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Center for Biologics Evaluation and Research (CBER)
176th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Web-Conference
Silver Spring, Maryland 20993

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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

COMMITTEE MEMBERS	
Hana El Sahly, M.D.	Baylor College of Medicine
Paula Annunziato, M.D.	Merck
Henry H. Bernstein, DOO., MHCM, FAAP	Cohen Children's Medical Center
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
David Kim, M.D., M.A.	U.S. Department of Health and Human Services
Arnold Monto, M.D.	University of Michigan
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H.	Seattle Cancer Care Alliance
Stanley Perlman, M.D., Ph.D.	University of Iowa
Jay Portnoy, M.D.	Children's Mercy Hospital
Eric J. Rubin, M.D., Ph.D.	Brigham and Women's Hospital
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine & Children's Healthcare of Atlanta
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Dean Follmann, Ph.D.	National Institutes of Health
Clifford L. McDonald, M.D.	Centers for Disease Control and Prevention
William Petri, Jr., M.D., Ph.D.	University of Virginia School of Medicine
Vincent Young, M.D., Ph.D.	University of Michigan Medical School

GUEST SPEAKERS	
Alice Guh, M.D., MPH	Centers for Disease Control and Prevention
Lindy Bancke, PharmD	Rebiotix Incorporated
Ken Blount, Ph.D.	Rebiotix Incorporated
Greg Fluet	Rebiotix Incorporated
Lee Jones	Rebiotix Incorporated
Sahil Khanna, MBBS, M.S.	Mayo Clinic
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Ms. Maryann Webb	

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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 176th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. I'm Mike Kawczynski. I will be helping facilitate today's meeting along with our chair and DFOs. Throughout the day, you may hear me jump in or interject just in case there's some technical issues. But keep in mind, this is an all-day event, so sit back and enjoy the ride.

That being said, I want to hand this off to our chair, Dr. Hana El Sahly. Dr. El Sahly, if you're ready, take it away.

DR. HANA EL SAHLY: Good morning, everyone, and welcome to the 176th meeting of the Vaccines and Related Biologic Products Advisory Committee.

During the meeting today, we will be discussing the safety and efficacy data of Rebyota, which is a live fecal microbiota product with the requested indication of reducing the recurrence of

Clostridioides difficile infection, and individuals will have been previously treated with antibiotics for *C. difficile* infection.

Now we have one of our conductors, Peter Marks, for the introductory remarks from the FDA. Oh, the administrative announcements first from Sussan. That's what I was looking for.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. SUSSAN PAYDAR: Yes. Thank you, Dr. El Sahly. Good morning, everyone. This is Dr. Sussan Paydar. It is my great honor to serve as the designated federal officer, DFO, for today's 176th Vaccines and Related Biological Products Advisory Committee.

On behalf of the FDA, the Center for Biologic Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone to today's virtual meeting. Today, the Committee will meet in open session to

discuss the Biologics License Application number 125739 -- BLA 125739 -- from Rebiotix Incorporated, for a product, Rebyota (Fecal Microbiota, Live) with a requested indication to reduce the recurrence of *Clostridioides difficile* infection, CDI, in adults following antibiotic treatment for recurrent *Clostridioides difficile* infection.

Today's meeting and the topic were announced in the Federal Register Notice that was published on August 9th, 2022. At this time, I would like to introduce and acknowledge outstanding leadership from my division director, Dr. Prabhakara Atreya, and the excellent work of my team whose contribution has been critical for preparing today's meeting.

Christina Vert is my alternate designated federal officer and will be supporting me throughout the meeting today. In addition to Christina, other staff who contributed significantly and provided excellent administrative support are Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lashawn Marks.

I also would like to express our sincere

appreciation to Dr. [sic] Michael Kawczynski in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings.

Please direct any press and media questions for today's meeting to FDA's Office of the Media Affairs at FDAOMA@fda.hhs.com. The transcriptionist for today's meeting is Ms. Linda Giles.

We will begin today's meeting by taking a formal roll call for the Committee members and temporary members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name. When finished, you can turn your camera off so we can proceed to the next person.

Please see the member roster slides in which we will begin with the chair, Dr. Hana El Sahly. Hana, you can start.

DR. HANA EL SAHLY: Good morning. Hana El Sahly, Baylor College of Medicine. I'm an adult

infectious diseases specialist. I see patients at Ben Taub Hospital, and my research expertise is in clinical vaccine development.

DR. SUSSAN PAYDAR: Great. Thank you. Dr. Paula Annunziato, our non-voting member industry representative.

DR. PAULA ANNUNZIATO: Good morning, everybody. My name is Paula Annunziatio, and I lead Vaccines Global Clinical Development at Merck. And as you just stated, I'm here today as the non-voting industry representative for the Committee.

DR. SUSSAN PAYDAR: Great. Thank you. Dr. Henry Bernstein. Hank?

DR. HENRY BERNSTEIN: Good morning, everyone. My name is Hank Bernstein. I'm a professor of pediatrics at the Zucker School of Medicine at Hofstra/Northwell. I'm a general pediatrician with expertise in pediatrics and vaccines.

DR. SUSSAN PAYDAR: Thank you. Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you. Good

morning. My name is Archana Chatterjee. I serve as the dean of Chicago Medical School and vice president for Medical Affairs at Rosalind Franklin University of Medicine and Science in North Chicago. I am a pediatric infectious diseases specialist and happy to be here. Thank you.

DR. SUSSAN PAYDAR: Thank you. Captain Amanda Cohn.

CAPT. AMANDA COHN: Good morning, everyone. I'm Dr. Amanda Cohn. I'm the pediatrician and medical officer at the Centers for Disease Control and Prevention with expertise in immunizations and vaccine-preventable diseases, and I'm happy to be here today. Thank you.

DR. SUSSAN PAYDAR: Thank you. Dr. Holly Janes.

DR. HOLLY JANES: Good morning. My name is Holly Janes. I'm a biostatistician faculty member at the Fred Hutch Cancer Center in Seattle with expertise in vaccine evaluations. Good morning.

DR. SUSSAN PAYDAR: Good morning. Thank you,

Holly. Captain David Kim.

DR. DAVID KIM: Good morning. This is David Kim. I'm the director of the National Vaccines Program in the Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health in the HHS. And I'm trained as an internist and versed in immunizations, in vaccine policy, and epidemiology.

DR. SUSSAN PAYDAR: Thank you. Dr. Arnold Monto, our acting chair.

DR. ARNOLD MONTO: This is Arnold Monto. I'm not acting chair today. I am at the University of Michigan School of Public Health where I work on epidemiology and prevention of respiratory infections.

DR. SUSSAN PAYDAR: Dr. Paul Offit.

DR. PAUL OFFIT: Yeah, good morning. I'm Paul Offit. I'm a professor of pediatrics at the University of Pennsylvania School of Medicine and a pediatric infectious disease specialist at Children's Hospital of Philadelphia. My expertise is in the area of vaccines. Thank you.

DR. SUSSAN PAYDAR: Dr. Steven Pergam?

DR. STEVEN PERGAM: Hey, everybody. I'm Steve Pergam. I'm a faculty member at the Fred Hutch Cancer Center, and my specialty is infections in immunocompromised hosts.

DR. SUSSAN PAYDAR: Thank you, Steve. Dr. Stanley Perlman.

DR. STANLEY PERLMAN: Well, good morning. I'm a professor of microbiology and immunology and a pediatric infectious diseases specialist at the University of Iowa. My specialty is virology, particularly corona virology.

DR. SUSSAN PAYDAR: Thank you. Dr. Jay Portnoy, our consumer representative.

DR. JAY PORTNOY: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri Kansas City School of Medicine. I'm an allergist/immunologist in the division of allergy/immunology at Children's Mercy Hospital in Kansas City.

DR. SUSSAN PAYDAR: Thank you, Jay. Dr. Eric Rubin.

DR. ERIC RUBIN: Morning, everyone. I'm Eric Rubin. I'm at the Harvard TH Chan School of Public Health, Harvard Medical School, the Brigham and Women's Hospital, and at the *New England Journal of Medicine*.

DR. SUSSAN PAYDAR: Thank you, Eric. Dr. Andrea Shane.

DR. ANDREA SHANE: Good morning. I'm Dr. Andrea Shane. I'm a pediatric infectious disease physician at Children's Healthcare of Atlanta, and I'm a professor of pediatrics at Emory University School of Medicine. My area of interest is in pediatric diarrhea and its prevention. Thank you.

DR. SUSSAN PAYDAR: Great. Thank you, Andi. Next, we'll do a roll call of our temporary voting members. Dr. Dean Follmann.

DR. DEAN FOLLMANN: Yeah, hi. I'm Dean Follmann. I'm head of biostatistics at the National Institute of Allergy and Infectious Diseases. My interests include vaccines and clinical trials.

DR. SUSSAN PAYDAR: Thank you, Dean. Next is Dr. Clifford McDonald.

DR. CLIFFORD MCDONALD: Good morning, everyone. Yes, my name is Dr. Cliff McDonald, and I am the associate director for science in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention. My background is internal medicine, infectious disease, clinical microbiology in medical and epidemiology, with many years' experience tracking *Clostridium difficile*.

DR. SUSSAN PAYDAR: Thank you so much. Dr. William Petri. Bill.

DR. WILLIAM PETRI: Yes. Bill Petri. I'm adult infectious diseases at the University of Virginia with an interest in *C. difficile*. And good morning.

DR. SUSSAN PAYDAR: Good morning. Thank you. Dr. Vincent Young.

DR. VINCENT YOUNG: Morning. My name is Vincent Young. I am a professor at the University of Michigan Medical School. I'm an adult infectious disease physician with a research interest in the microbiome and *C. difficile* infection.

DR. SUSSAN PAYDAR: Thanks, everyone. Thank

you so much. We have a total of 18 participants, 17 voting and 1 non-voting member. So, thanks, everyone. With that, I'll read the Conflict of Interest statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, September 22, 2022, the 176th Meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Hana El Sahly is serving as the voting chair for today's meeting.

Today, on September 22nd, 2022, the Committee will meet in open session to discuss the Biologics License Application number 125739 -- BLA 125739 -- from Rebiotix Incorporated for a product, Rebyota (Fecal Microbiota, Live), with a requested indication to reduce the recurrence of *Clostridioides difficile* infection, CDI, in adults following antibiotic treatment for recurrent *Clostridioides difficile* infection.

This topic is determined to be a particular

matter involving specific parties, PMISP. With the exception of an industry representative member, all standing and temporary voting members of the VRBPAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subject to Federal Conflict of Interest laws and regulations.

The following information on the status of this Committee's compliance with the Federal Ethics and Conflict of Interest laws including but not limited to 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

Related to the discussions at this meeting, all members, RGE and SGE consultants, of this Committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purpose of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development

agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with Federal Ethics and Conflict of Interest law.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential for a conflict of interest created by a financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by Committee members and consultants, there have been no Conflict of Interest

waivers issued under 18 U.S. Code 208 in connection with this meeting.

We have the following consultants serving as temporary voting members: Dr. Clifford McDonald, Dr. Dean Follmann, Dr. William Petri, and Dr. Vincent Young. Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting. Industry representatives are not appointed as a special government employee and serve as non-voting members of the Committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the Committee.

Dr. Jay Portnoy is serving as the consumer representative for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

The guest speaker for this meeting is Dr. Alice Guh, M.D. and Medical Officer, Division of Healthcare Quality Promotion from Centers for Disease

Control and Prevention, Atlanta, Georgia.

Disclosure of conflicts of interest for speakers, guest speakers, and responders followed applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firms, its products, and, if known, its direct competitors.

We would like to remind standing and temporary members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion. Their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. El Sahly. Thank you. Dr. El Sahly?

FDA INTRODUCTION

DR. HANA EL SAHLY: Thank you, Sussan. Next, we have the FDA introduction of the meeting today. This will be provided by Dr. Peter Marks, who is the center director at the Center for Biologics Evaluation and Research. Dr. Marks?

DR. PETER MARKS: Thanks very much, and good morning to everyone, or good day if you're located someplace else other than the east coast of the United States. We really appreciate everyone joining today. I want to, first of all, thank the Committee members for their time today, thank those from FDA who helped organize this meeting, thank our presenters, and we'll look forward to a productive meeting today.

This particular product that we'll be dealing with for consideration today from the sponsor Rebiotix is Rebyota, or BLA application 125739, is an interesting biologic product for consideration that I think will be very interesting for the Committee to discuss today. I would like to start -- and keep my

remarks relatively brief -- but start by noting that we are here today to discuss the Biologics License Application number 125739 for the product Rebyota.

There is, not today, going to be a discussion about our enforcement discretion policy. That is something separate. So I would ask today that, as we consider this and as we move forward, we can find our considerations to the biologics license application and to the information presented by the company, the FDA, and Open Public Hearing speakers in that regard and not wander into a discussion of our enforcement discretion policies, which is really a separate issue for separate consideration.

And with that said, I look forward to a very good discussion today. I think people will find the presentations quite interesting, and we really look forward to the Committee's considerations later today. Thank you very much.

DR. HANA EL SAHLY: Thank you, Dr. Marks. Now is the time to ask any questions to Dr. Marks. And I will begin by a question that, probably at the time of

submission of this packet, it probably wasn't an issue. And that is the emerging infectious diseases as we move along.

For example, a degree of circulation of poliomyelitis is going on in the U.S. and elsewhere. Who knows what the next vaccine-preventable or non-preventable disease that is going to start circulating in the population at the top clinical level? What are the, I guess, regulatory mechanisms that will be in place to continuously update the safety of such a product?

DR. PETER MARKS: Excellent question. I believe you'll hear considerations of this from both FDA and the sponsor because, obviously, biologic products have to be safe, pure, and potent. And in that, that means making sure that they are free from potentially communicable diseases. I think this will be a question of whether additional controls can be added into this.

This is not foreign to us at FDA because, if this were the Blood Products Advisory Committee, they

would've had to deal with the fact that we have similar things -- new infectious diseases come into the blood supply -- and if you're making plasma products and derivatives, one has to deal with those as they come in as well.

So I think this is one of these things that I think we can discuss today. But obviously, it has to be addressed in the manufacturing process given the nature of the product. And when I say manufacturing process, I mean including how one screens donors.

DR. HANA EL SAHLY: Okay. Thank you, Dr. Marks. My Committee members, any questions? I do not see any hands. Okay. Thank you, Dr. Marks.

Next is Dr. Qun Wang. Dr. Qun Wang is review committee chair at the Division of Vaccines and Related Biological Applications, DVRPA, Office of Vaccines Research and Review at the FDA. Dr. Wang.

BIOLOGICS LICENSE APPLICATION FOR REBYOTA

(FECAL MICROBIOTA, LIVE)

DR. QUN WANG: Okay. Thank you, Dr. El Sahly. Sound check -- can people hear me fine?

MR. MICHAEL KAWCZYNSKI: Yep, you're good.

DR. QUN WANG: Okay. Great. Good morning, everyone. We are here today at the Advisory Committee Meeting to discuss a Rebiotix Biologic License Application for Fecal Microbiota, Live, and also known as Rebyota. My name is Qun Wang from the Office of Vaccines Research and Review, CBER FDA. I'm the chair of the FDA review committee for this application.

During my talk today, I will give a brief introduction of the disease caused by *Clostridioides difficile* infection, followed by a description of the product, and an overview of the clinical package submitted through this BLA. I will then introduce today's meeting agenda and conclude with the voting questions to the Committee members.

Clostridioides difficile, or *C. diff*, is a spore-forming, rod-shaped, Gram-positive anaerobic bacterium that colonize through the fecal-oral route and causes *C. diff* infections. It is a common cause of

antibiotic-associated diarrhea and colitis. *C. diff* infection, or sometimes referred to as CDI, is an urgent public health concern associated with significant morbidity and mortality.

According to Centers of Disease Control and Prevention, there are about a half-million *C. diff* infections in the United States each year. In 2017, more than 12,000 deaths were associated to *C. diff* infection. And after the initial treatment of the *C. diff* infection, recurrent infection is common. About one in six of *C. diff* infections will recur in the subsequent two to eight weeks. This high recurrence rate of *C. diff* infections contributes to burden of disease and increased healthcare costs.

Recurrent *C. diff* infection is an episode of *C. diff* infections occurring within eight weeks of successful treatment of a previous episode. The most frequently reported risk factors for recurrent *C. diff* infections include advanced age for people older than 65 years old, prolonged use of antibiotics, and a weakened immune system, such as patients with severe

underlying diseases and immunocompromised conditions.

The treatment options for the recurrent *C. diff* infection include antibiotic treatments such as vancomycin and fidaxomicin. Bezlotoxumab is a human monoclonal antibody that binds to *C. diff* toxins and the only approved product for prevention of recurrent *C. diff* infection. It is indicated to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. Fecal microbiota for transplantation, or FMT, although unapproved by the FDA as the safe and effective for prevention of a recurrent *C. diff* infection, has been available under IND enforcement discretion.

The product Rebyota, or RBX2660, which is the name used under product development, is supplied as a pre-packaged, single-dose 150 mL fecal microbiota suspension containing 1 times 10 to the 8th to 5 times 10 to the 10th colony-forming units per mL. This product is for rectal administration, given 24 to 72 hours after the last dose of antibiotics for *C. diff*

infection, and the proposed indication is to reduce the recurrence of *C. diff* infection, or CDI, in adults following antibiotic treatment for recurrent CDI.

The applicant submitted a BLA to the FDA on November 30, 2021, to support licensure of Rebyota. The clinical package includes data from six clinical studies conducted in the United States and Canada. It includes three Phase 2 studies -- 2013-001, 2014-01, and 2015-01 -- and two Phase 3 studies -- 2017-01 and 2019-01 -- and then one retrospective study, 2019-02. Overall, 978 subjects exposed to at least one dose of Rebyota across all six studies.

The data from two randomized, double-blind, placebo-controlled studies, Study 2014-01 and 2017-01, highlighted in blue in this table, were contributed to a product effectiveness evaluation based on Bayesian analysis. In addition to these two studies, safety data from three open-label, uncontrolled studies -- 2013-001, 2015-01, and 2019-01 -- were pooled in the integrated summary of safety including six months of follow-up after the last dose of study treatment across

all studies. You will hear details of these clinical studies and data analysis from both the applicant and the FDA presentation today.

For today's advisory meeting agenda, after my introduction, Dr. Alice Guh from Centers for Disease Control and Prevention will discuss the current epidemiology of *C. diff* infection in adults in the United States. And then, the applicant's representatives will then present the development program of Rebyota.

After a short break, we will hear from Dr. Adewuni and Dr. Gao, the clinical and statistical reviewers of this BLA, to provide the FDA's presentation of the clinical safety and the effectiveness data.

We will take a lunch break shortly after 1:00 p.m. and then reconvene to start with the Open Public Hearing. We will take another short break before Committee members' discussion and voting. The meeting will be adjourned at around 5:00 p.m. this afternoon.

So the Committee is being convened today to

review and discuss presentations of safety and effectiveness data derived from studies conducted with Rebyota. The Committee will be asked to vote on the following two questions.

Question number one: Are the available data adequate to support the effectiveness of Rebyota to reduce the recurrence of *C. diff* infection, or CDI, in adults 18 years of age and older following antibiotic treatment for recurrent CDI? Please vote yes or no to this question.

Question number two: Are the available data adequate to support the safety of Rebyota when administered to adults 18 years of age and older following antibiotic treatment for recurrent CDI? Please vote for yes or no to this question.

And this concludes my talk. Thank you for your attention.

DR. HANA EL SAHLY: Thank you, Dr. Wang. Are there any questions from the Committee members to Dr. Wang? I do not see any raised hands. Thank you, Dr. Wang.

DR. QUN WANG: Thank you.

DR. HANA EL SAHLY: The current epidemiology of the *Clostridioides difficile* infection, CDI, in adults in the U.S. will be reviewed by Dr. Alice Guh. Dr. Alice Guh is at the Centers for Disease Control and Prevention. Dr. Guh. And I hope I said your name right. Dr. Guh is muted.

MR. MICHAEL KAWCZYNSKI: Ma'am, you have your own phone muted, Alice.

CDC PRESENTATION - CURRENT EPIDEMIOLOGY OF *CLOSTRIDIOIDES DIFFICILE* INFECTION (CDI) IN ADULTS IN THE UNITED STATES

DR. ALICE GUH: Sorry. Okay. I'm Alice Guh, and I'm going to be presenting the current epidemiology of *Clostridioides difficile* infection in adults in the United States. I have no financial disclosures.

The objective of my presentation is to describe the landscape of *Clostridioides difficile* infection, or CDI, in the United States in the past

decade.

I'm going to first begin with a brief background and a description of the epidemiology of CDI in earlier years. And then I'm going to focus on the current epidemiology, specifically changes in CDI incidence since 2011, the emergence of community-associated CDI, and lastly, review CDI recurrence and mortality.

Clostridioides difficile, or *C. diff*, is an anaerobic, Gram-positive, spore-forming gastrointestinal pathogen. Transmission usually occurs via the oral-fecal route. The clinical spectrum ranges from asymptomatic colonization to mild or severe disease with fulminant colitis and death. Risk of CDI increases with gut microbiome disruption and immunosuppression. Risk factors for CDI include antibiotic use, which is the primary risk factor, proton pump inhibitor use, advanced age, and chemotherapy.

Outbreaks of *C. diff* have been previously reported, including those involving clindamycin-

resistant strains in the late 1980s and early 1990s, but it wasn't until the emergence of ribotype 027 strain in the early 2000s that we saw a dramatic shift in the epidemiology of CDI with increased incidence, severity, and mortality. The number of hospital stays with CDI increased four-fold from 1993 to 2009, and *C. diff* mortality increased five-fold from 2000 to 2007.

During this period, CDI was also increasingly being detected in non-hospital settings in the community. In one state, more than 50 percent of healthcare-associated CDI had onset in nursing homes. And there were also reports of severe cases of CDI occurring in healthy individuals living in the community and among peripartum women.

This is just a little bit more information about ribotype 027. It first emerged in North America and was responsible for several hospital outbreaks with severe CDI in both the U.S. and Canada, with subsequent spread to other parts of the world. What's unique about ribotype 027 is it has high-level resistance to fluoroquinolones and produces more toxin than most

other strains. It's also more likely to be associated with severe outcomes and death. Although it's predominantly a healthcare-associated strain, it has been detected among community-associated cases.

To monitor the changing epidemiology of CDI in the U.S., the CDC has two surveillance systems for CDI: the National Healthcare Safety Network, or NHSN, and the Emerging Infections Program, or EIP. In 2013, CMS required acute care hospitals in all 50 states, D.C., and Puerto Rico to report CDI to NHSN. So, from NHSN, we have national data on a risk-adjusted measure of hospital-onset CDI which we refer to as a standardized infection ratio, which is derived by comparing the observed number of hospital-onset CDI with a predicted number of infections based on several factors. However, a large portion of CDI cases are not hospitalized and therefore would not be captured in NHSN.

So, to give us a more complete picture of the epidemiology of CDI in this country, we also utilized EIP which conducts active laboratory and population-

based surveillance for CDI in selected counties in ten states since 2011. EIP captures all healthcare and community-associated cases within the defined surveillance catchment areas, including those that are not hospitalized and diagnosed only in outpatient settings. They also receive isolates from a subset of cases. Because this is population-based and consists of diverse geographical areas, we've used EIP data to estimate national CDI burdens and to monitor changes in strain prevalence over time.

Now I'm going to focus on current epidemiology of CDI. We started the last decade with the burden of CDI near its highest level. 2011 was the first year that we used population-based surveillance data to estimate a national burden of CDI, and we estimated that there were 476,400 incident cases that occurred in the U.S. in 2011, with nearly 307,000 that were healthcare-associated cases and 170,000 that were community-associated cases. We also estimated that there were 239,000 hospitalizations with CDI in the U.S. in 2011. In fact, *C. diff* was the most commonly

reported healthcare-associated pathogen that year, accounting for 12 percent of healthcare-associated infections in U.S. hospitals.

Around that time, there were also changes in *C. diff* diagnostic testing practices that could've impacted CDI incidence rates. Nucleic acid amplification tests, or NAAT, used for *C. diff* diagnoses were first introduced in the late 2000s. There was also growing concern about the lower sensitivity of toxin enzyme immunoassays which led to increased use of NAAT for *C. diff* diagnoses.

Among EIP sites, CDI cases diagnosed by NAAT alone or as part of a multistep testing algorithm where NAAT is the final confirmatory test used increased from 55 percent in 2011 to 84 percent in 2016. Although NAAT use looked like it leveled off in 2017, it still remains consistently high for the subsequent couple of years.

NAAT is highly sensitive for toxigenic *C. diff* strains since it detects the toxin gene, although not the actual toxin, and it can lead to increased

detection of CDI. In fact, by switching from toxin EIA to NAAT, it's been shown that CDI incidence rates can increase by 43 to 67 percent. Therefore, it's important to account for the higher sensitivity of NAAT and changes in NAAT use when comparing CDI burden estimates over time.

With that in mind, this figure shows the national burden of CDI in the U.S. from 2011 to 2017. The dark-colored bars represent the annual burden estimate based on the NAAT usage rate for that year. You can see that, in some years, the burden of CDI exceeded half a million and decreased to 462,000 in 2017.

To account for changes in NAAT use over time, we adjusted the national burden of CDI by holding NAAT usage rate constant at the 2011 rate of 55 percent, and that's shown by the light-colored bars. We found that, after adjusting for NAAT, the national burden estimate of CDI decreased by 24 percent from 2011 to 2017.

This slide shows the national burden estimates of healthcare-associated CDI and community-associated

CDI from 2011 to 2017. After adjusting for NAAT, the national burden estimate of healthcare-associated CDI decreased by 36 percent from 2011 to 2017 whereas the adjusted national burden estimate of community-associated CDI remained unchanged during this period. This data indicates that the decrease in the total national burden estimate of CDI from 2011 to 2017 is primarily driven by the decrease in healthcare-associated CDI.

Similarly, when we look at data from NHSN, we see that from 2015 to 2020 there was a 48 percent decline in the national CDI standardized infection ratio, which again is the risk-adjusted measure of hospital-onset CDI. This supports not only the decrease in healthcare-associated CDI that we observed in EIP but also demonstrates continued decreases even beyond 2017.

Taking another look at data from NHSN, this figure shows the total number of hospitalized community-onset CDI as well as the total number of hospital-onset CDI reported to NHSN from 2015 to 2020.

This is the raw data without any adjustments made. You can see that there is continued decreases, even during COVID-19 pandemic, in both the number of hospitalized community-onset CDI, which declined by 55 percent over this period, as well as there was also a decrease in hospital-onset CDI which declined by 60 percent over this period.

When we look at what's been published regarding the impact of COVID-19 on the incidence of CDI in the U.S., we find that most studies reported no change or a decrease in healthcare-associated or hospital-onset CDI rates. Although, for some hospitals, especially smaller ones, the experience may have been different. In a large study of HCA Healthcare-affiliated hospitals, CDI was not found to be significantly associated with COVID-19 burden.

In another large study, this time including VA acute care and long-term care facilities, it was found that CDI rates significantly decreased during the pandemic compared to pre-pandemic period. However, the *C. diff* diagnostic test used by VA facilities have

changed which may have also contributed to the decrease. In a recent publication of NHSN data, the national CDI standardized infection ratio significantly decreased in all quarters of 2020 compared to 2019 with an overall decrease of 11 percent between these two years.

While there have been many studies looking at the impact of the pandemic on healthcare-associated CDI rates, there have been limited data available regarding community-associated CDI. We know from EIP that the 2017 to 2019 crude community-associated CDI rates remain relatively stable, but the 2020 data have not been finalized yet, although preliminary results suggest a decrease in community-associated CDI rates during 2020, which might be artificially low due to decreased outpatient visits and antibiotic use during the pandemic.

The decrease in healthcare-associated CDI is likely due to several factors. Over the past decade, there's been improvement in infection prevention practices in healthcare facilities with several

successful local and regional initiatives focused on CDI prevention. There's also been significant decline in ribotype 027 with *C. diff* in 2012, 21 percent being ribotype 027 compared with 15 percent in 2017. Nevertheless, ribotype 027 still remains the most common healthcare-associated strain in the U.S.

The decrease in ribotype 027 might have been partly driven by reduced fluoroquinolone use in U.S. hospitals as a result of intensified efforts to reduce inappropriate antibiotic prescribing. We know from the experience in England that restriction of fluoroquinolone prescribing can lead to drastic reduction of CDI. Importantly, there could have also been changes with *C. diff* diagnostic testing practices that might have impacted healthcare-associated CDI rates.

There has been increased emphasis on diagnostic stewardship, particularly in the inpatient settings, to reduce inappropriate testing due to the concern that NAAT might potentially overcall CDI. The continued decreases in healthcare-associated CDI might

also be partly driven by a recent shift back to toxin EIA over NAAT for reporting CDI. We noticed that, among EIP labs starting in 2019, there's been an increase in labs using a testing algorithm where toxin EIA instead of NAAT is the final confirmatory test. And this is similar to an algorithm used in England.

So what is known about community-associated CDI? There's a higher incidence of community-associated CDI among the younger population, although patients of community-associated CDI generally have a milder clinical course than those with healthcare-associated CDI. Those with community-associated CDI, about 31 percent may require hospitalization, and 11 to 14 percent may develop recurrence.

In terms of healthcare-related risk factors, two-thirds of patients with community-associated CDI had recent antibiotic use and more than 80 percent have had recent outpatient healthcare exposures. Although community-associated CDI patients have not had any recent inpatient exposures, those that are 65 years of age and older are more likely to have had remote

hospitalizations in the prior year.

Several non-healthcare sources of *C. diff* have been described. Toxigenic CDI strains have been isolated from various types of food, including root vegetables and retail meats, as well as from water and farm and domestic animals. Interestingly, there was a recent study in Europe of several *C. diff* strains where they found a distinct pattern of genetic relatedness that did not appear to reflect local person-to-person transmission but instead seems to suggest dissemination through another route, such as the food chain or from the environment.

Another way to look at the epidemiology of CDI in the U.S. is by this pie graph. As of 2019, 48 percent of CDI are healthcare-associated and 52 percent are community-associated. When we further stratified by location disease onset and healthcare exposures, we find that only 16 percent of all CDI are hospital-onset, 10 percent are nursing home-onset, 1 percent are LTACH-onset, and 21 percent are community-onset with recent inpatient exposures.

These four subgroups make up healthcare-associated CDI. When we look at the remaining half of the pie, 43 percent of all CDI are community-onset with recent outpatient exposures and only 9 percent are community-onset with no recent healthcare exposures. And these make up community-associated CDI.

So now I'm going to shift gear and talk about CDI recurrence. Majority of first recurrent episodes occur within eight weeks of the initial or prior episode. Risk of occurrence increases with each CDI episode as shown on the slide. When we looked at data regarding multiple recurrences that occur within 180 days after initial CDI diagnosis, we found that 5 percent may have 2 or more recurrences during this follow-up period, 1 percent may have 3 or more recurrences, and 0.2 percent were 4 or more recurrences.

Risk factors for recurrent CDI include advanced age, immunosuppression, prior CDI, infection with ribotype 027, and treatment of primary CDI with antibiotics can also be a risk for recurrence because

of disruption to the gut microbiome, although those treated with fidaxomicin have a low risk of recurrence compared to other antibiotic therapies. Recurrent CDI is associated with two-and-a-half-fold higher hospital readmission rate, four-fold longer hospital stay, and 33 percent higher mortality rate than primary CDI. Attributable healthcare costs for each recurrent case has been estimated to be nearly $11,000.

Most studies of CDI recurrence define it as a new CI diagnosis that occur within two to eight weeks of the prior episode. In one study that looked at trends of multiply recurrent CDI in the U.S. from 2001 to 2012 -- which, again, is the decade during which ribotype 027 had emerged and the epidemic of ribotype 027 peaked and incidence of CDI was at its highest -- we found that, during that period, multiply recurring CDI increased 189 percent.

The estimated national burden of first CDI recurrences was 84,600 in 2011 compared with 69,800 in 2017. However, after accounting for changes in NAAT use over this time period, there was no change in

adjusted recurrent CDI burden estimates.

In a subsequent analysis, we saw a 16 percent reduction and adjusted risk of 180-day recurrent CDI in 2018 compared with 2013. However, unlike previous analysis, this analysis used a longer follow-up period of 180 days instead of an eight-week period. And while it accounted for patient mortality, it did not adjust for NAAT use.

There might be several factors that could explain this decrease observed in 2018, mainly that there was a greater use or increased use of NAAT for diagnosing initial CDI in 2018 compared with 2013, which might have detected a greater proportion of patients with milder infections that might have been at lower risk for recurrence. In fact, when the analysis was restricted to patients with toxin-positive initial CDI, there was no change in recurrence rate between 2018 and 2013.

The observed decrease in recurrence rate in 2018 is less likely due to changes in treatment for initial CDI as only a very small fraction, 1.3 percent,

of initial CDI in 2018 were treated with fidaxomicin.

Looking at recurrence rates by epidemiologic class, this figure shows the crude CDI recurrence rates for healthcare and community-associated cases that were reported to EIP from 2011 to 2019. As expected, healthcare-associated cases had a higher rate of CDI recurrence compared to community-associated cases. But both healthcare and community-associated cases showed similar decreases in recurrence after 2016.

While we don't know the exact reason for this, I suspect that the increased use of NAAT during those years may have contributed to some of the decrease that we see in recurrence. As I previously mentioned, it wasn't until 2019 that we start to see an uptick in EIP labs switching back to toxin EIA from NAAT. So it'd be interesting to see whether the recurrence rate levels out or might even go back up a little bit after 2019.

Lastly, I want to give a brief overview of CDI mortality. All-cause mortality among patients with CDI has ranged from 11.8 to 38 percent. Since 2000, attributable mortality has ranged from 4.5 to 5.7

percent during endemic periods and nearly 7 percent to 16.7 percent during epidemic periods. Using the attributable mortality of 5.7 percent, we estimated that there were 11,500 deaths among patients hospitalized with CDI in the U.S. in 2019.

Several studies have shown increased mortality in older patients with CDI compared to those without CDI. In one study that used linked laboratory-confirmed CDI cases identified through EIP population-based surveillance with administrative data from CMS after adjusting for several factors, it was shown that persons 65 years of age or older have three times higher odds of mortality in the year following CDI compared to a matched cohort. And as you can see by the Kaplan-Meier survival curve, the higher probability of death among CDI cases was throughout the entire following year.

Several studies have utilized HCUP data to assess trends in CDI mortality, and most have found a decrease in in-hospital mortality among patients with CDI from the late 2000s to 2014. In one study, as an

example, as shown by this figure, in-hospital mortality decreased from 3.6 percent in 2004 to 1.6 percent in 2014. A greater decrease in mortality was observed in older patients compared to younger patients.

Decrease in mortality might be due to several factors, including decreased prevalence of ribotype 027. Also, there's potentially more patients being diagnosed that have milder infections since the increasing proportion of CDI are now community-associated and also due to increased diagnostic use of NAAT, which I've previously mentioned. It's unclear what role CDI treatment may have played.

In summary, the incidence of CDI and CDI mortality have declined in the U.S. over the past decade largely due to decrease in healthcare-associated CDI. There are several contributing factors, including decreased prevalence of ribotype 027 and increased emphasis on diagnostic and antibiotic stewardship. CDI recurrence rates appear to have declined in more recent years, again, likely due to several contributing factors including increased use of NAAT for diagnosing

initial CDI. Despite the decrease in incidence, the overall burden of incident and recurrent CDI is still substantial and is associated with high morbidity and costs.

An increasing proportion of CDI are now community-associated with a large portion of cases requiring hospitalization and could be contributing to transmission within the hospital setting. Majority of patients with community-associated CDI have had recent antibiotic and outpatient healthcare exposures, indicating that prevention efforts focused on healthcare delivery might still be effective for reducing community-associated CDI. Thank you.

Q&A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Guh, for this presentation. I want to invite my fellow Committee members to raise the hand electronically for questions directed at Dr. Guh. I will begin by asking whether the definition of CDI in your surveillance

system requires a two-step test? Or is it whatever that institution calls CDI?

DR. ALICE GUH: Right. So, for NHSN, it's really the final test that's put in the patient's medical record. So, irrespective of what kind of algorithm is used or whether it's a single test, it's whatever is determined to the final positive test.

Now, for EIP, it's any positive test. So, whether it's NAAT positive or toxin positive irrespective of what step of the algorithm, it does get captured within EIP so that we have an opportunity to look at the different ways that positivity of tests within the algorithm may or may not affect CDI rates.

DR. HANA EL SAHLY: Okay. All right. Thank you. Dr. Follmann?

DR. DEAN FOLLMANN: Yeah. Thanks, Dr. Guh, for the presentation. I had one question. You'd talked about a decrease in healthcare-associated CDI, also recurrent CDI. I was wondering if you had tried to correlate that with fecal transplant use in the U.S. and whether that has increased. And was that possible

to do?

DR. ALICE GUH: Yeah, that's a really great question, and that's something that, unfortunately, the way our surveillance system is set up, we aren't able to look closely at that information. Right now, we do chart reviews on only a subset of incident CDI cases. And often, these incident episodes are the patient's first primary episode and they have a recurrence; we are aware.

We capture whether they have a recurrence if it occurs within two to eight weeks from that incident episode, but we don't actually do chart reviews on those recurrent episodes. So, likely, if a treating clinician were to see the patient, if FMT were to be given, it'd probably be more for the recurrent episode which, unfortunately, our surveillance system wouldn't be able to capture.

But I can tell you, for what it's worth, sometimes patients may have more than one incident episode over time, as long as it's separated by about eight weeks. So, with subsequent incident episodes, we

sometimes may be able to do chart reviews on those.

So, when I did look at our surveillance data and understand the limitations I just described, a very small percentage -- it was about 1 percent -- had received FMT in 2019. But again, we mainly capture incident episodes. So, that, I think, is an underestimate of really how much FMT is being given in this country.

DR. DEAN FOLLMANN: Thanks.

DR. HANA EL SAHLY: Dean, thank you. Dr. Kim?

DR. DAVID KIM: Okay. Thanks very much. To help with the context of this entire discussion, I'd like to ask what incentives, and possibly disincentives, are there for healthcare facilities to report CDI for, say, CMS-quality measures and whatnot? And a related question to that is, do we have any information on asymptomatic cases of CDI and the impact that it might have on the overall CDI surveillance?

DR. ALICE GUH: Right. That's a great question. So, for the first question, I know that CMS, as part of their pay-for-performance, they have

required, in order for acute care hospitals to continue receiving reimbursement, that they do report hospital-onset CDI to NHSN. So, in that respect, we have pretty good confidence that the data reported to NHSN is fairly comprehensive in terms of hospital-onset CDI. In terms of -- and I'm sorry, your second question was about --

DR. DAVID KIM: Asymptomatic cases.

DR. ALICE GUH: Oh, asymptomatic. Sorry. Okay. So, in EIP, we don't require symptoms in order to meet the case definition. But as part of the chart review process, we do look to see if they have symptoms. And I'd say more than 90 percent, at least of the reported cases to EIP, do have diarrheal symptoms.

But I do understand what you're referring to in terms of the concern that, particularly with NAAT, it might be more likely to diagnose those who might be colonized or at least have mild infections. And I think that is definitely a growing concern and certainly contributing to the diagnostic challenges

experienced with *C. diff*.

DR. HANA EL SAHLY: Okay. Thank you. Dr. Portnoy?

DR. JAY PORTNOY: Thank you, Dr. Guh. That was a great presentation. I'm a little bit new to CDI infection in general. Am I correct in assuming that it's the toxin that actually causes the symptoms of CDI rather than some other factor? And if so, have you measured the amount of toxin produced by specific strains? Is there a way of doing quantitative measurements of that? And what factors would control how much toxin is actually produced?

DR. ALICE GUH: Yeah, no, those are really great questions. So, yes, you're right in that toxins, or the virulence factors of *C. diff*, are leading to a production of toxin and therefore causing disease. And we do know, from at least the experience of looking at ribotype 027, that it does produce substantially more toxins than most other *C. diff* strains. So there is a way to be able to measure that.

I'm trying to see if -- I don't know, there

might be more -- certainly, there has definitely been a lot of studies looking at that. I personally can't speak completely to the methods for how to do that. And in terms of what might lead to toxin production, we know that maintaining homeostasis in the gut microbiome is essential to preventing overgrowth of the vegetative cells of *C. diff*. That's the form that, once it germinates, can cause disease and lead to toxin production.

So, having a normal microbiome, minimizing disruption of the microbiome, and also the immune status of the patient -- if they're immunosuppressed and have disruption of the gut microbiome from other insults, whether it's antibiotics or other medication use -- could increase their risk of *C. diff*, therefore germinating and potentially causing disease or toxin production.

DR. JAY PORTNOY: But have you identified any factors from the innate microbiome that modulates the amount of toxin that's produced by *C. diff* if it's present?

DR. ALICE GUH: I know there have been a lot of studies looking at that. I don't know personally as well the field or the literature regarding that.

DR. JAY PORTNOY: Okay. Great. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Guh and Dr. Portnoy. Dr. Young?

DR. VINCENT YOUNG: Yes. In response to Dr. Portnoy, there are ways to quantify the amount of toxin both in *C. difficile* that has been grown in the lab in vitro as well as to directly measure the amount of toxin in feces. This is a number. They're bioactive. There are bioassays, and there are also some immunologic assays for that. And there are some controversies in the literature.

Generally, there's some papers that report that the greater amount of toxin might be associated with worse disease, but not all studies have shown that. So there are some. And it might be doing to the differences in methodology, whether or not they were looking at isolates in the lab, or they were trying to look in-site too within feces on a patient with

symptoms. But they can be measured.

DR. HANA EL SAHLY: Okay. One last question pertaining to fidaxomicin use. Are we seeing increasing use of fidaxomicin over time, especially in individuals at high risk of recurrence?

DR. ALICE GUH: Yeah. I mean, at least with our surveillance data, we haven't really seen, as one would expect, an increase in fidaxomicin use. But I know with recent updates to guidelines in more recent -- I think -- was it 2017 or '18? You know, it's possible, in the next couple years, we might start to see more of an increase. Our surveillance data does lag by a year or two, so it might still be too premature to really know.

As of 2018 at least, it was still a very, very small fraction. But I think also, with fidaxomicin always being a little bit more cost-prohibitive -- but I think, with further education, there may be other ways to make it more accessible to patients -- I could see that being used more often.

DR. HANA EL SAHLY: Okay. Thank you, Dr. Guh.

DR. ALICE GUH: Mm-hmm.

DR. HANA EL SAHLY: Thank you for the members. Next is the sponsor's presentation. We have five presenters on behalf of the sponsor. We're going to go through these presentations and then save the questions till the end. So I'm going to ask my fellow Committee members to jot down their questions, and we will be asking them after the five presentations.

So, on behalf of Rebiotix Incorporated, the first presentation is by Ms. Lee Jones who is founder and past president and CEO of Rebiotix. Ms. Jones is going to review Rebyota (Fecal Microbiota, Live) for patients with recurrent *Clostridioides difficile* infection.

SPONSOR (REBIOTIX INC.) PRESENTATION - REBYOTA (FECAL MICROBIOTA, LIVE) FOR PATIENTS WITH RECURRENT *CLOSTRIDIOIDES DIFFICILE* INFECTION

MS. LEE JONES: Good morning, Madam Chair, members of the Committee, and members of the FDA. I am

Lee Jones, founder and past president and CEO of Rebiotix Incorporated, a Ferring Company.

Over ten years ago, I founded Rebiotix to treat debilitating diseases by harnessing the power of the human microbiome, and I've worked closely with the Agency during our development program in this new therapeutic area.

We're pleased to be here today to share the data supporting the safety and efficacy of RBX2660 to finally provide patients with a treatment to end the recurrent *Clostridioides difficile* infection.

Recurrent *Clostridioides difficile* infection, or rCDI, is a rare, serious, and potentially life-threatening disease. CDI itself has been declared an urgent antibiotic-resistant threat by the CDC. It is the most common cause of healthcare-associated infections worldwide, affecting almost half a million people in the U.S. annually. It can result in diarrhea, colitis, and potentially sepsis.

Up to 30 percent of CDI cases recur at least once. Most often, patients are re-treated with

antibiotics, precipitating further episodes of the disease. Antibiotics contribute to the ongoing dysbiosis and do not address the underlying cause. This group of patients are those who have the highest unmet need. Because current choices for treating recurrent CDI do not address the underlying pathophysiology, desperate patients and their providers often turn to an unapproved fecal microbiota transplantation, or FMT, to end their vicious cycle of CDI recurrence.

The concept of FMT has been around for decades, and the promising results have made it a well-recognized platform, including in treatment guidelines. Despite the demand by patients and use by physicians, the accessibility of FMT remains limited. Additionally, there have been reported risks as both the donor screening and product manufacturing are at the discretion of the physician, which can lead to product variability. COVID has revealed further limitations of this industry, heightening the need for a scalable and regulated product, which is accessible

to patients with recurrent CDI.

Building upon the concepts of FMT, RBX2660 was designed to standardize microbiota restoration and address the underlying disease pathophysiology. RBX2660 is an intestinal fecal microbiota suspension delivered rectally that was developed as a drug product, including documented good manufacturing practices and quality controls.

It is standardized for potency with a controlled formula and manufacturing processes and stabilized for an extended shelf life. Lot-to-lot consistency is assured by release specifications for viable bacteria count, Bacteroide species growth, and phenotypic diversity count. Each pre-packaged 150 mL dose is manufactured from a single individual stool and contains a broad consortium of live microbes known to reflect a healthy microbiome.

RBX2660 was granted fast-track, breakthrough, and orphan drug designations based on the rarity and severity of disease and promising early results.

As with any regulated drug, oversight is

provided throughout the product's life cycle from donor screening, stool collection and validated quality control, manufacturing and shipping processes, through prescription, product receipt, and administration. With approval, pharmacovigilance would also continue to monitor for product safety.

Let me review the donor screening and collection processes in more detail, a key component to the development of RBX2660. Our donor screening process was built upon the foundation of other well-established programs such as that used in blood donations. Donors are routinely screened for infectious diseases, including COVID-19. They complete a health history questionnaire to access health and behavior at the time of every donation, and every donation is tested for 29 stool pathogens.

As with every regulated drug product, manufacturing processes and quality controls are in place, including but not limited to continuous process improvement, changed management, and product surveillance, all under the umbrella of the quality

management system. These processes have been developed proactively with input from the FDA as well as leading clinical experts in infectious diseases and evolved based on risks identified with emerging disease information. Together, these elements have provided a consistent drug product throughout our clinical program with no reports of disease transmission from the product to the patient.

RBX2660 is the first microbiota restoration therapy to demonstrate a statistically significant and clinically meaningful reduction in recurrent *C. difficile* with a favorable benefit-risk profile. The clinical efficacy is consistent with microbiome data showing restoration of gut diversity to a more normal composition.

The product has been thoroughly studied in a robust clinical development program consisting of six clinical studies beginning in 2013 and involving more than 900 patients. The body of clinical evidence collected demonstrates the safety and efficacy of RBX2660.

Later in this presentation, you will see that the overall data package supports the proposed indication to reduce the recurrence of *Clostridioides difficile* infection in adults following antibiotic treatment for recurrent CDI. You will know more at today's meeting with the following agenda: Dr. Sahil Khanna will describe the disease background and current unmet medical needs, Dr. Lindy Bancke will review the efficacy data in supporting this publication, Dr. Jonas Pettersson will review the safety data, and Dr. Colleen Kraft will conclude with her clinical perspective.

In addition to our presenters today, we have additional experts available to answer any questions you may have. All outside experts have been compensated for their time at today's meeting. With that, I'll now turn the presentation over to Dr. Khanna.

DR. SAHIL KHANNA: Good morning, everyone. Thank you for this incredible opportunity to speak today. I'm Sahil Khanna, a professor of medicine in the Division of Gastroenterology at the Mayo Clinic in

Rochester, Minnesota.

We've had a *C. difficile* clinic and a microbiome therapeutics program since 2012, managing over 500 patients a year who are suffering from recurrent or refractory *C. difficile* infections. My research has focused on the epidemiology, outcomes of *C. difficile*, along with development of model therapeutics and their outcomes for these patients.

As we heard, *Clostridioides difficile* is a serious infection that not only disrupts the patient's daily lives but can become life-threatening. There are an estimated half a million *C. difficile* infections and approximately 30,000 associated deaths in the United States every year.

Patients often wonder why they get *C. difficile* infection. The risk factors include use of antibiotics, advanced age, healthcare exposure, previous *C. difficile* infection, and several comorbid conditions.

Highlighting the severity of this infection, patients endure debilitating diarrhea, meaning anywhere

from 3 to 4 to upwards of 15 bowel movements throughout the day. These symptoms may last for months with recurrences. In addition to diarrhea, patients experience severe pain and fever, a decreased appetite, and the inability to eat leads to significant weight loss.

Patients experience severe dehydration and a sizable fraction, up to 40 percent from the community, end up in the hospital or in the intensive care unit. All of this often leads to patients developing anxiety, quarantining themselves from family and friends for fears of spreading the infection, and experiencing social isolation, greatly impacting their day-to-day life. *C. difficile* forces most patients to miss work and social activities.

Several options are available for patients to manage their first episode of infection. These include vancomycin or fidaxomicin or one of these antibiotics with added intravenous bezlotoxumab. Of these, vancomycin remains the most prescribed option, despite its known disruption on the gut microbiome.

Fidaxomicin is relatively gut microbiome-sparing and has lower recurrence rates compared to vancomycin.

Bezlotoxumab is another FDA-approved treatment when used concurrently with standard-of-care antibiotics for patients at high risk of recurrent disease. It reduces the risk of recurrence. Bezlotoxumab has extensively been studied in patients with one or two episodes of CDI and includes a warning for heart failure exacerbation. These treatment options do not address the underlying pathophysiology and do not restore the gut microbiome.

Despite treatment, upwards of 30 percent of patients will experience a recurrence of infection within eight weeks and then are most commonly treated again with antibiotics such as vancomycin with a taper-pulse.

This is now a smaller group of patients in the highest unmet need of treatment, yet still upwards of 50 percent of infections will recur because, while the infection is being treated, the microbiome is never being restored.

And if we continue to use antibiotics alone, we have upwards of 60 percent recurrence. However, now guidelines recommend restoring the microbiomes with the use of fecal microbiota transplant, or FMT, which drastically reduces the recurrence rates. Hence, the demand for FMT is so great.

Microbiome restoration is a viable fast way to prevent *C. difficile* recurrence. Patients in a healthy state have a diverse microbiome and a complex composition of bacteria. Upon exposure to risk factors for *C. difficile*, the microbial diversity lowers; the composition becomes simple. When people get exposed to *C. difficile* spores in the presence of a low diversity, the spores can germinate into vegetative forms leading to symptoms including diarrhea.

The antibiotics that are used to treat *C. difficile* infections are active against the vegetative forms but not the spores. These antibiotics, especially vancomycin, are active against the gut microbiomes from disposing people to a vicious cycle of recurrence. Restoration of the gut microbiota, both

through the diversity and composition with a microbiota-based therapy, often leads to resolution of *C. difficile* infection.

We've been using this approach successfully for many years. Despite not being an FDA-approved therapy, the demand for FMT from patients and the use by physicians is increasing. Here, I've plugged the FMT success rates after one treatment from various published trials -- treatment in green and controls, or the non-FMT group, in gray.

FMT has shown promising success rates among these patients that have failed first and second-line therapies. The overall evidence of efficacy mostly includes case theories, open-label clinical trials, or smaller randomized controlled trials, which were heterogeneous in methodology.

The increasing evidence supporting FMT has prompted updates to the U.S. treatment guidelines which now recommend FMT for treatment and prevention of recurrent *C. difficile* infection after multiple recurrences. The FDA additionally states, in the 2013

Guidance for Industry, the use of FMT to restore intestinal flora may be an effective therapy for the management of refractory *C. difficile* infection. The efficacy and safety profile of this intervention has not been yet fully evaluated in controlled clinical trials. To date, the use of FMT for CDI is under FDA's enforcement discretion.

Ideally, we'd like to restore the microbiomes sooner in the treatment landscape to help break the cycle of recurrence, but the field needs well-controlled studies to garner data supporting earlier use.

With screening processes in place, FMT is generally safe and serious adverse events attributed to FMT are rare. However, FMT in its current form has challenges due to its lack of standardization in donor screening, making the practice heterogeneous. At minimum, screenings should include a health screening for exclusion of conditions associated with an altered microbiome and exposure to infections.

Stool tests for donors should include enteric

pathogens, viruses, parasites, MDRO infections such as ESBL-producing organisms. Additionally, donors undergo blood tests for transmissible infections including HIV, viral hepatitis, syphilis, and many others. Any donor screening program should also be cognizant of emerging pathogens such as SARS-CoV-2.

While these procedures should be done, we know they're not consistently completed. Four separate FDA safety alerts have been published by the FDA since the June of 2019 which outline adverse events amongst recipients of FMT. Two alerts document transmission of pathogenic E. coli from donor to FMT recipients, some of whom became severely ill and some of whom died. These adverse events occur because testing for ESBL was not even being done, and insensitive tests for E. coli were being used. The other alerts concerned the potential for transmission of COVID-19, and most recently, monkeypox.

Due to all of these challenges, the inventory of FMT is limited. Most FMT distribution is now restricted to emergency use only or dependent on

individual physician development and administration, leaving many patients with recurrent CDI in need.

In view of current data, there are clear benefits of having a regulated, FDA-approved microbiome restoration therapy. Physicians and patients truly want and need a well-studied, well-characterized product with an efficacy and safety data that builds on our current understanding of FMT.

Approval of a microbiome restoration therapy would reduce variability and heterogeneity of the processes and preparation, improve access for this orphan patient population who suffer from debilitating symptoms, and finally give patients what they want -- the means to actively address the cycle of recurrence. Thank you. I'll turn the presentation to the sponsor to review the clinical data.

DR. LINDY BANCKE: Thank you, Dr. Khanna. I'm Dr. Lindy Bancke, head of clinical development at Rebiotix. I'll review the efficacy data for RBX2660 that was well studied in a robust clinical development program and demonstrated efficacy for the treatment of

recurrent *C. difficile* infection, a serious and rare disease in a very sick patient population. These data build on the established body of evidence from unapproved FMT.

The totality of evidence supporting RBX2660 comes from six clinical studies including two randomized studies, three open-label, and one retrospective study, all of which evaluated the reduction of CDI recurrence.

The Phase 2 Open-Label Study 2013 was the first in-human trial. This study demonstrated efficacy consistent with known treatment success rates from published FMT literature and a safety profile comparable to expectations for a microbiota restoration therapy. Based on this data, we began assessment of RBX dosing regimens to determine if one or two doses given one week apart would be optimal for the treatment of rCDI.

Today's presentation will focus mainly on data from the two randomized studies, Study 2014 and Pivotal Study 2017. Moving forward, we will refer to active

product simply as RBX.

Study 2014 was a Phase 2B prospective multicentered randomized double-blind placebo-controlled study, evaluating the efficacy and safety of RBX in adults with recurrent CDI. Patients were randomized one to one to one through three different treatment regimens. After completing a source of antibiotics to control their symptoms and prior to administering the first enema, all patients completed a 24- to 48-hour washout period.

In the first treatment course, all patients received two blinded doses or enemas. One group received two doses of RBX, a second group received one dose of RBX followed by placebo, and the third received two doses of placebo only. The second dose in all three regimens was administered one week after the initial dose.

Per CDC and clinical practice treatment guidelines, eight weeks is the standard definition of recurrence. Therefore, patients without any recurrence at eight weeks after the last dose were considered a

treatment success and continued follow-up for 24 months. Alternatively, treatment failures with a recurrence within eight weeks were offered the option to enter the open-label portion of the study which allowed patients to receive a second course of treatment consisting of either one or two doses of RBX with or without another preceding course of antibiotic therapy, and the clock for safety follow-ups was reset.

Study 2014 enrolled adults that met strict eligibility criteria to assess the efficacy of RBX. All patients had recurrent CDI with at least two recurrences following the primary episode and had completed at least two rounds of standard-of-care antibiotics, or they had experienced at least two episodes of severe CDI resulting in hospitalization.

This study excluded patients who were likely to experience recurrent diarrhea for reasons other than *C. difficile* infection, specifically those with a history of IBD, IBS, chronic diarrhea, or celiac disease. We also excluded patients who had a previous fecal transplant.

The primary efficacy endpoint was treatment success at eight weeks using the intent-to-treat analysis population defined as all randomized patients. Treatment success was defined as the absence of *C. difficile*-associated diarrhea at eight weeks after the last study enema. A CDI occurrence after this time was considered a new primary CDI event. Treatment failures were confirmed through lab testing, and outcomes were adjudicated by the DSMB. Those who discontinued prior to eight weeks after the last blinded study treatment or did not complete the assigned study treatment were also considered treatment failures.

Turning to demographics, baseline characteristics were representative of an adult patient population with recurrent CDI and were balanced across treatment groups. The mean age ranged from 58.8 to 63.6 years, and the majority of patients were female, primarily white, and enrolled from 21 sites across the United States and Canada. A mean duration of prior CDI events ranged from 17 to 20 days with an average of four previous episodes. About half of the patients

were hospitalized due to prior CDI episodes with a median duration ranging from 5 to 9.5 days. Most patients received vancomycin to treat CDI symptoms prior to blinded treatment.

Turning to the results, the two RBX treatment arms achieved treatment success rates of 56 percent and 57 percent at eight weeks compared to 43 percent of patients on placebo. The primary endpoint was not statistically significant at the final analysis. However, when comparing the two RBX treatment arms, we observed no meaningful difference in one versus two doses for the qualifying rCDI event. This provided the support needed to move forward with a single-dose regimen in the Phase 3 program.

We also allowed for a second open-label course of RBX treatment for patients experiencing CDI recurrence within the first eight weeks. Of the 19 failures in the single-dose RBX arm, 14 patients were eligible and opted for a second course of treatment. More than half of these patients reported treatment success after the additional eight weeks. Now I will

share the Phase 3 study.

Study 2017 was a Phase 3 prospective, multi-sensor, randomized, double-blind, placebo-controlled study. Due to the severity and rarity of disease, patients were randomized two to one to receive one dose of either RBX or placebo. Similar to Study 2014, all patients completed an antibiotic washout period followed by a single-blinded dose or enema in the first treatment course. Again, patients without any recurrence at eight weeks were considered a treatment success and were then followed for a total of six months after the blinded treatment.

Patients with a confirmed CDI recurrence were deemed treatment failures and given the option to receive open-label RBX within 21 days with or without another preceding course of antibiotic therapy or standard of care CDI therapy per the investigator's discretion. Those who received open-label treatment restarted the follow-up timepoints through six months.

Inclusion criteria allowed adults with only one or more prior recurrences of CDI to participate in

the study, or two episodes of severe CDI resulting in hospitalization in the last year. The trial excluded patients who were likely to experience recurrent diarrhea for reasons other than *C. difficile* infection, specifically those with a history of IBD, IBS, chronic diarrhea, or celiac disease. We also excluded patients who had a previous fecal transplant, investigational CDI vaccine, or monoclonal antibodies.

Baseline characteristics were well-balanced. Patients were, on average, 60 years of age, mostly female and white, enrolled from 44 sites across the United States and Canada. The mean duration of the qualifying CDI events was 25.5 days with three previous episodes. Twelve to 13 percent were hospitalized for a median of five days prior to study entry. And again, most received vancomycin as their antibiotic at screening.

The primary endpoint for Study 2017 was the same as prior Study 2014. Unlike Study 2014, the primary efficacy analysis was conducted in the mITT population. Patients who did not complete treatment or

discontinued prior to evaluation of treatment outcome, if not related to CDI symptoms, were excluded from the analysis. Discontinuations due to CDI symptoms during the blinded period were considered treatment failures. In order to evaluate durability of effect, we also identified loss of sustained clinical response through six months as a key secondary endpoint.

Shortly after enrollment began, increased availability of FMT products under FDA's enforcement discretion guidance unexpectedly made it even more difficult to enroll patients as there was limited desire for potential randomization to placebo. Originally, we planned to conduct two Phase 3 studies with approximately 300 patients each. Due to study enrollment challenges, we expanded the number of clinical sites. However, accrual rates continued to be far less than anticipated, significantly delaying completion of the pivotal Phase 3 study. Additionally, conducting another placebo-controlled study would have been challenging, as it would take about six additional years to complete.

FDA acknowledged these extenuating circumstances, and given the rarity of disease, agreed to the use of Study 2014 data by exploring other statistical approaches such as a Bayesian design. This approach would allow demonstration of substantial evidence of effectiveness for approval in a single Phase 3 trial. Incorporation of a Bayesian design was considered acceptable to the FDA, but this decision was not data-driven.

A statistical analysis plan was amended to include this approach while the study was still enrolling patients and before any data was unblinded for either interim or final analysis. The overall safety database also exceeded the number of patients required for thorough safety assessments and is particularly robust for an orphan-designated patient population. Additionally, this data is in the context of historical use and effectiveness of FMT.

The amended statistical plan used all data from Study 2017 and dynamically borrowed data from Study 2014. FDA agreed that use of an integrated

Bayesian efficacy analysis is supported by similarity of the studies and that the data are generally exchangeable. However, because the two studies are not identical, an approach based on hierarchical modeling with dynamic borrowing was considered appropriate. This means that the more similar the effect size observed in the two studies, the more the 2017 effect size would dynamically borrow for the final analysis. Only data from the single-dose RBX and placebo groups were borrowed, and this analysis applied only to the primary endpoint.

The outcome of the primary analysis is the posterior probability of a superior response rate for RBX in the 2017 study. The primary Bayesian analysis included two thresholds for statistical significance to assess the robustness of results. A higher threshold of 99.93 percent was used as the interim and final analysis and reflects a statistically very persuasive finding. Statistical significance of the primary endpoint would be met if the posterior probability at the final analysis was 97.5 percent or greater.

Now I'll review the disposition of patients in the primary analysis population. Of the 320 patients enrolled, 289 were randomized -- 193 to RBX and 96 to placebo. Twenty-two patients were not treated, and 5 discontinued prior to the eight-week efficacy analysis due to non-CDI related symptoms. Therefore, 262 patients are included in the mITT population -- 177 assigned to RBX and 85 to placebo. I will now review the results.

Here, I show RBX treatment success on the y-axis and placebo treatment success on the x-axis, a slightly different approach to a standard force plot. The diagonal line equals null benefits. Values above the line correspond to a superior response rate for RBX compared to placebo. The mean treatment different and 95 percent confidence interval from Study 2017 are plotted. And here is the treatment difference from 2014 alone. These lines reflect the independent analysis from the separate trials.

Now we add the Bayesian model treatment difference and credible intervals in light blue.

Notice the posterior distribution for the 2017 Bayesian analysis looks very similar to the 2017 data, with the reduction in the error bars largely attributed to the similar differentials in the treatment effect between the study. The model-estimated, treatment success rate was 70.4 percent in the RBX group and 68.1 percent in the placebo group.

The Bayesian interval does not cross the null, demonstrating that RBX is superior to placebo in the prevention of CDI recurrence through eight weeks of blinded treatment. In the initial primary endpoint analysis, this difference between RBX and placebo was 12.3 percentage points with a 98.6 percent probability that RBX was superior to placebo. While the higher significance threshold was not met, the 97.5 percent significance threshold was surpassed.

In addition to the initial primary analysis, here I show key analyses requested by FDA during BLA review. As noted in FDA's briefing documents, they recommended aligning the analysis populations and definitions to support a stronger claim of

exchangeability between Studies 2014 and 2017 and a more interpretable analysis.

Therefore, an updated primary efficacy endpoint analysis was performed using the Bayesian hierarchical model by applying the Study 2017 definition of the mITT population to the Study 2014 final efficacy data and also restricting the follow-up period in Study 2014 to eight weeks from first dose. The model estimated treatment success rates was 70.6 in the RBX group and 67.5 percent in the placebo group with a difference of 13.1 percentage points and a 99.1 percent posterior probability that RBX was superior to placebo.

FDA considers this to be the primary efficacy endpoint analysis. Additionally, we conducted a sensitivity analysis using these matched analysis populations and included number of prior CDI episodes as a covariant in the Bayesian hierarchical model. Once again, these results were very consistent with the refined primary efficacy analysis. Similarly, consistent treatment success rates were observed across

prespecified subgroups, including age, sex, race, previous episodes of CDI, and duration of vancomycin.

Moving to secondary endpoint results -- plotted here is time to CDI occurrence with the percentage of patients reporting an occurrence on the y-axis, which increased over time. As seen here, a greater proportion of placebo patients experienced CDI occurrence compared to RBX. We see early separation from placebo as reflected in the positive primary endpoint with the majority of occurrences observed during the first four weeks. This is the time period during which patients are known to be most vulnerable to CDI recurrence.

This separation between RBX and placebo was sustained with more than 90 percent of responders maintaining treatment success through six months of follow-up.

Similar to Study 2014, treatment failures within the first eight weeks could elect to receive a second course of open-label RBX treatment. Out of the 51 failures in the RBX arm, 41 patients were eligible,

and they elected a second course. More than half of these eligible patients reported treatment success after the additional eight weeks.

Further, in looking across the entire clinical development program, RBX demonstrated clinically meaningful treatment success with either one or two doses. Treatment success rates in the open-label and retrospective studies ranged from 75 to 83 percent. Results are consistent with our pivotal study, demonstrating positive treatment outcomes for patients with recurrent CDI.

In summary, the totality of data presented today offers substantial evidence of effectiveness supporting RBX2660. Pivotal Study 2017, using the Bayesian model, achieved statistical significance with a 99.1 percent probability of superiority of RBX over placebo. This result is supported by consistently favorable results across the entire clinical development program, a robust dataset for a serious and rare disease.

The statistically significant and clinically

meaningful results demonstrated by RBX build upon data from already used but unapproved FMT, providing a larger well-controlled dataset and a standardized approach for consistent efficacy and safety. With that, I will now invite Dr. Jonas Pettersson to present the safety results.

DR. JONAS PETTERSSON: Thank you, Dr. Bancke. My name is Jonas Pettersson, and I'm senior medical director at Ferring Pharmaceuticals. Today, I will present the safety data showing that RBX was well-tolerated with expected and manageable adverse events, and the safety profile was consistent across the clinical program.

The clinical development program provides a robust assessment of safety in more than 1,000 patients from the prospectively designed studies, including more than 900 RBX-treated patients.

The integrated safety population includes data from randomized controlled studies, open-label studies, and data from patients who received one or multiple doses of RBX. While the integrated safety population

provides the largest and longest assessment of safety, the placebo-controlled data from the Pivotal Phase 3 Study 2017 provides the best assessment of comparative safety data for the dose of treatment. It's also the largest controlled study in the program.

Study 2019-02 is a retrospective study. Therefore, it will not be presented today. However, this data can be found in your briefing materials.

First, I'll review the adverse events experienced by patients through the first eight weeks in Study 2017. We present these data slightly differently than the FDA, as this data censors patients if they are last to follow up or experience a CDI recurrence within this timeframe. This means that the adverse events after CDI recurrence are excluded regardless of presentation. Our conclusion and FDA's align.

Overall, RBX was well-tolerated with expected and manageable adverse events. The incidence of adverse events were higher in the RBX group compared to placebo. The imbalance was primarily driven by

patients with mild events across various system organ classes with no single class predominating. The incidence of moderate and severe adverse events were balanced between the two groups. Also, the incidence of serious adverse events were comparable.

One patient had an adverse event leading to death. Please note this is the same patient who discontinued and experienced a potentially life-threatening serious adverse event.

The most common adverse events occurring in greater than or equal to five percent of patients based on preferred terms were all from the gastrointestinal disorder system organ class and were balanced between treatment groups, as would be expected for the patient population with CDI. A similar proportion of patients experienced diarrhea, while more patients on RBX reported abdominal pain and nausea compared to placebo. These gastrointestinal events typically occurred early within the first seven days of starting treatment and were short in duration, lasting a median of two days for RBX and four days for placebo.

Overall, few patients experienced serious adverse events in either arm, none of which were deemed related to study drugs. Four patients on RBX experienced six serious adverse events, all of which were single events with no common etiology. One patient experienced a cardio-respiratory arrest that led to death. This is the death already shown on the earlier slide. One patient on placebo reported a serious adverse event. Other than the asthenia, which was noted as resolving a study exit, all non-fatal serious adverse events have resolved.

Let's now look at the safety data from blinded treatment through six months. The blinded safety profiles through six months aligns with the earlier profiles shown. More adverse events were reported in the RBX arm, which was driven primarily by mild adverse events. Four percent versus 2 percent of serious adverse events were reported. Here again, I show the one patient who experienced an adverse event leading to death through six months.

Here are the adverse events by severity in

Study 2017 for the first six months after blinded treatment, censored at CDI recurrence. Most adverse events occurred during the first two weeks on treatment. After this, the proportion of patients with adverse events declined in subsequent two-week intervals with consistent waves of adverse events between patients receiving RBX and placebo.

As a reminder, all treatment failures with a recurrence within eight weeks were offered the option to enter the open-label portion of the study, which allowed patients to receive a second course of treatment. Sixty-five total patients opted to receive an open-label second course of RBX -- 41 from the RBX blinded group and 24 from the placebo group. These patients were followed for six months from the point of re-treatment.

Here, we present the safety for those patients who experienced a CDI recurrence after a first course of treatment and elected to receive open-label RBX. When comparing these two groups, we see adverse events were comparable overall, serious adverse events were

higher in the group who received two courses of RBX, though again, no clear patterns were identified with single events reported across various preferred terms for these five patients. Adverse events leading to discontinuation were reported at five percent in the group who received two courses of RBX versus none in the placebo open-label RBX group, and one additional death occurred in this period.

Let me now review the deaths within this trial. One 75-year-old male died of cardio-respiratory arrest 37 days after RBX treatment. He suffered from a number of comorbid conditions, including multiple cardiovascular and central nervous system diseases. His death was reported as unrelated to the study drug as determined by both the investigator and the Data Safety Monitoring Board.

The second was a 79-year-old female with a history of cardiac disease, diabetes, cerebrovascular disease, and chronic kidney disease. She died 151 days after her last treatment with RBX. The cause of death was due to multimorbidity, and again, deemed unrelated

to study drug.

Now let's review the integrated safety population, first for the crude 2014 and 2017 blinded data, and then the full integrated population which includes 978 patients exposed to RBX across the five prospective studies. The total number of patients shown is the latest number, including the recent update from the ongoing study, 2019.

Please note that while all five perspective studies had six months of follow-up, Studies 2014 and 2015 had additional follow-up for 24 months. To standardize the duration of follow-up, the integrated analysis considers only adverse events with onset within six months of last treatment. This means that adverse events observed in 2014 or 2015 with onset beyond the six months after last treatment are not presented in this analysis.

Here is the pool data for blinded studies 2014 and 2017 through six months. Similar to the profile for each individual study, more adverse events were reported in the RBX arm, which was driven primarily by

mild events. Serious adverse events were balanced between groups. Adverse events leading to death occurred in five patients receiving blinded RBX, none of which were deemed related to study drugs.

Turning to the full integrated safety population, which provides the largest and longest assessment of safety, the "all RBX" group from the integrated safety population includes all patients who received one to four doses of RBX. This group represents a mix of the open-label and controlled studies.

It's also important to note that adverse events from patients that experience a CDI recurrence after receiving placebo are counted in the "all RBX" column if they received an open-label re-treatment. Again, most events were mild to moderate in severity and resulted in few discontinuations. The types of adverse events aligned with those observed in Study 2017 and were predominantly gastrointestinal-related.

Here I show a subset of the integrated safety database comparing those who received placebo only and

those patients who received a course of treatment that included only one dose of RBX. To be clear, those on placebo and RBX who failed first enema and received an open-label dose of RBX are not included in these columns. Across all studies, all patients who only received one dose of RBX had comparable outcomes to those who received placebo with the apparent exception of adverse events leading to death, which I will review on the next slide.

Here we present the adverse events with onset within six months after last treatment leading to death across all studies. Again, we must be cautious about making direct comparisons because the "all RBX" group includes the placebo patients who failed and were treated with open-label RBX. The placebo column does not contain these failures.

There were 18 adverse events leading to deaths, all of which occurred in the "all RBX" group. Fifteen of the 18 resulted in deaths within six months of last treatment. The other three adverse events occurred in the first six months but resulted in deaths

after that timepoint. Note the different observation of time in years for each group. The patients who received placebo had an overall observational time of 42 years, while the "all RBX" group had an observational time of 404 years.

That means that 91 percent of the overall observational time was from the "all RBX" group. Therefore, one would expect 91 percent of the deaths to be in the "all RBX" group. The observed distribution of death was within expectations. The numbers alone do not convey the full story. The adverse events leading to death were due to a broad diversity of causes. No clustering of pathologies occurred, indicating that the observed data do not constitute safety-related concerns with RBX. Finally, none of these deaths were plausibly related to RBX treatment. Each event has a narrative which was provided in your briefing materials.

There have been no confirmed infections transferred from a donor stool to a recipient throughout the clinical development program. As you heard, Rebiotix has worked to develop and implement

continued screening and active testing processes to mitigate the risk of transmissible pathogens and deliver a consistent drug product should RBX be approved. Furthermore, controls are in place to continually adapt the screening process of the donor program to mitigate any emerging pathogens. Additionally, with approval, a standard pharmacovigilance plan will be in place for RBX, an activity that does not currently exist for unapproved FMT.

So, in conclusion, overall, these data demonstrate that RBX was well-tolerated in an extensive safety dataset with expected and manageable adverse events. The overall safety profile was favorable with mostly mild to moderate adverse events. The types of events were mostly gastrointestinal-related, as expected. Serious adverse events and deaths were not plausibly related to RBX treatment, with most cases related to the underlying CDI and other comorbidities.

Importantly, the rigorous donor screening program successfully mitigated risks with no infections

transferred and will continue to be employed post-approval. Thank you. Dr. Kraft will now conclude the presentation with her clinical perspective.

DR. COLLEEN KRAFT: Thank you. I'm Colleen Kraft, an infectious disease physician and a professor of pathology in laboratory medicine at Emory University. I've been a faculty physician for 12 years and started our fecal transplant program in 2012. We have seen that use of FMT has been life-changing for so many of our patients. Antibiotics continue to be a mainstay in the treatment of *C. difficile*, but they can destroy the gut along the way. We usually think about the gut being like a garden, and instead of just continuing the weed killer, we also need to replant that garden.

Those of us who have spent years thinking and practicing in this realm have always understood that FMT, in its current variable form, is not a long-term answer for our patients. Given the amount of interest in probiotics and gut microbiomes, it was not hard to bridge that gap to a therapeutic that could work in

this fashion but be standardized enough to be regulated.

Recurrent CDI is a significant problem for patients and the healthcare community in general. There are no currently approved effective microbiome treatments available for recurrent CDI, though the severity of consequences makes it important that we find a treatment.

As Dr. Khanna noted earlier, the goal of treatment for CDI is to stop recurrence. And for many patients, this is indeed possible. For about 20 to 30 percent of patients, however, their CDI returns, and then the treatment paradigm becomes obscure and challenging.

Historically, antibiotics were used to treat recurrent infection and are still recommended, but we've learned that antibiotics can also precipitate the infection for some by destroying the natural gut microbiomes creating this ecological advantage for *C. difficile*. Bezlotoxumab, a monoclonal antibody, was approved to treat recurrent CDI but is not available to

or appropriate for all patients. And despite bezlotoxumab's approval in 2016, unapproved FMT is actually more commonly used as it's the only current therapy that acts on the underlying issue to restore the microbiome, and now it's included in the latest guidelines.

Microbiota restoration is an increasingly important type of therapy to end the cycle of recurrent infection, and now with RBX2660, we have an opportunity to make a well-tested, well-characterized treatment accessible to our patients.

RBX2660 offers meaningful and practical benefits. I've seen patients in the clinical setting go through rounds of antibiotics for over a year without success, and with each round comes recurrent debilitating diarrhea.

With RBX2660, you've heard that 71 percent of patients in Study 2017 were without a recurrence after only one course of treatment. This translates to a number needed to treat of eight, which is clinically meaningful. This means that, for every eight patients

I treat, RBX2660 will prevent one recurrence after only a single course of treatment. After two courses of treatment, additional patients are benefiting from RBX2660 treatment. Perhaps, most affirming is the full data package, which shows additional studies all demonstrating favorable response, and these data are aligned with what we'd expect of FMT.

In addition to the efficacy data, RBX2660 offers practical advantages that are tremendously satisfying for my patients and our clinic. It is an easy-to-administer treatment for a complicated disease that we've been dealing with for a long time. With RBX2660, physicians would have an in-office treatment via enema providing the patient with one less referral visit and a less invasive procedure than a colonoscopy.

For those of us who can administer FMT at our sites, it requires extensive mixing and complicated storage. And the potential for site-to-site variability and donor screening increases the safety risks.

RBX2660 comes pre-packaged and pre-mixed, and

the rigorous donor screening minimizes the risk of transmissible pathogens, allowing us to efficiently and consistently treat our patients.

I can't stress enough the importance of these practical benefits. While we know FMT can be successful, it can be challenging to develop or administer, so much so that we know some aren't using FMT due to its current complexity. Approval of RBX2660 would afford patients with access they're desperately seeking, particularly those in rural areas and areas in which there's a scarcity of donors, given COVID-19.

Now I'll turn to my review of the safety data. Overall, the safety data very much aligns with expectations for a microbiota restorative treatment. The events were mostly mild to moderate and were manageable. Long-term safety appears unchanged, and the safety of an additional course of treatment is consistent to the first without any accumulated risk.

Deaths on study were lower than the background rate observed for similar populations, which was reported to be around one to nine percent. And, while

the safety events are as good as or better than current FMT, the stringent donor screening and stool testing minimizes risks and provides a reliable safety profile without worry of transmissible pathogens.

So let me put all of this data into context. As you heard, RBX2660 builds on the knowledge already generated from FMT where we have efficacy and safety data supporting its use, robust enough to be recommended in treatment guidelines, but only after second recurrence since the data does not yet come from larger, well-controlled clinical trials. The RBX2660 dataset offers this well-controlled setting to corroborate our current understanding.

An approved product would also be scalable to meet the needs of patients and providers across the United States, something not currently available, and many of us are still mixing individual batches of FMT in our own centers or relying on expanded access treatment to treat our patients. The RBX product is generated under good manufacturing processes. And while individual centers can operate under GMP as well,

we have no way of knowing if it's consistently being done.

The same goes for the current screening processes. Yes, we have processes in place. But again, current FMT lacks accountability to ensure all execute to the same level of stringency. An approved product would allow for rigorous and consistent screening processes as well as safety surveillance to monitor the effectiveness of those processes. Approval without accountability is currently adapt in our treatment landscape. We need products like RBX2660 that are a clear advance on our current option of FMT.

To conclude, it's gratifying to see pivotal prospective data that in all ways substantiates and expands our earlier understanding of microbiome restoration therapies. The RBX2660 program has generated the type of rigorous evidence that could change practice and truly help our patients. Outcomes align with the goal of treatment -- to prevent recurrence. And the safety profile was well-tolerated by patients. The strict donor screening provides

reassurance to me that physicians like myself are able to treat patients effectively while minimizing inherent risks of donor-dependent products.

Approval of RBX2660 would be an important step toward meeting the unmet medical needs to provide a safe, effective, and importantly, consistent treatment to patients and physicians struggling to manage recurrent *C. difficile* infection. As I noted earlier, while antibiotics allow us to properly weed the gut garden, RBX2660 will concurrently allow us to restore the garden which is needed to maintain patient health. Thank you. Dr. Bancke will now return to moderate your questions.

Q&A SESSION

DR. HANA EL SAHLY: Thanks to the Rebiotix team for this presentation. Now I invite my fellow Committee members to raise the hand function in the system for questions to the team. We begin with Dr. Portnoy.

DR. JAY PORTNOY: Thank you. See, I learned my lesson. Hit the hand button before the presentation's over so I can ask the questions first.

As an evidence-based medicine thing, this is a treatment for a disease. So I always look for information about the benefits and the harms. You did mention a number needed to treat of eight, but I'm concerned about the difference between statistical significance and clinical indifference.

The difference in the improvement that the patients got -- the reduction in the frequency of recurrence -- was pretty modest, I think. It didn't look to me like it was a number needed to treat of eight; I'd like to see how that was determined. But that has to be compared to the number of harms, which is the number needed to harm, which you didn't present to us. It looked like, to me, that there was consistently more patients with adverse events with the treatment than with the placebo.

Now, what I want to know is, were the harms that occurred to those patients justified by the

improvements that the patients received by reducing their risk of developing a recurrence? And did you do a harm/benefit analysis? Because that's the kind of information I need to know in order to determine whether this product is safe -- is effective enough to justify the harms that could occur from it.

DR. LINDY BANCKE: The 13.1 percentage point treatment effect observed in a pivotal study does represent a treatment success rate for RBX of 70.6 percent, and that's compared to 57.5 percent of patients experiencing treatment success with placebo. Again, this does demonstrate statistical significance for a favorable Pivotal Phase 3 trial.

But to your question about clinical relevance, clinically meaningful impact of that treatment difference and the treatment success rates, I would like to ask Dr. Colleen Kraft to respond to your question.

DR. COLLEEN KRAFT: Thank you, Dr. Bancke. Colleen Kraft. While this study demonstrates the percentage we were looking at and the number needed to

treat that I already mentioned, this is indeed a very clinically meaningful result to our patients. Many of whom suffer, sometimes for years, with a debilitating diarrheal illness. And we also have really seen the interest in getting the standardized product and having the ability to trust what that treatment can do for them.

DR. JAY PORTNOY: But I wanted to make sure that the harms don't outweigh the benefits. Because if the patients are harmed by the treatment and they would be better off with just the placebo, then it's really not justified to use this product.

DR. LINDY BANCKE: Although we did not perform specifically a harm/benefit analysis that you had mentioned, I would also like to ask Dr. Sahil Khanna to provide his perspective on this data and clinical relevance to patients.

DR. SAHIL KHANNA: Dr. Khanna. When we look at the 13.1 percent point difference, we also start thinking about, what's the relative risk reduction? And doing the back end of calculations, relative risk

reduction is about 31 percent in this patient population. When I look at the risk-benefit ratio or the number needed to harm, I don't think that's a number that we can calculate because a lot of patients who initially receive placebo ended up getting the active RBX arms in open labels.

So the safety profile is the integrated safety profile. And when we look at the patients that we're treating in our clinical practice, I don't think there is going to be any additional harm because there is no difference in the data that we have seen in the active agent or placebos for the adverse events. The adverse events that we are seeing are (inaudible) very similar to what I see in my large FMT practice.

Over the last ten years, we've treated about 1,200 patients with fecal microbiota transplantation. We've done some studies looking at outcome adverse events. Predominantly, adverse events in the FMT profile are of gastrointestinal nature, similar to what we are seeing with this product. So there's no difference with the current unapproved FMT in terms of

the bigger adverse events that we are seeing from this product.

DR. JAY PORTNOY: Okay. Well, I have many more questions, but I'll get back in line and ask them later. Thank you.

DR. HANA EL SAHLY: All right. Dr. Offit.

DR. PAUL OFFIT: Yes. Thank you. I just had two questions; I'll ask them both and then listen to the answers. The first is there were statements made early on about making sure you had lot-to-lot consistency that you standardized through potency, but the range was fairly broad. From 1 times 10 to the 8th to 5 times 10 to the 10th colony-forming units is a 500-fold difference. I just wondered how one came to that range as an acceptable range.

The second question is a safety question. I know within our hospital when we do fecal transplants, we will occasionally see in patients who have long lines, a catheter-related infection presumably because there's a transient bacteremic event it seems, with the catheter. I just wondered whether or not you noticed

that as a possible problem when you did your studies. Thank you.

DR. LINDY BANCKE: For the first part of your question regarding lot-to-lot consistency and the specs that were identified for appropriate release of the product, I would like to ask Mr. Greg Fluet to respond to your question.

MR. GREG FLUET: Thank you, Dr. Bancke. Greg Fluet, CEO for Rebiotix, a Ferring Company. You're exactly correct. In our specification for product potency, we measure that based on CFU per mL. That potency range has been consistent throughout our clinical development program, and that was really defined early on in looking at the results of early experiments and formulation and stability testing to establish what was the range of potency we expected to see in that program.

Because of the desire to maintain that consistency throughout the clinical development, particularly because there's a complex biologic, the process itself is the product. We wanted to maintain

that consistency. We have not seen any justification to narrow it. It's actually reflective of a healthy human microbiome coming out of the processing of the manufacturing controls.

And I think, to your other question regarding the lot-to-lot consistency, this is also achieved not just from the release testing but from the consistent manufacturing process that we have used. We've used the same formulation and that same process throughout all the clinical studies.

DR. PAUL OFFIT: Thank you. And then, I guess, the safety question -- so I want you to answer that.

DR. LINDY BANCKE: And, Dr. Portnoy [sic], we may need to bring that back after the break or try to bring that data back after the break. I just wanted to confirm your question. Could you restate it just so we make sure that we have the right data pulled for you?

DR. PAUL OFFIT: Wait, Dr. Bancke, I just want to make sure that my catheter-related question gets -- I'm happy to go off-screen. I just want to make sure,

at some point, that I get the answer. But you can go to Dr. Portnoy. Sure.

DR. LINDY BANCKE: And can you restate the catheter question for us?

DR. PAUL OFFIT: Sure. Sorry, yeah. So, we do these fecal transplantations at our hospital occasionally. When that's happened, we've seen -- it's not common, but we've seen patients who have long lines that then develop catheter-related infections, presumably because with that fecal transplantation, there's a transient bacteremia. And then you see that line, and then you see a catheter-related infection with one or more of those organisms.

So I'm just wondering whether, in your extensive trials, you saw any of that. Thank you. And I'll go off-screen. I don't need to be on screen.

DR. LINDY BANCKE: Okay. We will try to come back to that question after the break. Thank you.

DR. HANA EL SAHLY: Okay. All right.

DR. JAY PORTNOY: What was the question again? You wanted me to restate my question about the number

needed to harm?

DR. LINDY BANCKE: No. My apologies. We got the information that we needed. I apologize; I called on you.

DR. HANA EL SAHLY: Thank you, Dr. Portnoy. Dr. Rubin.

DR. ERIC RUBIN: Okay. I think it's working. Can you hear me now?

DR. HANA EL SAHLY: We can hear you, yes. Please go ahead.

DR. ERIC RUBIN: Okay. All right. Thanks. Thank you for the presentation and showing us all those data. Essentially, what we're talking about here, though, is a standardized FMT product and it should work like FMT does. So, I'm just curious as to how -- there have been many RCTs of FMTs that have been published. How do your results fit in with all the other published material?

DR. LINDY BANCKE: Well, there is an established body of literature supporting the use and effectiveness of FMT. And again, we're building upon

that with our clinical development program with six studies. The real goal here is to provide a standardized product and process for consistent efficacy and safety. The FMT that has been utilized for decades now and is even included in the clinical practice treatment guidelines is heterogeneous and difficult to draw solid conclusions from.

So we've targeted a robust dataset to support a favorable safety and efficacy profile for RBX. We do not have head-to-head data with unapproved FMT, but I would like to ask Dr. Sahil Khanna to provide his perspective based on his extensive use of FMT and also his use of RBX.

DR. ERIC RUBIN: Yes. And, Dr. Khanna, I'm interested sort of more quantitatively. How do the efficacy and safety numbers fit in with other studies?

DR. SAHIL KHANNA: Absolutely. Sahil Khanna. I'm actually going to pull up a slide to show some numbers. A few years ago, our group did a systematic review and meta-analysis looking at various microbiome restoration therapies including FMT. And we had a very

interesting question to answer, which was, is the cure rate that you're seeing from FMT -- is it actually what is being shown in open-label trials or case series? We're seeing that 90 percent that gets said in the literature, and what we found was very interesting.

This was the slide from that meta-analysis that we did in our research group. When you look at clinical trials that are open-label, the cure rates are about 82.7 percent, much lower than even what you see in open-label case series. When we look at clinical trials that actually have a non-FMT competitor group, the cure rates are about 67 percent. And this has held true for many trials put together which have been done in the literature.

When we look at RBX clinical cure rates within the clinical paradigm of the trials that have been done, the numbers fall somewhere in between and are very close to the trials that are with the non-FMT competitor group.

I'm also going to pull up another slide here that's going to demonstrate just success rates with

some of the core presentation, CO-43, that looks at all of the different trials and their success rates, and ranges between 75 and 83 percent. And the clinical trial 2017-01 was in the same range.

So, when we're looking at FMT that's being done in a controlled setting, you're following patients in a controlled manner to actually see the lower cure rates which is very similar to what we are seeing in this clinical development program.

DR. HANA EL SAHLY: Okay. Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Thanks. I had a couple questions; I'll make them pretty brief. There's a description of the screening for stool pathogens, but as I went through the briefing, I could not see actually what that screening was and what specific pathogens are screened for. And then, as a second question, a lot of the descriptions of the populations at risk include immunosuppressed patients, but the studies did not include that population specifically.

I'm curious if either the company is planning

to do additional studies in those populations or if there's going to be, in the application, a specific black box warning for those groups. We know that there's been studies in microbiome in these populations and some have shown safety, but there is potentially additional risk in those groups, and I'd be curious how the company is going to be addressing that.

DR. LINDY BANCKE: Yes, we'll take both of your questions iteratively. We'll start with the first regarding the screening processes. And again, quality controls and a stringent donor screening process are really at the center of standardizing RBX for commercialization. I would like to ask Mr. Greg Fluet to provide a bit more detail on that process.

MR. GREG FLUET: Thank you, Dr. Bancke. Greg Fluet. I'd like to show one slide first just to review an element that was covered at a high level in our presentation. That is the extent of testing that is going on -- an ongoing basis for donor screening. As you mentioned, we do blood and COVID testing as well as the health questionnaires and donation testing in those

29 stool tests.

I would like to share another slide please. This is a full list of the tests that are being executed against, and this comprises all of the stool tests alone.

DR. LINDY BANCKE: And for the second part of your question, during the clinical development program, we have excluded some common comorbidities from the prospective trials simply so that we could test more robustly the safety and efficacy profile of RBX. With that said, we have iteratively expanded the eligibility criteria so that we can include a patient population more representative of the broader recurrent CDI population.

We actually have an ongoing, open-label Phase 3 trial, which is Study 2019-01, and in that study, we have allowed for some of these common comorbidities observed in the recurrent CDI population to be included. So we've included IBS, IBD, and importantly to your question, immunosuppressed patients who have also been allowed to enroll in the open-label trial.

So we do have some data to share from that patient population, and I would like to ask Dr. Jonas Pettersson to come to the podium for that.

DR. JONAS PETTERSSON: Okay. Jonas Pettersson, Ferring Pharmaceuticals. In the ongoing trial 2019, we have included patients with IBD and immunocompromised patients, and I would like to first show the results from the latest data cut and in patients with IBD. What we can conclude from that is the safety profile in patients with IBD appears comparable to that observed in patients without the disease.

However, because the number of patients with IBD was much smaller than those without IBD, there are limitations in this comparison. But overall, the data indicate that patients with IBD are not at higher risk than patients without IBD of treatment-related adverse events.

And then, to the immunosuppressed patients also eligible in the ongoing trial 2019, first, a slide where you can see which patient's onset of

immunocompromised that are included in this trial. We have patients with malignancies, end-stage renal disease, HIV, also patients on concomitant medications, corticosteroid use, and systemic immunosuppressive medications. And the safety, so far, are shown on the next slide.

Overall, the incidence of adverse events are comparable between immunocompromised and non-immunocompromised patients. We should note that we have 91 patients included in the immunocompromised group compared to 392 in the non-immunocompromised group. And we can see that we have, so far, more patients reporting serious adverse events in the immunocompromised group and also severe adverse events. But I think this is expected in this population with the diseases we saw on the previous slide.

DR. STEVEN PERGAM: Thank you.

DR. HANA EL SAHLY: Dr. Perlman.

DR. STANLEY PERLMAN: Yes. So I have a question about the study design. So, in all the studies that you did, you saw patients for eight weeks,

1 although mostly (inaudible) where you go for six
2 months. So does the efficacy disappear after eight
3 weeks? Or has this been designed over so many years,
4 so it's just based on the original non-controlled use
5 of these transplants? How do you end up with eight
6 weeks? In fact, is there efficacy beyond eight weeks?
7 **DR. LINDY BANCKE:** The minimum duration of
8 follow-up in the clinical studies in our program was
9 six months, and, in two of our Phase 2 studies, we
10 actually followed patients out to 24 months. I would
11 like to show you the slide from the core presentation
12 which provides a curve representing the sustained
13 clinical response rate in the Pivotal Phase 3 trial.
14 Again, this shows the full duration of follow-up.
15 So the eight weeks timepoint is denoted there
16 as the primary endpoint. We do see the separation
17 between active and placebo. However, we followed these
18 patients out to six months and essentially the last
19 timepoint collected for those individual patients. And
20 we see sustained treatment effects out to six months
21 with greater than 90 percent of (audio skip) still

reporting treatment success at that time.

DR. STANLEY PERLMAN: Okay. Thank you.

DR. HANA EL SAHLY: Dr. Janes.

DR. HOLLY JANES: Good morning. Thank you. I have two questions and perhaps a third, Dr. El Sahly, if you'll tell me if there's time for a third.

First question is rather simple. Thank you for the presentation. You mentioned this pre-specified Bayesian analysis which combines the data from the Phase 2B trial in 2014 and the Phase 3 trial in 2017, and you highlighted that it had been a pre-specified plan to do that combining of the data sources. I wanted you to elaborate on that. When you said pre-specified, was that pre-specified before the Phase 2B data analysis was done, before the 2014? Or only before the 2017 trial? So that's a clarification.

My second question is a bit more complex. It appears to me, from reviewing the data from these two studies that support the efficacy package, that the populations are potentially importantly different between the Phase 2B study and the Phase 3 study. So

it's notable that the treatment success rate is substantially lower in the Phase 2B population than in the Phase 3 population. And similarly, the adverse event rate is substantially higher in the Phase 2B population versus the Phase 3 population (audio skip) rated or has relevance in terms of the ability to combine data from the two studies for efficacy and safety.

So can you speak to that? Was that an expected result, or was it to be expected given the differences in eligibility criteria between the two studies? And then, Dr. El Sahly, I'll also have a statistical question about the manner in which the data were combined, but I can wait for that if you'd prefer.

DR. HANA EL SAHLY: I see that on the agenda there is mathematics and statistics later in the day. Maybe we should discuss that later. I have some questions on statistics too.

DR. HOLLY JANES: Great.

DR. LINDY BANCKE: So I'll start with your first question regarding incorporation of the Bayesian

analysis into the design. We were experiencing enrollment difficulties during the Pivotal Phase 3 study conduct, so that was Study 2017. We had initiated that trial and engaged FDA to discussion regarding our challenges. But also, with regards to the appropriateness of looking even at Study 2014 as an appropriate dataset to combine with the Phase 3 study, we believe that the data that was available at the time really gave us a good foundation for potentially looking at an innovative design for Phase 3 because it was so difficult to enroll.

So we discussed that with FDA and that was amended in the statistical analysis plan during active enrollment of Study 2017. So it was prior to any database lock, any data unblinding, for either interim or final analysis. We did not have any data in hand at the time other than the Phase 2B data, and that was incorporated into the final statistical analysis plan before any 2017 analyses were performed.

Regarding the populations, again, I think that's a really great question and part of the reason

that, during BLA review, we actually made some adjustments to the primary analysis for the primary endpoints. The two studies are substantively similar with regards to study design, patient population, the same product being used, route of administration, et cetera, so generally acceptable for exchangeability purposes.

However, it was noted by FDA that the studies could be further aligned by aligning the analysis population definitions, matching the populations for borrowing, as well as making sure that the primary endpoint assessment duration was equivalent when we made those adjustments.

Again, I would like to share the slide from the core presentation just so that we can compare what that data looked like relative to the initial primary analysis. We see, perhaps, more interpretable results with this FDA primary analysis in the middle row but very consistent treatment effects as well as posterior probability for the primary endpoint.

And then you also had a question with regards

to the safety of the Phase 2B study relative to the Phase 3 study. I would like to ask Dr. Jonas Pettersson to provide some additional detail around that comparison.

DR. JONAS PETTERSSON: Jonas Pettersson. We have, in the core presentation, presented pooled analysis of the 2017 and 2014. And the result from the 2014 alone is presented in your briefing materials. But I would like to show the data from the Phase 2 Study 2014 alone for the first eight-week, double-blind period. Patients were censored if they experienced a CDI recurrence within the timeframe.

Overall rates of adverse events, more moderate to severe adverse events in the RBX arms and more serious adverse events with RBX compared to placebo with higher rates in the two-dose group than one-dose. Those small number of events were reported across all arms. We looked into these events to assess for any discernible patterns. And I would like to show you the serious adverse event (audio skip) for period. And we can conclude that there were no clustering of serious

adverse events (inaudible) for short-term with only one patient experiencing any given serious adverse event.

Based on the narratives, which we reviewed, and types of events, we see no reason to believe a causal connection between these events. Investigators did not assess any of these serious adverse events as related to RBX. Based on these investigations as well as the fact that these trends were not recapitulated in the larger pivotal trial, our conclusion was that these findings in Study 2014, and especially in the group with two doses, are attributable to random chance events that can arise in small sample sizes.

DR. LINDY BANCKE: Thank you. I also would just like to remind the panelists that our proposed label will be for a single treatment course consisting of one dose of RBX for the treatment of a recurrent CDI episode, and again, that we have also incorporated first-recurrent patients for the very first time into the Pivotal Phase 3 trial where we had only included multi-recurrent patients, so a relatively sicker population in prior studies, including Study 2014.

But again, when adjusting for those prior CDI episodes, as a patient level covariant in the Bayesian model, we still see very consistent efficacy results.

DR. HANA EL SAHLY: Thank you. Dr. Bernstein?

DR. HENRY BERNSTEIN: Yes, thank you. I'm following up a little bit on the questions that Dr. Janes just asked. One of the things -- and I may have missed it, but could you expand a little bit of the details on why it turned out to be so challenging to enroll subjects if recurrent CDI is so common?

DR. LINDY BANCKE: Recurrent CDI is a subset of the overall CDI population, and it is a rare disease. We do have orphan designation for the reduction of recurrent CDI. During the course of the clinical development program, we did experience significant enrollment slowdown compared to the very first trial that we conducted. I would like to share a slide just to give you a visualization of that decreased enrollment.

As you can see in the very first study, 2013, we saw relatively high enrollment rates. It was around

that time that the Guidance for FDA Enforcement Discretion was finalized. And this began to have a significant impact on our ability to enroll the clinical trials, specifically the placebo-controlled trials. As you can see, Study 2014 here, as well as by the time we got to the Pivotal Study 2017, were very difficult to enroll because the potential randomization to placebo when other treatments, including FMT, may have been available outside of the clinical study paradigm.

DR. HENRY BERNSTEIN: Thank you. And then I had a second question, and that is, can you explain a bit more how you distinguish the severity of the treatment-emergent eight needs, including death, from treatment versus the pre-existing conditions? It seemed to happen right from the subjectivity of the investigators.

DR. LINDY BANCKE: These adverse events during the course of the clinical studies were assessed by the investigators as you noted with regard to severity as well as relatedness. However, in addition, we also had

DSMBs who were reviewing the data as well and did not find any of those investigator assessments to be inappropriate or needed to be changed. So it was all consistent with both investigator-level assessment as well as the oversight committee's assessment.

DR. HENRY BERNSTEIN: So there was consistency with the DSMB?

DR. LINDY BANCKE: That is correct.

DR. HENRY BERNSTEIN: Thank you.

DR. HANA EL SAHLY: Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: I have two questions. My first is actually concerning -- and I apologize, you're hearing my landline here from the background probably. But my first question is with regard to the lack of diversity among the participants in the clinical trials. It's of concern that there were very few people who were non-white that were included in the trials.

My question is, what is the sponsor doing to evaluate the product in non-white populations? The second question is, although recurrent CDI is really

relatively uncommon in the pediatric population, are there plans to study this product in the pediatric population?

DR. LINDY BANCKE: Thank you. To start with your first question regarding the lack of diversity in the clinical trials, we similarly noted, actually, very early on in the clinical development program, that the majority of patients enrolled were white. We did make deliberate attempts during the course of the clinical program to diversify the clinical study sites that we were selecting, in hopes that that would reflect similarly with a more diverse patient population being enrolled.

Unfortunately, we still continued to see the majority of patients being enrolled were white. We may attribute this to, unfortunately, healthcare disparities as this is not the only clinical program to see some of those disparities. Of note, we have paid very close attention to the post-COVID era. Although most of our studies were conducted pre-COVID, I think that there are some really key learnings that could be

applied for future trials in order to increase diversity of clinical studies in other clinical development programs for these microbiota-based products.

I also would like to respond to your second question regarding development in pediatrics. Because this does have an orphan designation, we are not required to have a pediatric development plan. So we do not have a pediatric plan at this time. However, we agree wholeheartedly with your notation that pediatrics are a very important part of this significant unmet need for recurrent CDI, so that will be considered moving forward.

DR. ARCHANA CHATTERJEE: Thank you.

DR. HANA EL SAHLY: Dr. Young?

DR. VINCENT YOUNG: Yes. I have a question regarding -- I'd like to return to the concept of consistency and potency. We have noted that potency was determined by determining CFUs present in each lot, which was a single donor human stool. And it's already been said that the process is consistent. But have

there been any analysis of the composition of the microbiota and trying to associate that with the variable efficacy seen from lot to lot?

DR. LINDY BANCKE: We have, in an exploratory manner, looked at the microbiome composition of drug products. We've also looked at the composition of patients themselves in order to identify, if possible, biomarkers or any baseline characteristics that may be indicative of a treatment outcome. We have not identified anything with regard to product or the patient characteristics themselves that would indicate that there is a predictive nature to the microbiome for either that would be predictive of response.

DR. VINCENT YOUNG: Okay. Thank you.

DR. HANA EL SAHLY: Does that include the microbiome at eight weeks?

DR. LINDY BANCKE: I'm sorry. Can you repeat that? The microbiome at eight weeks?

DR. HANA EL SAHLY: Yes, because that's the timepoint when the (inaudible).

DR. LINDY BANCKE: We did collect fecal

samples, again, in an exploratory way throughout the clinical trials. So we were able to look at both baseline as well as the eight-week timepoints and even out to six months. I would like to ask Dr. Ken Blount to provide additional detail around that data that was collected.

DR. KEN BLOUNT: Dr. Ken Blount, Chief Scientific Officer of Rebiotix, a Ferring Company. So, as Dr. Bancke indicated, we did conduct exploratory analyses of the microbiome composition. This included collecting fecal samples prior to and at various time points after treatment with RBX, sequencing them to determine the microbial composition at each time point. I'd like to share with you some of that data here.

What we observed in these studies was, first of all, on this graph -- I want to orient you. You're looking at the relative abundance of four key bacterial taxa that are normally found in the human gut. These are not the only four, but they are the four that we see the greatest changes in. Relative bacterial abundance of bacteroidia, as you can see, is denoted in

the baseline. This is a mean with confidence intervals.

At baseline, shown in red, bacteroidia and clostridia were decreased compared to a healthy population, representatives shown in green on those first two panels. In addition, the bacteria known as gamma-proteobacteria and bacilli were increased relative to a healthy population.

Now, specifically to your question, at least within one week after treatment, we saw a shift towards those healthier compositions. Specifically, you can see bacteroidia increasing, clostridia increasing as well, and gamma-proteobacteria and bacilli decreasing.

So, while these were exploratory analyses, they do show a shift back towards healthy composition, which was consistent with and supportive of the superior clinical efficacy for RBX.

DR. HANA EL SAHLY: So are -- what about the non-responders? They're not on this figure.

DR. LINDY BANCKE: Dr. Ken Blount.

DR. KEN BLOUNT: Per your question, the non-

responders are relatively limited. If we go back to Dr. Bancke's display of the clinical trial design, you'll recall that, upon recurrence, patients were treated with either an antibiotic by standard of care or an additional open-label dose. At that point, we were really required to censor the microbiome analysis.

So we had very few time points prior to that. Among the timepoints that we did observe for patients that occurred later, we saw less of the restoration that you observed here -- specifically less of bacteroidia, less of clostridia. Increasing with some persistence at four weeks, gamma-proteobacteria and bacilli.

DR. HANA EL SAHLY: Okay. Dr. Shane?

DR. ANDREA SHANE: Hi. Thank you very much for that great presentation. Actually, Dr. Chatterjee asked both of the questions that I was going to ask. So thank you very much for the responses to those. Thank you.

DR. HANA EL SAHLY: Thanks. And Dr. McDonald?

DR. CLIFFORD MCDONALD: Yes. Thank you for

that presentation. I have a question around the diagnosis of the primary or the precedent cases. I believe that in both studies, the Phase 2B and the Phase 3, you left it up to clinical practice whether they used a NAAT or an EIA or a toxin test or a nucleic acid test. And I think we've seen from other data that, when it's all based upon nucleic acid versus toxin, that you might see, in regression of the null, that maybe some of this is, in fact, colonization are more likely.

Now, of course, there's a difference in the Phase 2 -- so the question I'm asking you about is whether you've looked at the diagnostic assays used to diagnose the previous episodes and done any analysis on them. Now, specifically in the Phase 2B, I think -- and this is pointed out in your packet -- that the main difference between the Phase 2B and the Phase 3 study design was, I think, greater than two recurrences -- maybe you can help me there, exactly how you say that -- greater than two recurrences versus, I think, the first recurrence. And that may not be quite correct in

the Phase 3.

And so, again, in the Phase 3, I would be a little bit more worried about some regression to the null and just wondering if you looked at that at all, if you can follow that. So, just in terms of did you look -- do you have any analysis of the type of diagnostic assay used maybe in the most recent *C. diff* episode across these studies?

DR. LINDY BANCKE: Yes. As you noted, we did allow for a standard of care wherever possible to be implemented even as part of the clinical studies. So we did not dictate which antibiotic was to be used at screenings for the active infection, and we also did allow for standard of care testing for that active event to be standard of care. Predominantly, we see at least 70 percent of our patients coming into the study with PCR as the test method utilized for that qualifying event.

We did, post hoc, explore this as a sensitivity analysis, those patients that used PCR versus other methods. Again, small numbers in some of

those other categories because most were utilizing PCR for the qualifying event. We did not see any indication that that was having an impact on treatment outcome. But again, the intent, really, is to reflect what is being utilized as standard of care. And we still demonstrated, even with that approach, a statistically significant treatment effect in the Pivotal Phase 3 trial.

Before I answer the second part of your question with regard to the CDI episodes, I would like to give Dr. Sahil Khanna an opportunity as well to speak to his sort of clinical perspective with regard to evaluating these patients beyond just the test used.

DR. SAHIL KHANNA: Sahil Khanna. When we see a patient in clinic with suspected *C. difficile* infection, the diagnosis is clinical and not just reliant on a test. I'm going to pull up a slide that shows what my diagnostic practice within the clinic look like, and I think it's very similar to what's been used in this particular clinical development program.

One first needs to assess risk factors for *C.*

difficile, such as antibiotics and others that we've heard about earlier. One then needs to assess for presence of symptoms which was very well done on this clinical development program. Patients had diarrhea or abdominal pain or other symptoms. Then the third step is a positive test. I did a PCR on an enzyme immunoassay-based toxin assays.

And then, finally, if you're still confused in clinical practice, you try to get those patients a treatment for *C. difficile*, either vancomycin or fidaxomicin. And if, in a few days, their symptoms are low, then you consider those patients to have true *C. difficile*.

In this clinical program, it was very similar. Patients who were required to have a response to either vancomycin or fidaxomicin or a similar treatment before they could be randomized and they could be given a dose of this treatment. It's a very well-mirrored clinical practice -- very well-mirrored the real-world diagnostic and clinical setting.

DR. CLIFFORD MCDONALD: Thank you. Yeah, and

I would think that, if you had any -- there's another factor here, of course. It's not just the diagnosis but also the number of recurrences. And when you have more recurrences, you have a higher pretest likelihood of true *C. diff*. If anything, you'd probably be biased towards the null in your later study where you did not require as many recurrences.

Can I ask one more question about safety? Okay. Thank you for what we've seen in terms of the menu of tests being performed. And I think something that the chair mentioned right at the beginning, the reality that we live in now with emerging infections, especially emerging viral infections -- what's next? We don't know -- is there any quarantine period for product before release that you might -- do you have a process of, say, quarantine?

And I'm thinking specifically around when you have metagenomic samples ready to screen, as soon as some emerging disease came up where we had a sequence or you could start to look for sequence similarity. So, thinking a little bit ahead of the curve here for

safety in terms of maybe a quarantine interval where you don't release product right away. It's frozen anyway. Is there any intent on that or concept behind that or planning for that?

DR. LINDY BANCKE: Yes. That's a very relevant subject, especially considering where we are with COVID and monkeypox and some of these other things that we are monitoring for emerging threats so that we can ensure safety of the product and consistency of the product according to FDA guidelines. I would like to ask Mr. Greg Fluet to provide a little bit more detail around the process that we use for donor screening and manufacture.

MR. GREG FLUET: Thanks, Dr. Bancke. Thank you for that question, Dr. McDonald. It is dead on in how there are three really core elements of how we are maintaining an ongoing level of quality that we expect in safety and we expect of our product. But one is how we are monitoring for emerging threats and doing surveillance.

We have an active program that is part of our

quality management system -- again, part of our overall manufacturing controls as Dr. Marks referenced at the beginning of the talk -- that obligate us and we're committed to, and are auditable, to make sure that we are looking at CDC updates, Minnesota Department of Health updates, published literature on a monthly basis and reviewing it with our Medical Advisory Board to identify if there are any emerging threats. And this was kind of proved out in both the COVID and the monkeypox situations that Dr. Bancke referenced and how we were able to adapt our program in advance and in compliance with the FDA safety alerts.

We do have a quarantine period for all manufactured product. So, from the date of donation, that product is processed -- forward processed and stored in ultra-cold. And all product is quarantined until we have all of the completed testing in and (inaudible), and that typically is a four-month process. So we have that as a safety period associated with the quarantined product.

And in addition, because of the three-year

stability of the product because of the ultra-cold storage conditions, we maintained a goal of additional extra inventory on-hand, so that in the event -- and that's when we saw this in COVID and again with the hold for monkeypox -- we still have a sufficient inventory of product to maintain continuity of supply.

DR. CLIFFORD MCDONALD: Okay. Thank you.

DR. HANA EL SAHLY: I see no more questions from my members, so I'll ask a couple of additional questions I have here. In the two trials that are supporting the presentation today, there was a significant drop-off between ITT, mITT per protocol. And to get to per protocol, one, the subject has to be randomized to receive the product assigned and have follow-up at eight weeks to assess the endpoint. But the drop-off, at least in one of the studies, is almost half. Why is that? Why (audio skip)? Is it because we couldn't assess this eight-week mark? Or --

DR. LINDY BANCKE: Could I clarify that you're referring to the number of subjects in each of those populations?

DR. HANA EL SAHLY: Yes.

DR. LINDY BANCKE: So the approach utilized in the clinical program for ITT in the 2014 study was all randomized subjects. So any subjects who did not make it from randomization to treatment, which can be common because there is a gap between randomization and study drug administration, partly due to the fact that all subjects need to complete a course of antibiotics in that time, have a washout period, and then receive study treatment. So that required us to treat anyone who was randomized in the study but not treated as a treatment failure.

In the Study 2017 Pivotal Trial, we utilized the mITT population, focusing on lessons learned from that Study 2014, where the conservative approach even of treating those subjects that had dropped out from the studies, again, due to various reasons -- comorbidities, sickness of other types. That required us to take a very conservative approach. So, in the Study 2017, the pivotal trial, we identified mITT as the primary analysis population, where then we were

focusing only on subjects that had actually received treatment.

And those patients who were discontinuing from the study during that eight-week analysis period due to CDI-related symptoms were also treated as treatment failures. But if they discontinued due to a non-CDI-related symptom, they were excluded from the mITT population. So we tried to focus, as we moved through the program, on an analysis population that was really representative of those being treated with product.

DR. HANA EL SAHLY: Okay. Dr. Kim?

DR. DAVID KIM: I was following up on your response to Dr. Chatterjee's question earlier on characterization of the gut biome in different study subject and also in normal subjects. Our gut biome can change as we age and in response to external influences. In the Pivotal Phase 2B and Phase 3 clinical trials, the subjects were limited to adults aged 65 and older. I realize that these clinical trials do not have the power to address this question, but what consideration should there be regarding age-

matched donor-recipient correlation and possibly other variations in the product being offered?

DR. LINDY BANCKE: We do include, in both our donor screening program as well as the clinical programs, anyone who is 18 years of age or greater. We do see a greater preponderance in the clinical studies of more ages of patients being enrolled. But again, even in looking at, prospectively, these subgroups, I would like to share a slide, again, from the core presentation where we looked at age less than 65 or greater than or equal to 65.

And we do not see a difference between those two subgroups or an impact on efficacy. Again, we've only explored the impact of the donor in an exploratory fashion retrospectively. But again, we do not see any impact of donor on treatment outcomes either.

DR. HANA EL SAHLY: Okay. Thank you. So we reached the hour and a half for this presentation. Thank you to Rebiotix team and to the members for this engaging discussion. We will be taking a ten-minute break, and I turn the meeting over to Michael

Kawczynski.

MR. MICHAEL KAWCZYNSKI: All right. Thank you. And with that, members, remember just to stay online. But yes, we will be taking a 15-minute break. So please join us back here at 11:45 Eastern Time. Studio, if you would, please kill our audio.

[BREAK]

FDA PRESENTATIONS: REBYOTA (FECAL MICROBIOTA, LIVE): REVIEW OF EFFICACY AND SAFETY

MR. MICHAEL KAWCZYNSKI: Okay. Welcome back to the 176th Vaccines and Related Biological Products Advisory Committee meeting. I think I may have said we that we would've had a 15-minute break, but I only gave you 10. My apologies, but let's get started with our next portion of today's meeting. Dr. El Sahly, take it away.

DR. HANA EL SAHLY: All right. Thank you, Michael. The next item on our agenda today is the

presentation by the FDA. Dr. Omolara Adewuni will walk us through the Rebyota review of efficacy and safety. Dr. Adewuni.

DR. OMOLARA ADEWUNI: Good morning. I'm Omolara Adewuni, a medical officer in the Center for Biologics, Office of Vaccines Research and Review, Division of Vaccines and Related Products Application at FDA. I and my colleague will be presenting FDA's review of the effectiveness and safety of Fecal Microbiota, Live, RBX2660 in adults 18 years and older.

I'd like to start off by acknowledging the many contributions of my colleagues in CBER. This is the outline of the presentation today. I'll give an overview of the clinical studies that evaluated RBX2660. My colleague, Dr. Gao, from the Office of Biostatistics and Pharmacovigilance, Division of Biostatistics, will discuss the effectiveness of RBX2660. I will then discuss the safety of RBX2660 before concluding with an overall summary of the effectiveness and safety of RBX2660.

The clinical development program for RBX2660

included six studies that were conducted in the U.S. and Canada, all of which enrolled out of 18 years of age and older and would document their recurring C. difficile infection. The totality of evidence submitted to support live (inaudible) included five perspective studies, and one was the retrospective study.

The retrospective study was not included in our effectiveness or safety analysis. The perspective studies included two placebo controlled studies and three open-label studies. All of the perspective studies required subjects to have completed standard of care or antibiotic therapy with resolution of symptoms prior to initial treatment with RBX2660.

The number of subjects who received RBX2660 in the studies range from 34 in the first study, 2013-001, and 254 in the last ongoing study, 2019-01. There were two double-blinded placebo-controlled studies that support efficacy, the Phase 2 study, 2014-01, and Phase 3 study, 2017-01. These slides present the key differences between the two studies.

The treatment groups were different. So the 2014-01 had three treatment groups; Group A, where subjects received two doses of RBX2660; Group B, where subjects received two doses of placebo; and Group C, where subjects received one dose of RBX2660 and one dose of placebo; in comparison to Study 2017-01, with two groups of one RBX2660 dose and one placebo dose.

The number of doses were also different. In study 2014-01, subjects who received up to two doses of RBX2660 in the blinded phase and up to two additional open-label doses, for a total of four RBX doses in the study, one in Study 2017-01. Subjects who received one blinded dose of RBX2660 in the blinded phase and up to one additional open-label dose for a total of two RBX doses in the study.

The number of previous C. difficile infection at baseline was different. In Study 2014-01, subjects were required to have had two or more CDI recurrences after a primary episode and two or more rounds of standard of care antibiotic therapy at baseline prior to study entry. Once in Study 2017-01, subjects were

required to have had one or more CDI recurrence and one or more round of standard of care antibiotic therapy prior to study entry.

Administration of the dosage regimen was different. The two doses of RBX2660 was given seven days apart in Study 2014-01, while there was one dose in Study 2017-01. There was a 24-month safety follow-up in Study 2014-01 after the last dose, while there was a 6-month safety follow-up after the last dose in Study 2017-01.

RBX2660 was evaluated in several open-label studies and one retrospective study. However, interpretation of these open-label studies and the retrospective data was limited by lack of concurrent placebo control and the differences in the study population. Therefore, these open-label studies were not included in the discussion for RBX2660 effectiveness.

I will stop here and turn it over to my colleague, Dr. Gao, from the Office of Biostatistics, to discuss the effectiveness of RBX2660.

DR. ZHONG GAO: Hi, good morning. Thank you very much, Dr. Adewuni. So my name is Zhong Gao. I am from Division of Biostatistics, Office of Biostatistics and Pharmacovigilance, CBER, FDA. I am statistical reviewer on this BLA submission. My presentation will focus on the efficacy evaluation of the product. So let's start with Phase 2 Study 2014-01.

The primary objective was to evaluate the efficacy and safety of RBX2660 for prevention of CDI recurrence. The study population included subjects who had at least two recurrences after a primary episode and had completed at least the two rounds of standard of care antibiotic therapy or at least the two episodes of severe CDI resulting in hospitalization.

So, as Dr. Adewuni already introduced, this study included three treatment groups. The primary efficacy endpoint was treatment success. Treatment success was defined as the absence of CDI-associated diarrhea without need for retreatment with antibiotics or FMT at 56 days after administration of the last assigned treatment. The primary efficacy analysis was

the comparison between two enema of RBX2660 and the placebo group.

The secondary efficacy analysis included the comparison between the one enema of RBX and the placebo group and the comparison between the two enemas and one enema of RBX groups. Just to mention, the data from the one enema of RBX and placebo groups were to be borrowed for Study 2017-01 primary efficacy analysis. Here are the efficacy results of Study 2014-01. The primary efficacy analysis based on the ITT population yield an estimate of treatment effect 12.4 percent between the two enemas and the placebo groups.

For secondary efficacy endpoint analysis, the estimated treatment effect was 13.6 percent between the one enema group and the placebo group. However, the treatment effects were not statistically significant. Because Study 2014-01 did not demonstrate definitive evidence of effectiveness for a single dose of RBX2660, therefor, the applicant initially planned two independent Phase 3 trials. The planned sample size was about 300 subjects each trial. Total planned

sample size would be 600 subjects for 2 Phase 3 trials. Study 2017-01 was 1 of the 2 planned Phase 3 trials.

The primary objective was to evaluate efficacy of RBX2660 as compared to placebo in preventing recurrent episodes of CDI through eight weeks. The secondary objective was to evaluate the sustained clinical response rate of RBX versus placebo through six months. So, as the applicant already described in detail, the applicant encountered recruitment challenges. CBER and the applicant agreed to modify the study design to a Bayesian adaptive trial with data borrowing from Study 2014-01.

So, for Study 2017-01, the primary efficacy analysis was conducted on treatment success, which was defined as the absence of CDI diarrhea through eight weeks after the blinded treatment. So, regarding study population, 1 difference in eligibility criteria between Study 2017-1 and 2014-01 was that the Study 2017 included subjects with at least 1 recurrence of CDI and at least 1 round of standard of care oral antibiotic treatment for enrollment.

The intend-to-treat population included all randomized subjects, excluding those who exited prior to receiving blinded treatment. Modified intend-to-treat population -- Michael, you can hear me, right?

MR. MICHAEL KAWCZYNSKI: Yes, we can hear you, sir.

DR. ZHONG GAO: Okay. Great. The modified intend-to-treat population was the ITT population excluding subjects in whom treatment was attempted but not completed and the subjects who discontinued from the study prior to evaluation of treatment failure or success if the reason for exit was not related to CDI symptoms. The primary efficacy analysis was performed with a Bayesian hierarchical model formally integrating treatment success rates from Study 2014-01.

So this slide provides some very brief introduction on Bayesian Approach. The Bayesian Approach can help synthesize prior information with new information to update our knowledge about treatment effect. And there are three major components in the Bayesian Approach. First, historical data on treatment

effect provides information for prior distribution. Second, new data are acquired from a clinical trial which provides likelihood.

Even information from historical data in the clinical trial posterior distribution is generated to update probability distribution of treatment effect. So this slide provides some visualization of the Bayesian Trial design process. First, since the study would borrow historical data from Phase 2 Study 2014-01, it was important to evaluate exchangeability between 2 studies, so that is whether to studies are similar enough to warrant data borrowing. Second, a Bayesian model was formulated.

Third, simulation was conducted to evaluate a trial operating characteristics, including type one error, impact of historical data, study power. And the study success criterion were proposed for evaluation of treatment effect. Now we talk a little bit more about exchangeability of studies. So studies are considered to be exchangeable if clinical outcomes in future studies tend to be similar to those in previous

studies.

So this graph provides some visualization on the idea that exchangeable trials can be thought of as a representative sample of some super-population of clinical trials. So, in our case, both Phase 2 Study 2014-01 and the Phase 3 Study 2017-01 are considered as a part of a super-population of trials. The historical Phase 2 Study 2014-01 provides information on the super-population and, therefore, inform the current Phase 3 Study 2017-01. This enables Study 2017-01 to borrow strength from the historical Phase 2 Study 2014-01.

We acknowledge that the trials are similar but not identical in all aspects. Therefore, Bayesian hierarchical model was used to allowed dynamic borrowing, which means that the borrowing strength was dependent on similarity of effect of interest between historical and the target studies. In another words, the most similar between studies, more borrowing, less similar, less borrowing. This slide shows the Bayesian design of Study 2017-01.

Because of recruitment challenges, this study was modified to Bayesian adaptive design, borrowing efficacy data from Phase 2 Study 2014-01. And, at the design stage, the applicant and CBER evaluated similarity between those two studies. And the two studies evaluated the same product in dosage, route, and formulation, and were generally similar in study design and in study population. So, in this study design, there were two interim analysis that could stop the trial for futility or efficacy.

The posterior probability threshold for success at interim analysis was 0.99943. At the final analysis, the posterior probability threshold for success was set and adjusted at 2 levels, that is 0.9993 and 0.9750. And I will discuss more in the next slide. So the statistical evidence for the treatment effect was evaluated based on the posterior probability of superiority the for RBX group versus the placebo group.

The success thresholds were selected as analogues to frequentist the one-sided type 1 error

rate of 0.00125 and 0.025 without borrowing but utilizing the Bayesian posterior probabilities of superiority. The first and the more stringent success threshold may constitute statistical evidence that could potentially substitute two adequate and well-controlled Phase 3 studies. The second success threshold may provide the statistical evidence to declare success of the Phase 3 Study 2017-01.

As we discussed before, two studies were considered to be generally exchangeable. However, there are some differences between two studies, including analysis population definition, treatment success definition, and the primary efficacy endpoint assessment period. So, during the BLA review, FDA requested a refined analysis aligning these elements between studies. The goal was to improve exchangeability between two studies and to provide more interpretable information for regulatory decision making.

This slide shows Study 2014-01 efficacy data after alignment to Study 2017-01 definitions. The data

were incorporated into study 2017-01 primary efficacy analysis, that is the integrated Bayesian analysis. On this slide, the table shows the efficacy data for the mITT and ITT populations of Study 2017-01 only. For the mITT population, the treatment success rate was 71.2 percent for the RBX group while it was 62.4 percent for the placebo group.

So this slide shows the results of the refined analysis. The primary efficacy analysis using the mITT population yielded a model estimated treatment success rate of 70.6 percent in the RBX group and 57.5 percent in the placebo group. The difference in treatment success rates was 13.1 percent. The 95 percent credible interval was between 2.3 percent and 24.0 percent. This means that there is 95 percent probability that the true difference would lie between 2.3 percent and 24.0 percent.

The posterior probability that RBX2660 was superior to placebo was 0.991, which met the second success threshold but did not meet the first and the most stringent success threshold. The primary efficacy

endpoint analysis using the ITT population led to the same conclusion. So this slide shows the posterior probability distribution over different levels of treatment effect here, measured as the difference in treatment success rate between the RBX and the placebo group. And this is shown in the X axis.

And we're looking at the posterior probability for treatment effect in greater than the specific level. It is calculated as the cumulative probability or area under the curve to the right of the specific level. As we discussed before, the posterior probability of treatment effect being greater than zero percent was 0.991. The posterior probability of treatment effect being greater than 2 percent was 0.978. The posterior probability of treatment effect being greater than 5 percent was 0.930.

The posterior probability of treatment effect being greater than 10 percent was 0.715. Hopefully, this plot would provide a picture of posterior probability of different treatment effect levels. This slide shows the applicant's initial analysis on the

primary efficacy endpoint. The applicant initially used the non-final ITT data from Study 2014-01 as historical data because this data were used for evaluation of trial operating characteristics at the design stage.

The primary efficacy analysis using the mITT population yielded a model-estimated treatment success rate of 70.4 percent in the RBX group and 58.1 percent in the placebo group. The difference in treatment success rate was 12.3 percent. The posterior probability that RBX was superior to placebo was 0.986, which met the second success threshold but did not meet the first and most stringent success threshold. So, basically, the applicant's initial analysis led to the same conclusion.

And the applicant also conducted analysis on the secondary endpoint, which is the sustained clinical rate response in Study 2017-01 only. So sustained clinical response was defined as treatment success for the presenting CDI recurrence at eight weeks and no new CDI episodes during the six months of follow-up. For

the mITT population, sustained clinical response rate was 65.5 percent for the RBX group and 56.5 percent for the placebo group. The treatment difference was about 9.1 percent.

However, the difference was not statistically significant. The results for the ITT population were similar. The applicant also conducted additional analysis on the secondary efficacy endpoint. The applicant analyzed the time to CDI occurrence through six months after the blinded treatment. So it should be noted that this analysis was based on Study 2017-01 only. The (inaudible) plot showed some separation of curves between the treatment and placebo groups at eight weeks after treatment. The separation appears to have maintained until month five or six.

However, the difference was not statistically significant. So here is a very brief summary of efficacy evidence. Endpoint one, the primary efficacy analysis of Study 2017-01, which is integrated Bayesian analysis, showed that the treatment effect was 13.1 percent with 95 percent credible interval 2.3 percent

to 24.0 percent. And posterior probability of superiority was 0.991. The primary efficacy analysis results matched the less stringent second threshold for study success.

However, it did not meet the first and the most stringent success threshold. Point two, the secondary efficacy endpoint analysis yielded a similar trend with primary efficacy endpoint analysis. The treatment effect was about nine percent, but it should be noted that the difference was not statically significant. So this concludes the section of clinical effectiveness, and I will turn it back to Dr. Adewuni for clinical safety. Thank you very much.

DR. OMOLARA ADEWUNI: Thank you very much, Dr. Gao. I will now discuss the safety analysis and result. Safety assessment for the RBX2660 development program included solicited adverse events collected via subject diary in the first seven days after assigned treatment. The list of solicited events included gas or flatulence, abdominal distension or bloating, rectal irritation or pain, chills or severe shivering,

abdominal pain or cramping, increased diarrhea or constipation, rectal bleeding, nausea, vomiting, and fever.

In general, unsolicited adverse events were assessed for six months after the last RBX2660 exposure, whether it was blinded or open-label, and subjects were followed until the events resolved or they exited the study. Treatment emergent adverse events were unsolicited adverse events that occurred post RBX2660 exposure. The applicants retrospectively defined adverse events of special interest as terms identified using two standardized MedDRA Queries from multiple SMQs that we assessed for safety signal detection.

Serious treatment emergent adverse events were defined as adverse events that resulted in deaths, was life-threatening, resulted in persistent or significant disability or incapacity, resulting in hospitalization for 24 hours or more or prolongation of an existing hospitalization, congenital anomaly or birth defect, and an important medical event as defined as the

applicant.

FDA assessment of RBX2660 followed a tiered approach which included looking at individual studies and then drilling down to look at double blinded placebo-controlled studies, and then they integrated safety population, which included a single-dose population which is the proposed dose for licensure. The safety population included all subjects who received at least one dose of RBX2660. The blinded safety population from Studies 2014-01 and 2017-01 is presented on the left side on the slide.

In these two studies, a total of 83 subjects received at least 1 dose of blinded placebo, and 312 subjects received at least 1 dose of blinded RBX2660. The integrated safety population from the first perspective study is presented on the right side of the slide. In these studies, 749 subjects received one to four doses of blinded or open-label RBX2660.

As mentioned by the applicant, there were limitations and considerations when we interpreted the comparisons between the blinded and RBX groups in the

placebo-controlled studies, which included loss of randomization due to CDI recurrence. Randomization was no longer preserved between the blinded and placebo groups as a result of the exclusion of subjects who experienced CDI recurrence, and they moved onto the open-label RDX group, and the loss of placebo group due to the cross-over open-label RBX.

The subjects in the placebo-only group who experienced the CDI recurrence and received open-label RDX were removed from the placebo group. In the integrated safety analysis, there were additional limitations and considerations in the interpretating comparisons between the placebo and any RBX groups, which include the open-label nature of the many RBX2660 doses.

There was a higher proportion of subjects who received open-label RBX2660 due to the CDI recurrences, which may have slightly increased risk of adverse events from underlying risk factors that predispose to recurrent CDI or underlying comorbidities. And addition, subjects were followed for six months after

the last dose of study treatment, which resulted in longer follow-up duration for subjects who got multiple doses of RBX. Due to the differences in the design, a treatment course in the studies could result in one or two doses.

It could be open-label or blinded. And a subject could receive one or two treatment courses that represent a total of one to four doses of RBX. In this slide, safety population going forward is presented by treatment, dose, and study in this slide. In this table, I'm going forward in the safety analysis. I'll be presenting safety data by the following safety population. In the first column is the placebo-only group, where 83 subjects received 1 to 2 doses of placebo.

The next column is the blinded placebo group, where 193 subjects received 1 or 2 doses of blinded of RBX doses. The next column is the 1 dose RBX group, where 429 subjects received 1 dose of blinded or open-label RBX2660. And the last column is the any RBX2660 group, where 749 subjects received 1 to 4 doses of

blinded or open-label RBX doses. Shown here in the red box is the number of subjects who received one dose of double blinded or open-label RBX, which is the proposed dose for licensure.

The subjects here were mostly from the Phase 3 double-blinded Study 2017-01 and the ongoing Phase 3 open-label Study 2019-01. The subject disposition by treatment and dose in the safety population is displayed in this slide. The rate of completion between treatment and eight weeks follow-up was comparable but slightly lower in the RBX2660 group compared to placebo. The rates of completion between eight weeks and six months follow-up was slightly lower, more so in the RBX2660 group than in the placebo group.

Reasons for discontinuation was similar between the treatment groups and at eight weeks and six months, and the most common reasons for discontinuation was withdrawal by subject. The demographics and baselines characteristics are comparable between the placebo and the RBX2660 groups.

The mean age and range of age was similar between the placebo and the RBX2660 groups. However, there was a higher percentage of subjects that were 65 and 75 years of age and older in the RBX2660 groups compared to placebo.

The majority of subjects were white and non-Hispanic. The CDI characteristics at baseline is displayed in this table in this slide. Across treatment groups, most subjects had three or more CDI episodes before treatment compared to placebo. The main duration of qualifying CDI episodes were similar across the treatment groups with a mean duration of 24 to 30 days. Most subjects received Vancomycin alone for their qualifying episodes, with a smaller percentage receiving Fidaxomicin and Vancomycin in combination or other treatment.

The risk of solicited adverse events collected from day one through seven after assigned treatment was similar, and most of the events were mild or moderate. The most frequently reported event was flatulence, abdominal distension or bloating, and abdominal pain or

cramping. The most frequently reported solicited event were abdominal pain or cramping, increased, diarrhea, and abdominal distention or bloating. There were severe solicited events. These solicited events were more common in the placebo group compared to the RBX2660 group.

As stated earlier, safety data is presented by the following safety population. In first column is the placebo-only group of 83 subjects. The next column is the blinded RBX2660 group of 193 subjects. The next column after that, the 1-dose group of 429 subjects. And the last column is the any RBX2660 group of 749 subjects. As we move into the safety analysis, I would like to have a remainder that one of the limitations for safety analysis from prior slide is that subject in the blinded studies, after CDI recurrence, moved on to get open-label RBX.

Thereby, subjects in the placebo-only group had less recurrences, and they had less comorbidities. So subjects in the RBX group had more recurrences and more comorbidities. So keep that in mind as we go

through the safety analysis. This table shows the frequency of at least one other TEAEs in five precent of more subject across treatment groups. The rates of unsolicited TEAEs were slightly higher in the RBX group, ranging from 60 percent to 70 percent, 60 in the placebo groups to 70 percent in the RBX2660 groups, with diarrhea and abdominal pain being the most frequent.

Most of the TEAEs were mild or moderate. Across treatment groups, gastrointestinal disorders were reported more frequently. Diarrhea, abdominal pain, nausea, and flatulence were the most common TEAEs in the RBX2660 group. And diarrhea was the most common TEAE in the placebo group. As stated earlier, the applicant looked at multiple standardized MedDRA Queries to evaluate for consultation of unsolicited adverse events to enhance detection of any potential safety signals.

There were no patterns or clusters of events that were observed to identify a safety signal that would suggest an adverse event of special interest. In

this table, serious TEAEs in five or more subjects by preferred term are presented. The frequency of serious TEAE was similar between the placebo groups and one dose RBX2660 group but higher in the blinded RBX2660 and any RBX2660 group. C. difficile infection that required hospitalization for 24 hours or more was considered a serious TEAE at this time by the applicant.

And C. difficile infection was the most common serious TEAE in the RBX2660 groups. Overall, there were low rates of reported serious TEAE for preferred term, and the majority was considered unrelated to RBX2660. There were five serious TEAEs that were considered to be related back to RBX2660 by the investigator, as listed here.

After review of the case reports and narratives, FDA's assessments found three of the serious TEAEs to be related to a recurrent C. difficile infection and two to be related to preexisting conditions in a case of relapsed acute myeloid leukemia and a case of Parkinson's disease with chronic

constipation.

There were a total of 18 deaths in the safety population of 749 subjects who received at least 1 dose of RBX2660 and no deaths in subjects who received placebo. Two of the deaths occurred within 30 days after the last RBX2660 dose. One was a 94-year-old female with recurring C. difficile infection on day 14 and died on day 24, after the second dose of RBX2660, and a 63-year-old male with MRSA (inaudible) pneumonia who developed bacteremia on day 25 and died on day 29, after the third dose of RBX2660.

The investigator reported a serious event of sepsis and bacteremia as unrelated to RBX2660, and FDA concurred with this assessment. Furthermore, in depth review of the individual case report and narratives with aggregate analysis did not reveal any patterns to suggest a causal relationship between the reported deaths and RBX2660 exposure. The increased death rates in the RBX2660 groups may reflect the small sample size of the placebo group comparator and the severity the underlying C. difficile infection in subjects who

received multiple RBX2660 doses.

There was an increase serious TEAEs with increase in age, including the frequency of TEAE leading to death. Serious TEAEs were reported by a higher proportion of subjects who is 75 years of age and older, 24 percent, compared to subjects who were less than 65 years of age, so just 11 percent. Serious TEAEs leading to death were reported more frequently in subjects who were 75 years of age and older, 12 out of the 18 deaths, with a lower number of deaths in subjects who were less than 65 years of age, which is 3 out of the 18.

The TEAEs in the older population, in the older age group, were related to recurrent C. difficile infection and preexisting conditions and unrelated to RBX2660. The applicant provided a safety update six months after the BLA submission. In the safety update, there were additional 229 subjects exposed to at least 1 dose of RBX2660 from the ongoing Study 2019-01. In the safety update, there were no additional deaths reported and there were no additional serious TEAEs

that were considered to be possibly related to RBX2660 by the investigator.

However, the FDA considered the event to a plausible alternative etiology of recurrent C. Difficile infection. The FDA did not consider this event to be related to RBX2660. There were no new safety concerns identified in the safety update. In summary, the results of the integrated Bayesian analyses for Phase 3 Study 2017-01 met the specified success threshold for a single adequate and well-controlled Phase 3 study but did not meet the specified success threshold for a single study to substitute for 2 adequate and well-controlled Phase 3 Studies.

There were imbalances in gastrointestinal TEAE and serious TEAEs, including deaths, between RBX2660 and placebo groups. Most of the TEAEs were mild to moderate. There were no serious TEAEs or deaths found to be plausibly related to RBX2660. Most were related to recurrent CDI and underlying comorbidities. Limitations in the safety analysis included a small placebo comparator group to the

RBX2660 group with loss of subjects that cross-over from the placebo group for open-label RBX2660 treatment after CDI recurring. Thank you.

Q&A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Adewuni and Dr. Gao. I invite the Committee members to start putting hands up pertaining to questions for this presentation. And I will begin with a few that I have. The first question, how many of the 2014 subjects were borrowed for the Bayesian analysis? And, if we were to conduct a treatment-success treatment-failure simple analysis, what would the efficacy be and the confidence interval, understanding that you cannot choose these terms as such?

But, still, it would give us an idea of a frequent approach, more like a pooled analysis as opposed to a Bayesian analysis. Dr. Gao?

DR. ZHONG GAO: Oh, okay. Yeah. Okay. Sure. So, for the primary efficacy endpoint analysis for

Study 2017-01, the Bayesian hierarchical model was used. And, also, this model would allow dynamic borrowing, which means that, if the effect of interest more similar, would be more borrowing, less similar with less borrowing from the historical data. So just with regard to the detailed analysis, I would like to invite the applicant to provide additional information. Thank you.

DR. OMOLARA ADEWUNI: Okay. The Rebiotix team?

UNKNOWN FEMALE SPEAKER: We would like to address the question with regards to the Bayesian analysis versus a pooled analysis. I'd like to ask Dr. Scott Berry to respond to that.

DR. SCOTT BERRY: Scott Berry, biostatistician and consultant to Rebiotix. I'll show you a little bit. I want to reenforce that the borrowing is done on the effects side. It's not individual patients grabs or it's not a set of patients. But on the effect side is the borrowing. I'll show you a couple things related to your question. I'd like to bring up a

slide. This builds on a core slide that Dr. Bancke showed. This is a two-dimensional graph of the posterior distribution. One thing you asked about is the pool.

The borrowing is dynamic depending on the similarity. The model judges two ways. One is the similarity of the placebo response, and the other one is in the odds ratio or the difference from that line. So it borrows in those two dimensions. I've added to this graph. Where the posterior Bayesian model is shown in yellow, the purple shows the pool results, which is what you asked about. In terms of the dynamic borrowing, I'll add an additional slide that tries to summarize the amount of borrowing being done.

I mentioned that it's done in the dimension of the placebo but also in the difference or the odds ratio. We refer to the effective sample size and the effective sample size borrowed. In the posterior, its approximately 16 patients borrowed in the estimate of the placebo. But, in the difference, it's equivalent to borrowing approximately 75 patients, which is a

large amount of that given the similarity in the difference or the odds ratio between placebo to treatment in the different arms.

DR. HANA EL SAHLY: Okay. So the more data from 2014 resembles the data from 2017, the more you can borrow?

DR. SCOTT BERRY: That's right. And Dr. Gao described the super population. If there's little variability between the trials, they all inform each other more, and there's more borrowing. If study-to-study variability is large, there's less information in the prior to inform 2017. So that's exactly correct.

DR. HANA EL SAHLY: Okay. We have many statisticians on the call today, but that sounds like excluding data that could be more informative by excluding the patients who did not demonstrate the effect size seen in 2017. Know what I mean?

DR. SCOTT BERRY: Yeah. Sorry. To be clear, it isn't self-selecting patients; it's about the effect size. So the effect size seen in 2014 is what's being borrowed in that case. So it's not self-selecting or

grabbing certain patients and excluding them. It's borrowing on the relevant effect size seen in the two trials and the similarity of that.

DR. HANA EL SAHLY: But I'm sure that your team and -- once these data are published and in public domain, a lot of clinicians and statisticians are going to pool these two trials and look for the efficacy because, quite frankly, there's a temporal difference, but the inclusion-exclusion the -- even in order to get to the post-analysis, there was some harmonization. Someone can get to that pooled effect size as opposed to a Bayesian or estimated effect size. And would it be still in the range of 10 to 13 with the lower bound being larger than 1?

DR. SCOTT BERRY: So I'll bring back up a slide that I showed in the pooled, and I 'll come back to the question. The pooled analysis, if we were to just combine the trials together, does show similar effect size. You can see the purple line and its distance from the curve to slightly larger effect size. But it does show a similar benefit, statistically

significant at that one trial level.

I don't doubt that there will be separate analyses of these separate analyses and trials. I think this is the ideal circumstance for a Bayesian analysis where we have a good bit of information about FMG, which is a rare scenario in a setting like this, that it was deemed scientifically appropriate to use all of the information to inform 2017.

DR. HANA EL SAHLY: Okay. Thank you.

DR. ZHONG GAO: Yeah. I just wanted to briefly add a comment here. I think at the study design stage, a major question is how much information we would borrow from historical data, Phase 2 Study 2014-01? So keep in mind, at that point, we didn't know anything about the results of 2017-01. So that was a prospective design at that stage. But we wondering how much information we could borrow from the Phase 2 Study 2014-01.

So there are some other approaches to prespecify how much information we really borrow from that historical data. But, at that point, it's really

premature, and we were not really informed to set that specific threshold for how much information we borrow and how much discount we should apply to the historical data. So, at that time, we didn't have yet that information. In that case, we thought that the hierarchical model with dynamic borrowing made sense because we didn't know the data from the Phase 3 study at that time.

So we just set up a framework that is dynamic borrowing. If the ongoing of future Phase 3 study are similar to the historical study, we would allow more borrowing. However, if they are different, then we would give a little bit more discount to the historical information. So I think that was the thought process at the design stage. We didn't know the Phase 3 study result at that time. So that's the thought process. I just wanted to share that information. Thank you.

DR. HANA EL SAHLY: Okay. Thank you, Dr. Gao. We acknowledge that the majority of the adverse events fell into the mild-to-moderate category. However, whether mild, moderate, severe, life threatening,

death, it's all favored -- or I'm not going to use the word favor. It (inaudible) mostly in the Rebiotix arm, whether we include only blinded or pooled or more than dose.

So I want to point that out, and I wonder if there's a particular Bayesian statistic that allow for the probability that we will see more of these serious adverse events and not-so-serious adverse events in patients who get the Rebiotix.

DR. ZHONG GAO: Oh, yeah. So this is about clinical safety. I would like to defer to my colleague, Dr. Adewuni.

MR. MICHAEL KAWCZYNSKI: I'm sorry. Who did you want to refer to?

DR. HANA EL SAHLY: Dr. Adewuni from the FDA.

MR. MICHAEL KAWCZYNSKI: Can that person raise their hand because I can't understand. I'm sorry. Oh, there we go. There we go. I couldn't hear you. My apologies.

DR. OMOLARA ADEWUNI: Yes, thank you for that question. Specifically, on answering question on

Bayesian statistics for serious TEAEs with a preference for RBX, I would like to have my colleagues in Rebiotix to answer that.

UNKNOWN FEMALE SPEAKER: The safety data for RBX2660 in this clinical data package was pooled and integrated across the prospective studies in the clinical development program. However, we did not apply Bayesian statistics to the safety data, only to the efficacy data in the program.

DR. HANA EL SAHLY: Okay. All right. A few of my colleagues are waiting. Sorry I kept you waiting. Dr. McDonald.

DR. L. CLIFFORD MCDONALD: Thank you, all, for the presentation today, the two presentations. Very good. Thank you. And, actually, I have a question both on the efficacy and the safety as well, if I may. First, on the efficacy for Dr. Gao, I brought up this morning with the sponsor this area where the two studies are not as comparable. And it comes back to -- really what I'll say is the certainty that C. difficile is the etiology of the process. I mentioned testing

this morning, but let's leave that off the table.

Let's talk just about the difference being, in the 2014 study, you had to be on the second recurrence, third overall episode or greater; in the 2017 study, first recurrence, second overall episode or greater. What generally is seen is -- there's an old clinical adage. I'm not sure how correct this still is -- that the first risk of recurrence is, it was said today, one in six. We used to say one in five. Maybe it's probably lower, one in six. And that has something to do with diagnostic testing also.

But let's say for a moment it's one in six, the first episode. So you have your first recurrence. One in six people have their first recurrence. A second recurrence probably again happens at about a frequency of one in six. But about after the second recurrence, third overall episode, you start to see an increased risk in subsequent episodes, probably at the point of the fourth overall case, third recurrence. If you've had a third recurrence, you're looking at probably a 50 percent chance of a subsequent

recurrence.

So the probability of having a recurrent C. difficile syndrome seems to go up with number of recurrences. All that to say that, let's say for a moment, the 2014 study had a greater certainty of being something treatable with the Rebiotix Rebyota product. Therefore, would likely have an increased effect size, or maybe at least an increased frequency of events in the population.

I'm just asking the question, what does that do the -- just getting down to is what does it do to the Bayesian inference if you're saying that the first study was a study designed where a priority would have a greater instance of the effect of interest in the placebo group and, I guess, would have a greater effect size? Do you follow that? Again, it comes back to probably misclassification bias or maybe it's just people without the condition.

But, when you have a greater likelihood of a condition that is treatable with the intervention that -- first of all, it probably had a higher frequency of

recurrence in that pool. People with two or more recurrences are going to have a greater frequency of recurrence than people with only their first recurrence. And, probably, the treatment would have a greater effect. Does that do anything to the Bayesian approach? I guess it would say the borrowing should decrease.

If there was more similarity in those two studies by design, the borrowing would've increased. But the borrowing, it sounds like, is done statistically when you're looking at the effect size. So there's no one making that decision. Am I correct about that?

DR. ZHONG GAO: So I think this is a really great question. I think, during the review process, we were also thinking about that question. However, within the scope of this particular BLA submission, we didn't see any clear evidence of consistent relationship between number of prior CDI episode and the effect size in Study 2017-01. But I have to say, this is only within the scope of this particular BLA

submission and especially Study 2017-01.

So I guess it's very likely that there are additional views on this or additional evidence beyond this BLA submission. So, here, I would like to invite the applicant to provide your view on this issue. Thank you.

UNIDENTIFIED FEMALE SPEAKER: Yes, thank you. I would echo what you noted, Dr. Gao, which is that, during the review process, we also acknowledged that one of the key differences between Study 2014 and 2017 was the inclusion of first-recurrent patients into the pivotal Phase 3 study where we had not included in Study 2014. That was the idea around a slide I'd like to show again from the core, which was adjusting the Bayesian analysis for prior number of CDI episodes.

Again, as you can see shortly -- again, I'd like to try to share this slide. You can see in the bottom row that, when making the adjustment for prior CDI episodes at the patient level covariant in the model, we still see very consistent results with the FDA primary analysis in the middle. With that said, I

would like to ask Dr. Scott Berry to provide a little bit of additional information around how the Bayesian model handles the fact that these studies are not identical.

They are somewhat different, and that is accounted for in the dynamic borrowing nature of the Bayesian model.

DR. SCOTT BERRY: Scott Berry. A couple important aspects of this -- and I'll bring up the core Slide 38 that shows this 2 parts. First all, within the algorithm, it determines similarity in amount of borrowed, so it's not a human making that decision. It was all part of the prospective model built into this. In this analysis, you brought up this notion that, if you go in and start treating populations where the placebo rate is higher, it's harder to get a larger absolute effect.

The model actually borrows on the odds ratio difference. So a similar effect going from 50 to 60 might be exactly the same as going 70 to 76, for example, and it borrows on that odds ratio. So, I

think, actually, in here, it's quite similar in its odds ratio. One's a little bit higher on the curve, but the odds ratio is quite similar. Hence, the model did borrow more on that, reducing the variability in the odds ratio.

DR. L. CLIFFORD MCDONALD: Okay. Thank you. Can I still ask my question about safety, or should I pass?

DR. HANA EL SAHLY: Please go ahead.

DR. L. CLIFFORD MCDONALD: Okay. Our Chair has noted already the number of deaths and other adverse events, more of them in the Rebiotix. I think, FDA, you did a very good job of pointing out again that a lot of this -- the cross-over design, there was very few placebos left standing -- we will say it that way -- because, unfortunately, this is a disease where there is no other option at this point. People are tired of it, and they want to get the treatment, and so they're going to cross over.

I guess, for FDA, is there anything you can think of that you can do to try -- so what you have is

the placebos left standing are healthier and healthier and maybe never had C. diff. I mean, God forbid. Maybe they didn't, or they had something else, or they just got better. Then you have these other people who are -- because maybe they're even recurring more than once. I don't know if you even looked at people who got multiple doses. I think you were looking at any exposure.

But I guess I'm just asking -- the question is, is there any way to really do a more fair comparison of adverse event rates with this kind of data when you have everyone crossing over to get the treatment?

DR. OMOLARA ADEWUNI: Thank you, for that question. Let me start by saying that we did look at the different doses. Apart from looking at the individual studies, we did look at the blinded, and we did look at the different doses. When I say "any doses," that was the one to four doses. The three and four doses, specifically, was in Study 2014-01, which was the second study, one of the blinded study. And,

of course, as you would expect, there were more sick. They were not healthy; let me put it that way.

They have more comorbidities. And those had more serious adverse events also. And also subjects who had, let me just say, two or more also, we did look at the one RBX. Another way that you could do this, especially when subjects know that they have multiple recurrences, and they know that there's a treatment, I guess that might a (inaudible) question, and I'll let Dr. Fink take that question. But this is a disease that is recurring, and it can be life-threatening. So I'll let Dr. Fink take it up from there. But we did look at multiple doses.

DR. DORAN FINK: Hi, Dr. McDonald, I think you've raised what has been a very challenging issue for us, which is how to really get at a controlled safety evaluation in this disease, in this patient population, given the demand for this particular type of product, and how to really run a clinical trial that would be able to recruit subjects, which already has other challenges going against it.

I guess what I can say is that, given the realities of how the trial could be designed, I think it's fair to say that we would the placebo-controlled safety data to be most useful for examining those adverse events that are occurring relatively frequently and in close temporal relationship to administration of the product. We solicited -- or not we but Rebiotix solicited a set of those types of adverse events.

For the less common but potentially serious adverse events that we would worry about with any clinical development program, it becomes especially important for us as FDA to look closely at the case scenarios for each of those events and to make our own independent assessment based on the details of those cases. What is the plausible association with the study product?

I think what you've heard from both Rebiotix and from our own independent review is that we attribute those serious adverse events, including the deaths, to the underlying disease process or to underlying comorbidities. We have not found, really,

anything in the way of concerning signals for serious adverse events or deaths that we would be concerned were due to the study product. Over.

DR. L. CLIFFORD MCDONALD: Thank you.

DR. HANA EL SAHLY: Okay. Thank you, all. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you. Where should I start? My statistics professor always taught me that, if you torture the data enough, it will confess to just about anything you want it to. Had this Bayesian borrowing approach been agreed to in a priori before the studies were done I would feel more confident with it. But it looks to me like the company didn't study; it didn't show what they wanted. They tried another study; it wasn't showing what they wanted.

They asked you, is there any way we can statistically torture the data so that we can get better data that shows what we want to? Eventually, they were able to eek by with just a slightly statistically significant result, but a very modest

treatment effect. A number needed to treat of eight means you have to treat eight people for one person to benefit. That's not a terribly affective treatment, and it's a pretty big deal when doing this.

I'm not inclined to give this treatment the benefit of the doubt because it's a new treatment. The onus is really on the company to show us that it really does work and that it's safe enough to justify giving the treatment. Everybody before me has mentioned that the adverse effects all happened in the treatment group and not in the placebo group. I'm not inclined to say that something isn't positively associated with it.

We don't know what changing the gut microbiome does to your risk of having a heart attack or a stroke or dying from some other reason. It could very well be causally related. We just don't know about it. We have to be very, very careful. The number needed to harm hasn't really been fully defined by our statistical analysis.

But I was wondering is there any way that you can combine the expected mild, very modest benefit from

the treatment with the adverse effects that we have seen, the risk of having these bad outcomes, to come up with a treatment threshold, which is the harms over the harms plus benefits, so that I can know whether it's actually justifiable to treat my patients with this treatment as opposed to not treating them because, otherwise, I'm not feeling very comfortable that the company has actually proven their case?

DR. ZHONG GAO: I think this is a good question. I think this is also a very challenging question we have to face. From my personal view, I think I just only can speak of the review process. I think the Bayesian analysis was prespecified, and we did a very careful review based on merit and also circumstances. Regarding some other aspects of your question, I think perhaps I would invite applicant to provide their review. Thank you.

UNIDENTIFIED FEMALE SPEAKER: The risk in this very sick patient population is that these cycles of recurrence continue. And that is the benefit that we are looking at with regards to the pivotal Phase 3

trial. We talk about a 13.1 percentage point difference. Again, I think it's very important to consider the clinical meaningfulness of that as shared with Drs. Khanna and Kraft this morning.

It's also important to note that the adverse events reported in this trial are very consistent and not unexpected for a product of this type in a patient population of this type who had just experienced an infection that was then treated with antibiotics. They are just coming off of antibiotic treatment for that infection.

So the mild to moderate adverse events that are reported in the clinical studies, as well as the transient nature of those adverse events, is very consistent with a favorable safety profile that's also in alignment with the favorable benefit from the efficacy effect creates a (audio skip) for really (audio skip) treatment option for patients. I would also like to ask Dr. Sahil Khanna to provide his perspective again from a clinical standpoint.

DR. SAHIL KHANNA: Well, we can agree, when we

look at treatments like this, we need to keep our patients front and center and discuss with them the possibility of the benefit, the potential of harm, especially when patients have had months and months and months and sometimes years of suffering of recurrency (inaudible) infection.

If I present this to one of my patients and say, "You could get placebo, and you could get active arm, and the treatment difference is 13 percent," or "The relative risk reduction of 31 percent, meaning 31 percent few chances of having the recurrence if they give you the active arm," all of the patients will choose to get an active arm because, for patients, when they have suffered for several years, this is not a small percentage for them. This is actually a huge percentage for them for them to be able to get rid of their suffering.

When you look at the potential harm -- and we've shown that earlier there are more adverse events and more deaths, as you mentioned, in the RBX arm. But that's because all the patients were followed for a

longer period of time. The patient here were followed for longer periods of time. And, in addition, when you look at the background death rate for these patients, that is much higher that what we've seen in this clinical development program.

In my clinical opinion, I would say the difference that we're seeing in the treatment benefits is clinically meaningful for patients. It's something the patients will choose for, something the patients will be looking for a standardized treatment program where the donor screening is standardized, the donor testing is standardized. We've seen with unregulated FMT there's actually been harm that has been attributed to FMT cells.

Based on the FDA alerts that we've seen, ESBL producing E. coli happened from unregulated FMT. Patients died where we know that that's happened, which was directly related to FMT. Gene sequencing was done for the organism. It actually came from the FMT. We've not seen any of this in this particular clinical development program. And the way the pharmacovigilance

is set up for going future, I don't think we'll see something like this. I think we'll be ahead of the game if we had a regulated product like this.

So I firmly believe that this is meaningful for my patient population that I see day in and out.

DR. JAY PORTNOY: Okay.

DR. HANA EL SAHLY: Thank you.

DR. JAY PORTNOY: Thank you.

DR. HANA EL SAHLY: In the interest of time, we have two more --

DR. DORAN FINK: I'm sorry. Could I just add one more point? Is it okay?

DR. HANA EL SAHLY: Sure. Is that Dr. Fink?

DR. DORAN FINK: Yeah. Thank you. I just wanted to respond to Dr. Portnoy on a couple things. First of all, with regard to the comment about torturing the data in many different ways, I just want to make sure that it's clearly understood that the Bayesian analysis that Rebiotix has presented and that FDA had independently analyzed and confirmed, this was prespecified. It was agreed to as a measure to deal

with difficulties in recruiting the ongoing Phase 3 trial.

It was not done as an attempt to rescue a failed trial after the fact. So I just want to make sure that point is understood. I really do hear your concern about weighing the benefits versus risks. And what I think I hear you saying is you'd like some sort of quantitative benefit-risk assessment similar to maybe what has been shown for some of the COVID vaccine meetings that we've had recently. We don't have that to present here today, but I think we can certainly take that suggestion under advisement. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Fink. We have two more questions. Maybe we can discuss later. There has been trials since, and we've seen publications. Dr. Follmann. You are muted, Dean.

MR. MICHAEL KAWCZYNSKI: Yeah. Dr. Follmann? I'm not sure --

DR. HANA EL SAHLY: Not yet.

MR. MICHAEL KAWCZYNSKI: Make sure your phone isn't muted, sir. Your phone. Unmute your phone, sir.

All right. We'll come back to Dr. Follmann. We'll go to the next one.

DR. HANA EL SAHLY: Dr. Janes.

DR. HOLLY JANES: Okay. I have two questions. Also, I just wanted to take an opportunity to thank tremendously the FDA team for the enormous amount of work that goes into reviewing these packages and validating the analyses and presenting it so clearly for all of us. Thank you so much. One, I wanted to follow up on this notion of borrowing information from the Phase 2B trial in order to estimate efficacy after (audio) and questions that Dr. El Sahly was raising around how that (audio skip).

So I wanted to share my interpretation (audio skip) and ask the FDA folks to check if (audio skip). So, what I'm seeing in the numbers, basically (audio) -

-

DR. HANA EL SAHLY: You're breaking up a quite

--

MR. MICHAEL KAWCZYNSKI: Yeah. Dr. Janes, you're breaking up a little bit.

DR. HOLLY JANES: Okay. Can you hear me now?

DR. HANA EL SAHLY: Yes, ma'am.

MR. MICHAEL KAWCZYNSKI: Yeah. Now we can hear you.

DR. HOLLY JANES: All right. so the information borrowing comes from both in estimating the placebo success rate and in estimating the effect size. And it appears to me that it's important to recognize that, because of the unequal size of the Phase 2B and the Phase 3 trial design, also because of the randomization ratio being a one-to-one randomization in the Phase (audio skip) you're getting reasonably similar amounts of information from the two studies.

Whereas, when you're borrowing information to estimate the success rate for the treatment arm, because the Phase 3 study is larger and used a two-one randomization ratio, most of the information is coming from the Phase 3 study. So that seems to be borne out when you look at the estimates from the Bayesian analysis, that the Bayesian analysis posterior estimate of the success rate in the treatment arm is 71 percent,

very close to what you've estimated in the Phase 3 study, nearly identical.

But the estimate of the success rate in the placebo arm, based on the Bayesian analysis, is 58 percent, which is somewhere in between the success rate from the Phase 2B and the success rate in the Phase 3. As we would expect, it's sort of a weighted average. But, basically, the success rate in the Phase 3 is getting dragged down because it was much lower in the Phase 2B trial. As pointed out by Dr. McDonald, the overall success rate of Phase 2B was lower.

So it appears to me that this information borrowing sort of hinges on one's belief in the ability to borrow the placebo information across these trials because the success rate in the treatment arm is not really changing, but the estimated success rate in the placebo arm is getting dragged down with incorporation of the historical data. So that suggests to me that it's critically important to interrogate this assumption as to whether or not the placebo rate in the Phase 2B trial is reflective of the population enrolled

in the Phase 3 study.

And, because of the differences in eligibility criteria between the two studies, I'm concerned about that assumption. So the success rate in the placebo arm in the Phase 2B was 44 percent, and it was 62 percent in the Phase 3. So I'm concerned about that assumption about the ability to share the placebo success rate across the two studies. Can the FDA folks comment on that interpretation?

DR. ZHONG GAO: Yeah. I think you brought up a very good point. I think that that could be one of the statistical interpretations of the results. I would like to invite the applicant to provide their review on this. Thank you.

UNIDENTIFIED FEMALE SPEAKER: That (audio skip) placebo response rate -- and just to remind us, a placebo in our trials is actually reflective of standard of care because all patients entering our trials are receiving standard of care antibiotics for the active infection. Because these studies were conducted sequentially and there's, of course,

advancements in clinical practice and treatment guidelines, it's not all that unexpected that the placebo response rate might evolve over time.

With that said, I would like to ask Dr. Scott Berry to respond to your question about how that is handled in this borrowing (audio skip).

DR. SCOTT BERRY: Scott Berry. I'll bring up the core slide that shows this. So, Dr. Janes, the borrowing is in two dimensions, as I mentioned before. One is the placebo; one's the odds ratio. As you see the Bayesian estimate here, it's really moving in two dimensions. It's moving together. And the 2014 estimate that comes out of that model moves a little bit towards 2017 within that setting. It is largely borrowing on the odds ratio difference between that which pushes that.

And to get the right odds ratio, it kind of moves the placebo down as well. So had the model reflected a little bit what you're saying, that the placebo rates were different, then the borrowing of that was less than the borrowing in the odds ratio,

which gravity had to pull them together. So it's not just the placebo doing that work. It's as much the odds ratio. The odds in the 2014 was just over 2, moving it up, and it was about 1.5 observed in the 2017 trial, moving to 1.7 as a posterior estimate.

DR. HANA EL SAHLY: Okay. Thank you, all.

DR. HOLLY JANES: Sorry. Can I make one more question just real quick?

DR. HANA EL SAHLY: Okay.

DR. HOLLY JANES: I think that it's critically important. I apologize for dragging this out, but this has been mentioned several times, this notion of a prespecified analysis. And I think it is important that we're all clear on what that was. So my understanding from the discussion is that the analysis was prespecified after the Phase 2B trial results were available and perhaps public, which is different from prespecifying from the get-go, as I think Dr. McDonald or perhaps Dr. Portnoy mentioned.

So, to me, this is somewhat analogous to something like an noninferiority trial, which is

designed and contingent on some set of historical data. And, in that context, it would be typical to do an analysis that's conservative in terms of the assumptions that it makes about the exchangeability of that historical data. So I'm wondering here can FDA folks comment on this pre-specification? It was prespecified after the Phase 2B but before the Phase 3.

And has any analysis been done that is making the less stringent assumption about the exchangeability of that historical data? Thanks, El Sahly.

DR. ZHONG GAO: Yeah. So I would invite Dr. John Scott to make comment on this.

DR. JOHN SCOTT: Hi. Thanks. John Scott, Division of Biostatistics at FDA. These are all very good points. You're right that the pre-specification happened after the Phase 2 study. So it's not prespecified in the sense of having thought ahead about a sequential data collection procedure that would lead to a pooled analysis. It was more, we've seen the Phase 2 results, and we think those are informative to the Phase 3 analysis and incorporating that in the

Phase 3 analysis in order to help overcome some of the recruitment difficulties.

I hear what you're saying about the noninferiority comparison. To me, that's not quite an accurate -- the analogy doesn't really work for me because I think, in noninferiority, what we're being conservative about is making sure that we're not overestimating the active controlled versus placebo comparison. But, here, we're explicitly using the information we have about the same treatment effect we're trying to estimate in Phase 3.

So it doesn't quite mesh for me, but you're overall point about the pre-specification is right. The model was proposed early in the Phase 3 study. Thanks.

DR. HANA EL SAHLY: Okay. So we did not forget Dean Follmann. However, we will get to the break. There will be more time for more questions. And both the FDA and the applicants will be in the afternoon. In the interest of time -- sorry, Dean -- you will be the first to deliberate in the afternoon.

We will take a lunch break, and I think it was for 40 minutes but may be a little shorter now. Right, should we do 30?

MR. MICHAEL KAWCZYNSKI: All right. Let's see. Yeah. I have to make sure. Yeah. We're going to do a 30-minute break. So everyone, stay here, though, while I get the studio to put us on break. Studio and captioner, please put us on a 30-minute break. Studio, make sure you pull up your slides as well and tell us when we're clear. Everybody in the meeting, please wait until we are.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: All right. And welcome back. We are now going to start off our Open Public Hearing session. I'll hand it back to Dr. Hana El Sahly. Dr. El Sahly, take it away.

DR. HANA EL SAHLY: Thank you. Thank you all

for logging back in. Now we begin the second half of our day, and we kick it off with the Open Public Hearing.

Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency of the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written and oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its products, and if known its direct competitor.

For example, the financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, the FDA encourages you at the beginning of your statement

to advise the Committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking. Would then, Dr. Paydar, kick it off?

DR. SUSSAN PAYDAR: Great. Thank you, Dr. El Sahly. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing (OPH) session during which interested persons may present relevant information or views.

Participants during the OPH session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this Open Public Hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made.

With that guidance, I would like to begin. Every speaker will have only three minutes to make their remarks. Let's begin with our first OPH speaker, Ms. Patricia Alonso. Patricia, go ahead.

MS. PATRICIA ALONSO: My name is Patricia Alonso. I do not have a financial stake in this hearing. I am married with two young children. I am speaking today to share my experience as a *C. diff* survivor and to encourage you to approve this treatment.

In October of 2018, I experienced horrible diarrhea and severe abdominal pain. I was unable to leave my house as I was using the bathroom so frequently. I was too weak to work or to care for my children, who were seven and five years old at the time.

After a week of experiencing these symptoms, I went to my doctor. I provided a stool sample and was diagnosed with *C. diff*. My doctor prescribed an antibiotic. I had never heard of *C. diff*, but a Google search gave me enough information to terrify me as I

was already experiencing several of the horrible effects. It was then that I learned that this illness could lead to hospitalization and even death.

My symptoms went away with the help of the medication. A month later, I had my first recurrence. Once again, I was unable to work or care for my family as the pain was so extreme. I was prescribed a different antibiotic, and my symptoms eventually subsided.

The following month I experienced yet another recurrence. This time the prescribed antibiotic was not effective, so I had to take an additional course of antibiotics. The second course did provide relief of my symptoms, but I was left feeling terrified that this illness that had affected me three times in three months would come back again. I was worried that the treatments would stop working, and I was also worried about what the antibiotics were doing to my immune system.

My biggest fear was spreading this superbug to my children or husband. During the time that I had *C.*

diff, I confined myself to one location in my house and would not allow my children to come near me. My young children do not understand why I was denying their requests for hugs and cuddles. The picture I have attached to this slide was taken very shortly before my first bout of *C. diff*.

We are a family that heavily celebrates holidays. Because of *C. diff*, I was unable to attend Thanksgiving dinner at my sister's house with my husband and children. I was unable to decorate the house for Christmas with my children, decorate gingerbread houses, visit Santa, or participate in so many of our Christmas traditions. Those were the big things, but the saddest times for me were turning my children away from my affection or to play with them.

I received a fecal transplant in January of 2019. I experienced no side effects or pain. To this date, I have not had a recurrence of *C. diff*. I credit that entirely to the fecal transplant.

I lived my life in fear in extreme pain for three months. I thought of *C. diff* constantly. Now,

with the exception of speaking to you today, I do not think of *C. diff* at all. I urge you to approve this treatment. Thank you.

DR. SUSSAN PAYDAR: Thank you, Patricia, for sharing your experience. Next is Kathleen Bischoff. Kathleen, go ahead.

MS. KATHLEEN BISCHOFF: Good afternoon. I'm Kathy Bischoff, and I survived seven *C. diff* infection reoccurrences following my first diagnosis throughout the course of two and a half years.

I have no financial disclosures.

My journey started because of an ongoing struggle with reoccurring diverticulitis and excessive antibiotics. Upon my discharge from the hospital, I was told I had *C. diff*. My treating physician just casually mentioned it before I left, saying, "Oh, by the way, you have *C. diff*." That was the first time I had ever heard of it.

When I asked him for additional information, he said it was an infection in my colon, and he had given me a prescription for it. I didn't know how

serious the infection was, what to expect, or what precautions to take.

I had seven reoccurrences of *C. diff* over the next two years; three of them required hospitalization. During each infection, my life was turned upside down, and unfortunately, without fail, *C. diff* would return about two weeks after each treatment course was finished. My system had become so weakened I was unable to conquer the infection or restore the needed beneficial microbes to my microbiome after treatments. I had no way to fight *C. diff* from reoccurring.

After my last treatment, a lengthy taper, I started to experience symptoms that by this point were all too familiar. I tried desperately to convince myself that it was not a *C. diff* reoccurrence. The symptoms worsened, and I got tested. "It can't be *C. diff* again," I thought. "Please, please no." You can imagine my disappointment when I found out that I tested positive for yet another *C. diff* infection.

I was devastated. I was physically, emotionally, and psychologically exhausted. I was

questioning, could I even go through this again? I knew I could no longer continue down the same path. The specialists treating me were at a loss of what to do next. Sick and frightened about my future, I made a decision that I had to advocate for myself and for my survival.

While searching for information online, I found the *C. diff* Foundation's website. I called into one of their support sessions. For the first time, I felt gratified, and I was relieved I was finally receiving so many of the answers I was looking for. I learned about recommendations on nutrition, environmental safety, and so much more. The foundation told me that there were clinical trials available and being conducted. There was hope. I applied, and I was accepted.

The trial treatment was successful in conquering the infection. It saved my life. I am here this afternoon because there are many, many others just like me, and we are all anxiously awaiting FDA approval of medications to treat and prevent a reoccurrence of

this debilitating and sometimes fatal infection.

I ask you please, please think of us today as you make your decision. Thank you very much.

DR. SUSSAN PAYDAR: Thank you, Kathy. I appreciate you sharing your journey. Next is David Bischoff.

MR. DAVID BISCHOFF: Good afternoon. My name is Dave Bischoff. I have no financial disclosures.

I'm here to share my experience as a primary caregiver for my wife, Kathy, whose sheer survival probably stands as a statistical anomaly. She endured two and a half years of ordeals of seven consecutive major *C. diff* episodes.

Now, every patient suffering with *C. diff* focuses on trying to survive the ordeal, and at their side is the caregiver providing vital assistance and support functions 24/7. With every *C. diff* reoccurrence, which in our case struck without fail within two to three weeks after every temporarily successful regimented treatment, the endless nightmare bouts of nausea, blinding pain, depression,

despondency, and growing hopelessness would reestablish and grow exponentially in magnitude.

Witnessing a loved one undergoing unrelenting physical pain and suffering plus dealing with their inevitable depression and mood swings is something I hope for you or your loved ones never have to endure. A caregiver must simultaneously deal with the daily challenge of orchestrating the complex logistics of care and support of a critically ill *C. diff* patient's often rather unique needs and requirements along with life's normal ongoing routine.

Quite literally moment to moment your loved one's situation can drastically change. The caregiver had better be prepared to instantly adapt and respond often with but brief moments to contemplate and comply. There is a constant ongoing battle with dehydration, searing pain, the uncontrollable muscle spasms, cramping, and the hours spent literally screaming in pain while curled up in a fetal position on the bathroom floor at home and nothing to do but hope that a cure will soon be found.

Something normally as simple as leaving the protective boundaries of the home becomes a complex undertaking in many ways. The fact needs to be recognized that a *C. diff* patient and those who care for them are subject to constant and severe physical and psychological stresses. That's the impact of reoccurring *C. diff* and a way of life for the *C. diff* afflicted.

The therapy before you today means hope for tens of thousands of other people like my wife and myself, who continue to live in fear of the potential next bout of *C. diff* and the lack of options currently available to them to survive it. Please remember our story and those tens of thousands like us as you consider your decision today. You have a chance to help so many *C. diff* afflicted: past, present, and future. Thank you for your time and dedication.

DR. SUSSAN PAYDAR: Thank you, David, for sharing the caregiver perspective. Appreciate it. Next is Kee Kee Buckley.

MS. KEE KEE BUCKLEY: Hello. My name is Kee

Kee Buckley, and I'm a filmmaker from Hampton, New Jersey. My financial disclosure today is that I have been a paid patient spokesperson for Ferring Pharmaceuticals.

In September of 2019, I was prescribed a ten-day course of mebiquine for a sinus infection, and a week later I had a routine colonoscopy screening that took place at a hospital.

The week after my colonoscopy, I saw my gastroenterologist and complained that my diarrhea hadn't stopped after the colonoscopy prep and that I had horrendous gut pain. She ordered a fecal test, and the next day she phoned to say that I was positive for *C. diff*.

I started a ten-day course of vancomycin, and I was afraid to leave the house because I was having diarrhea seven or more times a day and I never knew when I would need a bathroom. I was terrified of getting my husband sick.

I finished the first round of antibiotics, and I was feeling a bit better. But then five days later,

I relapsed, and it was worse this time. I had extreme abdominal pain. I was nauseous, and I completely lost my appetite and, of course, continued to have severe diarrhea.

Towards the end of my second course of vanco, I had a morning where I felt good enough to leave the house and do some errands. When I returned home, I took a sudden turn for the worse, and, over the next hour, I vomited five or six times in addition to having diarrhea. I was literally just lying on the bathroom floor in between episodes because I didn't have the strength to stand up. I was delirious with fever, and I was in the most pain I've ever felt, literally moaning with every breath.

My husband rushed me to the hospital where I was admitted with sepsis, and the shocking thing to me is how fast that happened. I went from in the morning doing errands to the evening being septic. I spent a week in isolation, and I don't remember much of that hospital stay. I was on high doses of three different antibiotics. I was also on IV fluid, heparin shots in

my belly, antinausea drugs, pain drugs, potassium, and a host of other things that I can't recall.

They couldn't get my fever down, and they couldn't figure out why my body wasn't getting better. My face and limbs swelled. I had trouble breathing. It felt like I had a weight on my chest. I had blurred vision, brain fog, a vaginal yeast infection, and thrush that made my tongue look like a lion's mane and made it difficult to talk.

When my fever finally broke five days into my hospital stay, the worry on my doctors' faces finally made it register how serious this was. I could have died.

After a week, I was being stable enough to be discharged. I had lost so much weight that my clothes were falling off of me. I was on a tapered dose of two different antibiotics for the next four weeks, only I didn't make it that long. Two weeks later, I relapsed again, and, at this point, I was finally eligible for a fecal transplant. It was a miracle, and it instantly cured me by restoring a healthy gut microbiome.

Without an FMT, I don't know if I'd be here talking with you today. Three years later, I'm still *C. diff* free. Thank you so much for inviting me to share my story.

DR. SUSSAN PAYDAR: Thanks, Kee Kee, for sharing your story. We appreciate it. Dr. Teena Chopra.

DR. TEENA CHOPRA: Yes, hi. Good afternoon, everyone. My name is Dr. Teena Chopra. I'm an ID physician -- infectious disease physician -- and I'm also a hospital epidemiologist for an eight-hospital system in Detroit, where I not only see *C. diff* patients, but I also monitor our *C. diff* rates. I have been here for 17 years.

Over the years, recurring *C. diff* has become more and more challenging to treat. My community is underserved and very high risk for recurring *C. diff*. We serve over 13 housing homes and long-term acute care facilities in the area that serves some of the highest risk patients who are older than 65 years of age and carry high morbidity and mortality.

We also see a very high percentage of patients with recurring *C. diff* which even carries a higher mortality. Our recurrent rate is as high as 50 percent, and, since the pandemic, we have seen more and more patients of *C. diff* and COVID coinfections. I happen to have reported the first nine cases of COVID and *C. diff* coinfections, out of which six of the patients passed away.

The currently available treatment options are ineffective at restoring the gut microbiome. Not only do we need a microbiome biotherapy product, but we need a standardized FDA-approved product.

Currently, we are giving antibiotics to treat *C. diff,* which are actually causing more harm by disturbing the microbiome and putting the patient at high risk for recurring *C. diff*. I run our FMT program here, but we don't have a standardized FDA-approved product, so I have not been able to offer FMT to my patients. My patients have poor quality of life from repeated *C. diff* episodes, and some of them are unable to work or even live independently.

I think restoring the microbiome is key in preventing the vicious cycle of recurrence, and our community can really benefit from this innovation. I really thank the FDA for all their support.

DR. SUSSAN PAYDAR: Thank you, Dr. Chopra, for your clinical perspective. We really appreciate it. Next is Candace Cotto.

MS. CANDACE COTTO: Good afternoon, everyone. My name is Candace Cotto. I have been a registered nurse for over 43 years and a clinical research nurse for 20 of those years. I do not have a financial stake in this product.

I am here today to speak on my personal experiences with patients suffering with recurrent *C. diff* and how the investigational product you are reviewing today, Rebyota, has significantly changed their lives.

I previously worked with patients suffering with Alzheimer's, Parkinson's disease, and cancer, and I had never seen anyone cured from those devastating diseases. Since working with patients with *C. diff*

treated with a Rebyota product, I am able to see patients cured of a devastating disease.

When I first started working with *C. diff* patients, I had no idea how it affected every aspect of their lives. Often when I speak with a patient suffering with *C. diff*, they are very frightened, discouraged, and feel helpless. Many have been hospitalized numerous times and are afraid that their next bout with *C. diff* will kill them. They are afraid to be around other people. They feel isolated and feel as though they are a bother to their loved ones and friends. Many can no longer leave their home or work for fear of when the next episode of diarrhea will occur. Their activities of daily living that we take for granted are completely disrupted. They feel as though their life will never be back to normal again.

When I speak to the patients for the first time about a fecal transplant, I try to alleviate their fears about the next steps that we are about to take. On the day of the Rebyota procedure, the patients always have a look of mixed fear and relief. The

procedure itself takes minutes, and, while I am preparing them, I chat with them about their families and things that they are interested in to take their minds off of the procedure. While they are talking, I'm administering the product, and, when it's complete, they exclaim, "I can't believe that it's over and it was that easy."

I always follow up with them to see how they have done, and every patient has told me how this has changed or saved their lives. One patient, in particular, chose to drive over seven hours to have treatment with the Rebyota product. She'd experienced numerous episodes of *C. diff* and felt as though she may not make it through the next time. She was an avid gardener, raised bees, and loved to go out with her friends for lunch and shopping. She hadn't been able to do that for many months.

She always celebrated her birthday, Fourth of July, with many friends and family and was afraid that she wouldn't be able to celebrate this year. She had planned to go across the country to celebrate her

special day with dear friends and family. The Rebyota procedure gave her hope. The day of the procedure we chatted, and, when she told me that she raised bees, well, we had something in common; I love bees.

When I called her to check on her the next day, she told me that she couldn't believe how wonderful she felt. She stated that she hadn't felt so good in months. The first thing she did that morning was to call all her girlfriends and tell them that she was back and to get ready to go out for a day of shopping and lunch. She told me that she was going to name her queen bee after me so she would always remember how this procedure changed her life.

When I spoke to her months later, she told me that she had been able to go cross country to celebrate her special birthday as she had hoped she could.

She is only one of the many patients that I have treated with this amazing product with similar stories to tell -- all positive and their words are often the same: "Thank you, Candy (phonetic). You have changed my life."

As a nurse of 43 years, it is so touching to know that I have helped so many people with this devastating disease. Please remember this as you consider your decision. You have the ability to help so many more patients with a recurrent *C. diff* today. Thank you for your attention and your time.

DR. SUSSAN PAYDAR: Thanks, Candy, for sharing your experiences, such a caring nurse. We really appreciate it. Next is Dr. Eric Debburke. I hope I'm pronouncing your last name correctly.

DR. ERIC DEBBURKE: Debburke. Thank you for the opportunity to speak here today. My name is Eric Debburke. My disclosures are I have enrolled patients into trials of Rebyota, and I have received payments as a consultant from Rebiotix and Ferring.

I'm an infectious diseases physician and professor of medicine at Washington University in St. Louis School of Medicine. I do clinical, translational, and epidemiological *C. difficile* infection research.

In addition to doing *C. difficile* research, I

have a clinic where I only see patients with recurrent *C. difficile* infection. I routinely have patients travel hundreds of miles to see me and have had a few that have traveled over a thousand miles. I mention the distance patients travel to see me not to boast but to highlight how devastating recurrent *C. difficile* infection can be to patients and their families.

My research has helped to document the objective impact recurrent *C. difficile* infection can have on patients in the healthcare system, leading to increases in days hospitalized, healthcare costs, and deaths. However, one of the more difficult to quantitate is the subject of experience recurrent *C. difficile* infection has on my patients.

I commonly hear from my patients that they are afraid to leave their homes out of fear of urgently needing to use the bathroom. They often have debilitating abdominal pain and cramping, and they no longer have family and friends visit out of concerns for infecting them. Based on this, you may not find this surprising that I frequently hear *C. difficile*

infection is the worst thing that they have ever experienced.

One patient in particular sticks out in my mind had just been diagnosed with recurrence of a cancer that had no known effect or treatments, but she was actually more afraid of having additional recurrences of *C. difficile* infection than the recurrence of this cancer.

There are some people who proselytize about the effectiveness of microbiota restoration therapies, such as fecal transplantation and Rebyota, but I do not consider myself to be one of these people. However, there are clearly decades of experience on the efficacy and safety of microbiota restoration therapies for the prevention of recurrent *C. difficile* infection. And I do see microbiota restoration therapy as an essential tool in a very limited (inaudible) to prevent recurrent *C. difficile* infections. My patients are in desperate need for an FDA-approved and regulated microbiota restoration therapy product.

The landscape with a continued absence of such

a product, I think, is frightening. As demonstrated by the over 62,000 people who have received an OpenBiome product, people will continue to seek out a microbiota restoration therapy in the absence of an FDA-approved product.

Unfortunately, there are providers willing to administer and have had patients who have received microbiota restoration therapies from unscreened donors. FDA approval of Rebyota will be the best method to ensure patients with recurrent *C. difficile* infection have access to the efficacy of microbiota restoration therapies from properly screened donors. In addition, approval will facilitate our ability to monitor the efficacy and safety of these products into the future. Thank you.

DR. SUSSAN PAYDAR: Thank you, Dr. Debburke, for your viewpoint as a physician. Next is Dr. Paul Feuerstadt.

DR. PAUL FEUERSTADT: Thank you. Hello. My name is Dr. Paul Feuerstadt, and I am an assistant clinical professor of medicine at the Yale University

School of Medicine and an attending gastroenterologist at the PACT Gastroenterology Center.

Thank you so much for giving me the opportunity to speak today. My disclosures include that I have enrolled in patients in clinical trials for Rebiotix and RBX and have received consulting speaking honoraria from Ferring.

Within my practice, I spend a portion of my time in academia and the remainder in private clinical practice. I learned about the microbiome initially during my fellowship when working at Montefiore Medical Center with Dr. Lawrence J. Brandt. Over my 12 years in practice, *C. difficile* infection in patients with recurrent and multiply recurrent disease has been my clinical and research focus.

Following the guidance of this organization, in 2013, I spearheaded the fecal microbiota transplantation program here at the Yale New Haven Hospital and obtained institutional review board approval to perform FMT under enforcement discretion. Although very rudimentary and labor-intensive, the FMTs

worked beautifully, and the results were incredibly gratifying. I saw the power that this treatment could have. As our research center engaged with clinical research trials, we learned about RBX and saw similarly exciting results both in clinical trials, open-label studies, and through enforcement discretion.

One very poignant patient comes to my mind when thinking back about the impact of RBX. This is a 26-year-old man with no past medical history who presented to me with recurrent *C. difficile*. He had seen another provider who gave him four courses of vancomycin, and he was not responding, recurring one to two weeks after treatment each time. The patient moved out of his home with his wife and one-year-old daughter for fear he would give them *C. difficile*.

He got to the point with numerous recurrences of diarrhea that he called my office and said he felt suicidal since he felt he would never get rid of this. I referred the patient to the psychiatric ER. He ultimately received RBX through the enforcement discretion, and today he is better, back to normal, and

living with his family again.

Another example came with a 35-year-old woman who had multiple occurrences of disease. She came depressed and frightened about her future and feeling like she could not break the cycle of recurrence. One provider went so far as to tell her she would never be able to conceive. She had never had children, so this really hit her hard. She ultimately received RBX and now is better, back at work, and collaborating with fertility awaiting an implantation later this fall.

These are just a few examples of the impact recurrent *C. difficile* can have on a patient's life. You are hearing many more stories like them today. Our broad experience with this product in clinical trials and through enforcement discretion has proven to us the ease of usage and the impact this can have on our patients breaking the burdensome cycle of *C. difficile*. Thank you so much for your attention.

DR. SUSSAN PAYDAR: Thank you, Dr. Feuerstadt, for your clinical perspective. Next is Christina Fuhrman.

MS. CHRISTINA FUHRMAN: Hi. My name is Christina Fuhrman, and I'm from Columbia, Missouri. I have no financial stake in this hearing.

Exactly ten years ago today in the woods, I married a man that I love. Our wedding pictures depict us smiling and happy, but, upon a closer look, my eyes are dark and I'm very thin. In the background, a chair rests against a tree in case I'm no longer able to stand.

A few months prior to my wedding, antibiotic use had landed me in the hospital with a *C. diff* infection. Antibiotic therapies to treat this infection failed me, which caused a seven-month, unending, merry-go-round ride of antibiotic treatment for *C. diff* and *C. diff* recurrences. If I wasn't hospitalized, I was at the GI office getting fluids for dehydration.

If I had to describe my illness in two words, it would be cruel and degrading -- degrading because of the type of sickness. In lieu of a blushing bride, I was confined to a hospital bed with diarrhea. And

cruel because with each script and method of antibiotic therapy to treat *C. diff*, I quickly realized we were all just kicking the can down the road. I came close to death, so a fecal transplant was finally given to me, and I fully recovered.

A year after my recovery, I gave birth to a healthy baby named Pearl -- Pearl because she is precious to me. However, by the time Pearl was 20 months old, she was hospitalized with a severe *C. diff* infection probably catching it from our home.

Watching her endure the pain of being sick with *C. diff* was nothing compared to watching her endure the cruelty of the infection recurrences. I was nine months pregnant with my son at that time while Pearl, with curly brown hair and hazel eyes, fought for her life against *C. diff* unable to understand what was happening to her.

Upon bringing her to the Mayo Clinic and given a fecal transplant, she quickly recovered. In the realm of *C. diff*, if we currently have the knowledge of two things; one, microbiome-like therapies work in a

large majority of cases, and, two, we also know that antibiotic therapies are failing us. For example, Flagyl is no longer the first line of defense for *C. diff*, and we have found vancomiant-resistant strands.

That begs the question, what are we going to do about this? If microbiome therapies hadn't existed, then neither would I and neither would my precious Pearl, and today would be just another day and not one celebrated in the wood ten years ago. Please consider approving this therapy and thank you for your time.

DR. SUSSAN PAYDAR: Thank you, Christina, for sharing your heartening and personal experience. We really appreciate it. Next is Ana Goetsch.

MS. ANA GOETSCH: Hello. This is Ana Goetsch. I have no financial disclosure. Thank you for this opportunity to share my experiences with RBX2660.

I'm a clinical research coordinator at a gastroenterology clinic here in Idaho. I had been working with this product since 2014, and we have performed over 250 administrations in patients 18 all the way up to 85. I had been working with *C. diff*

patients for over 14 years in clinical research, and I have first-hand knowledge of how this infection really impacts the patient's quality of life.

During my first interaction with recurrent *C. diff* patients, they're highly discouraged, depressed, or even have feelings that this infection will be the death of them. These patients are fragile and have felt isolated and alone due to their *C. diff*. Patients often feel embarrassed by their infection and because of that keep to themselves. These patients have tried and failed many courses of antibiotics, those antibiotics coming with their own side effects.

On the day of administration, patients are a little nervous but eager to be rid of this infection. The procedure takes one to two minutes, and the most common thing patients say afterwards is, "I can't believe that's it." Some even joke that they will take a second one just for good measure. There were minimal adverse events, and many patients didn't experience any adverse events.

At the one-week follow-up, it isn't uncommon

for patients to show a major shift in both their health and their quality of life. By the time we get to the Week 8 visit, the patients have their hope back. They are sharing with me all the things they have done that they have missed out on and their future plans, whether that is by getting back to college or being able to spend time in their garden or with their grandkids.

I can't even count the number of times patients have saying to me, given hand-written notes expressing their gratitude, and crediting us with saving their life. The patients who really stand out to me are the elderly patients who come into their visits with their family and to see how much joy has been restored to that family following successful treatment of *C. diff*.

I feel this product has saved many lives and improved their quality of life in some way or another. Patients are becoming more informed and reaching out to their doctors in hopes to get this type of treatment. The administration is very easily performed onsite in a short amount of time with great results. Prior *C. diff*

patients are now advocates for others, and we have had many instances where patients actually refer other *C. diff* patients to us for treatment.

I'm so excited for this product to have the ability to reach the many people who can't access this treatment just yet and how this product will transform the treatment for CDI for years to come. Thank you.

DR. SUSSAN PAYDAR: Thank you, Ana. Next is Christian Lillis. Christian, are you there? Maybe we can move to the next speaker and then we come back.

MR. MICHAEL KAWCZYNSKI: I got it. Hold on one second. You there? Christian, you there?

MR. CHRISTIAN LILLIS: Hi. Sorry. I was -- can you hear me?

DR. SUSSAN PAYDAR: Yes.

MR. MICHAEL KAWCZYNSKI: Yes, we can. Go ahead.

MR. CHRISTIAN LILLIS: Okay. No problem. Okay. Thank you. Good afternoon and thank you for the opportunity to address the Committee. I am Christian John Lillis, Executive Director of the Peggy Lillis

Foundation for *C. Diff* Education Advocacy. My brother and I founded PLF in response to my mother's death from her *C. diff* infection in April 2010.

Our mother, Peggy, was a single parent, a kindergarten teacher, and just 56 years old when *C. diff* took her life.

I want to disclose that Ferring has supported our organization financially, but I have no financial interest in the company or received any compensation for my appearance today.

C. diff causes an estimated half million infections and nearly 30,000 deaths annually. While Mom did not survive her first infection, over the past 12 years we have heard from thousands of people with recurrent *C. diff* infection.

An initial *C. diff* infection can be distressing with violent and painful diarrhea up to 20 times daily. Other symptoms may include fever and nausea and fatigue. Imagine suffering for seven to ten days while being treated, feeling a bit better for a while, and then having the infection and the symptoms

return days or weeks after treatment ends. This is recurrent *C. diff* or rCDI, and it affects around 130,000 Americans every year.

rCDI is a torturous disease. Those afflicted can suffer weeks, months, or even years with diarrhea, GI pain, and fever. They are at a heightened risk for sepsis. rCDI prevents patients from working, caring for their families, and even leaving their homes.

Our organization helps recruit CDI patients for a 2020 study to examine rCDI's social, emotional, and financial impacts. We showed that 94 percent of people say CDI impacted their daily activities, and 72 percent said CDI impacted their professional lives with almost half having to stop working entirely during their infection.

Patients with recurrence had higher rates of physical and psychological consequences, greater impacts on daily and work activity, and more work stoppages. Those with a greater number of recurrences showed a trend of reporting more harmful effects at higher rates. Even once they've been successfully

treated, over 80 percent of rCDI patients live in fear of it returning.

Finally, rCDI is expensive. On average, study participants spend $4,000 in out-of-pocket costs. This is egregious when nearly half of Americans cannot afford a sudden bill of $500.

Fecal microbiota transplant has been a treatment of last resort for rCDI patients. While inelegant, many patients feel like FMT saved or destroyed their lives, but the COVID-19 pandemic and most recently Monkeypox have made FMT very difficult to access.

Peggy Lillis Foundation hears from rCDI patients every day. They are suffering; they need help. But most of all, they need better treatment options. While we could not save my mother, an approved microbiome therapeutic for recurrent *C. diff* will prevent pain, suffering, and death for tens of thousands of people every year. Thank you so much.

DR. SUSSAN PAYDAR: Thank you, Christian, for sharing your story. Sorry about your loss. Next is

Pamela McCollister.

MS. PAMELA MCCOLLISTER: Yes. Hi. My name is Pam McCollister. I have no financial disclosures.

I'm a mother, a wife, and advocate for the Peggy Lillis Foundation, a member of the Oregon Health Authority Healthcare-acquired Infection Advisory Committee, and a *C. diff* and sepsis survivor. My life forever changed in 2017 when I was diagnosed with *C. diff* from the overuse of antibiotics. I was prophylactically placed on antibiotics to ward off an infection following spine surgery. Little did I know that decision would change my life forever. Over the next year, I would suffer a total of four recurrences, each one worse than the previous and each one landing me in the ICU with sepsis.

Like so many patients diagnosed with *C. diff*, I had never heard of it, yet it is the most common healthcare-associated infection. I wasn't given any information about it: what may have caused it, what can I do to prevent it from spreading, is it contagious, how will I know if the treatment is working? I was

left with countless questions and to find the answers on my own. Three bouts with *C. diff*, three stays in the ICU, and three different antibiotics to combat *C. diff* had all failed. My hope of getting rid of this was fading fast.

A fecal matter transplant was (audio skip) me, and the operating room was reserved for the next day. I started feeling better within a day or two, almost back to myself. I wasn't running for the bathroom constantly. I wasn't feeling quite as tired as I had for the last eight months. I had a pep back in my step. I felt like I had rounded a corner, and the worst was behind me.

This feeling was short-lived; in just ten days, I would find myself back in the ER with the worst bout of sepsis I had seen and diagnosed with *C. diff* again. I was admitted to the ICU and this time fighting for my life. I had run the course of antibiotics to treat *C. diff* from Flagyl to Dificid and then FMT. My options were running out. My care was transferred to an infectious disease doctor, and I was

given an infusion of Zinplava. I credit this and her for saving my life and ending my ongoing battle with *C. diff*.

I won't say that I am cured of *C. diff* because I honestly don't believe I ever will be. I am left with countless ramifications from post-infectious IBS and colitis to the endless foods that I can no longer digest. I've dealt with numerous issues from my bouts of sepsis, and the mental burden this has taken on me and my family is something that will stay with us forever.

I ask you to remember all the stories you hear today when making your decision. Thank you.

DR. SUSSAN PAYDAR: Thank you, Pamela, for sharing your experience. Next is Dr. Robert Orenstein.

DR. ROBERT ORENSTEIN: Thank you. My name is Dr. Robert Orenstein, and I'm speaking on behalf of my work with patients with complicated *C. difficile* infection. I have enrolled patients in trials of the product we're describing today, and I've also served as an advisor to Rebiotix and Ferring.

I'm a professor of medicine at the Mayo Clinic and chair of the Division of Infectious Diseases at Mayo Clinic in Arizona. I've been engaged in the care of people with *C. difficile* for over 25 years, and I've witnessed the impact this has had on many lives. I've been involved in studies to diagnose, prevent, and treat this awful infection, and, during my tenure in Rochester, we developed environmental cleaning protocols, which help prevent the spread of *C. difficile* in the healthcare setting.

However, I continue to see persons with CDI who despite our best antimicrobial therapies could not rid themselves of this illness. I have seen realtors stuck in their homes because they're afraid to go out with clients, Olympic horsemen who had to wear diapers to their equestrian training, chefs who couldn't work, young moms who couldn't take care of their newborns, previously active and well older adults who lost their autonomy and ended up in skilled nursing facilities, hospitalized patients who nearly or did lose their colon after undergoing an elective surgery.

Imagine being a highly functional person and then to be relegated to spending your days on a toilet or living in fear that anytime you might receive an antibiotic, you could potentially get sick enough to end up in the ICU or die. These are the stories I hear every day from patients who come to see me to seek out new solutions.

In 2011, after seeing the effectiveness of fecal transplant performed by a colleague in Duluth, Minnesota, we embarked on developing a program to offer FMT to patients whose recurrent disease -- who are unable to clear their infection by conventional means. We performed the first FMT by colonoscopy in 2011 in a man who spent weeks with severe diarrhea in the hospital only to see him recover in 24 hours and return home. The success stories of this procedure are some of the most gratifying.

To ensure the safest and most operationally effective process, we developed standardized protocols and shared these with our colleagues at numerous healthcare institutions across the United States. We

continue to work with others to better understand the safety and the microbial mechanisms by which this therapy was so effective. We provided this treatment to over 450 patients here at Mayo Clinic in Arizona and to thousands across Mayo Clinic sites nationally.

The 93 percent open-label success of FMT at curing even the most challenging cases let us and others to envision a safe and regulated pathway for these human biologic products to be developed, understood, and more widely accessible.

DR. SUSSAN PAYDAR: (Inaudible).

DR. ROBERT ORENSTEIN: There really is a clear need for safe, effective, accessible, and affordable microbiota-based therapeutics, and it's my hope that products like the one being reviewed today will become available to our patients in the near future. Thank you for the opportunity to hear my experience.

DR. SUSSAN PAYDAR: Thank you, Dr. Orenstein. I appreciate it. Next is Rebecca Perez.

MS. REBECCA PEREZ: Thank you and good afternoon. I appreciate the opportunity to share some

thoughts from the professional case management community.

So case managers are licensed healthcare professionals, registered nurses, social workers who are often very intimately involved in the care of individuals that are challenged with *C. diff* infections. So I'm happy to represent them today and also the nearly 450,000 people that suffer with infection every year.

C. diff and its complications often are overlooked and not included in care coordination or transition management strategies. But case managers are there, and they are directly involved in these particular activities, so it's important that they are included in the transition processes and in education and prevention of recurrence.

I've had the opportunity to share some information with case managers recently about *C. diff* infections, and hearing some of the patient statements today reinforces what I have seen in my practice as a registered nurse and as a professional case manager.

These individuals are often left with significant problems and weaknesses, poor outcomes, and they often self-isolate due to the concern that they're going to make some else ill. They often have antibiotic resistance, so the infections are recurring at all times. Antibiotics are sometimes expensive or the antibiotic that a physician orders is not approved by a payer. They experience multiple admissions, and, as case managers, we try to prevent those readmissions and we also try to make their transitions safe so that an admission can be prevented. But unfortunately, with *C. diff*, that doesn't always happen.

We'd really like to see the microbiota treatment be approved to help better manage CDI so that people are not so horribly affected, that they're not returning to the hospital multiple times, and that their quality of life is improved. Oftentimes, this requires an interdisciplinary approach, and so the availability of this treatment will just help case managers to also advocate for that treatment once it's approved hopefully and it will be approved. Thank you.

DR. SUSSAN PAYDAR: Thank you, Rebecca, for a case manager perspective. We appreciate it. Next is Freda Pyles.

MS. FREDA PYLES: Good afternoon. I have no financial disclosure.

As a result of a dentist-prescribed oral antibiotic for a tooth infection, I suffered my first bout of *C. diff* infection in September 2021. Prior to that time, I was an active 73-year-old woman. After being misdiagnosed with diverticulitis in an ER, I spent five days in a hospital in complete isolation on IV fluids and appropriate antibiotics for the correct diagnosis of *C. diff* colitis. I was so sick that a consultation was done for a possible surgical invention for a total colectomy as I had fulminant *C. diff* colitis.

Still with diarrhea, I was allowed to go home after some improvement. For weeks, I would get brief respite for days after a course of oral vancomycin when I could leave our home to go grocery shopping and adventure outside. After the diarrhea resolved, I

would think I was cured and start regaining some strength.

Unfortunately, a week or ten days later, the symptoms would begin again with severe diarrhea, making it impossible to eat or regain any strength I had lost previously. I was confined to my chair in my living room closest to the bathroom. This recurred three times after being treated with vancomycin, and I became weaker and weaker losing weight and strength rapidly.

After the fourth bout of *C. diff* recurrence, I was convinced I was not going to survive. I had lost 45 pounds and was a prisoner in my own home, essentially chained to the toilet. My husband, a retired ER physician, and close friends who are medical professionals were doing extensive research on what the next steps should be for help.

Finally, they found a study concerning microbiotic treatment for *C. diff* in the then current issue of *The New England Journal of Medicine* where we learned Dr. Paul Feuerstadt was the lead author. We contacted him and arranged a video appointment after he

reviewed all of my recent medical records. I was told I would be a good candidate for the microbiotic fecal replacement procedure, and an appointment was scheduled quickly. I was also started on fidaxomicin as an alternative to vancomycin. This drug, by the way, was $1,500 out of pocket for a ten-day course despite having Medicare Part D.

DR. SUSSAN PAYDAR: Freda, if you could please wrap it for us.

MS. FREDA PYLES: After the fecal transplant procedure with the Rebyota material, I felt better quickly. I have had no problems, have gained weight, my appetite is normal, am traveling, working out of our YMCA again, gardening, keeping my bees, and have resumed all normal activity.

MR. MICHAEL KAWCZYNSKI: Please wrap it up.

MS. FREDA PYLES: I'm absolutely con- --

DR. SUSSAN PAYDAR: Freda, if you could please wrap it for us, please, that would be great.

MS. FREDA PYLES: I'm absolutely convinced the Rebyota treatment saved my life. Thank you very much.

DR. SUSSAN PAYDAR: Thank you for making time to share your personal experience with us. Next is Dr. Kelly Reveles.

DR. KELLY REVELES: Good afternoon. My name is Dr. Kelly Reveles, and I have served as a paid consultant for Ferring Pharmaceuticals, but then today speaking on my own behalf. I'm an associate professor at the University of Texas at Austin and the UT Health Science Center at San Antonio.

As an infectious diseases pharmacist and academic researcher, I've been working in the *C. diff* and microbiome space for ten years evaluating the national *C. diff* epidemiology and then fecal transplant for both infectious and noninfectious diseases. I do believe that one of the primary areas of unmet need for *C. diff* patients is the treatment and prevention of recurring infection.

While we currently have approved antibiotics for *C. diff*, these therapies continue to deplete our healthy gut microbes and contribute to risk for recurrent *C. diff* infection. Really the most effective

way to break this cycle is to replenish healthy gut microbes with the use of microbiome-targeted live biotherapeutic products like Rebyota.

In my group's work, we've documented high rates of poor *C. diff* infection health outcomes, including severe infection, recurrence, prolonged hospital stays, and mortality. Notably in the U.S. veteran population, we found a significant increase in the incidence of *C. diff* recurrence over a ten-year period. We also found that patients who experienced *C. diff* infection more often require higher levels of healthcare after hospital discharge, including long-term care, skilled nursing, or hospice. And particularly concerning is the impact of *C. diff* on patient quality of life as you've heard repeatedly from the patient advocates today.

And then finally in a more recent publication, our group found that the use of fecal transplants nationally has declined in recent years likely due to reduced access. So given these data, I believe there's a critical need for an FDA-approved live biotherapeutic

to improve access to these life-saving medications.

Published data indicate that Rebyota restores the healthy microbiome in the gut, significantly prevents future recurrences of *C. diff*, and improves patient quality of life. Additionally, my work in the microbiome and fecal transplant space demonstrate promise for the use of microbiome-targeted therapies for many other biological processes. We now have evidence that disruptions in the gut microbiome are associated with more than two dozen health conditions, and that microbiome-targeted therapies may be effective in altering the course of these diseases.

So not only can live biotherapeutics substantially reduce *C. diff* infections, they may also open the doors to important scientific advancements in other areas as well. So I believe that Rebyota will provide an important and life-saving therapy that will make a significant and sustained positive impact on patient health. Thank you.

DR. SUSSAN PAYDAR: Thank you, Dr. Reveles. Next is Lisa Serwin.

MS. LISA SERWIN: Thank you for the opportunity to speak today. I have no financial conflicts.

My name is Lisa, and I'm speaking to you as a healthcare executive and patient who has had *C. diff* and was subsequently cured with FMT via a colonoscopy. I want to start by saying it's exciting; there could be a newly approved treatment on the market.

C. diff is an insidious disease. As we have heard here today from so many, it robs you of everything: career, finances, emotion and behavior, social life, family relationships, and dignity. All you are left with is watching yourself disappear knowing you might die as you shrink into nothingness. By the time I received my FMT, I weighed a little over 92 pounds.

FMT saved my life. I credit OpenBiome and the product they provided. With that life, I have worked hard to make sure no *C. diff* patient goes through unnecessary suffering to access treatments they need. The formal approval of a new treatment by the FDA

represents a win for patients.

However, I would like to offer my voice for those for whom the approved product may not work. I would like to encourage the FDA's continued thoughtfulness before making changes to the enforcement discretion framework. My concerns focus on patients being able to access alternative treatment options, those for whom this enema product may not be appropriate, e.g., pediatric patients or for whom this enema product fails.

FMT has proven itself as a successful efficacious and necessary weapon against what is a truly horrific disease. Please leave as many treatment options as possible open to patients and their providers. Thank you for your time today.

DR. SUSSAN PAYDAR: Thank you, Lisa, for your participation. Next is Dr. Miguel Sierra Hoffman.

DR. MIGUEL SIERRA-HOFFMAN: Hello. I thank you for the opportunity to speak. I am Dr. Sierra-Hoffman. I'm an infectious disease and critical care specialist. I have no financial disclosures, but I

have to disclose that I was invited to a scientific meeting around 2020 to provide my opinion in regards to this product. I didn't get a fee for my opinion.

The good thing is that that same opinion I gave two years ago is the same opinion that will hear right now. *Clostridium difficile* remain in the urgent list of organisms in the serious illness. If we take a quick look -- a better look -- at those five organisms, *Clostridioides* is the only one that is not eradicated with antibiotics. We all know that the real elimination and solution of severe disease or recurring disease and the fastest one is to replace the fecal microbiome.

This concept is not new; what might be overlooked is that the fecal matter biome restoration is done in (inaudible) healthcare centers by far. That means that 99 percent of the facilities in the United States do not benefit directly from these well-established (inaudible).

As of September 22, 2022, I'm yet to see that procedure or that technology performed in Victoria,

Texas. (Inaudible) of the infectious diseases --

DR. SUSSAN PAYDAR: Dr. Hoffman, it helps if you speak a little bit. Your voice is very low. We can't hear you well. Just speak a little louder.

DR. MIGUEL SIERRA-HOFFMAN: Sorry.

DR. SUSSAN PAYDAR: Could you just speak a little louder for us? That's all.

DR. MIGUEL SIERRA-HOFFMAN: Okay. As of September 22nd, 2022, I'm yet to see that procedure performed in Victoria, Texas. I see the whole spectrum of the disease from recurrent disease to toxic megacolon and (inaudible). These (inaudible) are extraordinary opportunities to transfer that technology to the hands of the rest of the country and stop depending on (inaudible) healthcare center referrals in the hope that finally someone would perform the procedure or the technology in small communities.

And last, I would like to close with we cannot forget that in the prior decade, *Clostridium difficile* was the number one cause of mortality from an infectious disease cost. Thank you very much.

DR. SUSSAN PAYDAR: Thank you, Dr. Sierra-Hoffman. Our last OPH speaker is Maryann Webb. Maryann, please go ahead.

MS. MARYANN WEBB: Good afternoon and thank you for allowing me the opportunity to share my experience as a *C. diff* patient with you today.

I have no financial disclosures to make at this time.

My name is Maryann Webb, and I contracted a *C. diff* infection after a diverticulitis diagnosis and treatment. A few weeks later, I came down with severe abdominal pain, cramping, vomiting, and explosive diarrhea. This was not anything remotely like a stomach bug or even the diverticulitis that I had just recovered from. It was incessant and persistent. I went to the emergency room and was admitted. I was put on additional antibiotics and sent home to quote recover, but that's not what happened.

I didn't get better; in fact, I got worse. No hydration, intolerable pain, vomiting, explosive diarrhea, weakness, and brain fog moved in. I had

trouble retaining and understanding information. I was alone in the hospital almost all the time. I tested positive for *C. diff* and then was put into complete isolation. This was the never-ending cycle of infection, hospitalization, treatment, and recurrence that would claim three years of my life. The antibiotic treatments of Flagyl, vancomycin, Dificid were very difficult to tolerate, and they came with their own side effects. They didn't cure my *C. diff* infection, yet this is the treatment routine that I was given each time I was hospitalized.

No one explained to me or my family that I was likely to have a recurrence with the first *C. diff* infection or that, with each recurrence, the next one would become more likely. I felt like I was going crazy and that I was alone and isolated. Layer by layer, my humanity was being shed, like the peeling of an onion as I watched people live their lives outside my window.

All that was left of me was just a bag of bones and a series of failing biological functions. My

hair was falling out and sometimes I felt my body shutting down and I knew I was dying. I received an FMT, and, since its emergency use authorization only, it was covered after years of suffering through failed treatments. I fit into that category unfortunately, but I still had to fight to get the authorizations.

Eight hours after my FMT, I became reborn. My symptoms disappeared, gone. I never looked back, except that I did look back. I was angry. It didn't have to happen. It didn't have to be that way. Why should we have to suffer so many recurrences when there are other effective treatments available? Had the FMT option been available to me with the first or second recurrences, I would have reclaimed three years of my life.

As a *C. diff* survivor, I'm now committed to use my experience to explain to anyone who will listen. We deserve better testing and better treatments and access to those treatments delivered in a timely and humane manner. Thank you so much for this opportunity.

DR. SUSSAN PAYDAR: Thank you, Maryann, for

your participation and sharing your personal experience with us.

Thank you, everybody. And this concludes the open public hearing session for today, and now I hand over the meeting back to our chair, Dr. El Sahly. Dr. El Sahly, go ahead.

DR. HANA EL SAHLY: Thank you, Sussan. Next, we get a ten-minute break. It's 1:59 Central time. Let's reconvene at 2:09 Central time.

MR. MICHAEL KAWCZYNSKI: So ten minutes. All right. You all deserve that. All right. We are officially -- let's take us to a ten-minute break. Studio, please take us to break and, captioner, no captions at this time for ten minutes.

[BREAK]

MR. MICHAEL KAWCZYNSKI: All right. And welcome back to the 176th Vaccines and Related Biological Products Advisory Committee meeting. We just concluded our OPH session, and now we're going to

hand back to our chair Dr. Hana El Sahly for some additional Q&A.

DR. HANA EL SAHLY: Thanks, Michael. And thank you all for joining in the last part of our meeting today. So we begin with this part of the meeting with Rebiotix providing some answers to questions that were posed by some of our Committee members earlier today. Rebiotix.

DR. LINDY BANCKE: Thank you. We do have a brief follow-up in response to a question asked by Dr. Offit during this morning's Q&A regarding catheter-related infections. I would like to ask Dr. Jonas Pettersson to respond to that question.

DR. JONAS PETTERSSON: Jonas Pettersson. We have searched for catheter-related infections during the break, and we found one event. The narrative to this event is already provided in your briefing materials. In short, this was a 53-year-old male with multiple chronic conditions, including end-stage renal disease and dialysis. He experienced an event of sepsis with a positive blood culture for MRSA.

Perspective source including the dialysis perma-catheter. Please note that RBX is tested for MRSA, excluding the event from being related to treatment.

DR. LINDY BANCKE: That is the only additional follow-up that we had from this Q&A session.

DR. HANA EL SAHLY: Okay, thank you. Dean. Dr. Follmann, you didn't get a chance to ask some of your questions so please proceed.

DR. DEAN FOLLMANN: Yeah. Thanks, Dr. El Sahly. I had a comment that had to do with, were there sensitivity analyses or other approaches to try and weigh the evidence from the two studies? So, on my own, I did a fixed-effects meta-analysis using a permutation approach. I came up with a P value of 0.003, and this sort of helped me understand or put in context the posterior probability that you guys had calculated. And I was wondering if you had done an analysis like that, like a different method of combining the evidence or frequentist approach. Either you or the FDA had done this which would, I think, help

us deconstruct in some ways what you had done.

DR. LINDY BANCKE: I would like to ask Dr. Scott Berry to respond to your question regarding other analyses that we've performed.

DR. SCOTT BERRY: Scott Berry. Dr. Follmann, the analysis you did -- in a way this Bayesian borrowing is a meta-analysis, prospectively set up before the results were there in the estimate of 2017. We've done a range of power priors, fixed borrowing, and sensitivity analyses, much of them similar to the primary analysis that was set up.

DR. DEAN FOLLMANN: And then the same question for the FDA. Had they done an analysis like this, you know, beyond what the Bayesian analysis that Dr. Berry had done?

DR. ZHONG GAO: We didn't do the analysis you mentioned or conducted by you.

DR. DEAN FOLLMANN: Thanks. And then I had a follow-up question. I might've seen a slide somewhere that did a summary of randomized trials that people transplant versus a control intervention. Does either

the sponsor or the FDA have information about what that summary of other studies that have been done or a meta-analysis or something?

DR. LINDY BANCKE: From the sponsor perspective, I can tell you that we have looked at FMT literature that is available. Of course, we do not have head-to-head data available for an approved FMT, but I would like to ask Dr. Sahil Khanna to speak to that data that he presented earlier today.

DR. SAHIL KHANNA: Sahil Khanna. Our research group a few years ago did a systematic immune meta-analysis answering a very important question: what is the actual cure rate of FMT? Because we were seeing numbers all over the place.

DR. DEAN FOLLMANN: Yeah.

DR. SAHIL KHANNA: They were openly showing 90 plus percent. There were open-label studies showing somewhat lower in control trials, some showing somewhat lower. Pull up the slide again that you're referring to.

This is a meta-analysis that looks at cure

rates of studies that have --

DR. DEAN FOLLMANN: I see. I mean, this is just a cure rate. There's no comparison here, so we can't get sort of comparative evidence from this.

DR. SAHIL KHANNA: There's no competitor cure rates that were in this study at this time that I can show.

DR. DEAN FOLLMANN: Okay. Thank you. That's all the questions I have. I have discussion points, but I think we'll do that later.

DR. HANA EL SAHLY: I have a clarification question on the inclusion criteria in the trial. I know in one trial the patients had to have at least two recurrences and one trial that had to be either one recurrence or two hospitalized *C. diff* episodes. Upon enrollment, did the patient have to have *C. diff*? Or is it just in the past at any time they've had *C. diff*, and now we're enrolling them? Or is it, oh, they're coming down with another episode; they need to include an exclusion criteria, and hence we're going to enroll them?

DR. LINDY BANCKE: For all prospective trials, with the exception of study 2019-01, which is the ongoing open-label study, a very strict criteria was required for a positive stool test to be performed within 30 or 60 days depending on the study. It had been 60 days. We narrowed that to 30 days for the pivotal Phase 3 trial. And that stool test was required upon study entry, and patients needed to be actively being treated with antibiotics for that infection or being put on antibiotics at the time of enrollment in the study.

So, yes, they did come into all studies with an active recurrence of CDI.

DR. HANA EL SAHLY: All right. Thank you. I think that concludes the Q&A session, which is a bit of a leftover from the morning. Next, the Committee will be discussing the two questions --

MR. MICHAEL KAWCZYNSKI: Oh, you -- Dr. El Sahly, you do have another hand up.

DR. HANA EL SAHLY: Andrea. Okay, they changed the color. Andrea.

DR. ANDREA SHANE: Sorry. Sorry. I just had a question. I couldn't raise my hand fast enough. So I just wanted to ask, in the trial was there any limitations that were placed on -- in any of the trials -- on what other products patients could take? For example, was any assessment done of whether patients were taking probiotic products at the same time, or simultaneously, with the treatment? Thank you.

DR. LINDY BANCKE: In the clinical studies, we did prohibit use of concomitant probiotics that were supplements. We did not exclude dietary probiotics such as yogurt, et cetera. So only over-the-counter supplement probiotics were excluded.

DR. ANDREA SHANE: Thank you.

DR. HANA EL SAHLY: Dr. Young.

DR. VINCENT YOUNG: Yes. I did have a quick question left over from the morning, and it was regarding the different response rate of patients who received placebo. I don't remember finding the ratio of patients who received placebo with regards to the number who had gotten -- or percentage who had gotten

vancomycin as standard of care versus fidaxomicin, especially given the different time period. Was that in there and I missed it?

DR. LINDY BANCKE: For both studies, it was --

DR. VINCENT YOUNG: Yes. For -- okay, sorry.

DR. LINDY BANCKE: No. I do have a slide that I can share so that you can actually see the two studies side by side: Study 2014 and Study 2017. And as you can see on the bottom is pertinent to your question, the vancomycin during screening for both studies was very similar.

DR. VINCENT YOUNG: Thank you.

DR. HANA EL SAHLY: Okay. Any follow-up questions from the Committee members before we move to the questions deliberation? I see no hands. Thank you all. Prabha or Sussan, do you mind putting the two questions on the screen?

COMMITTEE DISCUSSION AND VOTING

DR. SUSSAN PAYDAR: Thank you, Hana, I'll take

it from here. Let me read my blurb, and then we go from there -- the instructions.

So we only have our 13 regular members and 4 temporary voting members, a total of 17 will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the final voting question for the record, and afterwards I'll ask all regular voting members and temporary voting members to cast their votes by selecting one of the three voting options, which includes yes, no, or abstain.

You have one minute to cast your vote after the question is read. Please note that once you have cast your vote, you may change your vote within the one-minute time frame. I'll announce when the voting poll has closed. At that point, all votes will be considered final. Once all of the votes have been tallied, we will broadcast the results and read the individual votes aloud for the public record. Does anyone have any questions related to the voting process before we begin?

DR. PRABHAKARA ATREYA: Sussan?

DR. SUSSAN PAYDAR: Yes.

DR. PRABHAKARA ATREYA: Sussan, can I speak?

DR. SUSSAN PAYDAR: Yes. Please, go ahead.

DR. PRABHAKARA ATREYA: We have to start the discussion first. It's not about the voting at this point in time. So the question will be on the screen, but the members will discuss the various aspects of the questions before they vote.

DR. SUSSAN PAYDAR: Okay, great. So now they have the instructions. We do the voting right after the discussion is over. Thank you, Prabha.

DR. HANA EL SAHLY: Okay. So, on the first voting question that we will be deliberating on prior to voting, "Are the available data adequate to support the effectiveness of REBYOTA to reduce the recurrence of *Clostridium difficile* infection in adults 18 years of age and older following antibiotic treatments for recurrent CDI?" Next voting question.

DR. ERIC RUBIN: Am I up?

DR. HANA EL SAHLY: Just a second so we can read the two questions and we can deliberate them.

"Are the available data adequate to support the safety of REBYOTA when administered to adults 18 years of age and older following antibiotic treatment for recurrent CDI?"

So now we will go around the table discussing these two questions, and I will begin with Dr. Eric Rubin.

DR. ERIC RUBIN: Thank you.

DR. PRABHAKARA ATREYA: Mike. Mike -- I'm sorry. Mike, can you keep the question on the screen, please, when they discuss?

DR. ERIC RUBIN: Okay. Thank you. Just to frame my thinking here. We heard a lot about a trial that was imperfect and necessarily imperfect because of the other options that patients had to have FMTs outside of the study and switch from a frequentist to a Bayesian analysis and the addition of other data which a little imperfectly matched, and they knew about the results before they mixed those data in.

And in the end, the effect size was pretty modest. That being said, thinking about what this

product is -- it's an FMT, it's a defined FMT. There's no reason to think that it's either better or worse than products that have not been selected perhaps on the safety side, but not from the efficacy side, because it's not designed to have a change in efficacy. And so I kind of look at it as fitting into the FMT landscape.

I think the evidence out there for FMTs is a little bit uneven, but it's pretty good, and most practitioners would say that. And the members of the public were commenting would say that there certainly are advantages and some really excellent responses to FMT. So I'm a little less worried about the specific efficacy data and feel more comfortable with a well-controlled product in terms of safety to be supportive of this product. Thank you.

DR. HANA EL SAHLY: Thank you. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you. I guess my concern is about the two questions is that the answer to the questions is really a linkage between those two. Is the efficacy -- does it justify the

risks related to the safety? So I can't really vote for question one without taking into account the vote for question two. It seems like there should be a third question, does the safety justify the efficacy? Is it worthwhile having this product for patients giving them that slight benefit of being cured but taking a risk that they might be harmed also?

There's no way to really express that combination of factors with just two questions.

DR. HANA EL SAHLY: Okay. I think the sponsor and the FDA did not provide an analysis of risk to benefit, and we all -- the concern that those who ended up getting more FMTs are likely to cure patients so they can't be compared to people who didn't go on to getting more FMT. But, nonetheless, we have to weigh in the data as presented.

DR. JAY PORTNOY: I know. But is the treatment justified given the risks? And there's no way to combine those two to a third question, otherwise both of those -- one and two -- seem like you could vote in favor of them. But the third question is

really the one, I think, is the most important, and that's the question that's just not available. So I'm going to have a hard time figuring out how to vote.

DR. HANA EL SAHLY: Okay. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Sahly. I listened to Eric's comment, and I thought to myself -- and listening to the public comments and I think what threw them --

DR. HANA EL SAHLY: Speak louder.

DR. STEVEN PERGAM: Oh, sorry. Can you not hear me well? Is that okay?

DR. HANA EL SAHLY: Yeah. It's very soft.

DR. STEVEN PERGAM: Yeah. Sorry. I don't know why I'm soft. I'm using the same headphones I've been using this whole time. But yeah, so I would say listening to Eric's comment and the public comments that were made, there are places where current available therapies are not sufficient to treat patients, and there is a need for this product. I think what people need to understand is that if this product doesn't exist, fecal transplants will still

happen. They are still happening through different centers, just not with a regulated product.

And one of the advantages that I see is that there is a need for something that is more standardized in terms of its approach. Organizations like OpenBiome, which used to provide microbiome solutions for individuals and for centers no longer is making that available. So it becomes much more of a -- not a level playing field -- but a very difficult mishmash of different approaches in terms of screening or how people and centers are doing this. And so I think having a product that's more consistent would make more sense, and that's an advantage to this.

I guess my question about the voting question one is, when does this approach take place? Is it really after the first event and after the first episode of *C. diff* is this given? Is that the approach that's being offered, or is this sort of a non-specific answer? Is it after two episodes? It's not clear to me in the questions if that's been defined or if that's just an open-ended issue. That's just my only concern

about how the question is worded.

DR. HANA EL SAHLY: Well, the question says for recurrent *C. diff*, so at the minimum, the patient should have recurrent, which is one or more.

DR. STEVEN PERGAM: Fair enough. Yeah.

DR. HANA EL SAHLY: I don't think the just one episode either. Dr. Fink is on.

DR. DORAN FINK: Yeah, hi. Yes, Dr. El Sahly, you have it right. The proposed indication is for use after a recurrent episode, and it could be the first recurrence, it could be the nth recurrence.

DR. STEVEN PERGAM: Okay. Great. Thanks.

DR. HANA EL SAHLY: Dr. McDonald has a question next. And I want to encourage all our Committee members to pose their questions and their viewpoints of the presentations and reading so far.

DR. CLIFFORD MCDONALD: Yes, thank you. I'll give my viewpoint, and I think that I will consider these questions in the context of the world in which we live and the situation these patients find themselves in. And I do think that hearing from the patients has

been so important. As I think we heard from the patients back in -- I don't know what it was -- 2015 or was it 2012 or '13 -- when the FDA first discussed this publicly, the issue of FMT and then soon thereafter came to the conclusion of enforcement discretion.

And I think we've heard about, you know, the many people who have benefitted from enforcement discretion. And then some of this goes into this theme that I've been asking about throughout the day that -- especially there's a subset within this population that we're studying in these efficacy trials which are the people who've had it three, four, five times or more and, of course, there is no other treatment for them in that situation.

Some other clinical experts, if they were here, would say that some of these early recurrences could perhaps be better managed with the antibiotics, and some of them wouldn't even come onto a third or fourth recurrence. Sometimes maybe the primary episode could be better managed with the antibiotics we have. But, that being said, there's clearly this unmet need,

especially in the multiply recurrent population where probably the efficacy is a little even better than we've seen today.

Anyway, so this is where I look at it and I also look at it again with the (inaudible) these patients have nowhere else to go. They're going to be going to FMT regardless. This is, to me, an improvement in safety and standardization. Over.

DR. HANA EL SAHLY: I want to ask you a question. So this is the second time you indicate that the potential better niche for this particular product is for individuals with multiple recurrences. But do we have those data or is it --

DR. CLIFFORD MCDONALD: No. No, we don't. And I think that it'll be increasingly difficult. I mean, why would anyone? I think this situation I've heard from these patients, too. It's just miserable. Their life stops, and the last thing they want to do is be randomized to placebo in those situations, especially as you go on to multiple and multiple recurrences. So I think that some of it's looking at

historical data in that the likelihood of recurrences mount in number in looking at that.

DR. HANA EL SAHLY: Okay. All right, thank you, Dr. McDonald. Dr. Young.

DR. VINCENT YOUNG: Yes. I mean, it's clear that patients with recurrent *C. difficile*, they represent a patient population in desperate need, and I think that we have made some advances with FMT in the past. And I think what we had presented to us today is, as I mentioned earlier, a kind of reproducible, codified system for preparing FMT. But it's not in either of the voting questions, but the term consistency has been brought up and reproducibility has been brought up.

But I have some hesitation about using those kinds of terms because we are not being consistent because as we know, patients vary from the composition of their microbiota. And even within a person over time, there's variation. And I think that we need to accept what is being presented to us, that this is a version of the unregulated FMT where the procedures are

more consistent, where the screening is more consistent. And the screening can vary as we understand more things. For example, we are presented with monkeypox or we're presenting with SARS-CoV-2 is something that we need to consider.

I think that's the niche that we are trying to fill a little bit here with a product like this, but it still fundamentally has some of the inherent variability and somewhat unpredictability that's going to be inherent in using a product where you start with feces as the initial input into the whole system. So I just think that's something that sometimes got not glossed over, but I think it's something that should be considered as we talk about this type of product. And it's different. It's different than something that's been presented before, right? It's quite a bit different. So, thanks. That's all.

DR. HANA EL SAHLY: Understood. Dr. Shane.

DR. ANDREA SHANE: Yes. Thank you very much. I just also wanted to just raise the point again I think that Dr. Chatterjee also mentioned about

representativeness. And I do have some concerns that -- about the composition of the people -- participants in the trials as well as how that might relate to the fact that their *C. diff* and recurrent *C. diff* does not seem to really -- the people who are experiencing recurrent *C. diff* did not seem to be completely represented in terms of racial and ethnic composition in the trials.

And so, in our voting questions, we're asked to consider adults 18 years of age and older. That applies to all adults, and so I would've really appreciated seeing some more data from a greater composition and more variety of people with different racial and ethnic backgrounds, and, I think, we know that *C. diff* affects people from these different backgrounds. So I just feel that there's a little bit of a loss in not having those individuals represented in the trials.

And we've talked a lot about variability of microbiome across racial and ethnic groups and ages and various impacts. So I just wanted to raise that as

well as one of my concerns. Thank you.

DR. HANA EL SAHLY: Thank you. Dr. Follmann.

DR. DEAN FOLLMANN: Yeah. Just a couple comments. Regarding the efficacy, I appreciated sort of a conundrum you had planned to do two 300-person trials, and yet that was not possible because it's so difficult to recruit. And so what do you do then? And I thought the approach of blending the Phase 2 study with a Phase 3 study was reasonable/defensible of this Bayesian kind of blending approach. The difference in the placebo event rate in the two trials was noticeable to me and Holly and I think others, but at the end of the day -- and partly supported by this meta-analysis that I did that had a P value of 0.003; I thought the evidence was sufficient.

Also, I noticed that the success rate in, I think it was 2014 following placebo failure, was 57 percent. It was a little bit more evident I would say. And then also I'm sympathetic to the unmet need for this condition.

Regarding safety, earlier you had mentioned,

can you do statistics on this? And actually, you can. And so, for example, the 18 to 0 split in death looks alarming, but there's a very big difference in the person-years of follow-up. And if you do a binomial test on this, you get a P value of 0.336. So the -- you know, you can sort of formalize whether there's a difference there.

And similarly, if you look at -- I think it was Table 24 -- the SAE rates are ten percent and seven percent, which aren't statistically different either. And so I understand we don't want to do a lot of inference about this, but still I think it helps to put the 18 to 0 in context that it's not statistically all that alarming. Thank you.

DR. HANA EL SAHLY: Well, I mean, yes. A lot of the individuals in that 18-person group who eventually died are people who got multiple doses of FMT, meaning they were sick from the start. But, nonetheless, it's across the board the adverse events are in the FMT group. And while a lot of it may not be reaching severity and death -- seriousness and death --

it would've been more informative if we had some statistical analysis or risk/benefit analysis around it. Yeah. Thank you for the --

DR. DEAN FOLLMANN: Yeah, I would agree with that. I would agree with that.

DR. HANA EL SAHLY: Yeah. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. Thank you, Dr. El Sahly. This time I am going to reiterate Dr. Shane's question, which is the concern about the non-inclusion or very few people of color that were included in the trials. So I do think that that is a concern that needs to be addressed in future studies at least.

Having said that, I would concur with many of the opinions that have been expressed that recurrent *C. diff* is not only a miserable disease, but potentially a life-threatening disease. The treatment options for this condition are very few and in a small proportion, at least, of the cases seem to be not very effective.

So, from that standpoint this product serves as an option that perhaps might work, and, for people

who are desperate, I agree with some of the comments that have been made by fellow Committee members that this, at least, appears to be a somewhat better-regulated product than the other methods of FMT that might be applied in those cases.

With regard to safety, I share some of the concerns that you have raised, and I would also like to see a little bit more data on that. But given what we're given, we do not have more data on that.

So going back to earlier comments that were made about risk/benefit analysis, which is not really being asked here, but I think all of us who are clinicians are used to doing this on a regular basis in our minds when we're thinking about therapeutic interventions. To me, it appears this is a safer product than the current ones that are available for FMT. And so those were my thoughts and remarks. Thank you.

DR. HANA EL SAHLY: Thank you, Archana. I have a question to some of my fellow statisticians on the Committee before we go to the next question. So,

the analysis -- the Bayesian analysis met one criterion but not the other. Where does this leave us?

I mean, we are familiar with an approach where a margin or a statistical analysis is put forward in the beginning -- be specified at what margin we would consider a success or what endpoint is reached is considered a success without specific error rate. But here, the biostats have specified two probabilities -- two (inaudible) probabilities, I should say, and one was not.

So where does this leave us? How certain are we of the finding which is a modest improvement of recurrence and give or take ten percent if we look at both clinical trials compared to placebo? So that's Holly and Dean in the hot seat.

MR. MICHAEL KAWCZYNSKI: Who are you asking, Dr. El Sahly?

DR. HANA EL SAHLY: Yeah, I'm asking Dean or Holly. Would you mind putting them on?

MR. MICHAEL KAWCZYNSKI: Dean. Okay, I'll put Dean on. And who's the other one? And Holly, here we

go.

DR. HANA EL SAHLY: Dr. Janes.

DR. HOLLY JANES: All right. You know, I'll share some thoughts, but I was actually going to raise this as a question for our FDA colleagues. You know, the FDA has set forth a standard for approval of products based on two adequately powered and well-conducted Phase 3 trials and that standard hasn't been met here. I think all have agreed on that point, and yet they were presented suggesting that under a certain analysis that the standard was met for the statistically significant efficacy equivalent to one adequately powered and well-designed Phase 3 trial.

So, taken at face value, to me, that would suggest that the FDA criteria for approval have not been met here, unless there's a different standard that we ought to be applying given the severity and significance of this clinical context.

DR. HANA EL SAHLY: Okay. See, that's why (inaudible) put it in statistical wording like you are here, okay. Dean?

DR. DEAN FOLLMANN: Yeah, I had sort of the same question, really. It met one bar but not the other, and so how do we deal with that? And then I tried to think how close we were to meeting the bar, and I did an analysis where, if you switch three treatment failures to successes, then you would meet the bar with this analysis that I had done. That's three out about 340 patients, I guess, in the total studies. To that, that was one bit of evidence.

I've also, it seems, lately been in situations where unmet need and the inability to do studies is effectively, I guess, weakening the strict bar, and that's part of my thinking about this as well.

As a practical matter, I don't know that we'll get more studies like this. You know, I don't really know that. But it seems like they wanted to do two 300-person studies; they couldn't. The FDA didn't say, oh, you're just making it up. They said, let's try to find a path forward here with this kind of blending, which I thought was reasonable. And then, it didn't quite meet the bar. But there's I don't see a good way

to get additional evidence.

Part of that reason was I was interested in meta-analysis of other studies, not this particular product. Just trying to cast the net widely in terms of additional efficacy information because I think this is the sort of the fixed hand we're dealt with, more or less. And, anyway, that was my struggle with this.

DR. HANA EL SAHLY: Okay. All right. Thank you. Dr. Perlman. Thank you both.

MR. MICHAEL KAWCZYNSKI: I think Doran has a question. There we go. Go ahead, Dr. Fink.

DR. DORAN FINK: Hi, sorry. Before Dr. Perlman speaks, I just wanted to make sure that -- it seems like Dr. Janes and Dr. Follmann wanted to have FDA weigh in with some direction on how to consider these discordant statistical results. I think we entered the data that this question might come up, and so I'm happy to do that.

And I think Dr. Follmann really did lay out the considerations very well. We do expect a standard of substantial evidence of effectiveness to support

licensure of a biological product, and what constitutes substantial evidence of effectiveness can vary according to the disease and patient population and other factors.

We actually have published a draft guidance that speaks to many of these considerations. We do accept, in certain situations, single adequate and well-controlled trials to provide substantial evidence of effectiveness. Usually -- usually, those single trials provide what we would call a statistically very persuasive result, which is the bar that the Bayesian analysis did not meet in this situation. But we do have the regulatory flexibility to, again, consider the patient population, the disease, and other circumstances.

We also have the regulatory flexibility to consider other avenues of evidence, and some of those avenues of evidence have been discussed today as well.

But to sum up, this question of substantial evidence of effectiveness and how we apply it is really a regulatory policy question, and we don't usually ask

the Advisory Committee to weigh in on regulatory policy questions. Instead, what we're asking is for your clinical and scientific expertise to help advise us on how you see the strength of the evidence overall given the context of how the study was conducted and the challenges and also the patient population and unmet need. Thank you.

DR. HANA EL SAHLY: Okay. Thank you, Dr. Fink. There was Dr. Perlman. Sorry we cut you off.

DR. STANLEY PERLMAN: Yeah, I don't feel cut off since I never started. So I don't really have very much to add, but I'm swayed by all the arguments that have been made so far. It seems to me that this treatment will be very useful for a subset of patients, which are hard to identify in advance. Some of the placebo patients seem to recover without therapy, even though we wouldn't expect them to. But I think that on one hand, the efficacy was proven.

We've discussed how it wasn't great. Just the analyses did not stir the strongest possible support, but on the other hand, I think that we've heard over

and over that there's so many products on the market that the sooner we can get this into a regulated situation, I think the better everyone will be. So that's really all I have to say.

DR. HANA EL SAHLY: Thank you, Dr. Perlman. I would like to point out that what happens to the other drugs on the market may or may not be affected by what we say today, and I would like us to focus on the strength of the data on efficacy and safety as presented. But there are a lot of things that are happening actually in the field. It's probably beyond what we're doing today, but it's important to refocus on strictly what was presented. Dr. Cohn?

CAPT. AMANDA COHN: Hi. Thanks. I agree, (inaudible). I agree that you're in the -- I agree that the evidence is not overwhelming, but it is adequate to support the use of this product in this particular context and in this patient population. I would love to see there be some requirements for additional studies, including to enroll persons of color and to monitor the safety and effectiveness in

those groups, as well as to ensure there's strong information in the labeling of this product so that providers can make clinical decisions about which patients would most benefit from this product.

We use the word recurrent, and I know that Dr. Fink nicely stated that this means that more than one occurrence. But just because something is indicated, does not mean that that's the clinical recommendation, and I think there will be a lot of clinical decision-making on the providers given each particular patient context that will determine the number of episodes that a patient may have before using this product.

DR. HANA EL SAHLY: Thank you. Dr. Janes.

DR. HOLLY JANES: Thank you. I wanted to summarize my thinking around how to interpret this. I think the clinical context and the unmet need are really striking, and it was really tremendously helpful to hear the patient perspectives that were shared. But I guess what I feel is that the clinical package that's been presented here (inaudible) somewhat disappointing that it's not stronger.

It's based on a relatively modest number of participants, and the efficacy analysis and inferences based on it are sensitive to the data that are included in the analysis, whether one includes the historical data or makes inference based solely on the Phase 3 trials. And we haven't been provided with sort of sensitivity analyses that would relax assumptions or allow for the potential that there are different effects and historical study versus the Phase 3 trial, for example, due to differences in patient population evolution and standard of care, or even regression to the mean, which is a real issue in these small studies.

And the primary efficacy analysis that's been presented is subject to this assumption of exchangeability of the effects and even the placebo response rate in the two studies. And so, I really would've liked to have seen some analyses that relax that. And even taken at face value, as it's been mentioned, the effect size is rather modest, and it's hard to line it up, as has been mentioned, with the significant rate of adverse events in the patient

population and to make a cost-benefit assessment.

The inclusion of a very homogenous patient population, exclusion by and large of racial/ethnic groups that represent the demographics of the U.S. is rather just disappointing in this era. And as Dr. Follmann brought up in one of his questions, we haven't also seen that there's strong supportive evidence coming from other studies that the observational data that are out there are apparently uncontrolled observational studies. So it's really not possible to strengthen the inference based on external data, at least as far as been presented here.

So, in sum, I come back to this as thinking that this is certainly not supportive evidence that's equivalent to two Phase 3 studies and perhaps rather weak evidence for a single Phase 3 study. And as Dr. El Sahly just mentioned, I think the question that's been posed to us is not, is this product an improvement upon the FMT situation that's out there in clinical practice today, but rather is it demonstrated to be safe and effective on its own -- this product on its

own -- and I feel it's rather weak evidence of (inaudible) based on the package.

DR. HANA EL SAHLY: Thank you, Holly. I would also like to bring up another point that we didn't get to discuss before, although it was presented in the packet and was touched upon by both the FDA and the sponsor in two different ways, which is what happens after eight weeks. Even with the importation of the -- the borrowing of data that took place from 2014 to 2017 clinical trials, after eight weeks the difference narrows between placebo and active recipients, and even with the importation, it's no longer significant.

So I would just like to keep that in mind, understanding that this was actually a key secondary analysis, not a primary analysis. Thank you. Dr. McDonald.

DR. CLIFFORD MCDONALD: Thank you. Yes, in regards to some of the questions -- well, maybe in the context -- for FDA, does the Agency have any experience either in review or approval of a drug sourced from humans? Maybe pooled immune coagulant or other human

source drugs, and specifically any insights in post-marketing surveillance either as a drug versus a tissue or blood product?

So this is a question for FDA about if this were approved as a drug, the strengths and benefits of it being approved as a drug versus -- not that it's even being discussed as a tissue or blood product, I'm not making that point. I'm just saying that -- I'm guessing that the Agency's experience with approving human-sourced materials in humans is probably more in the realm of tissue or blood. Over.

DR. DORAN FINK: I believe that's a fair statement. We don't regulate any of those products in Offices of Vaccines, and so I'm wondering if Peter Marks perhaps is on the line and available to answer that question.

DR. PETER MARKS: Yeah. So, if I understand the question correctly, is there a way that we could think about regulating these in a manner that would be more akin to how we do this for our tissue products, if I understood it correctly? Is that what --

DR. CLIFFORD MCDONALD: Specifically, the post-marketing safety surveillance. Over.

DR. PETER MARKS: I think, actually, in some ways, our tissue products for post-marketing surveillance, I mean it's not actually quite as easy as it might be if we have a biologic product, which will have an actual code associated with it which allows us to follow that through our large database. So ultimately, I think in terms of safety surveillance on a product, rather than -- it may actually be easier in the long run to have this. And, Doran, feel free to speak up.

I think that's my take on this is that we should actually -- it can be challenging when we have products where we don't have things like NDC codes to be able to follow. Whereas here, we'll be able to use our surveillance systems and large databases, claims databases, because this is something that will go through claims databases and should be able to then pluck out people who have received these.

Should also allow us, besides doing safety

surveillance, potentially even do some exploration of real-world effectiveness.

DR. DORAN FINK: I'll add it as I've been thinking about this a little bit as Dr. Marks has been talking. We do have human-derived products that are licensed under BLA, so immunoglobulin-based therapies, for example, they may be big for treatment of neo-natal *Clostridium* infections.

We do have experience with human-derived products being out there in the market where we can track the safety. It is a bit of a different situation here because, for a product like an immunoglobulin-based product, there's not supposed to be any living organisms in it at all. And yet, the active ingredients for this product we understand are mostly, if not all, living organisms. So it becomes more challenging. But I think we --

DR. PETER MARKS: Yeah, immunoglobulin is also -- we have cellular products are the same way. Allogeneic cell products, so yeah. You're right; those are generally cells. Those are generally considered

sterile ones.

DR. CLIFFORD MCDONALD: Yeah. I mean, of course, it's new territory. We understand that that's been sort of mentioned, but actually, might have some benefits for safety surveillance over other human-sourced tissues, at least. But you actually answered my question both ways that, yes, you do have human-sourced materials under BLA.

DR. DORAN FINK: So bottom line, yes. We do.

DR. CLIFFORD MCDONALD: I do have one other question that's not related to surveillance safety. So, chair, if I could just bring it up. I mean, it's been mentioned or it's out there among the group that there is no other RCT of FMT, and there are other FMT RCTs, the van Nood study, for example. And so I thought that I heard someone say that there have been no other RCTs of FMT and there have been.

DR. HANA EL SAHLY: Yes, indeed. So, you know, you mentioned -- Dr. Marks, if I may have you for a minute -- effectiveness studies that can help us understand the role of this product. So one of the

cited reasons for the clinical trials not being able to enroll is the wide use of the (audio skip) product actually in the field. So do we (audio skip) there that were (inaudible) obtained?

DR. PETER MARKS: I'm sorry, you broke up a little bit. Do we have effectiveness data from what came in that made it difficult for these trials to enroll, is that what you were saying?

DR. HANA EL SAHLY: Yeah. A lot of the serologists' clinics, whether this product or other products are being used widely for years now, do we have any effectiveness data that are available?

DR. PETER MARKS: You know, I'll ask Dr. Fink to chime in, but aside from things that have appeared in journals, unfortunately, that's been the issue with having individual practitioners do this on a one-off basis. They may feel that the product is working for them, but we don't have, essentially, a trial design here. And, in fact, because we don't trace the product quite the same way, as we will be able to if it is a licensed product, it's hard to actually pick up those

people into using our surveillance systems to be able to make inference.

But Dr. Fink may want to comment on that as well, if I may have missed something. But I think that the fact that it's been done on an individual practitioner basis with enforcement discretion has not allowed us to gather the kind of evidence that we might like.

DR. HANA EL SAHLY: Okay. Thank you.

DR. DORAN FINK: I'm not aware of much in the way of trials that have been conducted. Dr. Khanna has this meta-analysis that he's shown slides of, but there really hasn't been much enthusiasm for conducting rigorous trials of the product administered in an unregulated manner.

DR. HANA EL SAHLY: Got it. Thank you both. Dr. Annunziato.

DR. PAULA ANNUNZIATO: Hi. Thanks so much. So I have a question with regards to the fact that this is a product for an orphan population. I work in vaccines, obviously, and so we never really think about

orphan populations, orphan disease populations. So perhaps the FDA could comment a bit on in that context what should we be expecting in terms of the number of subjects exposed. In fact, there were almost a thousand in these tables exposed to this product. That struck me as actually being a bit large for an orphan population program.

But perhaps I'm not thinking about that right. And then, also, does the fact that this is a product that's targeted to an orphan population -- does this in any way, should this, or does this make us think differently about the need to meet a substantial evidence bar versus a significant evidence bar? So that's intended for the FDA, perhaps, to answer.

DR. PETER MARKS: This is Peter Marks. I can start with one of these while Dr. Fink comes on. Thank you for throwing me some softball questions.

Congress has been very generous with what we consider an orphan product, and an orphan-designated product simply has to affect less than 200,000 individuals in the United States. So, I think we're

well under that. But on the other hand, FDA has traditionally -- although we have some discretion, we generally use the same standards for safety and effectiveness that we use for non-orphan populations for orphan populations.

And that means that we do have a safety and effectiveness standard as -- well, it's an effectiveness standard and we look at safety, but the effectiveness standard that we apply is similar. And as I've noted, there is some discretion given to the Agency, but we use the same standard. And, Dr. Fink, feel free to -- I think that's the way we think about things here but --

DR. DORAN FINK: Yeah. I guess the only thing I'll add is that even regardless of the orphan designation question, I do think that it helps to maybe make a distinction between this product and the preventive vaccines that this Committee is used to seeing. So preventive vaccines are administered to healthy individuals, and so we have a very high bar for safety and would typically ask for safety database of

at least 3,000 individuals in prelicensure trials.

This is a product that is intended for use as prevention of recurrent *C. diff*, but it's secondary prevention. These are patients who have already suffered from at least two episodes of *C. diff* and have -- we understand that they have disordered intestinal microbiota, and so they have a disease. They're not healthy. And so even disregarding the flexibilities that we might extend to orphan products, the safety database for this program is actually consistent with what we would typically see for or expect for therapeutic drugs.

And I think that's important for the Committee to understand.

DR. PAULA ANNUNZIATO: Thank you.

DR. HANA EL SAHLY: Thank you all. I see one last hand risen, but we have not heard from everyone, so please let us know your thoughts. Dr. Rubin.

DR. ERIC RUBIN: Hi, thanks again. I just wanted to point out because it's been raised several times, that there are RCTs out there of this therapy.

Not with this product, but with donor stool. I know that one journal that I know quite well has published one, but I think there are about eight others out there. They're relatively small. They're all positive. They all point in the same direction.

So it's not as if there's no high-quality evidence out there. There is some high-quality evidence out there for donor stool, not obviously for this product.

DR. HANA EL SAHLY: Okay. Thank you. Dr. Offit.

DR. PAUL OFFIT: Thanks, Hana. What I would say is pretty much what Eric and Steve have already said and many have already said. I mean, we have a fecal microbiota transplant program in our hospital. Now we see this isn't going to affect us much because we deal with children less than 18 years of age, but when we do that, the donors are invariably the parents. And we have through the therapeutic standards committee, have a pretty tortured protocol to make sure that we're not inadvertently transplanting in

pathogens.

I think, as far as I'm concerned, that's the biggest advantage here, which is that you have a defined product in terms of a potential pathogen. So that's all I have to say.

DR. HANA EL SAHLY: All right, thanks, Paul. Dr. Bernstein.

DR. HENRY BERNSTEIN: Yeah. It's been a fascinating conversation. For me, I'm disappointed to hear that enrollment was so challenging, which resulted in the need to, so-call, borrow data. But that being said, despite spotty data demonstrating modest benefit and safety, there appears to be a real need for this option that's in this unique patient population, so it's hard not to think about it in those terms and think positively for issue to population.

DR. HANA EL SAHLY: All right. Thank you. Dr. Petri.

DR. WILLIAM PETRI: Yes. Just to echo what's been said sort of as a subject matter expert on this, I find the efficacy data convincing and find the product

safe. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Petri. Dr. Young.

DR. VINCENT YOUNG: Just following up a little bit on what Dr. Rubin and others have said about the existence of randomized control trials. I think there's something that people have been following this for a while, like up to a decade or more, have noticed at the same time as these small trials come up. The placebo effects tend to rise, and I think there's a couple things going on there.

One is that in some of the cases there's such a long delay in getting people into these small, randomized control trials is that they're going through multiple rounds of vancomycin, or they're maintained on drugs over time. And at the same time, I think that we've learned a lot because there is a desperate need for these patients, and I think that the standard of care has evolved over that same time. I think people need to understand that short of giving FMT, our care and the use of antibiotics has also evolved over that

time.

So I think all of these things make it to the point that our standard of care has gotten better, but what we still have shown here is that in those select subgroup of patients that the FMT does give additional benefit to those patients who have failed our evolving standard of care.

DR. HANA EL SAHLY: Thank you, Dr. Young. I think we've heard from most everyone on the Committee. Let me see. Okay. Any final thoughts before we proceed to the voting, and after the voting we each have -- we can explain why we voted the way we did. If you have any final thoughts to share, please raise your hand. Okay, I will hand it over to our FDA colleague to proceed with the voting. Let me know --

MR. MICHAEL KAWCZYNSKI: You have Cliff.

DR. CLIFFORD MCDONALD: Sorry. One question would be, if this were approved, FDA's consideration for what they would do with enforcement discretion and specifically maintaining ready availability for some product in this area. It's been brought up in some of

the public comments. Actually, not the one we've heard from today, but it was from some of the written comments, specifically, from OpenBiome, I think.

I would just second from what I see with OpenBiome talking about trying to toss through this in such a way to drive the benefits of a more regulated and standardized product if this were approved. But at the same time, to maintain ready availability of some form of FMT in all nooks and crannies of this country and rural settings, et cetera. Over.

DR. PETER MARKS: I guess from the FDA perspective we can simply say, point well taken. And obviously, after this Committee votes, we will obviously -- that policy issue that we will be having to go back and, again, we often have to adjust policies in light of evolving regulatory approval from that and that's what we'll have to do here.

DR. HANA EL SAHLY: Okay.

MR. MICHAEL KAWCZYNSKI: All right. No more hands up, Dr. El Sahly.

DR. HANA EL SAHLY: So, Sussan, you want me to

read the questions and then begin the voting?

DR. SUSSAN PAYDAR: I would like to read the instructions once again and then we proceed with the question.

DR. HANA EL SAHLY: All right. Great.

DR. SUSSAN PAYDAR: Only our 13 regular members and 4 temporary voting members, a total of 17, will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the final voting question for the record, and afterwards, I'll ask all regular voting members and temporary voting members to cast their votes by selecting one of the three voting options which include yes, no, or abstain.

You will have one minute to cast your vote after the question is read. Please note that once you have cast your vote, you may change your vote within the one-minute timeframe. I'll announce when the voting poll has closed, and that's when all votes will be considered final. Once all of the votes have been tallied, we'll broadcast the results and read the individual votes aloud for the public record. Does

anyone have any questions related to the voting process before we begin? If no, let's go ahead.

Hana, if you could please read the voting question one for the record.

DR. HANA EL SAHLY: "Are the available data adequate to support the effectiveness of REBYOTA to reduce the recurrence of the *Clostridium difficile* infection, CDI, in adults 18 years of age and older following antibiotic treatment for recurrent CDI?"

DR. SUSSAN PAYDAR: At this time, please go ahead and select yes, no, or abstain. Okay, the one minute is up. It looks like all the votes are in. Michael, please end the vote by closing the poll and broadcast the results. Great.

So I'm going to read the individual votes. There are 17 total voting members for today's meeting; we have 13 yes and 4 folks who have voted no. I'll read one by one: Amanda Cohn, yes; Archana Chatterjee, yes; Dr. Arnold Monto, yes; Dr. Cliff McDonald, yes; Dr. David Kim, yes; Dr. Dean Follmann, yes; Dr. Eric Rubin, yes; Dr. Hank Bernstein, yes; Dr. Paul Offit,

yes; Dr. Stanley Perlman, yes; Dr. Steven Pergam, yes; Dr. Vincent Young, yes; Dr. William Petri, yes; Dr. Andi Shane, no; Dr. Jay Portnoy, no; Dr. Hana El Sahly, no; Dr. Holly Janes, no.

So, okay, that concludes this part of the voting section. Dr. Hana if you could please read the second voting question for the record?

DR. HANA EL SAHLY: Our second question today, "Are the available data adequate to support the safety of REBYOTA when administered to adults 18 years of age and older following antibiotic treatment for recurrent *C. diff*?" 01:12:25)

DR. SUSSAN PAYDAR: Okay, at this time you can go enter your votes. Timer is already on. Okay. The one minute is up; it looks like all votes are in. Michael, if you could please end the vote by closing the poll and broadcast the results. Okay, we have 17 total voting members for today's meeting. We have 12 yes and 4 who have voted no and 1 who have abstained from voting.

The answers are: Dr. Paul Offit, yes; Dr.

Vincent Young, yes; Dr. David Kim, yes: Dr. Cliff McDonald, yes; Dr. Arnold Monto, yes; Dr. Eric Rubin, yes; Dr. Archana Chatterjee, yes; Dr. Hank Bernstein, yes; Dr. William Petri, yes; Dr. Dean Follmann, yes; Dr. Steve Pergam, yes; Dr. Amanda Cohn, yes; Dr. Andi Shane, no; Dr. Holly Janes, no; Dr. Stanley Perlman, no; Dr. Jay Portnoy, no; Dr. Hana El Sahly, abstain.

That concludes our voting session. I'll now hand over the meeting back to Hana. Thank you so much. Hana.

DR. HANA EL SAHLY: Thank you all for voting and now we explain our vote. So I'm going to invite the participants one by one. Maybe I should begin with myself to explain my votes for the effectiveness question.

Were the data adequate? My answer was no. There were a couple of bars that were substituting an RCT that is double-blind, randomized and controlled, and even with that, the -- one of the two bars were not met, the statistical bars which would allow us maybe to consider an alternate. And a key secondary endpoint

was not met either.

When we put that in the context of how this whole FMT literature has evolved, I mean one of the most rigorous RCTs that were controlled with vancomycin being the control, it had to be stopped because FMT was inferior to a standard of care in recurrent *C. diff*.

So, when I put all of this in context, the evidence was probably not yet. Maybe an RCT or an alternate approach needs to be taken to affirm the effectiveness of this approach.

When it comes to safety, this is a sick population, and those who got more FMT are the sicker ones. But yet, there was no particular analysis that demonstrated that; it was our conclusion from looking at the data. So I abstain from voting on the safety because I thought it was just not enough data to comment or data presentation to comment on.

And now we'll go around the table. Dr. Kim has his hand raised, so I guess he wants to explain his vote first. Dr. Kim.

DR. DAVID KIM: Hello. Thank you so much.

For me, the bottom line I have from today's discussion is Rebyota has shown, despite limitations in clinical trials, an incremental benefit in preventing recurrent CDI in clinical trials. The evidence for our RBX's efficacy is far from obvious or evidential or convincing. But given today's discussion, I'm convinced that there is benefit. Also, I'm not overly concerned about RBX's safety profile.

I appreciate the written and oral testimonials provided by patients and providers in support of this product today. The current standard of care for recurrent CDI can be life-altering for many people. It's clearly not ideal. Repeatedly wiping out the gut biome to get rid of the weeds, to use the garden analogy provided by Dr. Kraft this morning, I want you to see that the weed overgrowth occurred before the normal flora come back.

The product is safe and easy to administer and can be beneficial for many patients with recurrent CDI. So RBX's is innovative and adds to the current small arsenal of treatment options available. To be sure,

the concept here is its prevention as treatment. So the data we're presented with today obviously don't say that RBX works for everyone or most people with CDI; it's far from it. But I do think that it's important to have a treatment option more readily available and more easily accessible to patients with recurrent CDI, and so I voted yes in both accounts.

DR. HANA EL SAHLY: Thank you, Dr. Kim. Dr. Portnoy.

DR. JAY PORTNOY: Great, thank you. I want to thank the FDA and the Committee members for this interesting discussion. I learned a lot and found it to be very stimulating.

In terms of my vote, I voted no. I was one of the four no voters. For safety, my concern was that this is a vulnerable population. These patients are desperate to get a treatment for which they don't have one, and the last thing I wanted to do is to subject them to a treatment that's not effective. They're going to be desperate to get it. Every doctor's going to feel obligated to prescribe it. Every patient's

going to demand it, and yet only one out of eight patients are going to benefit from it.

If we knew which patients those were, we would only treat them, but we don't know. Lots of patients are going to be treated with this product with no benefit. It's a really very moderate, beneficial effect. Also, statistically, it just squeaked by. As far as I know, it's not much better than placebo. It really is just a marginal benefit. Because it really didn't meet these requirements for effectiveness, I felt an obligation to vote no in order to protect patients from a treatment that I don't think is terribly effective even though they may desperately want to receive it.

In terms of safety, it asked, "given the data that was presented," so we're not supposed to assume data that wasn't presented. That's what lots of us are doing. I want to see evidence that this is a safe product. That these adverse events that occur in patients who receive this weren't caused by the fecal transplant. I don't know what fecal transplant does to

your risk of other diseases. We just don't know, and so we can't assume that things aren't causally related to it. We have to just take the data for what it is.

But telling us that they just didn't have the data and asking us to extrapolate and make assumptions, I don't think is fair. So I didn't feel comfortable voting yes with the safety issue either. So my two votes were no for safety, no for efficacy, and that's just how I vote given the data that I was presented with.

DR. HANA EL SAHLY: Thank you, Jay. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. Thank you, Dr. El Sahly. I don't really have a lot to add. My vote was yes for both questions based on the data that were presented and my interpretation of them as well as the discussions that took place today.

As Dr. Kim pointed out, the data are thin in support of this product being efficacious, however, this is a terrible disease for which we don't have very many therapeutic options, and, for certain patients, it

might actually be lifesaving, perhaps. And so that was my reasoning for the first yes vote.

With regard to the safety question, I did not feel that the data were terribly concerning, and so, given the status of these patients, I was convinced that weighing the risks versus the benefits, the risk was not high enough for me to vote no on that question. Thank you.

DR. HANA EL SAHLY: Thank you. Dr. Pergam.

DR STEVEN PERGAM: Thanks. I kind of (inaudible) giving a little bit of a background about why I voted the way I did. I think this was an area that there isn't a somewhat regulated product that there's going to be a lot of use of transplants (inaudible) it might be more dangerous for these patients. I think, in some ways, it almost feels like we're voting for a concept of screening and safety from potential pathogens that could be transmitted through fecal transplant. I'm not sure what this product is as well as what sort of mechanism of delivery of fecal transplants that would otherwise be used.

So I'm thinking about it in a (inaudible) in a little bit of a different way. But I think the other thing that I just want to bring up is the particular ways these trials were organized excluded a large number of patients that are potentially high risk for developing recurrent *C. diff*.

And so it'll be important to have the FDA put barriers around this or thinks about this or caveats to the approval is for people to look specifically at an (inaudible) criteria because, once something is FDA approved, people can look for a lot of different reasons and it would be important to note the specific exclusion criteria for patients who are involved in this trial (inaudible) a lot.

DR. HANA EL SAHLY: Okay. Thank you. Now I'm going to call on the rest of us. Dr. Cohn. Dr. Cohn, are you on?

CAPT. AMANDA COHN: Can you hear me?

DR. HANA EL SAHLY: Yes, I can now.

CAPT. AMANDA COHN: Sorry. I apologize, my video camera is being messed up.

My reason for voting yes is similar to what others have already said, that this is very limited and thin data. I appreciate the transparency of the sponsor, and I felt like given the context and the lack of other options for persons with recurrent CDI, that this was reasonable to approve. But I do encourage FDA to ask for continued post- -- if they do license this product, to ask for continued post-licensure safety and effectiveness data. Thank you.

DR. HANA EL SAHLY: Thank you. Dr. Shane.

DR. ANDREA SHANE: Yes. Thank you very much. So, I voted no for both questions. And while I really, really appreciate the challenges of this disease and also the moving testimonials that were presented, I also really felt obligated to vote on the questions, and I did not feel that the data that was presented was adequate based on a number of reasons. For effectiveness, I was concerned about the short term of follow-up and also the lack of diversity in participant enrollment.

And in the safety, I did have some concerns

about the events that occurred in the group that received -- or in the groups that received the active FMT. And so, for those reasons, I felt that -- and based on the wording of the questions -- that the best option would be no. But I did just want to say that I do really appreciate the challenges of this disease and the lack of options for patients.

And so, I hope that we will continue to move this field forward. Thank you.

DR. HANA EL SAHLY: All right. Thank you. Dr. Rubin.

DR. ERIC RUBIN: Hi. I voted yes on both questions, and I want to echo some of the things that other people said that the trials were not particularly well designed out of necessity. It's not -- I'm not trying to place blame here -- and the size of the effect was modest. And you can't rule out some safety issues from the data that were presented to us.

On the other hand, many of us have had a lot of experience caring for these patients and having FMTs. So, remember right now what's out there for

patients is they can get an FMT from their roommate, or if this is available, they can get a defined FMT that has undergone some sort of quality control.

And I think that if we have that product, it's going to actually enhance our ability to tell how well it works because one of the issues, and I think Dr. El Sahly brought this up before, is that the RCTs aren't great and they're small in part because the donor pools are really very, very diverse. And without having a product to look at, it's going to be difficult to tell. Now, we aren't going to be able to do placebo-controlled trials, and that was evident here because this will always be an option for patients at this point.

But I think that doing comparative trials of antibiotics versus a product like this will be good, and I think it will be -- and I want to echo what everyone else said, it'll be really important to expand this to other populations, including diverse populations.

DR. HANA EL SAHLY: Okay. Thank you, Dr.

Rubin. Dr. McDonald.

DR. CLIFFORD MCDONALD: Reiterating several of the things that have been stated already, we are in the world we're in and that there aren't other options. This already is widespread as an unregulated product, and there is evidence that, again, goes -- which is outside of this conversation today for some of that practice. And I do think this will be incrementally safer.

And I think that we're still looking for something better, too, but this is better than what we have.

DR. HANA EL SAHLY: If I may tangentially ask you something? So we have observed over the years sort of the CDC data, the (inaudible) data with the changes and the outcomes of placebos. The standards of (inaudible) to recurrences have decreased, mortality has (inaudible) and it's with other standards of care for primary and recurrent. Understanding that the potential niche for such a product is what you've been mentioning since this morning, would you be worried

about this product taking sort of the place of other proven therapies?

DR. CLIFFORD MCDONALD: I don't know that we really have -- again, I've sort of talked about the third or fourth recurrence and I do want to reiterate that there is historical data that suggests an increase in risk or recurrence with each sequential episode, and I could share some references on that. But that is historical. I don't -- I'm not saying I've seen a recent reference to that. But, you know, in those patients, we don't have anything else proven. I mean bezlo is it right now.

And you could especially imagine situations where someone has received bezlo previously, along with maybe fidaxomicin, which would be probably from the evidence the best standard of care for preventing another recurrent episode. But then, if someone has another recurrence, this makes sense.

Also, we really haven't talked a lot about that, but Vince Young could tell you much about that, of course, in terms of the pathophysiology and the

etiology and the pathogenesis -- I should say the pathogenesis of this disease.

And where other data -- again it's not part of this package, but -- shows that restoring key members of the fecal microbiota change what we call an index -- a risk index around bile acid metabolism and other things, which is really, you know, pretty worked out. This is not a black box, and we didn't really go into that. That there is always this lab evidence that comes from understanding the pathogenesis of disease. And we can't discount that as well.

DR. HANA EL SAHLY: Okay. Thank you. Let's see, Dr. Monto, who was silent today.

DR. ARNOLD MONTO: I'm taking a rest today. Whoops, wrong camera just got turned on. Now you can see me. I was taking a rest today from other activities.

I think everybody has really brought up the points that I would bring up today. It's always uncomfortable to the lay public when you have to go through statistical gyrations to come up with the

conclusion. I understand why it had to be done.

I'm uncomfortable with the fact that the placebo group was different in the different phase studies, but I think the bulk of evidence supports a yes vote because -- and we're not supposed to think about this -- but what's out there and what is being used is really unregulated, and it's much better to have a regulated product which can be followed over time to see how well it's working.

I am concerned if it displaces other things, but I don't know that there's a whole lot out there that really is any more effective than the modest effect of this product.

Safety, again, we heard things to explain findings such as there was a longer period of observation in the treated than the placebo group. But there doesn't seem to be a strong safety signal, which explains my yes vote which was, I think, a measured vote because this is not an ideal situation nor is it an ideal situation for the patients who are, as we know, long-suffering.

And thank you for letting me catch up on an FDA meeting where I didn't have to sit and in a tense situation where you are now sitting all day.

DR. HANA EL SAHLY: All right. Thank you, Arnold. Let's see, who did we not hear from? Dean. Dr. Follmann.

DR. DEAN FOLLMANN: Yeah, thanks, Hana. I think most of the reasons I gave for voting yes on both efficacy and safety are articulated when you and Holly and I were talking -- sort of laid that out. And I just wanted to make a couple of additional points. One thing was that Dr. Rubin brought out that there were several randomized studies where they did have control arms. I think that would be interesting to look at and maybe a meta-analysis could be done of that to support -- I know it's a different product, but, to me, that would provide additional evidence.

I would say that the safety data -- it seemed to me that you could do a person-years analysis to adjust for the duration of follow-up, and also there's statistical methods to adjust for the drug-exposed

group, including people who had failed on placebo and thus being in some since sicker, and there's no analysis like that done, but I think that would've been helpful.

And then finally -- who was it -- Dr. Portnoy sort of lamented the fact that there wasn't an integrated analysis of safety and efficacy. There are ways to do that as well that are sometimes done, particularly in the infectious disease world and also the cardiovascular world known as DOOR analysis or win ratio analysis. And so that might've been helpful evidence to have at this meeting as well. And that's all I have.

DR. HANA EL SAHLY: All right. Thanks, Dean. Dr. Young.

DR. VINCENT YOUNG: Yes. I voted yes on both questions, and we've talked a lot about phasing inference, and I have to -- as brought in as a subject matter expert, I have probably some warped priors that I had to try to ignore and address the questions exactly as they were said.

But I think that given the evolution of our care of recurrent *C. difficile* -- like I said, they were changes in our standard of care -- and the fact that the sponsor had done the best I think that they could during a time where patients' willingness to enroll in placebo-controlled trials and difficulties of getting people to be recruited into such trials; I think that the data were adequate.

Are they exactly what we wanted? No. But I did feel that the analysis of the data that were presented was accurate to allow me to vote yes on both questions. So thank you.

DR. HANA EL SAHLY: Thanks. Dr. Janes.

DR. HOLLY JANES: Thank you, Hana. I was one of the folks who voted no on both counts. I find it sort of impossible to disentangle the safety and efficacy which are inextricably linked and need to be balanced one against another. I think that's previously articulated that I found the package to be relatively weak in terms of the level of statistical evidence, the general eligibility of the study

populations, and the robustness of these analyses to the assumptions.

And the arguments that I heard presented that were really compelling were really around the suffering that these patients are experiencing and a strong desire for additional clinical options for these patients and perhaps some level of dissatisfaction with the current clinical context around unregulated use of FMT and dissatisfaction with the current regulatory situation. But that's not the question we're asked to consider, which was really the safety and efficacy of this product in particular and so, on that basis, I voted no.

And I guess, finally, I was not fully convinced that we could not have been presented with a stronger package of data either by drawing in additional literature if it exists or by considering a different source of evidence going forward if this question is pursued and presented again to the Committee. Thank you.

DR. HANA EL SAHLY: Thank you, Holly. Let's

see. Dr. Bernstein. We did not hear from you.

DR. HENRY BERNSTEIN: Thanks, Hana. So I have to say that having reviewed all the materials before the meeting, I was actually leaning towards two nos. And I really felt that the data were thin, and I also continue to struggle as I've mentioned earlier in the meeting about why enrollment was so challenging resulting in quote/unquote borrowed data. It just made me think "no" as I came into the meeting.

But ultimately listening to both the presentations that were made as well as the conversations around the table, it swayed me that they're really -- although it's modest benefit in safety, I really felt that there was a real need for these patients to have this option, so I switched from two nos to two yeses.

DR. HANA EL SAHLY: Very good. Thank you. Dr. Offit.

DR. PAUL OFFIT: Thanks, Hana. So vaccines are easier because they're generally given to healthy young people. This is a product that's given to people

who aren't healthy, some who are quite unhealthy, who've already failed one or two rounds of an existing therapy. So it's not surprising then that the efficacy is not going to be dramatic, but I think there was efficacy, and so I do think this does meet a need. And as I said earlier, I do think that this product certainly offers advantages over some of the things that we're doing in our hospital in terms of trying to make sure that we're not inadvertently inoculating someone with a pathogen.

And then in terms of the safety, there wasn't anything really that jumped out at me. So I do think, to me, the benefits of this product outweigh the risks. So I was two yes votes.

DR. HANA EL SAHLY: All right. Thank you. Dr. Petri.

DR. WILLIAM PETRI: Yes. First of all, it's my first FDA meeting ever, so as a member of the public, I'm very pleased with how open and rigorous the discussion was, and I voted yes on both things.

I found that the product was safe. The side

effects are -- nausea and abdominal pain were the two things that really sort of stood out, and unfortunately, that is part and parcel of having *C. diff*. And the effectiveness, yeah, I mean, I think that the statistical analysis was prespecified before the Phase 3 study, and so I found that convincing. Thank you very much.

DR. HANA EL SAHLY: All right. Thank you. I think all members had a chance to explain their vote. The votes are in, and I hand it over to the FDA. Dr. Marks, you're on mute.

MEETING ADJOURNED

DR. PETER MARKS: Yeah. Sorry. Thanks a lot. Thanks for getting me unmuted there. It kept going back and forth there. Okay, thanks very much.

So, I just wanted to thank everyone today. First of all, want to thank the members of the Committee for a very thoughtful discussion here. In addition, obviously, to the votes, there was some very

important discussion that we will note and make use of. Really appreciate that. Want to thank also the sponsor, other presenters, and the Open Public Hearing speakers.

Also want to really sincerely thank the FDA presenters and the advisory Committee's staff for making this happen today. We very much appreciate all of the effort, and we'll look forward to going back and looking over all the advice from today. So thanks very much to everyone, and thank you, Dr. El Sahly, for chairing today. Thanks very much.

DR. HANA EL SAHLY: Thank you. All right. Sussan, I think it's yours.

DR. SUSSAN PAYDAR: Adjourned.

MR. MICHAEL KAWCZYNSKI: Sussan?

DR. SUSSAN PAYDAR: I'm muted.

DR. HANA EL SAHLY: Okay, now we hear you.

MR. MICHAEL KAWCZYNSKI: We hear you.

DR. SUSSAN PAYDAR: You can hear me? Okay, great. For closing comments, I wanted to thank the Committee and CBER staff for working so hard to make

this meeting a successful meeting. I now call this meeting officially adjourned at 4:53 p.m. Eastern Time. Thank you, everybody. Have a nice evening.

MR. MICHAEL KAWCZYNSKI: All right, thank you. And with that, this meeting is concluded. Feel free studio to take us offline.

[MEETING ADJOURNED]