr. Yu, about the fallacy and the argument that this
9 regulatory requirement to demonstrate individual
10 benefit and the contribution of the individual
11 components is moot. There's a lot of historical
12 precedence to why this approach is necessary for
13 combination projects.

14 So ultimately what do we do given the data? I
15 felt you either deny a combination product where there
16 is evidence it is benefiting some patients or you
17 expose patients to this theoretical added benefit that
18 hasn't been demonstrated that meets the regulatory
19 requirements. And I felt given where we are today, I
20 decided to err on giving patients access to the
21 medicine given the tremendous unmet medical need.

22 I don believe that there is need or benefit

1 for greater prospective clarity, if you will, on what
2 is clinically meaningful benefit. I think part of my
3 struggle with this is that you're seeing as this drug
4 is being used in different types of genetic
5 defects -- as expected, you're going to see different
6 levels of efficacy, and so to what degree is enough
7 enough? So is a 2 to 3 percent increase one time on
8 average in a year good enough in light of a continual 1
9 to 3 percent annual decline over a lifetime and so
10 forth?

11 We saw evidence of 10 percent versus 5, versus
12 thresholds of 2 percent. And I think it would help in
13 the future to have a better sense of if 2 percent is
14 really a meaningful benefit, then it should be stated
15 from the front.

16 DR. HARKINS: Michelle Harkins. I voted yes.
17 I did think that there was efficacy. I do think this
18 is a much needed advancement for patients with CF. I
19 also enjoyed Dr. Connett's comment of the hierarchical
20 studies. I'm not a statistician, but the fact that
21 there are still positives, even though they're not
22 really allowed to be looked at, is something that we

1 really should think about.

2 DR. OWNBY: Dennis Ownby. I voted yes. I
3 felt that while no drug is ever perfect, this is a
4 group of patients that almost a hundred percent are
5 taken care of in specialty centers. And I have a lot
6 of faith in my colleagues who run those centers that
7 they will monitor the patients and will quickly decide
8 which patients are getting substantial benefits and
9 which may be having adverse effects.

10 I also think, as I mentioned earlier, that the
11 long-term potential here is wonderful for patients, but
12 also the potential that this will lead to continued
13 investment in this area and hopefully the development
14 of much better agents in the not-too-distant future.

15 DR. TRACY: Jim Tracy. I voted yes. From the
16 very beginning I've struggled with the 2 to 3 percent
17 and what that really meant clinically. Those concerns
18 were relieved. The study did meet its primary
19 endpoints in spite of a myriad of issues regarding
20 study design. As a result, I felt it met the
21 regulatory requirements for both efficacy and safety,
22 and I'm reassured by this as a very closely followed

1 group of highly devoted patients and families.

2 DR. OWNBY: Ms. Motenko, are you with us?

3 MS. MOTENKO: Can you hear me?

4 DR. OWNBY: Yes.

5 MS. MOTENKO: Great. This is Stacy Motenko.

6 I voted yes. I really feel that there is strong
7 evidence for the efficacy and safety data for the
8 approval of the combination. I heard from patients
9 that there were a lot of benefits described today that
10 really provided proof the efficacy is made
11 [indiscernible].

12 As a CF patient myself, I really can truly
13 understand how much a small amount of FEV1 increase can
14 impact the quality of life and how meaningful that can
15 be. So definitely yes, please.

16 DR. OWNBY: Thank you.

17 DR. GRAYSON: Mitchell Grayson. I voted yes
18 for pretty much all the reasons that have been stated.
19 I can't say whether monotherapy would be equal or
20 better or not, but that really wasn't the question.
21 The question is what we have in front of us now, and
22 from the data I saw, it to me seems efficacious and

1 safe.

2 DR. CASTILE: Bob Castile. I voted yes. I
3 was particularly impressed with the lack of decline in
4 FEV1 over the 48 weeks of data that were presented, and
5 probably even more impressed with the steady increase
6 in the BMI over the same period. I think any reduction
7 in exacerbation is extraordinarily important to this
8 patient group. Balancing that against what I think was
9 minimal risk with appropriate monitoring made it very
10 easy to vote yes.

11 DR. OWNBY: Thank you all. Before we adjourn,
12 are there any last comments from the FDA, Dr. Durmowicz
13 or Dr. Chowdhury?

14 DR. DURMOWICZ: There are no major comments.
15 I think that we would like to thank the advisory
16 committee members and ad hoc members for coming and
17 sharing their viewpoints on what we thought was kind of
18 a difficult issue at times to tease things out, as well
19 as the CF community for coming and sharing their
20 feelings and viewpoints as well.

21 I'd also like to apologize to the people at
22 home for the issues regarding the telephone situation,

1 but fortunately it didn't deter us too long. Thanks.

2 **Adjournment**

3 DR. OWNBY: We will now adjourn the meeting.

4 Panel members, please take all your personal
5 belongings. Don't do what I did and forget my computer
6 last meeting. All materials left on the table will be
7 disposed off. Please remember to drop off your name
8 badge at the registration table so it may be recycled.
9 Thank you all for your attendance and your attention.

10 (Whereupon, at 3:53 p.m., the meeting was
11 adjourned.)

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